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Cocaine conditioning and sensitization: The habituation factor

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Abstract

The behavioral and neurobiological impact of cocaine can be strongly influenced by the environmental context in which the cocaine effects are experienced. In this report, we present the results of an experimental study in which the effects of environmental context in terms of novelty/familiarity upon locomotor stimulant effects of cocaine were examined. In the first phase of the study, two groups of naïve rats (N=10/group) received either cocaine (10 mg/kg) or saline immediately prior to a 20-min test in a novel open-field environment. After three daily cocaine/saline test sessions, both groups received a saline test to evaluate cocaine conditioned drug effects. In the second phase, two groups (N=10/group) were administered a 20-min saline test 1 day prior to receiving the same cocaine and saline testing regimen as in the first phase. Cocaine sensitization effects were not observed when the cocaine treatments were initiated in a novel environment but were observed when the same cocaine treatments were preceded 1 day by a single 20-min test environment exposure. The maximal locomotion sensitization effects observed, however, did not exceed the locomotor stimulant effects induced by cocaine administered in a novel environment. Thus, the cocaine sensitization manifested following a brief 20-min exposure to the test environment 1 day prior to cocaine administration represented a reversal of an inhibitory habituation effect. Cocaine-conditioned effects were also observed in both phases. These cocaine conditioned effects approximated, but did not exceed, the activation effects generated by a novel environment.
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With repeated exposure to a novel open-field environment laboratory rats typically exhibit a decline in locomotor activity. This well-known habituation phenomenon (Cerbone and Sadile, 1994; Lubow and Kaplan, 2005) has been extensively studied and constitutes an adaptive inhibitory behavioral response. Conversely, if animals are given repeated tests in an open-field environment but with psychostimulant drugs, there can be an amplification of the initial drug-induced locomotor response (Kalivas et al., 1992; Heidbreder and Shippenberg, 1994; Mattingly et al., 1994). The potent but opposite behavioral effects of drug-induced locomotor sensitization and habituation can interact in several important ways. When the same psychostimulant drug treatment is administered in a novel environment vs. in a highly familiar home-cage environment, the differential effect upon neurobiological processes can be dramatic. If the drug treatment is administered in a novel environment, structural changes in selected brain areas can be observed but these changes are markedly attenuated when the same drug treatment is administered in a familiar home-cage environment (Klebaur et al., 2002; Uslaner et al., 2001; Li et al., 2004). Similarly, behavioral studies have shown that acute psychostimulant drug treatments have potent psychomotor stimulant effects if testing is performed in a novel environment but these same drug treatments are markedly attenuated if the animals have been previously habituated to the same environment (Kiyatkin, 1992; Montanaro et al., 1983; Carey et al., 2005). In several recent studies (Carey et al., 2003, 2005), we have reported that cocaine sensitization and cocaine conditioned drug effects can be strongly influenced by the degree of prior habituation to a test environment. We also have reported (Carey et al., 1998) that even a single brief exposure to a test environment can induce a persistent habituation effect. In the present investigation, we assessed the interaction between

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habituation effects and cocaine sensitization and cocaine conditioning. In the first phase of the study, we examined the effect of repeated cocaine treatments upon sensitization and conditioning when treatments are initiated in a novel environment. In the second phase, we assessed the effects of the same cocaine regimen upon sensitization and conditioning but after the animals had received, 1 day earlier, a single brief prior exposure to the test environment. This report presents evidence that even a single brief exposure to a test environment can have a substantial impact upon cocaine sensitization and cocaine-conditioned effects.

1. Materials and 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 $48 \times 27 \times 20$ cm^3 clear polycarbonate cages in a climate-controlled room at 22–24 °C with a 12-h dark and 12-h light cycle. During the 1st 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 0.9% saline (1.0 ml/kg) in order to acclimate the animals to the injection procedure. At this point, the animals were subdivided into four groups ($N=10$) equated on body-weight. All experiments occurred during the 12-h light cycle (6 a.m.–6 p.m.). This protocol (IACUC 4-E) was approved by the Veterans Administration Medical Center's 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 10.0 mg/ml. Cocaine injections were administered i.p. in a volume of 1.0 ml/kg. Saline injections (0.9% sodium chloride) were administered in a volume of 1.0 ml/kg (i.p.).

1.3. Apparatus

All of the behavioral tests were conducted in square $60 \times 60 \times 40$ cm^3 or round (68 cm × 40 cm [diameter × height]) open-field compartments of approximately equal area. Testing was conducted in two similar subsections of the testing room with a circular and square chamber in each subsection. While we had previously found that there were no differences in activity levels related to chamber shape or room section, we always equated these factors across groups and treatments to eliminate the possibility that chamber shape or room section could be potential uncontrolled variables. In the present experiments, neither test room subsection nor test chamber shape were statistically significant variables on any behavioral measure ($P>0.05$). Closed-circuit video cameras (Sanyo VCB-5123B) were mounted 50 cm above the open-field enclosures. All signals were analyzed by a video tracking system using a distance criterion of 2 cm for a movement to be scored (Ethovision, Noldus Information Technology, Inc, Leesburg, VA). The accuracy of the system for the measurement of distance was validated by moving objects a fixed distance and confirming that the tracking system generated the same distances. The walls of the chamber were white and the floor of the open-field was covered by plain white paper, which was changed after each animal. Masking sound (75 dB) was provided by a white noise generator (San Diego Instruments, San Diego, CA) and was turned on immediately prior to placement of the animal into the test chamber and turned off upon removal from the test chamber. Each chamber is illuminated by two overhead 12 V projection lamps placed 50 cm above the chamber adjacent to the video camera. Each lamp contains a red filer so that testing could be conducted under conditions of red light illumination to avoid the possible aversive quality of white light and to enhance the contrast between the subject and background as well as to reduce the animal's shadow. The testing under red light conditions is less stressful and also favors locomotor activation as the rats are transferred from the ambient light of the vivarium to the red light of the testing room (Nasello et al., 1998). The animal's head was blackened with a non-toxic marker and the camera tracked only this feature of the rat's body while the animal was being tested in the open-field environment. During each session, data were calculated every 2.5 min by the software. The computer screen tracings of the animal's patterns of locomotion were constantly present on monitors outside of the test room and saved by the software. In a previous report (Carey et al., 1995), we have presented the tracing of the locomotion patterns generated by animals in this test environment. In the present study, the locomotion patterns were similar to those previously presented. The tracings recorded by the tracking system could readily be used to identify small repetitive movements. Such tracings occurred infrequently and idiosyncratically. The complete test procedure was conducted automatically without the presence of the experimenter in the test room. In addition, a VHS VCR was connected to each camera to videotape sessions. The videotapes were always reviewed after each session in order to validate that the recording of the tracings represented the animals' locomotor patterns. In addition, the videotapes were evaluated by trained observers to score grooming behaviors less amenable to video tracking. Two experimenters uninformed of the treatment protocols scored behaviors observed in the videotapes which include facial and flank grooming. Prior to viewing the videotapes from the experiments, the experimenters were trained on other similar videotapes until they achieved inter and intra-experimenter reliability correlations of $r>0.9$.

1.4. Design and procedure

1.4.1. Phase 1. Novel environment

In the first phase of the experiment, two groups ($N=10$) received either saline or cocaine (10.0 mg/kg, i.p.) injections immediately prior to their first placement in the open-field test environment. Each group received three 20-min tests. These three tests occurred over 3 days with one test session per day. On

the fourth day, both groups received saline injections immediately prior to testing to assess cocaine conditioning effects.

1.4.2. Phase 2. Test environment pre-exposure

Phase 2 was a replication of Phase 1 except that prior to the initiation of the cocaine treatments, all animals received a single 20-min test session. For this test session, all animals were administered a saline injection immediately prior to testing. On the next day, the same protocol as in Phase 1 was followed. One group ($N=10$) received cocaine (10.0 mg/kg, i.p.) injections immediately prior to a 20-min test which was repeated once/day on 3 successive days. The other group ($N=10$) received saline immediately prior to 20-min testing once/day on 3 successive days. One day following completion of these test procedures, both groups received a saline injection immediately prior to a 20-min test to assess possible conditioned cocaine effects.

1.5. Statistical analysis

Two-way between–within-S analyses of variance (ANOVA) were used to assess the cocaine drug treatment effects upon the behavioral responses. Duncan's multiple range tests were performed for specific group comparisons. In test sessions in which groups in Phase 1 and in Phase 2 received saline, independent *t*-tests were used for specific between group comparisons. Paired *t*-tests were used for specific within-group comparisons. $P<0.05$ was the statistical criterion for null hypothesis rejection in these *t*-test comparisons.

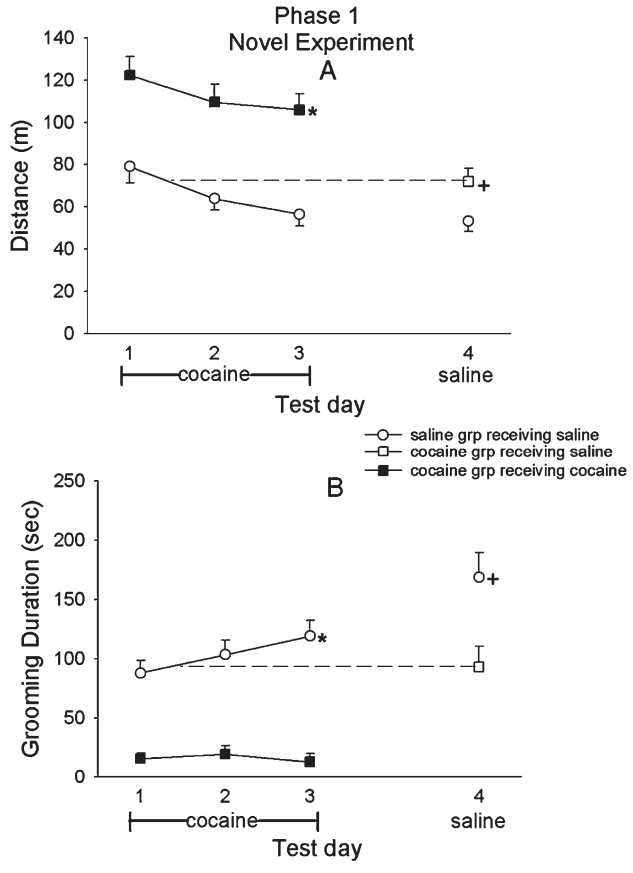

Fig. 1. Means ± S.E.M. for locomotion distance (A) and grooming (B) on the 20-min test sessions of Phase 1. Tests were initiated in a novel environment and then were administered on 4 successive days. On the first 3 days, the cocaine treatment group received 10 mg/kg (i.p.) cocaine immediately prior to testing and the saline group, saline. On the 4th day (conditioning test), both groups received saline. *$P<0.001$ vs. saline group over the first 3 test sessions. $^{+}P<0.01$ vs. saline group on the saline conditioning test.

2. Results

Fig. 1A,B presents the results of the first phase of the experiment in which cocaine (10.0 mg/kg) treatments were initiated in a novel environment. As is apparent from Fig. 1A, the cocaine treatment had a marked locomotor stimulant effect on distance traversed. Group differences over the three cocaine test sessions were statistically significant ($F_{1/18}=27.7$, $P<0.001$) but the group × test session interaction was not significant ($F_{2/36}=0.21$, $P>0.05$). The non-significant group × test session interaction indicates that locomotor sensitization to repeated cocaine treatments did not occur. As is evident in Fig. 1B, however, cocaine also had a marked suppressive effect upon grooming behavior ($F_{1/18}=67.8$, $P<0.001$); again, however, the group × test session interaction was not statistically significant ($P>0.05$). The fourth test session was a saline test for conditioned drug effects. As can be seen in Fig. 1A,B, the cocaine group exhibited the typical conditioned drug effect in that the cocaine group had higher locomotion distance scores and lower grooming scores compared to the saline group ($t_{18}=2.6$ and 2.9, $P<0.01$, respectively). In examining Fig. 1A,B, it can also be seen that the saline group underwent a typical habituation effect from test 1 to test 4, decreased locomotion and increased grooming ($P<0.05$ paired *t*-tests, sessions 1 vs. 4). Furthermore, as can be seen in Fig. 1A,B, the cocaine group scores on the saline conditioning test session in session 4 (which was its first saline test) approximated the locomotion and grooming scores of the saline group on test session 1 when the test environment was novel ($t_{18}=0.7$ and 0.2, $P>0.05$, for distance and grooming, respectively). Thus, the habituation effect expressed in changing response levels from test 1 to test 4 in the saline group appears to be the principal contributor to the difference between the cocaine and saline groups on the test for cocaine-conditioned drug effects.

The results of the second phase of the experiment in which both the saline and cocaine groups were given a single brief (20 min) saline test session 1 day prior to the cocaine/saline treatments are shown in Fig. 2A,B. As can be seen in Fig. 2A,B, the groups were closely matched on the initial saline test session ($t_{18}=0.01$ and 0.20, $P>0.05$, for distance and grooming, respectively). On the next 3 sessions in which one group continued to receive saline whereas the other group received cocaine (10.0 mg/kg), the cocaine treatment enhanced locomotion and suppressed grooming ($F_{1/18}=22.7$ and 29.5, $P<0.001$, for distance and grooming respectively). The group × test session interactions were significant for distance ($F_{2/36}=18.0$, $P<0.001$) and grooming ($F_{2/36}=3.6$, $P<0.05$). These results are indicative of a pronounced cocaine sensitization effect. In fact,

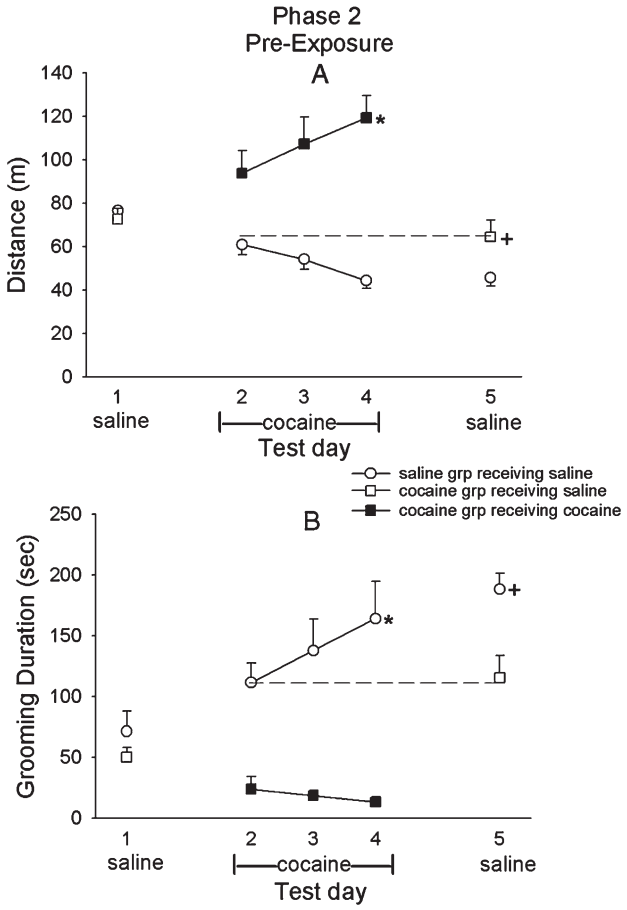

Fig. 2. Means±S.E.M. for locomotion distance (A) and grooming duration (B) in Phase 2 on the five 20-min test sessions. On the first test session, both the cocaine and the saline treatment groups received saline immediately prior to testing. On test sessions 2–4, one group received cocaine (10 mg/kg) immediately prior to testing and the other group, saline. On the 5th test session (conditioning test), both groups received saline. *$P<0.001$ vs. saline group over test sessions 2–4. $^{+}P<0.01$ vs. the saline group on the saline conditioning test.

the locomotion distance scores for the cocaine group on test session 4 were statistically higher than its distance scores on test session 2 ($P<0.01$, paired t-test). Grooming scores for the cocaine group were suppressed to a very low level across cocaine treatment sessions. Therefore, increase in locomotion in the cocaine group could not be accounted for in terms of decreased grooming as a possible competing behavior. Test session 5, in this experiment, was a saline conditioning test; and, as can be seen from Fig 2A,B the cocaine group had higher distance scores ($t_{18}=2.4$, $P<0.05$) and lower grooming scores ($t_{18}=3.2$, $P<0.01$) than the saline group. As was the case for Phase 1, the saline group underwent a substantial decline in locomotor distance and an increase in grooming behavior from test session 1 to test session 5 ($P<0.05$, paired t-tests for day 1 vs. day 5 in the saline group for locomotion distance and grooming, respectively). These changes are consistent with a habituation effect. It can also be seen in Fig. 2A,B that the distance and grooming scores for the cocaine group on the saline conditioning test (session 5) were quite comparable to the scores of the saline group on test session 2 ($t_{18}=0.4$, 0.1, $P>0.05$ for distance and grooming, respectively). For the cocaine group, the saline conditioning test was its second test with saline.

The locomotion distance and grooming scores for the saline group in Phase 1 and the saline group in Phase 2 over the first four test sessions were virtually identical ($F_{1/18}=0.24$ and 0.04, $P>0.05$, for distance and grooming, respectively). Similarly, for the cocaine groups over the 3 test sessions in which the cocaine groups in Phases 1 and 2 received cocaine, there were no overall differences between the groups ($F_{1/18}=0.43$ and 0.10, $P>0.05$, for distance and grooming, respectively) but there was a significant cocaine group × test session interaction for locomotor distance scores ($F_{3/36}=7.6$, $P<0.01$). Comparisons between the two cocaine groups on each cocaine drug test indicated statistically significant group differences on the first ($P<0.01$) but not on the second or third cocaine treatment sessions.

3. Discussion

The findings in the present studies are relevant to both cocaine sensitization and cocaine conditioned drug effects. We found that when the cocaine treatments were initiated in a novel environment locomotor sensitization effects were not observed; on the other hand, one brief prior exposure to the test environment 1 day before the cocaine treatments were administered was sufficient to promote the development of sensitization. For non-drug animals, one exposure to the test environment also impacted substantially upon the second test and inhibited locomotor activity. Evidently, this inhibitory habituation effect was the major variable influencing the locomotor response to cocaine. Seemingly, this behavioral inhibitory effect induced by the prior exposure to the test environment was able to interact with cocaine and attenuate its locomotor stimulant effect by initially reducing the cocaine locomotor stimulant effect compared to the novel environment group. Thus, it appears that the cocaine sensitization effects in the pre-exposure group represented a reversal of the inhibitory habituation effect induced by prior exposure to the test environment. Considered in this way, the relevant control group for the demonstration of a sensitization effect should be a cocaine group without any prior exposure to the test environment rather than the conventional saline control group. Thus, a conventional unpaired cocaine control group which controls for cocaine exposure per se also adds the inhibitory effect of prior exposure to the test environment. The inhibitory effect of habituation to a test environment upon the initial stimulant impact of cocaine observed in the present study is well-documented (Kiyatkin, 1992; Carey et al., 2005) and is most pronounced when cocaine is administered in a familiar home-cage environment. Our results are consistent with these reports and show that even a single brief prior exposure to a test environment can substantially attenuate the initial locomotor stimulant effect of a cocaine treatment.

A possible mechanistic way to account for such effects is in terms of the neurochemical impact of a cocaine treatment. 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 transport

proteins which resorb released DA, 5-HT, and NE. The neurochemical impact of cocaine, therefore, is indirect and dependent upon the released DA, 5-HT, and NE. Presumably, the intense neuronal activity 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, the cocaine re-uptake blockade would have a larger impact on neurotransmission. This differential neurochemical effect of cocaine could account for the differences we observed in the cocaine groups tested in the novel environment vs. testing in the same environment following a single brief prior exposure to the test environment. Such a mechanism, seemingly, would also account for the more profound differences observed between cocaine administered in a novel vs. a highly familiar home-cage environment. However, repeated cocaine treatments in the same environment could induce conditioned activation effects, and thereby increase the baseline level of neural activation and enhance the neurotransmitter impact of re-uptake blockade by subsequent cocaine treatment and lead to an apparent sensitization-like effect. The present results as well as other reports (Carey et al., 2005) suggest that the increase in the baseline activation level induced by a cocaine association to the test environment may increase but does not exceed and may not even equal the high level of activation induced by a novel environment. Indirect support for this assessment is provided by the conditioning test results in which the level of behavioral activation did not exceed that induced by the novel environment. While increased motoric activation is induced by repeated cocaine treatments in a familiar environment, we have previously shown that even 10 cocaine treatments do not increase the level of locomotor activation above that of an acute administration of the same cocaine treatment in the same test environment when that environment is novel. This important issue, however, needs increased experimental attention.

Inhibitory habituation effects appear important not only for cocaine sensitization effects but for cocaine conditioned effects as well. On the saline conditioning tests in both experiments, we obtained findings consistent with the occurrence of a cocaine conditioned behavioral response. The cocaine groups exhibited higher locomotor distance scores and decreased grooming as compared to their respective saline control groups. Importantly, however, the saline control groups had undergone substantial changes in their behavioral responses with repeated testing (i.e., decreased locomotion and increased grooming). These behavioral changes appear to represent a typical behavioral habituation effect to a novel environment (Cerbone and Sadile, 1994). In fact, the scores of the cocaine groups on the saline conditioning test were quite similar to their respective saline control group when comparisons were made in terms of saline tests alone. That is, for the cocaine treatment group which received cocaine on the initial exposure to the novel environment, the conditioning test scores were similar to those of the saline control group on its first exposure to the novel environment. For the cocaine group which received its first cocaine treatment following one saline treatment exposure to the test environment, its conditioning test scores were similar to its' saline control group on the second session in the test environment. Thus, the cocaine groups performed in the conditioning tests as if they had not acquired any habituation effects during their cocaine treatment sessions. This consideration appears to fit with drug state dependent effects (Jarbe et al., 1981; Lal and Bennet, 1989). That is, cocaine induces interoceptive drug cues (Rapoza, 1993) so that when the animals are subsequently tested without cocaine, the acquired environmental familiarity that developed during the cocaine drug state does not transfer to the saline state. As a result, the animals behave appropriate to the saline state (i.e., the environment was completely novel for the cocaine group which had no prior saline exposure in the test environment, whereas for the cocaine pre-exposure group, the conditioning test was comparable to a second saline test in the novel environment). The difficulty with a drug state dependent argument is that it appears to work as a mechanism to block the transference of habituation from the drug state to the saline state but it does not work in the opposite direction. That is, the habituation acquired in the saline state should not transfer to the drug state; yet, in this report and in other reports (Carey et al., 2005), the inhibitory habituation effects acquired in the saline state transfers to the cocaine state. Rather than drug state dependency, the present results indicate a behavioral equivalence between the activation effect of cocaine associative effects and the behavioral activation induced by a novel or partially habituated environment.

In the pre-exposure cocaine group, we found that the cocaine locomotion response increased substantially with subsequent cocaine treatments. This is a prototypical behavioral sensitization effect. Importantly, however, the increased cocaine locomotor activation reached only the level of the group which had received its initial cocaine treatment in the novel environment. Since the novel environment cocaine group did not have an enhanced response to cocaine with repeated cocaine treatments, it is difficult to argue that the increase which was manifested by the cocaine group which had received the single saline prior exposure was exhibiting an enhanced cocaine response (i.e., sensitization). Instead, it appears that the exposure to the test environment in a cocaine state leads to the acquisition of an enhanced activation state possibly linked both to the cocaine interoceptive drug cues and to the associated environment cues. We suggest that this acquired activation effect reverses inhibitory habituation effects and creates the appearance of a cocaine sensitization effect. We have reported previously (Carey et al., 2005) that if 10 cocaine treatment sessions are administered, this acquired activation or sensitization effect reaches its asymptote within 3 to 4 cocaine treatments and approximates but does not exceed the response to the same treatment given acutely in a novel environment. The present findings, however, are limited to one moderate dose level of cocaine. At high dose levels of psychostimulant drugs context may become less important. On the other hand, high drug dose levels may be of primary importance for neurotoxicology (Itzhak and Stein, 1992; Carey et al., 1995) but of little relevance to behavioral processes pertinent to drug use and drug addiction.

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