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Cocaine effects on behavioral responding to a novel object placed in a familiar environment

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Abstract

It is well established that cocaine stimulant effects are potentiated in a novel environment. The relationship between cocaine and novel stimuli, however, remains poorly understood. In this study, we examined the effects of different dose levels of cocaine (5.0, 10.0 and 20.0 mg/kg) administered to separate groups of rats ($N=10$) on attentional behavior to a small novel object stimulus placed within a central zone (CZ) of a familiar open-field environment. This method has been used to assess attentional function in young animals, brain damaged animals and drug treated animals. In previous studies, we have shown that attention to a novel object stimulus can be quantified by an animal's contact time with the object. Following a series of pre-exposures to the test environment without the novel object, we found that cocaine in a brief 10 min test session with the novel object present produced a dose related decrease in mean contact time with the novel object. In contrast caffeine (5.0, 10.0 and 20.0 mg/kg), which induced a locomotor stimulant effect equivalent to cocaine, did not impair novel object contact time. Correlational analyses indicated absence of significant negative correlation coefficients of locomotor activity and contact time with the novel object. These considerations indicate that the observed cocaine impairment of attention to the novel stimulus is not attributable to hyperactivity *per-se*. Furthermore, cocaine, but not caffeine, induced a dose related decrease in the duration of spontaneous grooming. Thus, cocaine appears to diminish an animal's overall capability to maintain a behavioral process (i.e., investigate a novel object stimulus and/or engage in spontaneous bodily directed activity such as grooming). Altogether, the findings obtained in the present study indicate that cocaine impairs an animal's ability to sustain attention to stimuli and suggest a behavioral state analogous to an attention deficit disorder.
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Keywords: Attention; Cocaine; Caffeine; Novel stimuli; Open-field Environment; Grooming; Locomotion

Cocaine is a potent stimulant drug which also can be highly addictive. In animal models, the stimulant effects of cocaine are readily quantified in terms of an increase in locomotor activity. While the measurement of locomotor activity is readily accomplished, it is also influenced by organismic variables (e.g., age, gender, etc.) as well as environmental variables (e.g. size of open-field test arena, ambient sound, light intensity, etc.). One environmental variable of particular relevance to cocaine stimulant effects is the novelty/familiarity of the testing environment (Cerbone and Sadile, 1994). A number of studies have shown (Kyatkin, 1992; Carey and Damianopoulos, 2006) that the locomotor stimulant effect of cocaine is substantially greater in a novel environment *vs.* a familiar environment. Furthermore, when the same dosage of cocaine or a related psychostimulant drug such as amphetamine is administered prior to placement of an animal into a novel *vs*. a highly familiar environment such as the homecage (Klebaur et al., 2002; Uslaner et al., 2001; Li et al., 2004), then, not only is activity enhanced in the novel environment, but in addition, structural changes occur in catecholaminergic-dense brain areas. Combining a novel environment with a psychostimulant drug treatment, therefore, can induce lasting changes in the brain. A novel environment not only potentiates the stimulant effects of drugs such as cocaine but it has also been suggested that responsiveness in a novel environment in a non-drug state is, at the same time, a predictor

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of an animal's degree of response to drugs such as cocaine (Nadal et al., 2005; Dellu et al., 1996; Deroche et al., 1993; Piazza et al., 1990).

Seemingly, a common mechanism by which novel environments and psychostimulant drugs induce behavioral activation is by increasing the arousal level of the animal. As has been long known (Koe 1976; Ritz et al., 1990), cocaine increases extracellular dopamine (DA), 5-hydroxytryptamine (5-HT), and norepinephrine (NE) by binding to neurotransmitter transport proteins to prevent the re-uptake inactivation of released DA, 5-HT, and NE. Presumably, the arousal level generated by a novel environment would evoke a larger release of DA, 5-HT, and NE than exposure to a familiar habituated environment. As a consequence, following placement in a novel environment, cocaine re-uptake blockade would be expected to produce a larger increase of transmitters in the extracellular space. This potentiated neurochemical effect of cocaine could account for the enhanced behavioral activation observed when the cocaine treated groups are tested in a novel *vs.* a familiar environment. Functionally, the novel environment effect could be viewed as equivalent to an increased dosage of a psychostimulant drug. While the increased arousal level elicited by a novel environment potentiates cocaine stimulant effects, it remains to be determined if the reverse is the case; that is, animals in the cocaine drug state are also more responsive to novel stimulus features of a test environment.

A well-established manipulation by which one can assess an animal's behavioral response to a novel stimulus object is to introduce a new object into an environment with which the animal is already familiar (Cheal, 1980). Typically, the novel object elicits investigatory behavior. This proclivity to explore a novel object in a familiar environment has been applied to assessments of attention deficits in brain-injured animals (Hayne et al., 1992) and to study the development of attention processes in young animals (Cheal, 1987). The introduction of a novel object in a familiar environment can readily be adapted to image analysis systems by creating a sub-sector of the test environment that contains the stimulus object. This general approach has also been used to study the effects of stress hormones on exploratory behavior in rats (Oitzil and de Kloet, 1992).

In several earlier reports (Dai and Carey, 1994a,b), we have used a methodology which employed novel stimuli but in the context of a familiar environment. In this testing protocol, we place a small novel object into a computer-defined central zone of an open-field. This relatively small change in the environment does not increase locomotor activity or frequency of entry into the central zone. Rather, the presence of the novel object reliably increases the average duration of each entry into the central zone. This increase in the duration of entry into the central zone is characterized by contacting and sniffing the novel object. This research protocol, therefore, provides a useful tool to determine whether or not cocaine alters animal responsiveness to novel stimuli. In a previous study, (Dai and Carey, 1994b) we found that the NMDA antagonist, dizocilpine, (MK-801) severely impaired an animal's responsiveness to the novel object in the central zone. In fact, MK-801 treated animals failed to attend to the presence of a novel object. In the present study, we assessed the effects of different dose levels of cocaine (5, 10, and 20 mg/kg) on responsiveness to a novel object. In that the effect of cocaine could be considered as secondary to increase in locomotor activity, we also tested animals with similar dose levels of caffeine as an alternative stimulant drug but with a different neurotransmitter profile not linked to an impairment of attention (Holtzman and Finn, 1988; Choi et al., 1988; Katims et al., 1983; Snyder et al., 1981).

1. Methods

1.1. Animals

Forty naive male Sprague–Dawley rats from Taconic Farms (Germantown, NY), 4 months old and weighing approximately 400 g at the start of the experiments were used. Upon arrival, the animals were housed in individual 48×27×20 cm clear polycarbonate cages in a climate-controlled room at 22–24 °C with a 12-h dark and 12 h light cycle. During the first week after arrival, all animals were handled and weighed daily for 7 days. During the second week, the animals received three injections I. P. of .9% saline (1.0 ml/kg) in order to acclimate the animals to the injection procedure. All experiments occurred during the 12-h light cycle (6AM–6PM). The experimental protocol was approved by the Syracuse Veterans Administration Medical Center Subcommittee for Animal Studies.

1.2. Drugs

Cocaine hydrochloride (Sigma Chemical Co., St. Louis, MO) was dissolved in sterile distilled H_2O to a concentration of 5, 10 or 20 mg/ml. Caffeine (Sigma Chemical Co, St. Louis, MO) was dissolved in sterile, warm, distilled H_2O to a concentration of 5, 10 or 20 mg/ml. Cocaine and caffeine injections were administered I.P. in a volume of 1 ml/kg.

1.3. Apparatus

All of the behavioral tests were conducted in a square open-field compartments (60×60×45 cm). A closed-circuit video camera (RCA) TC 7011U) was mounted 50 cm above the center of the open-field arena. Signals were analyzed by a video-tracking system (Ethovision, Noldus Information Technology, Inc., Leesburg, VA) and stored into a PC compatible computer. The walls of the test chamber were white as well as the floor of the open-field arena. After each test session, the floor was cleaned with warm water and then dried. Testing was conducted under conditions of red light illumination to enhance the contrast between the subject and background as well as to reduce the animal's shadow and to facilitate exploratory behavior (Nasselo et al., 1998). A central zone (CZ) comprising 1/9 of the floor area was monitored independently from the rest of the arena and distinguished only by the computer.

A solid foam block of 4×4×2 cm (Block Builders, Geoffrey) was fixed in the center of the CZ with Velcro for each of the object-present test sessions. The rationale for this

arrangement was to create an environment in which the rat would have a low but reliable probability of entering the CZ regardless of the presence or absence of an object. In order to insure that penetration of the CZ could be related to the animal's attention to the object, the animal's head was blackened by a non-toxic black marker pen so that the overhead camera monitored only this feature of the rat's body whether the animal was outside or inside the CZ. The test sessions were of a 10 min duration. The behavioral measurements included: (a) total distance traveled in the chamber; (b) number of entries into the CZ; (c) total duration in the CZ; and (d) a derived measure — average duration/CZ entry. The complete test procedure was conducted automatically without the presence of the experimenter in the test room. In addition a VCR was also connected to the camera and each test session was videotaped. Subsequently, the videotapes were scored by two experimenters to provide an independent measurement of the animal's contact with the novel object. In addition, spontaneous behaviors not effectively quantified by the video image analysis system were subsequently scored by two experimenters from the videotapes;

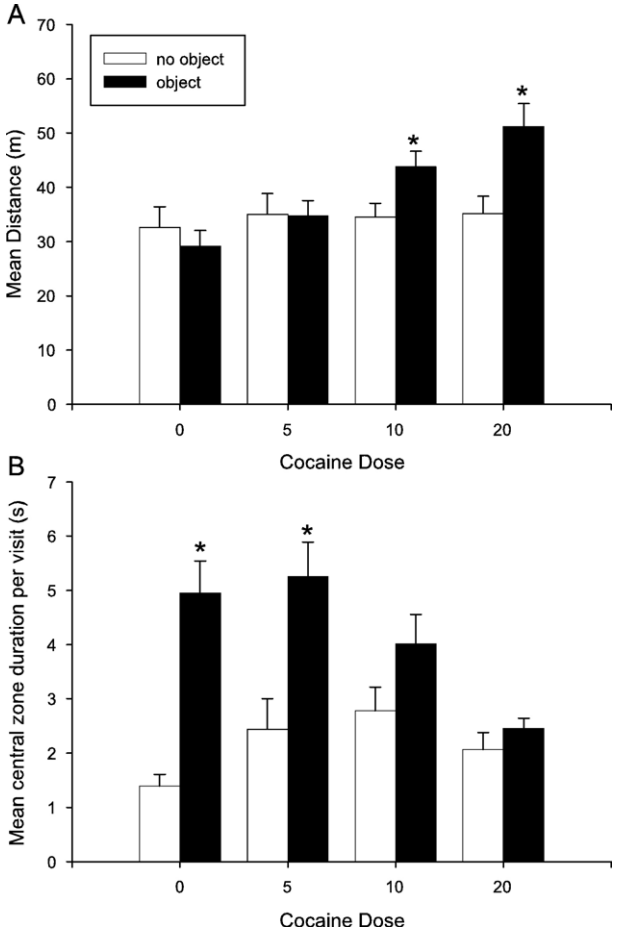

Fig. 1. *Cocaine Test.* Means and SEMs for (A) locomotor distance (m) and (B) mean duration/CZ entry (s) for separate treatment groups injected with cocaine (.0, 5.0, 10.0 or 20.0 mg/kg 10 min prior to 10 min open-field object-present tests. Open bars are for non-drug, no-object present test; filled bars are for the object present drug test with cocaine in the four groups. *$P<.05$ in correlated *t*-test comparisons.

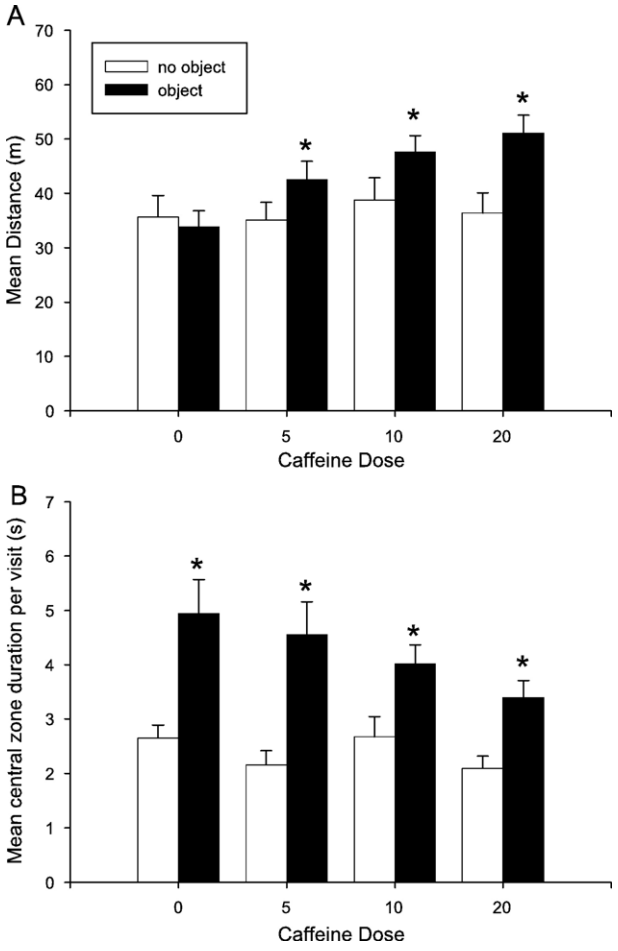

Fig. 2. *Caffeine Test.* Means and SEMs for (A) locomotor distance (m) and (B) mean duration/CZ entry (s) for separate treatment groups injected with caffeine (.0, 5.0, 10.0 or 20.0 mg/kg 10 min prior to 10 min open-field object-present tests. Open bars are for non-drug, no-object present test; filled bars are for the object present drug test with caffeine in the four groups. *$P<.05$ in correlated *t*-test comparisons.

specifically, grooming, open-field rears and wall rears. Grooming was specified as any self-directed activity such as licking, rubbing or scratching. Rearing was categorized as *wall rears* if the rat touched the wall with both paws or leaned up-against the side wall; all other rears (head-up with torso and front paws off the floor) were categorized as *non-wall rears.* The experimenters also recorded the frequency and duration of contact with the novel object. All scoring was performed without knowledge of the treatment. Intermittently, a subject previously scored by one experimenter was scored by the other experimenter. Scores were compared for agreement and/or drift in scoring criteria over the duration of the scoring protocol. Inter-experimenter agreement was high: Pearson-*r* correlation was >.95.

1.4. Design and procedure

Initially, seven 10 min no-object present test sessions were conducted so that animals were familiarized with the test environment without an object being present. On the basis of

this familiarization testing, four groups ($N=10$) were formed, equated for bodyweight and locomotor distance traversed in the open-field. In our previous reports (Dai and Carey, 1994a,b) we showed that a reliable response to an object placed into the CZ occurs not only in the initial 10 min test but also in subsequent tests in which there was a novel object present. In the present study, we conducted 3 novel object tests spaced 4 days apart with intervening no-object-present test sessions. On the initial object-present test session, the groups received one of four treatments 10 min prior to testing; saline, 5.0, 10.0, or 20.0 mg/kg cocaine. On the second object-present test, the treatments were: saline, 5.0, 10.0, or 20.0 mg/kg caffeine. On the third object-present test the saline/cocaine treatments were repeated: saline, 5.0, 10.0, or 20.0 mg/kg cocaine. The saline treatment was administered to the same group on each test session and the drug (cocaine or caffeine) groups received the same dose level of drug on each of the three drug tests.

1.5. Statistical analysis

One-Way analysis of variance (ANOVA) and paired *t*-tests were used. The dependent variable measures included, distance traveled, and average duration per entry into the CZ (image analysis scores), average duration of proximal contact with the novel object and frequency and duration of grooming (videotape scores). $P<.05$ was used as the criterion level (α-level) of statistical significance. The Pearson-*r* statistical method was used to calculate correlations between locomotion distance and mean object contact time.

2. Results

The image analysis results of the three drug treatment test sessions with the object present in the central zone are shown in the first three figures. To provide a contrast, the results of the non-drug 10 min no-object session, which preceded each drug treatment test, are also shown in these figures. Fig. 1 presents (A) the locomotion distance scores and (B) average duration per central zone entry (mean CZ duration/entry) for each group in the no-object saline test and in the initial object-present cocaine test. As can be seen in Fig. 1A, the distance scores for the groups on the non-drug, no-object, saline test were similar ($F_{3,36}=.5$, $P>.05$); but, on the object-present cocaine test, the locomotion distance scores increased as a function of dose level of cocaine ($F_{3,36}=8.7$, $P<.001$). For the mean CZ duration/entry, Fig. 1B, the non-drug, no-object test indicated a significant difference among groups ($F_{3,36}=4.4$, $P>.01$). This statistically significant effect was due to the higher scores of mean CZ duration/entry during the saline no-object test for the group that subsequently received the 10.0 mg/kg cocaine treatment on the object-present test. In view of this difference in baseline scores, the object-present results were evaluated by paired *t*-tests (no-object *vs.* object-present tests). To be consistent, the distance scores were also statistically evaluated using paired *t*-tests. For the group that received saline on both tests, the differences in locomotion distance scores were not significant ($P>.05$); but, the mean CZ duration/entry scores were significantly different ($t_{9df}=6.4$, $P<.001$). Similarly, for the cocaine 5.0 mg/kg group, the distance scores were not different ($P>.05$), but CZ duration/entry scores were significantly different ($t_{9df}=3.1$, $P<.01$). In contrast to this pattern, for the cocaine 10 and 20 mg/kg groups, the distance scores were higher on the cocaine tests ($t_{9df}=4.1$, 5.1, respectively, $P<.01$), but the mean CZ duration/entry scores were not different ($P>.05$). The results of the caffeine tests are presented in Fig. 2A, B. The saline group results were comparable to those shown in Fig. 1A, B. For the saline group, the difference between the locomotion scores on the object *vs.* no-object tests were not significant ($P>.05$); but, the mean CZ duration/entry scores were substantially higher on the object-present test ($t_{9df}=4.4$, $P<.01$). However, for the caffeine treated groups, 5.0, 10.0 and 20.0 mg/kg dose levels, all the differences between object *vs.* no-object tests were statistically significant; for distance ($t_{9df}=3.3$, 4.2, 5.1, respectively, $P<.01$); as well as for mean CZ duration/entry ($t_{9df}=4.2$, 3.1, 3.0, respectively, $P<.01$). While it is evident that there was an overall decrease in mean CZ duration/entry for the caffeine treatment, a One-Way

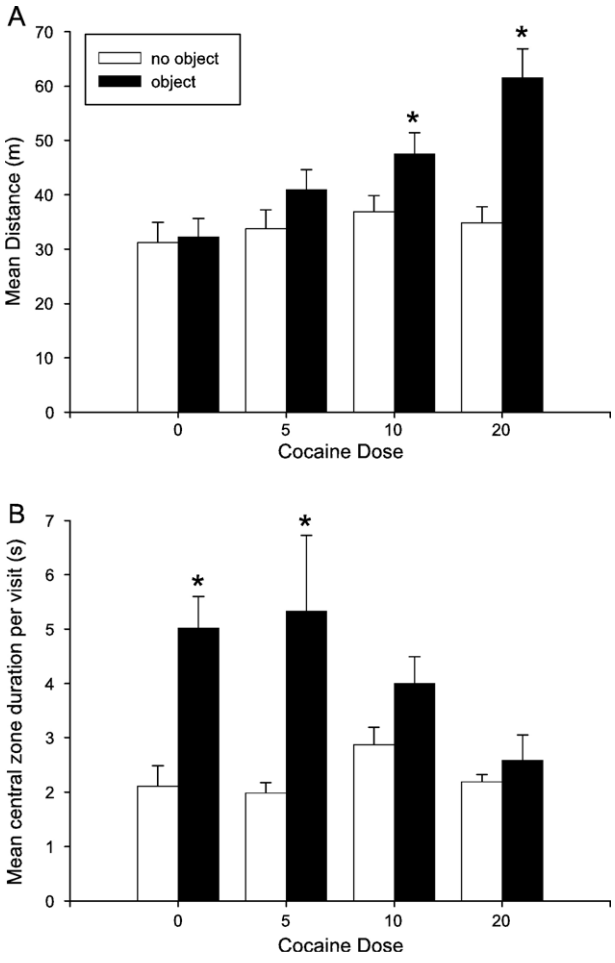

Fig. 3. *Repeat Cocaine Test.* Means and SEMs for (A) locomotor distance (m) and (B) mean duration/CZ entry (s) for the four separate treatment groups injected with cocaine (.0, 5.0, 10.0 or 20.0 mg/kg 10 min prior to 10 min open-field object-present tests in the repeat cocaine test. Open bars are for non-drug, no-object present test; filled bars are for the object present drug test with cocaine in the four groups. *$P<.05$ in correlated *t*-test comparisons.

ANOVA indicated that these mean differences were not statistically significant ($P>.05$). However, the relevant observation is the change in duration from when there was no object present to when the object was present in the central zone. A statistically significant difference indicates that the presence of the object had a behavioral impact. The results of the second cocaine test are presented in Fig. 3A, B. Overall, the results were comparable to those of Fig. 1.

In order to provide an independent validation of the central zone duration/entry scores as being reflective of the time spent by the animal attending to the object, the results of the videotaped scoring of the animal's contact with the object were evaluated. The mean time spent contacting the object for the saline group on the first object test was 5.2±.45 s. This compares favorably with the image analysis scores of mean CZ duration/entry, 4.95±.58 s. Thus, the image analysis scores of mean CZ duration/entry provided a reliable measure of an animal's contact with the object. When the videotape scored contact times for cocaine treatment test results were evaluated using a One-Way ANOVA, the cocaine treatment reliably decreased contact time with the object ($F_{3,36}=6.6$, $P<.001$). In contrast, the caffeine treatment did not decrease mean contact time with the object ($F_{3,36}=1.4$, $P>.05$). The differences in contact time were not related to detection of the object in that in each of the tests, there were no differences among the groups in the initial latency response to the object ($P>.05$).

Another method to assess the impact of locomotion upon contact time with the object is to correlate mean CZ object contact time with locomotion distance scores. When correlations were performed for each treatment group on the cocaine and caffeine test, the correlations were low and not statistically significant ($P>.25$). The measurement of the spontaneous behaviors of rearing and grooming indicated that neither caffeine nor cocaine had statistically significant effects on rearing behavior but there were effects upon grooming. When grooming behavior was evaluated in terms of duration of grooming, there were marked drug effects and differences between cocaine and caffeine. There were no differences in mean grooming durations (s) for the saline group on the drug test days: 64.7±15.8, 84.3±16.3, 79.3±15.2 ($F_{2,27}=.4$, $P>.05$)

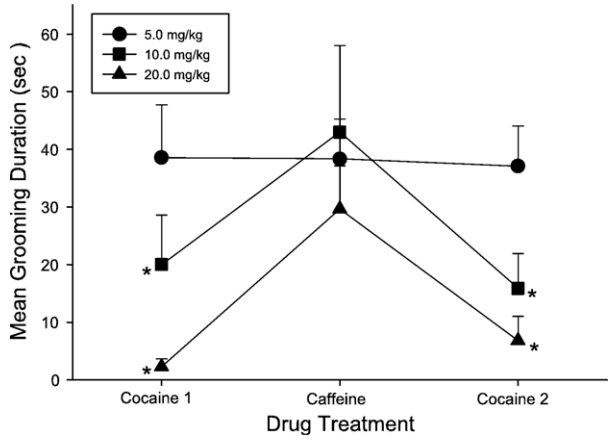

Fig. 4. *Grooming.* Means and SEMs for grooming (s) in the two cocaine tests and the caffeine test. *$P<.05$ *vs.* cocaine 5.0 mg/kg and three caffeine doses.

and these grooming duration scores were higher than each of the drug treatment groups. Accordingly, a statistical comparison was made only of the three groups that had received either cocaine or caffeine on separate test days. Cocaine induced a dose-dependent decrease in the duration of grooming ($F_{2,27}=9.2$ and $F_{2,27}=10.1$, $P<.001$ for cocaine tests 1 and 2, respectively), while caffeine had no statistically significant effect ($F_{2,27}=.4$, $P>.05$). Fig. 4 compares the grooming durations on the cocaine and caffeine tests. As can be seen in Fig. 4, the duration of grooming was decreased substantially more by cocaine than by caffeine.

3. Discussion

The cocaine and caffeine locomotor activation effects observed in the present study were in agreement with the expectations. Both drugs induced hyperlocomotion. The important finding, however, was that cocaine, but not caffeine, impaired responsiveness to a novel object in a familiar environment. The behavioral response to the novel object obtained in the present study for the non-drug treated animals were in agreement with our previous findings (Dai and Carey, 1994a,b). The introduction of the novel object did not increase locomotor activity but, rather, increased the amount of time an animal spent per entry into the central zone. Previously, we had shown from the tracings of paths of animals in an open-field, that, without an object present, the animals did not stay in the central zone but simply moved through the central zone (Dai and Carey, 1994a,b). With an object present, the animals stayed for a brief period to sniff and contact the object in the central zone. From videotape recordings, the animal's behavior toward the object were subsequently viewed and scored. The results showed that the animals sniffed and contacted the object upon entering the central zone. This is the expected result when the animal encounters a novel stimulus object. In agreement with our previous reports (Dai and Carey, 1994a,b), we found that, with brief tests spaced several days apart (interspersed with non-drug tests without the object for heightened familiarity with the test environment), the response to a novel stimulus object could be sustained over several test sessions; i.e., the presence of an object in the central zone retained its novelty.

Overall, the results obtained in the present study were reminiscent of our earlier finding with the NMDA antagonist, MK-801 (dizocilpine) (Dai and Carey, 1994b).That is, at higher dose levels, cocaine like MK-801, induced hyperlocomotion and diminished responses to the novel object. For both drug treatments, the drug treated animals appeared not to respond to the novel object as they passed through the central zone in that their paths and time spent in the central zone were similar to those when no object was present. It can be argued that the drug state that induced hyperactivity also prevented the animals from inhibiting movement to allow the animals to stop and explore the novel object. Considered in this way, the absence of response to the novel object simply confirms the drug-induced hyperactivity. In our previous investigation with MK-801, we found that even at dose levels that did not evoke hyperactivity, the animals, still did not respond to the novel object. In contrast,

however, low dose cocaine treated animals of the present study did not show hyperactivity and there was no interference with the response to the novel object. At the same time, caffeine treatments while inducing a level of hyperlocomotion which was similar to the cocaine treated animals permitted a reliable investigatory response to the object. Furthermore, there were no statistically significant negative correlations between cocaine induced hyperactivity and contact time with the object. Altogether, these considerations suggest that, in addition to hyperlocomotion, cocaine diminishes an animal's capability to respond to a small change in its environment. A novel stimulus object that was selectively attended to by the non-drug animals apparently was not sufficiently salient to the cocaine hyperlocomotion animals. Possibly, the cocaine treatment disinhibited the animal's familiarity to the stimulus complex of the open-field environment, thereby, making the small object less distinctive as a novel feature. As we have shown previously (Dai et al., 1995) animals do not respond to the addition of a small novel object to the environment if the environment itself is novel. On the other hand, when the duration of grooming bouts was measured, cocaine, but not caffeine, decreased grooming bout duration. The reduction in grooming bout duration and the response duration to a novel stimulus object could be indicative of an impaired capacity to sustain attention to stimuli (i.e., to unique features in the environment or to bodily surface stimuli). When considered from this perspective, the cocaine treatment could be viewed as inducing a state analogous to an *Attention Deficit Hyperactivity Disorder* (*ADHD*).

The findings obtained in the present study point to the need for a more comprehensive examination of the cocaine effects in an open-field behavior beyond locomotor activation effects. If cocaine treated animals are not only hyperactive but, in addition, more distractible and less attentive in detecting details of their environment, such a behavioral impact would have substantial implications for conditioning and context specific sensitization effects associated with cocaine treatment. It may be that cocaine treated animals and non-drug animals given similar exposures to a novel environment could acquire different information about the environment. If such animals are subsequently compared for their response to the same environment without drug, the environment may seem relatively more novel to the animals that had experienced the environment under the influence of cocaine. An enhanced activation response in the group previously treated with cocaine could then be mislabeled as a conditioned cocaine activation state. The same consideration applies to context-dependent sensitization effects, where groups are first tested in an environment either with a high dose of cocaine or vehicle and then, in a subsequent challenge test in the same environment, both groups are tested with a lower dose of cocaine (Pert et al., 1990). The enhanced response of the group previously treated with cocaine may not represent a context specific cocaine sensitization effect, rather, the enhanced response may be attributable to the environment being relatively more novel for the group which had previously been exposed to the environment under a high dose of cocaine. Since cocaine stimulant effects are enhanced in a novel environment, this possibility can provide an alternative explanation for a context-specific sensitization effects. This line of reasoning could also be extended to conditioned place preference (CPP) experiments in which environments experienced in the cocaine drug state are subsequently preferred in the non-drug test compared to environments which had been experienced in association with vehicle treatment (Spyraki et al., 1987; Nomikos and Spyraki, 1988; Koob, 1992). Instead of a cocaine conditioned reward effect, the CPP effect could represent a preference for a relatively more novel (cocaine-associated) over a more familiar (vehicle-associated) environment. A preference for a novel *vs*. a familiar environment in a CPP test has been suggested as a factor in the study of CPP (Scoles and Siegel (1986). In fact, novel stimuli can induce a CPP effect (Bevins and Bardo, 1999; Carr et al., 1988). Of course novel stimuli have been long known to have reward potency (Berlyne 1966, 1969) and the present analysis does not change the fact that a CPP effect does represent a reward effect. However, a treatment effect that induces CPP by interference with the acquisition of familiarity with an environment is a vastly different effect compared to one that generates CPP by directly inducing a positive hedonic state that becomes associated to environment cues. These examples highlight the need to examine the impact of cocaine treatments upon attention processes and acquisition of information.

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