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Sensitization to the Psychomotor Stimulant Effects of Amphetamine: Modulation by Associative Learning

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The authors investigated the influence of associative pairing of contextual stimuli with amphetamine administration on the expression of psychomotor sensitization. Animals received *d*-amphetamine or saline in group-specific environments. Amphetamine produced robust behavioral sensitization in all environments, but when an amphetamine challenge was given in a test environment that was novel for some groups but not others, the expression of sensitization was completely context specific. An injection of saline in the amphetamine-paired environment produced a conditional response (CR), but this was quite small compared to the magnitude of the sensitized response, and sensitization remained completely context specific following extinction of the CR. Results are discussed in relation to 3 models of how context may modulate the expression of sensitization: an excitatory conditioning model, an inhibitory conditioning model, and an occasion-setting model.

In behavioral pharmacology, the word *sensitization* refers to a progressive and persistent increase in a drug effect produced by repeated drug administration, without regard for the mechanism or mechanisms underlying the increased effect (Robinson & Becker, 1986; Segal, Geyer, & Schuckit, 1981; Stewart & Badiani, 1993). In recent years the sensitization produced by psychostimulant drugs has attracted considerable attention, in part because sensitization-related neuroadaptations are thought to play an important role in the development of psychostimulant psychoses (Robinson & Becker, 1986; Segal et al., 1981) and in the development of the compulsive patterns of drug-seeking and drug-taking behaviors that characterize addiction (Berridge & Robinson, 1995; Piazza, Deminière, Le Moal, & Simon, 1989; Robinson & Berridge, 1993). However, despite considerable research on psychostimulant sensitization, the exact conditions required for its induction and expression are still not well understood. Indeed, there is an ongoing discussion in the field regarding the fundamental nature of drug-induced sensitization.

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By one view, sensitization is the behavioral manifestation of neurobiological adaptations produced by the direct pharmacologic actions of drugs on a specific neural substrate (e.g., Kuczenski, Segal, Weinberger, & Browne, 1982; Robinson & Becker, 1986). Or, in behavioral terms, sensitization represents a progressive increase in an unconditional response (UR) to a drug, presumably because of drug-induced changes in the neural substrate that mediates the UR. This is a *nonassociative* view, and by this view, conditional stimuli (CSs), including contextual stimuli, are thought to have little or no influence on the induction and expression of sensitization, except under limited conditions.

By another view, sensitization reflects the outcome of *associative learning* processes involving drug-environment conditioning (Hinson & Poulos, 1981; Pert, Post, & Weiss, 1990; Siegel, Krank, & Hinson, 1987; Tilson & Rech, 1973). According to this associative view, when drugs are administered in association with a unique environment, contextual cues acquire the properties of a CS, with the drug acting as the unconditional stimulus (US). After pairing of the CS with the US, the CS alone (the context) can acquire the ability to produce druglike effects, a phenomenon first reported by Pavlov (1927). With regard to psychostimulants, the conditional response (CR) can resemble the unconditional psychomotor response (UR) to the drug (Beninger & Hahn, 1983; Carey, 1986; Hiroi & White, 1989; Pickens & Crowder, 1967; Ross & Schitzer, 1963; Schiff, 1982; Tilson & Rech, 1973; cf. Martin-Iverson & Fawcett, 1996). Thus, it has been suggested that sensitization may reflect the acquisition of a progressively increasing CR, which adds to the unchanging UR produced by the drug (Hinson & Poulos, 1981; Siegel et al., 1987; Tilson & Rech, 1973).

Finally, a third view of sensitization incorporates elements of both associative and nonassociative models. By this view, drugs induce neural sensitization by a nonassociative process, but CSs associated with drug administration

(including contextual stimuli) play a critical role in modulating the expression of sensitization (Pert et al., 1990; Stewart & Vezina, 1988; also see Baker & Tiffany, 1985, for a similar analysis of tolerance). Thus, associative learning determines whether sensitization is expressed at any particular time or place. This latter view may accommodate reports that under some conditions sensitization is context specific but under others it is context independent (Pert et al., 1990; Post & Weiss, 1988; Stewart & Badiani, 1993).

The purpose of the experiments reported here was to further explore the role of contextual stimuli on the *expression* of amphetamine sensitization. We hypothesized that if procedures were used that induced robust sensitization, the expression of sensitization would be entirely context independent. Indeed, in most studies that report context-specific sensitization, relatively low doses were used, and often the drug was given only once or just a few times (Ahmed, Stinus, Le Moal, & Cador, 1993; Drew & Glick, 1988; Mazurski & Beninger, 1987; Post & Weiss, 1988; Stewart & Vezina, 1991; Weiss, Post, Pert, Woodward, & Murman, 1989). These conditions are optimal for quantifying drug-induced changes in locomotor responses or turning behavior in neurologically intact rats, but they produce weak sensitization. Would the expression of sensitization still be context specific if animals were given numerous treatments with a relatively high dose of amphetamine?

To address this question, we needed a paradigm in which repeated injections of a relatively high dose of amphetamine produced a large, progressive, and sustained increase in a behavioral response that could be accurately quantified (i.e., a paradigm that produced robust sensitization). This paradigm is provided by the rotational behavior model of Ungerstedt (Ungerstedt & Arbuthnott, 1970), in which the rotational response to amphetamine is quantified in animals with a unilateral 6-hydroxydopamine (6-OHDA) lesion of the nigrostriatal dopamine (DA) system. In such animals amphetamine produces vigorous turning (rotational) behavior, and the rate of rotation is thought to be dependent on the degree of DA receptor activation in the nucleus accumbens (Kelly & Moore, 1976). Furthermore, sensitization of rotational behavior is characterized by a large and progressive increase in behavioral response (Robinson, 1984). The rotational behavior model offers a number of advantages over more traditional measures of locomotion and drug-induced stereotypies in studying sensitization (these are discussed in the Method section), and therefore, amphetamine-induced rotational behavior was used here as an index of psychomotor activation.

It was found that even after amphetamine treatments that induced very robust sensitization, the expression of behavioral sensitization was completely context specific. Exposure to the drug-paired environment produced only a small CR, and after extinction of the CR the expression of sensitization remained context specific. The results are discussed in the context of three different models of how associative learning could contribute to sensitization: (a) an excitatory conditioning model, (b) an inhibitory conditioning model, and (c) an occasion-setting model.

Method

Subjects

Male Holtzman and Sprague-Dawley rats purchased from Harlan Sprague-Dawley, Inc. (Indianapolis, IN), weighing 175–300 g at time of surgery and 350–550 g when behavioral testing began, were used in all experiments. They were housed in pairs before surgery and individually after surgery in wire-hanging cages located in an animal colony maintained on a 14:10-hr light–dark cycle (lights on at 7 a.m.). They had unrestricted access to food and water. Before surgery all of the rats were allowed to acclimatize to the animal facility for at least 1 week.

Behavioral Measure and Rationale

Rotational behavior in rats with a unilateral 6-OHDA lesion of the nigrostriatal DA system was used as an index of psychomotor activation, because this measure has a number of advantages over more common measures of locomotor activity or stereotyped behavior. First, dose–effect relations for amphetamine-induced rotational behavior in rats with a unilateral 6-OHDA lesion are relatively linear over a wide range of doses (Costall & Naylor, 1975; Ungerstedt & Arbuthnott, 1970). Thus, with sensitization, a progressive increase in drug effect is seen as a progressive increase in rotational behavior (Robinson, 1984). By contrast, the dose–effect curve for amphetamine-induced locomotor activity is quite complex, having an inverted U-shaped function over a relatively narrow dose range (Kelley, Winnock, & Stinus, 1986; Russell & Pihl, 1978). Thus, with measures of locomotor activity, a progressive increase in drug effect is not necessarily characterized by a progressive increase in behavior (Damianopoulos & Carey, 1992; Leith & Kuczenski, 1982; Segal & Mandell, 1974). This is also true for rotational behavior in rats without a unilateral lesion, because in this preparation rotation is seen over only a very narrow dose range (Jerussi & Glick, 1976). Second, rotational behavior is easily quantifiable, and the measure constitutes an interval scale, rather than the less desirable ordinal scale associated with stereotypy activity rating scales. Third, the unconditional rotational response to a saline injection in a novel test environment is negligible and unchanging across trials, but the unconditional locomotor response is usually very large and may change over time (Badiani, Anagnostaras, & Robinson, 1995). This latter situation can make it difficult to dissociate a small CR from an already large UR to the environment alone and, thus, to tease out the influence of factors such as habituation to the activating properties of the test environment (Damianopoulos & Carey, 1992).

6-OHDA Lesion Procedure

Before behavioral testing, all of the rats received a unilateral 6-OHDA lesion of the nigrostriatal pathway by use of procedures similar to those described previously (Robinson, 1984). In brief, rats were given atropine methyl nitrate (0.04 mg/kg, ip), anesthetized with sodium pentobarbital (50 mg/kg, ip, supplemented with methoxyflurane when necessary), and then were given 15 mg/kg (ip) of desipramine HCl (Breese & Traylor, 1971). Thirty to 60 min later, a 29–30-g stainless steel cannula was lowered into the nigrostriatal bundle where it coursed through the posterior lateral hypothalamus. This was used to infuse 8 µg of 6-OHDA hydrobromide in 4.0 µl of a saline-ascorbate solution (0.9% saline with 0.1 mg/ml l-ascorbic acid) over an 8-min period.

Following a recovery period of at least 10 days, the rats were screened for apomorphine-induced rotation. Each rat was attached to a sensor unit by a wire tether attached to an elastic harness located around its torso. They were allowed to habituate for 10 min to the test environment, which consisted of a cylindrical clear plastic flat-bottom bucket (Rubbermaid No. 6222, 25 cm lower diameter, 31 cm top diameter, 36 cm height) with Bed-o'-cobs (granulated corn cobs) on the floor. The chamber was located in a quiet room. Rats then received an injection of 0.05 mg/kg apomorphine HCl, administered subcutaneously, in the nape of the neck. Rats that did not make at least 50 full rotations in the direction contralateral to the lesion during the 30-min test session either received a second 6-OHDA lesion (and were screened again) or were dropped from the experiment. Only rats with greater than a 90% to 95% unilateral depletion of striatal DA rotate to this dose of apomorphine (Marshall & Ungerstedt, 1977). Overall, 14% of the total number of rats that received surgery were not included, either because they did not meet criterion or because of other postoperative complications.

Unless noted otherwise, we quantified behavior using the automated computer and photocell-based rotometer system described by McFarlane, Martonyi, and Robinson (1992). The system was configured to report data in 5-min intervals, and full turns (defined as four consecutive 90° turns in the same direction) in the dominant direction were the dependent measure.

Groups

Table 1 illustrates the groups used in each of the four experiments described here, and in particular, the environment in which the rats received injections of amphetamine and saline during the conditioning (pretreatment) phase of the experiment. Detailed descriptions of the environments are given below.

Statistics

We analyzed data using analyses of variance (ANOVAs), unless otherwise noted. When the data were averaged over an entire test session, one-variable univariate ANOVAs were used, followed by multiple post hoc Fisher's protected least significant difference (PLSD) tests as appropriate. Time-course or repeated-measures data were analyzed using the general multivariate analysis of variance (MANOVA) followed by appropriate univariate comparisons. Within-group comparisons between two means were made by

using paired two-tailed *t* tests. The results of all statistical analyses are given in the figure legends to enhance readability of the Results section. In the text of the Results section, no statements are made regarding group differences unless they are supported by statistical analyses.

Experiment 1. The Influence of Context on the Expression of Sensitization to Amphetamine

The purpose of Experiment 1 was to determine whether the expression of behavioral sensitization induced by an amphetamine-treatment regimen that produces robust sensitization is context specific.

Experimental Design and Protocol

Treatment. There were three treatment groups in this experiment (Groups 1, 2, and 4 in Table 1). Rats in the *saline control* (R^-H^-) group were transported from their home cages in the animal colony, given an intraperitoneal injection of 0.9% saline (0.5 ml/kg), and placed into the rotometers. Rats in the *rotometer paired* (R^+H^-) group were also transported to the rotometers, where they received 3.0 mg/kg of *d*-amphetamine sulfate (weight of the salt; 0.5 ml/kg ip). Rats in the *third-world* (3^+H^-) group were transported from their home cages to the "third-world" environment (see later), where they received 3.0 mg/kg of amphetamine. After 90 min, all rats were returned to their home cages in the animal colony, where they received an injection of saline. These procedures were repeated 10 times, once every 3 to 4 days. During this phase of the experiment, rotational behavior was recorded only from saline control and rotometer paired rats, because they were the only groups tested in the automated rotometers.

Challenge test. The extent to which context influenced the expression of sensitization was determined on an "amphetamine challenge" test day, which took place 3 to 4 days after the last (10th) treatment day. On the test day, all of the rats in all groups were transported to the rotometers, where they received 1.5 mg/kg of amphetamine. Note, however, that only rotometer paired rats had previously received amphetamine in this environment. Rotational behavior was recorded for 90 min, and the rats were then returned to their home cages and given an injection of 0.5 ml/kg of saline. Three to 4 days following the amphetamine challenge, the rats

Table 1

Conditioning: The Location Where Each Group Received Injections During the Training Phase of Each Experiment

Group	Environment				Experiment			
	Rotometer (test)	Home cage	Third world	Other worlds	1	2	3	4
$R-H^-$, saline control	Saline	Saline	—	—	×	×	×	×
$R+H^-$, rotometer paired	AMPH	Saline	—	—	×	×	×	×
$R-H^+$, rotometer unpaired	Saline	AMPH	—	—		×	×	×
$3+H^-$, third world	—	Saline	AMPH	—	×			×
$H+H^-$, home	—	AMPH/saline	—	—			×	×
$M+H^-$, multiple worlds	—	AMPH/saline	AMPH	AMPH				×
NH, nonhandled	—	—	—	—		×		

Note. R = rotometer; H = home cage; 3 = third world; M = multiple worlds; AMPH = amphetamine. During the conditioning phase, rats in each group received injections of AMPH or saline in the environments indicated, and a dash indicates that rats were never exposed to that environment. A plus sign (+) indicates location of AMPH injections; a minus sign (−) indicates location of saline injections (e.g., $R+H^-$). All "challenge" tests for context-specific sensitization took place in the rotometer (test) environment.

received a "saline challenge." On this day, all of the rats were transported to the rotometers, where they received 0.5 ml/kg of saline (instead of amphetamine), and rotational behavior was recorded for 30 min.

Contexts (environments). The environments in which rats received injections were as follows. (a) The *home cages* consisted of stainless steel sliding-drawer type cages with a wire mesh front and floor (23 × 20 × 18 cm). Pine wood shavings were located below the cages (i.e., not on the floor), and food and water were available at all times. (b) The *rotometers* consisted of cylindrical clear plastic flat-bottom buckets (Rubbermaid No. 6222). Each bucket was located within a 25-cm tall blue laundry basket with wide mesh walls. Pine wood shavings were placed on the floor, and white noise was played continuously. In addition, rats were attached to a sensor unit fixed over the chamber using a tether described previously (McFarlane et al., 1992). (c) The *third-world chambers* consisted of rectangular white (opaque) Nalgene tubs (41 × 23 × 20 cm) with wire lids and Bed-'o'-cobs on the floor. They were located in a busy surgery room, and classical music was played continuously. These rats were not tethered.

Results

Figure 1A shows that the amphetamine-treatment regimen used here did indeed produce robust sensitization. The rotometer paired group showed a large and progressive increase in amphetamine-induced rotational behavior with successive injections of amphetamine (see Figure 1A). The 1st injection of amphetamine produced an average (\pm SEM) of 11 ± 2 rotations per 5 min, and the 10th injection produced 50 ± 5 rotations, a fourfold increase. Rats given saline in the rotometers (the saline control group, R⁻H⁻) made few rotations in this environment, and there was no change in their behavior across test sessions (1st injection = 1.3 ± 0.2 rotations per 5 min; 10th injection = 1.1 ± 0.3).

The effect of an amphetamine challenge on the test day is illustrated in Figures 1B and 1C. It is obvious that the rotometer paired group showed a much larger behavioral response to the amphetamine challenge than did the saline

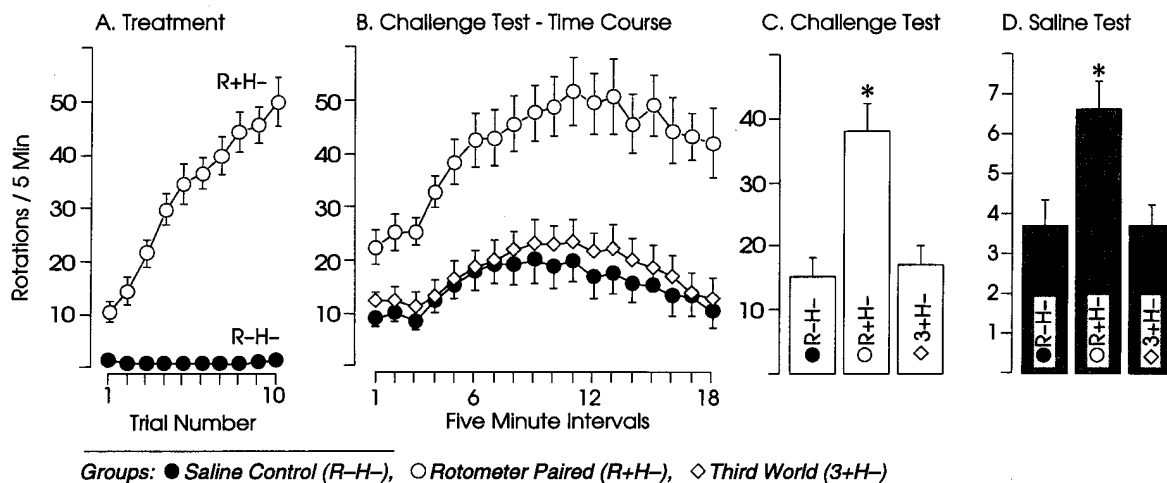


Figure 1. The influence of context on the expression of sensitization to amphetamine. A: The effect of repeated treatment with amphetamine or saline. The mean (\pm SEM) number of full rotations in the dominant direction per 5-min interval averaged over each of ten 90-min treatment sessions (one session/3–4 days). Rats that received 3.0 mg/kg of *d*-amphetamine in the rotometer test environment (the rotometer paired group, R⁺H⁻, open circle; $n = 12$) showed a large increase in amphetamine-induced rotations with successive injections (1st vs. 10th injection), paired two-tailed *t* test, $t(11) = 9.7$, $p < .0001$. Rats that received saline in this environment (the saline control group, R⁻H⁻, solid circle; $n = 12$) showed little rotational behavior, and their response to the 10th injection of saline did not differ from their response to the 1st injection, $t(11) = 0.6$, $p > .5$. The behavior of rats in the third-world group (3⁺H⁻, open diamond; $n = 13$) was not recorded during this phase of the experiment. B: Effect of an amphetamine challenge. The time course of amphetamine-induced rotational behavior over 5-min intervals on the amphetamine challenge test day, when all rats received 1.5 mg/kg *d*-amphetamine in the test (rotometer) environment. C: Same data as in B, but averaged over the entire test period. There were significant group differences in rotational behavior: Overall univariate analysis of variance (ANOVA), main effect of group, $F(2, 34) = 17.5$, $p < .0001$. The rotometer paired (R⁺H⁻) rats, which previously received amphetamine in this environment, made significantly more rotations than either saline control (R⁻H⁻) rats (Fisher's protected least significant difference [PLSD]: $p < .0001$) or third-world (3⁺H⁻) rats ($p < .0001$). Third-world rats, which had the same drug history as rotometer paired rats but received amphetamine in a different environment, did not differ from saline control rats ($p > .7$). D: Effect of a saline challenge. The mean (\pm SEM) rotations per 5 min for each of the three groups averaged over the 30-min test session following an injection of saline in the test environment. Note the scale for the y-axis is different from in C. There were significant group differences: univariate ANOVA, $F(2, 34) = 8.4$, $p = .0011$. Rotometer paired rats made significantly more rotations than either saline control rats (Fisher's PLSD: $p = .0013$) or third-world rats ($p = .001$), which not differ from each other ($p > .9$).

control group. In contrast, rats that were treated with amphetamine in the third-world group (3^+H^-) did not differ from saline control rats and made significantly fewer rotations compared with rotometer paired rats (see Figures 1B and C). Thus, only rotometer paired rats expressed behavioral sensitization in the test environment.

Three to 4 days following the amphetamine challenge, all of the rats were given a saline challenge in the rotometers. Figure 1D shows that rotometer paired rats made significantly more rotations in response to saline in this context than either saline control or third-world rats, which did not differ from each other; that is, only the rotometer paired group showed a CR. (Note that the scale on the y-axis is different in Figures 1C and 1D.)

Experiment 2. Context-Specific Sensitization: Dose-Effect Analysis

In Experiment 1 the expression of sensitization was completely context specific. However, only a single challenge dose of amphetamine was used, and it is possible that sensitization would not be context specific if other challenge doses of amphetamine were used. In this experiment, therefore, rats were challenged with different doses of amphetamine so that the extent of sensitization could be quantified by determining whether any of the treatment regimens produced a shift in the amphetamine dose-effect curve.

Experimental Design and Protocol

Treatment. The design of this experiment was essentially the same as in Experiment 1 in that rats received amphetamine (3.0 mg/kg) or saline every 3 to 4 days in different environments for a total of 10 treatments. There were, however, two changes in the composition of the groups tested. First, an *explicitly unpaired* group was used (see below), which is the standard CS^- control group in Pavlovian conditioning experiments (Rescorla, 1967). Second, a *nonhandled* (NH) control group was included to assess the potential effects of the injection and handling procedure itself. Thus, there were four groups (Groups 1, 2, 3, and 7 in Table 1). The saline control (R^-H^-) group and the rotometer paired (R^+H^-) group were treated exactly as in Experiment 1. In addition, there was a rotometer unpaired (R^-H^+) group. For each treatment session, these rats were transported to the rotometers where they received saline, and, after the 90-min test session, they were returned to their home cages, where they received 3.0 mg/kg of amphetamine. Rats in the fourth group (NH) were left undisturbed in their home cages during this phase of the experiment (i.e., they received no injections).

Challenge test. As in Experiment 1, the extent to which context influenced the expression of sensitization was determined on a series of amphetamine challenge test days, the first of which was given 3 to 4 days after the last treatment day. On the first test day, all of the rats received 1.5 mg/kg of amphetamine in the rotometers followed by saline in their home cages 90 min later. Three to 4 days later, all of the rats received a second challenge of 0.5 mg/kg amphetamine in the rotometers (followed by saline in their home cages), and 3 to 4 days later they received a final 4.5 mg/kg challenge of amphetamine in the rotometers. We are aware that this design may underestimate the extent of the shift in the dose-effect curve in sensitized animals, because the first and

second challenge injections of amphetamine would sensitize the control animals. We assumed, however, that the effect of treatment with 10 injections of 3.0 mg/kg of amphetamine would be much greater than the sensitization in saline control rats produced by one injection of 1.5 mg/kg followed by one injection of 0.5 mg/kg amphetamine. The results (see below) suggest that this assumption was warranted.

Results

As in Experiment 1, successive injections of amphetamine given at 3–4-day intervals produced a marked and progressive increase in rotational behavior in the rotometer paired group (1st injection, 12 ± 2 rotations per 5-min, 10th injection, 55 ± 4 ; Figure 2A). Saline control and rotometer unpaired rats, which both received saline in this environment, made few rotations (0.7 ± 0.2 and 1.1 ± 0.2 , respectively) and did not differ from each other (see Figure 2A).

Figure 2B shows the dose-effect curves for amphetamine-induced rotation when rats in all groups received an amphetamine challenge in the test (rotometer) environment. Relative to both the saline control group and the rotometer unpaired group (R^-H^+), there was a marked shift to the left in the amphetamine dose-effect curve in rotometer paired rats (R^+H^-). There was no difference between rotometer unpaired rats (R^-H^+) and saline control rats (R^-H^-). Thus, rotometer paired rats expressed sensitization, and this was context specific. In addition, nonhandled rats made significantly fewer rotations than rotometer unpaired rats and saline control rats when given 0.5 mg/kg. In summary, analysis of the dose-effect curves revealed there were group differences in the response to amphetamine on the challenge test day, such that rotometer paired > rotometer unpaired = saline control > nonhandled.

Experiment 3. Effect of Extinction

The main purpose of this experiment was to determine whether the influence of contextual stimuli on the expression of amphetamine sensitization could be abolished by an extinction procedure, as suggested previously (Jodogne, Marinelli, Le Moal, & Piazza, 1994; Stewart & Vezina, 1991). In addition, it has been suggested that giving amphetamine injections in the home cage should minimize the influence of conditioning factors on the expression of sensitization (Browne & Segal, 1977; Segal & Mandell, 1974), so a group was included that received all injections in their home cage.

Experimental Design and Protocol

Treatment. The treatment phase of this experiment was exactly as described for Experiments 1 and 2. Groups 1, 2, 3, and 5 from Table 1 were used, which included a saline control (R^-H^-) group, a rotometer paired (R^+H^-) group, and a rotometer unpaired (R^-H^+) group. These were treated exactly as described for Experiment 2. In addition, a fourth group (*home*; H^+H^-) was included. For each of the 10 treatment sessions, home rats received 3.0 mg/kg of amphetamine in their home cages and an injection of saline in their home cages 90 min later. These rats were not exposed to the

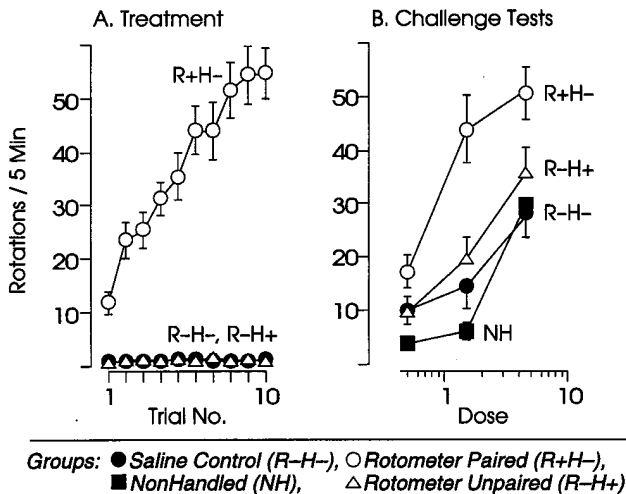


Figure 2. Context-specific sensitization: Dose-effect analysis. **A:** Effect of repeated treatment with amphetamine or saline. The mean (\pm SEM) number of full rotations per 5-min interval averaged over each of ten 90-min treatment sessions. Rats that received 3.0 mg/kg of amphetamine in the rotometers (the rotometer paired group, R^+H^- , open circle; $n = 9$) showed a large progressive increase in amphetamine-induced rotational behavior (1st vs. 10th injection), paired two-tailed t test, $t(8) = 13.3$, $p < .0001$. For rats in the saline control group (R^-H^- , solid circle; $n = 8$), there was no change in rotational behavior between the 1st and 10th treatment with saline, $t(7) = 1.75$, $p = .13$, as was also the case for rats in the rotometer unpaired group (R^-H^+ , open triangle, $n = 9$), $t(8) = 0.7$, $p > .5$. Rats in the nonhandled (NH, solid square; $n = 8$) group were left undisturbed during this phase of the experiment. **B:** Amphetamine dose-effect curve. The mean number of rotations per 5 min averaged over the entire test session following a challenge injection with one of three different doses of amphetamine in the test environment. There was a significant Conditioning Group \times Dose interaction: general multivariate analysis of variance analysis of variance, two-way interaction, $F(6, 60) = 4.5$, $p = .0008$. There was a significant simple main effect of conditioning group at every dose: univariate analyses of variance, 0.5 mg/kg, $F(3, 30) = 13.2$, $p < .0001$; 1.5 mg/kg, $F(3, 30) = 5.8$, $p = .0030$; and 4.5 mg/kg, $F(3, 30) = 4.6$, $p = .0096$. The dose-effect curve for rotometer paired rats was shifted significantly to the left of that for saline control rats (Fisher's protected least significant differences [PLSDs] at each dose: 0.5 mg/kg, $p < .0001$; 1.5 mg/kg, $p = .079$; 4.5 mg/kg, $p < .0001$), rotometer unpaired rats (at each dose, $p < .0001$; $p = .06$; $p = .0003$), and nonhandled rats ($p < .0001$; $p = .0014$; $p < .0001$). Rotometer unpaired rats did not differ from saline control rats at 0.5 mg/kg or 1.5 mg/kg ($p > .15$; $p > .9$) but differed marginally at 4.5 mg/kg ($p = .044$). Rotometer unpaired rats made somewhat more rotations than nonhandled rats at 0.5 mg/kg ($p = .0010$) but not at higher doses ($p > .10$; $p > .15$). Nonhandled rats also differed marginally from saline control rats at 0.5 mg/kg ($p = .044$) but not at higher doses ($p > .13$; $p > .5$).

rotometers or any other environment except their home cage during this phase of the experiment.

Challenge test. To determine the effect of amphetamine treatment, we administered to all rats a challenge injection of 1.5 mg/kg amphetamine in the rotometers 3 to 4 days after the last treatment day, followed by saline in their home cages 90 min later.

Extinction. Beginning 3 to 4 days after the amphetamine challenge test, rats received 10 extinction trials, each one given 3 to 4 days apart. For each extinction trial, all of the rats were taken to the rotometers and given an injection of 0.5 ml/kg saline, and

behavior was recorded for 90 min. Following this, the rats were returned to their home cages, where they received a second injection of saline. To determine the effect of this extinction procedure on the response to amphetamine, we gave all of the rats a second challenge of 1.5 mg/kg amphetamine in the rotometers 3 to 4 days after the 10th saline extinction trial.

Results

Figure 3 illustrates the development and expression of sensitization in the four groups before extinction training. As in Experiments 1 and 2, there was a marked increase in amphetamine-induced rotational behavior between the 1st and 10th injection of amphetamine, and repeated saline injections produced a negligible behavioral response (see Figure 3A). Figures 3B and 3C illustrate the effect of an amphetamine challenge on the first, "preextinction" amphetamine challenge test day. As expected from Experiments 1 and 2, rotometer paired rats expressed robust sensitization. They made significantly more rotations than the saline control, rotometer unpaired, and home groups, which did not differ from one another.

Figure 4A shows the effect of the 1st of 10 extinction trials, during which all rats received an injection of saline in the test (rotometer) environment. On the 1st extinction test, the rotometer paired group made significantly more rotations than all other groups, which did not differ from one another (see Figure 4A). That is, only the rotometer paired group showed a CR. This CR extinguished by 10th extinction test, at which time there were no group differences, and all groups showed only very low rates of rotation.

Three to 4 days following the last extinction trial, all rats were taken to the rotometers for a second, postextinction amphetamine challenge test, and the results of this test are shown in Figure 4C. The results of the postextinction amphetamine challenge test were similar to the preextinction test in many ways. First, only rats in the rotometer paired group (R^+H^-) expressed sensitization, showing a significantly greater behavioral response than the saline control group (R^-H^-), the rotometer unpaired group (R^-H^+), and the home group (H^+H^-). Second, the latter two groups did not express sensitization, as they did not differ from the saline control group or from each other. Thus, following the extinction procedure the expression of sensitization remained context specific.

On the other hand, there were also differences between the pre- and postextinction amphetamine challenge tests. The saline control group, the rotometer unpaired group, and the home group showed a significant increase in rotational behavior between the two amphetamine test sessions, as illustrated in Figure 4D. This may have been due to sensitization produced by a single exposure to amphetamine in the test environment on the preextinction test day. In contrast, the rotometer paired group showed a significant decrease in rotational behavior between the two test sessions (see Figure 4D). This effect was greatest during the first 5-min interval after the injection of amphetamine (data not shown), although it was evident throughout the test session. Although it is possible that the rotometer paired group did

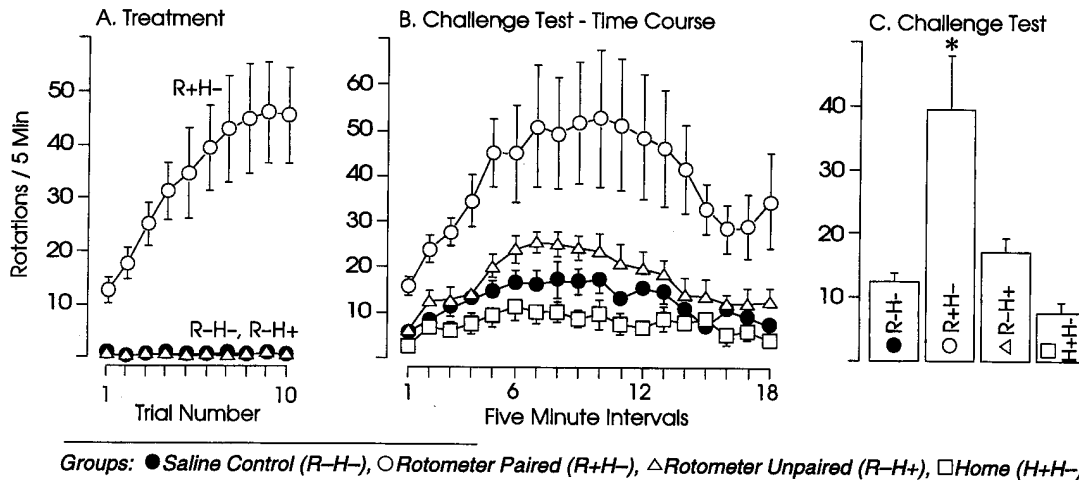


Figure 3. Development of context-specific amphetamine sensitization (Experiment 3). A: Effect of repeated treatment with amphetamine or saline. The mean (\pm SEM) number of rotations per 5-min interval averaged over each of ten 90-min treatment sessions. Rats that received 3.0 mg/kg of amphetamine in the test (rotometer) environment (the rotometer paired group, R⁺H⁻, open circle, $n = 8$) showed a large progressive increase in amphetamine-induced rotational behavior between the 1st and 10th injection: paired two-tailed t test, $t(7) = 4.2$, $p = .0042$. Saline control (R⁻H⁻, solid circle, $n = 7$) and rotometer unpaired (R⁻H⁺, open triangle, $n = 7$) rats, which received saline in this environment, made few rotations, and there was no change in rotational behavior between Trials 1 and 10, $t(6) = 0.7$, $p > .5$, and $t(6) = 0.9$, $p > .3$, respectively. The behavior of rats in the home group (H⁺H⁻, open square, $n = 7$) was not recorded during this phase of the experiment. B: Effect of an amphetamine challenge. The time course of amphetamine-induced rotational behavior over 5-min intervals during the first, preextinction amphetamine challenge test day, when all rats received 1.5 mg/kg of amphetamine in the rotometers. C: Same data as in B, but averaged over the entire test period. There were significant group differences in rotational behavior, $F(3, 26) = 9.1$, $p = .0003$. The rotometer paired rats made significantly more rotations than saline control rats (Fisher's protected least significant difference: $p = .0005$), rotometer unpaired rats ($p = .003$), and home rats ($p < .0001$). Rotometer unpaired rats were not statistically different from saline control rats ($p > .5$). Home rats did not differ from saline control rats ($p > .4$) and rotometer unpaired rats ($p > .10$).

not show an increase in behavior between the pre- and postextinction amphetamine challenge tests because of a ceiling effect, this would not explain why there should be a significant decrease, paired two-tailed t test; $t(7) = 2.5$, $p = .0421$.

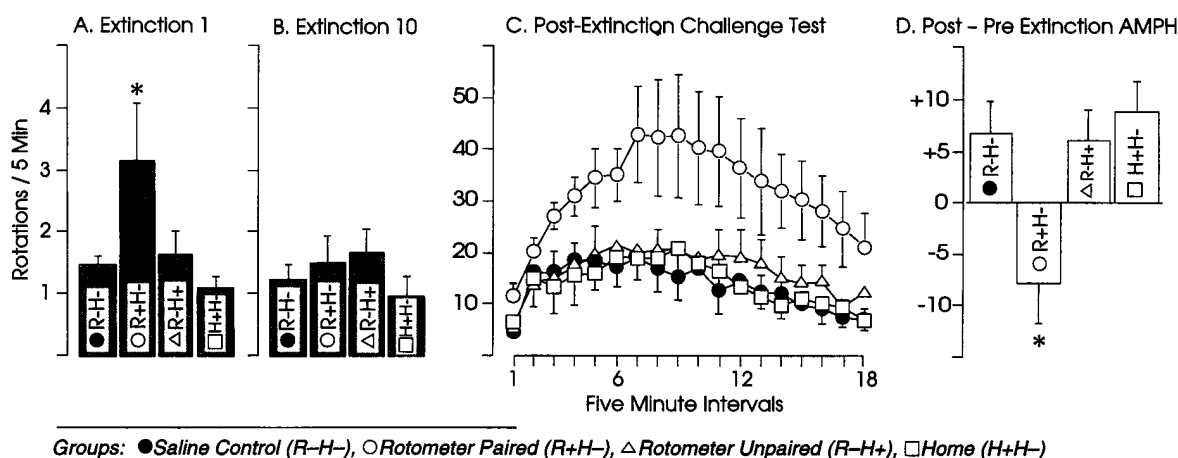
Experiment 4. Development of Sensitization in the Drug-Paired Context and Effect of a Noncontext Contingent Treatment Procedure

In Experiments 1–3 only the rotometer paired group expressed behavioral sensitization on the “test” day. The purpose of this experiment was twofold. First, we wanted to determine the effect of repeated injections of amphetamine in the environments in which different groups received amphetamine, that is, to determine whether they developed sensitization to a comparable degree in their respective “drug-paired” environments. Second, we included a group in which no particular environment reliably predicted the drug, to determine if a noncontext contingent treatment procedure would abolish the influence of context on the expression of sensitization. Third, we sought to replicate the effects of extinction described in Experiment 3.

Experimental Design and Protocol

Treatment. The protocol was essentially the same as for the previous experiments, with the following modifications. (a) Castrated male rats, which show more robust sensitization than intact male rats, were used (Camp & Robinson, 1988; Robinson, 1984). (b) Rats were treated and challenged with the same dose of amphetamine (2.0 mg/kg). (c) Treatment injections were given daily instead of every 3 to 4 days. (d) The test session on the amphetamine challenge test day lasted 120 min instead of 90 min.

There were six treatment groups, Groups 1–6 in Table 1. The saline control group (R⁻H⁻), the rotometer paired group (R⁺H⁻), and the home group (H⁺H⁻) were treated exactly as described for Experiments 1–3, aside from the procedural changes mentioned above (also note below that the rotometer environment was modified). There was also a rotometer unpaired group (R⁻H⁺) treated as in previous experiments, except that these rats lived in specialized home cages (buckets described below). This allowed us to videotape their behavioral response to each injection of amphetamine. The third-world group (3⁺H⁻) was treated as in Experiment 1, but in this experiment these rats received amphetamine treatments in the buckets that served as home cages for rotometer unpaired animals. In addition, a fourth group was included in this experiment, which we call the *multiple-worlds* group (M⁺H⁻). Multiple-worlds rats were treated with amphetamine in five different environments (all of which were distinct from the



Groups: ●Saline Control (R-H-), ○Rotometer Paired (R-H+), △Rotometer Unpaired (R-H+), □Home (H-H-)

Figure 4. Context-specific sensitization: The effect of extinction (Experiment 3). A: Test for a conditional response during extinction training. The mean (+ SEM) number of rotations per 5-min interval during the first extinction test averaged over the entire 90-min test session. Note the scale for the y-axis is different from the scale in Figure 3. There was a significant Group \times Extinction Trial interaction: general multivariate analysis of variance with Extinction 1 and 10 responses as dependent variables, $F(4, 26) = 3.8, p = .0141$. The main effect of group at Extinction 1 was nearly significant (one-way analysis of variance [ANOVA]); $F(3, 26) = 2.87, p = .0556$. Post hoc comparisons revealed that rotometer paired (R^+H^- , open circle, $n = 8$) rats made significantly more rotations than saline control (R^-H^- , solid circle, $n = 7$) rats ($p = .0426$) and home (H^+H^- , open square, $n = 8$) rats ($p = .0107$), and were nearly statistically different from rotometer unpaired (R^-H^+ , open triangle, $n = 7$) rats ($p = .0609$). All other comparisons were not significant ($ps > .4$). B: Test for a conditional response following extinction training. The mean (+ SEM) response during the 10th extinction test. There were no significant overall group differences, $F(3, 26) = 0.8, p > .5$. The response on Trial 10 differed from that on Trial 1 only for rotometer paired rats, which made significantly fewer rotations on the 10th extinction trial: paired two-tailed t test, $t(7) = 2.7, p = .0297$; every other group, $ps > .3$. C: The effect of an amphetamine challenge following extinction. The time course of amphetamine-induced rotational behavior over 5-min intervals during the second, postextinction amphetamine challenge test, when all rats received 1.5 mg/kg of amphetamine in the test environment. There were significant group differences in rotational behavior, $F(3, 26) = 3.9, p = .0193$. Rotometer paired rats made significantly more rotations than saline control rats ($p = .0078$), rotometer unpaired rats ($p = .0224$), and home rats ($p = .0072$). Rotometer unpaired rats did not differ from saline control rats ($p > .6$) or from home rats ($p > .7$), which did not differ from each other ($p > .9$). D: The difference in rotational behavior between the pre- and postextinction amphetamine challenge tests. The overall rate for the preextinction amphetamine challenge test was subtracted from the rate for the postextinction challenge test for each rat. Mean differences between the two tests are depicted for each group. There were significant group differences: univariate ANOVA, $F(3, 26) = 5.6, p = .0043$. Saline control, rotometer unpaired, and home rats all showed an increase in rotational behavior on the postextinction test day and did not differ from each other (Fisher's protected least significant difference: $ps > .5$). Rotometer paired rats showed a decrease in rotational behavior and differed from all other groups ($ps < .01$).

rotometers; see below), followed by saline in their home cages (the standard wire hanging cages located in the animal colony). The behavioral response of these rats was videotaped following the 1st and 10th injection of amphetamine.

Videotapes were scored for full rotations in the dominant direction using the same criteria used by the automated rotometer system (one rotation = four consecutive 90° turns in the same direction).

Challenge test. The effect of amphetamine treatment on the expression of sensitization was determined on an amphetamine challenge test day, which took place 5 to 6 days after the last treatment day. On this day, all of the rats in all groups were transported to the rotometers, where they received 2.0 mg/kg amphetamine. Beginning 1 day later all of the rats underwent the same extinction procedure described for Experiment 3 (except they were left in the rotometers for only 60 min and extinction training took place daily), followed 1 day later by a postextinction amphetamine challenge test.

Contexts (environments). The environments in which rats received treatment injections were as follows. *Animal colony home cages* were the same as the wire-hanging home cages described in Experiment 1. All of the rats in all of the groups lived in these cages except for rotometer unpaired rats, which were moved from the animal colony home cages to buckets 10-days before beginning treatment injections. The buckets (Rubbermaid No. 6222) were located in a different room, and they were made from cylindrical clear plastic equipped with a flat wire-grid floor. Pine wood shavings were located beneath the floor. Each bucket had blue vertical stripes, several small holes in the side, and a wire-mesh lid. Food and water were available at all times, and white noise was played continuously at a moderate volume. The buckets were arranged in groups of five and were located under a video camera mounted near the ceiling. Rotometer unpaired rats lived in these buckets for the duration of the experiment.

The rotometers differed from those used in Experiments 1–3. Here they consisted of clear Plexiglas hemispherical bowls (23-cm

high, with a top diameter of 38 cm). A 25-cm tall blue laundry basket was placed inverted onto the top of these, forming a cover. The floor of each bowl was covered with Bed-'o'-cobs, and rats were tethered as usual to the automated recording device (McFarlane et al., 1992). White noise played continuously, and the entire room was scented with Prevail Powder Room scent (Bissell Co., Grand Rapids, MI).

Multiple-worlds rats were treated in five different environments, all of which were distinct from the rotometers. The first environment was their home cage (animal colony), where they received the 4th and 9th treatment injections. The second environment, where they received the 1st and 10th injections, consisted of cylindrical white plastic flat-bottom buckets (Rubbermaid No. 6222) with pine shavings on the floor. These were arranged in groups of five under a video camera. The third environment, where they received the 2nd and 6th injections, consisted of a glass aquarium (76 × 31 × 46 cm) filled with ~20 cm of Styrofoam shipping "popcorn," which was scented with Prevail Citrus Orchard scent (Bissell Co.). The aquarium was placed in a dimly lit room, and rats were placed into the aquarium in groups of 5. The fourth environment, where they received the 3rd and 7th injections, consisted of clear rectangular Plexiglas containers (23 × 31 × 23 cm) with wire-mesh lids and Fresh Step cat litter (Clorox Co., Oakland, CA) on an aluminum floor. The fifth environment, where they received the 5th and 8th injections, consisted of cylindrical white plastic flat-bottom buckets (Rubbermaid No. 6222) with Bed-'o'-cobs on the floor. The Bed-'o'-cobs were scented with a Fresh Coconut scent (Medo Industries, Mt. Vernon, NY), and the chambers were located in a completely dark room.

Results

In Experiments 1–3 only the rotometer paired group (R^+H^-) showed any evidence of behavioral sensitization when administered amphetamine in the rotometers on the test day. In this experiment we were able to quantify the effect of repeated injections of amphetamine in the environments in which the other groups received amphetamine treatments. Furthermore, the multiple-worlds rats, which received amphetamine in five different environments during treatment, allowed us to test the effect of a noncontext contingent treatment procedure on the context specificity of the expression of behavioral sensitization.

Figure 5 shows that, as in the previous experiments, rotometer paired rats showed a large and progressive increase in amphetamine-induced rotational behavior in the test environment. Of particular importance, however, Figure 5 shows that the other groups also developed robust sensitization in their respective drug-paired environments. It is not appropriate to directly compare the absolute number of rotations across all treatment environments, because they were physically very different. The exact physical dimensions of a test chamber can have a large effect on drug-induced rotation and other behaviors (Beck, Chow, & Cooper, 1986; Sahakian, Robbins, Morgan, & Iversen, 1975; Schallert, De Ryck, & Teitelbaum, 1980; Willner, Papp, Cheeta, & Muscat, 1992). Nevertheless, Figure 5 shows that the groups developed sensitization in their respective drug-paired environments to a comparable degree as the rotometer paired group.

Figures 6A and 6B show the results of a 2.0 mg/kg amphetamine challenge test when all rats received amphet-

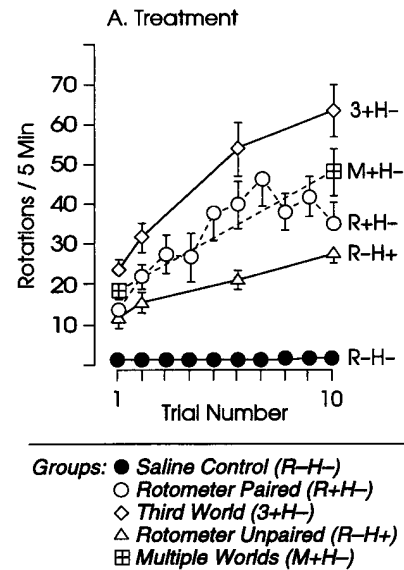


Figure 5. The development of sensitization in different drug-paired contexts. The mean (\pm SEM) number of full rotations per 5-min interval averaged over 90-min treatment sessions are shown as a function of injection number. All the amphetamine-treated groups showed a progressive enhancement in rotational behavior with repeated injections of 2.0 mg/kg amphetamine given in their respective drug-paired environments: rotometer paired (R^+H^- , open circle, $n = 10$, 1st vs. 10th injection), paired two-tailed t test, $t(9) = 4.7$, $p = .0011$; third-world ($3+H^-$, open diamond; $n = 8$), $t(7) = 7.7$, $p < .0001$; rotometer unpaired (R^+H^+ , open triangle, $n = 10$), $t(9) = 4.23$, $p = .0022$; and multiple-worlds (M^+H^- , $n = 8$), $t(7) = 6.9$, $p = .0002$. Saline control (R^-H^- , solid circle, $n = 10$) rats made very few rotations, and there was no difference between the 1st and 10th injection of saline, $t(9) = 0.9$, $p > .3$. Behavior was not recorded from home rats (H^+H^- , open square, $n = 8$) during this phase of the experiment.

amine in the rotometers. As in Experiments 1–3, rotometer paired rats expressed robust sensitization in this environment, making significantly more rotations than saline control, rotometer unpaired, third-world, multiple-worlds, and home rats. Also, as in Experiments 1–3, the saline control, rotometer unpaired, third-world, and home groups did not differ from one another. It is especially important to note that the multiple-worlds rats did express sensitization in the test environment (which they had never visited before), making significantly more rotations than all other groups except the rotometer paired group. Although they expressed sensitization, the multiple-worlds rats made significantly fewer rotations than the rotometer paired rats.

The rats in this experiment also underwent the same extinction procedure (10 extinction sessions) as described for Experiment 3 (except in this experiment, they were daily instead of every 3 to 4 days). As in Experiment 3, only rotometer paired rats showed a significant CR when given saline in the context alone (see Figure 6C). The extinction procedure abolished this CR by the 10th extinction trial (data not shown); general MANOVA with Extinction 1 and 10 responses as dependent variables, Group \times Trial interaction, $F(5, 49) = 3.9$, $p = .0050$ (see Figure 6C for the

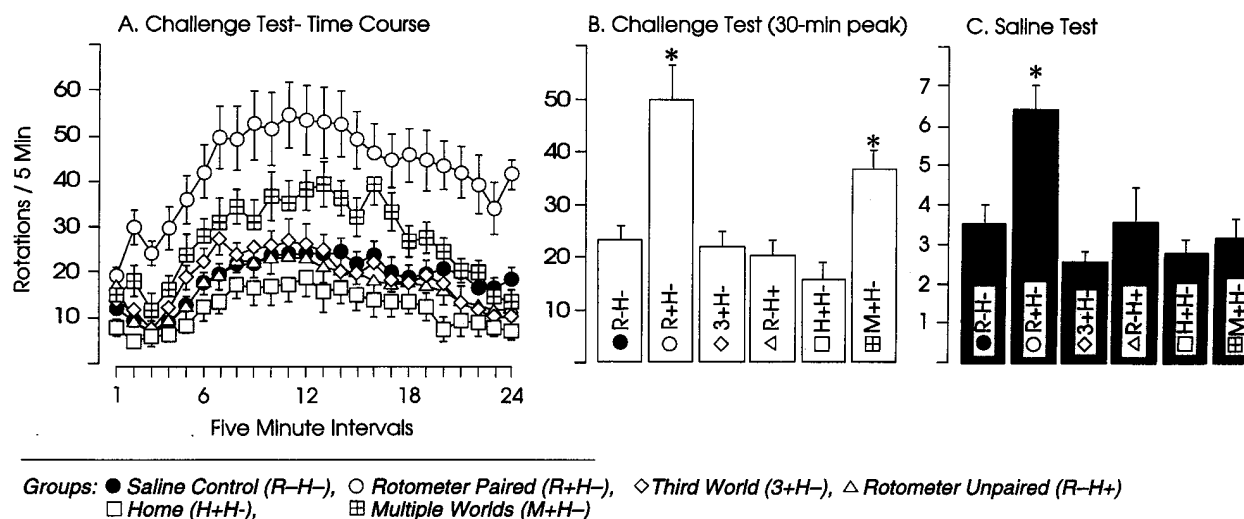


Figure 6. The effect of a noncontingent treatment procedure on the expression of sensitization. A: Effect of an amphetamine challenge. The time course of amphetamine-induced rotational behavior over 5-min intervals on the amphetamine challenge test day. On this day, all rats received 2.0 mg/kg of amphetamine in the rotometers. B: The mean (\pm SEM) number of rotations per 5-min interval averaged over the 30-min period during which rats showed the maximal behavioral response (average of intervals 12–17). The peak response is depicted because the long test period used in this particular experiment resulted in a strong Group \times Time Interval interaction ($p < .0001$), especially for comparisons involving the multiple-worlds group, as is evident on inspection of A. During the period of peak drug effect, there were significant overall group differences: univariate analysis of variance (ANOVA), $F(5, 49) = 10.0$, $p < .0001$. Rotometer paired rats made significantly more rotations than saline control ($p < .0001$), rotometer unpaired ($p < .0001$), third-world ($p < .0001$), multiple-worlds ($p = .0278$), and home ($p < .0001$) rats. Multiple-worlds rats also made more rotations than saline control ($p = .0265$), rotometer unpaired ($p = .0077$), third-world ($p = .0158$), and home ($p = .0021$) rats. Saline control, rotometer unpaired, third-world, and home rats did not differ from each other ($ps > .2$). Note also that 1 rat was excluded from the home group because it was an outlier: Its score of 58.2 rotations per 5 min (entire 2-hr period) was 2.3 standard deviations from the mean for this group. The range for all other rats was 6.9 to 23.5 rotations per 5 min. Excluding this rat did not affect the pattern of results or statistical conclusions. C: On this day, rats were injected with saline in the rotometer environment, and their behavior was assessed for 60 min. Note the different y-axis scale than in B. There were significant group differences: overall ANOVA, $F(5, 50) = 5.8$, $p = .0003$. Only rotometer paired rats showed a conditional response to the context alone. They differed from all other groups ($ps < .001$, Fisher's protected least significant difference), which did not differ from each other ($ps > .2$).

univariate ANOVA for Extinction Test Session 1, $p = .0003$; univariate ANOVA for Extinction 10, $F(5, 49) = 0.87$, $p > .5$. The response for paired rats on Extinction Trial 10 was 3.9 ± 0.4 rotations per 5 min, and the range for the other groups was 2.5 to 3.7 rotations per 5 min. Also, as in Experiment 3, rotometer paired rats showed a small but significant decrease in their response to amphetamine on the postextinction challenge test, whereas all other groups showed a small but significant increase (data not shown); $F(5, 49) = 5.1$, $p = .0008$, and the expression of sensitization remained context specific; that is, the main effect of group remained significant, $F(5, 49) = 2.5$, $p = .0414$. The rotometer paired rats made significantly more rotations than the saline control and rotometer unpaired rats ($ps < .05$), which did not differ from one another ($p > .6$).

General Discussion

It was hypothesized that although the expression of weak psychostimulant sensitization may be context specific, con-

textual stimuli would have a negligible effect on the expression of sensitization following an amphetamine treatment regimen that induced robust sensitization. In most studies reporting context-specific psychostimulant sensitization, animals were treated with relatively low doses of the drug only once or just a few times (Drew & Glick, 1988; Mazurski & Beninger, 1987; Post & Weiss, 1988; Stewart & Vezina, 1991; Weiss et al., 1989). In the present experiment, therefore, procedures were used that induced a robust and progressive increase in drug response (rotational behavior), as indicated by an approximately fourfold increase in rotational behavior in rats given 3 mg/kg of amphetamine 10 times in the test apparatus. Contrary to our hypothesis, however, the expression of sensitization was completely context specific despite robust sensitization. Rats with the same drug history as rotometer paired rats but that received amphetamine treatments in a different environment responded the same as saline-pretreated controls when given an amphetamine challenge in the rotometers (with one

exception), and significantly less than rotometer paired rats. This was true even though most groups developed comparable sensitization to rotometer paired rats when they were observed in the environment in which they received their initial drug treatments.

These findings have a number of implications for how behavioral sensitization is conceptualized. It is clear that a strong version of a simple neuroadaptationist or nonassociative view (see the introduction) is not tenable. By this view, sensitization represents only unconditional neurobiological adaptations produced by the pharmacologic actions of drugs on a specific neural substrate. In the experiments reported here, however, context was the major determinant whether sensitization was expressed. The question that needs to be addressed, therefore, concerns the mechanism by which contextual stimuli modulate the expression of sensitization.

There are at least three different psychological models of how associative pairing of a specific context with drug administration could allow contextual stimuli to modulate the expression of sensitization. Two of these have been proposed previously as explanations of context-specific drug sensitization. A third is applied to the phenomenon of sensitization, to our knowledge, for the first time here. We refer to these three models as (a) the excitatory conditioning model, which posits that context acts as an excitatory CS; (b) the inhibitory conditioning model, which posits that context acts as an inhibitory CS; and (c) the occasion-setting model, which posits that context acts as an occasion setter (occasion setters, or modulators, are CSs that may not themselves elicit a behavioral response but can modulate the ability of other stimuli to elicit behavioral responses; e.g., Holland, 1992). The first model is a purely associative view, whereas the latter two incorporate elements of both associative and nonassociative processes. The ability of each of these views to explain the context-specific sensitization described here is discussed next.

Excitatory Conditioning Model

One of the earliest explicit models of how context contributes to sensitization is a Pavlovian excitatory conditioning model (Hinson & Poulos, 1981; Pert et al., 1990; Siegel et al., 1987; Tilson & Rech, 1973). According to this associative model, sensitization is context specific because sensitization is due to Pavlovian conditioning. By this view, amphetamine acts as a US, producing a number of URs, including locomotor activity, stereotyped behavior, rotational behavior, and enhanced dopamine activity. The context acts as a CS, and after repeated pairings with amphetamine the context comes to elicit CRs, which can resemble the drug's URs. Indeed, conditional locomotor activity, stereotyped behavior, rotational behavior, and dopamine activity have all been demonstrated (Annett et al., 1992; Beninger & Hahn, 1983; Carey, 1986, 1988; Drew & Glick, 1987; Fontana, Post, & Pert, 1993; Herz & Beninger, 1987; Hiroi & White, 1989; Post, Lockfeld, Squillace, & Contel, 1981; Schiff, 1982; Stewart, 1984; cf. Martin-Iverson & Fawcett, 1996). Thus, according to a simple excitatory conditioning model, sensitization represents the progressive

acquisition of a CR elicited by contextual stimuli, which is added to the unchanging UR produced by the drug (i.e., the "sensitized" response = UR + CR).

It is worth pointing out, however, that some authors have suggested that the apparent locomotor CR reported in many studies may reflect an impairment in a habituation process rather than an associative learning process (e.g., Ahmed, Cador, Le Moal, & Stinus, 1995; Damianopoulos & Carey, 1992). This is clearly not the case here. First, there was no change in the rotational behavior produced by repeated saline injections in the test environment (e.g., see group R⁻H⁻ in Figure 1A). The absence of a large UR upon mere exposure to the test environment, and thus of subsequent habituation of this response with repeated exposure to the test environment, is a major advantage of rotational behavior over locomotor activity for this type of study (see Badiani, Anagnostaras, & Robinson, 1995; Badiani, Morano, Akil, & Robinson, 1995). Second, in a number of instances, the unpaired group did not receive drug injections in the test environment (e.g., the third-world and home groups), precluding the opportunity to habituate to the test environment.

Indeed, the data reported here are consistent in many ways with an excitatory CS model of sensitization. First, with the exception of the multiple-worlds group, the expression of sensitization was completely context specific. Second, after repeated pairings of a specific context (the rotometer) with amphetamine administration, an injection of saline in the rotometer environment was sufficient to elicit a CR (rotational behavior). Third, extinction training eliminated the CR, and in the rotometer paired group also resulted in a significant decrease in rotational behavior during the postextinction amphetamine challenge test (all other groups showed a significant increase in rotation between the pre- and postextinction challenge tests). The decrease in the rotometer paired group may reflect the loss of the contribution of the excitatory CR to the amphetamine response in this group. The increase in the other groups could be due to sensitization induced by a single injection of amphetamine in the rotometer environment during the preextinction challenge test, as a single injection is known to be sufficient to produce some sensitization (Robinson, 1984).

On the other hand, a simple excitatory CS model has difficulty dealing with many reports that sensitization is not always context specific. For example, in the present experiments the multiple-worlds group expressed sensitization in the rotometer environment. We envisioned this group as similar, in principle, to a contextual version of Rescorla's (1967) "truly random" control group, for which the US (the drug) is not contingent on the CS (the context). In this group, context should not develop excitatory CS properties and, thus, should not produce a CR. But rats in this group did express sensitization when given an amphetamine challenge in the test environment (which they had never encountered before), albeit less robust sensitization than paired rats. An excitatory CS model could potentially explain this by evoking the concept of stimulus generalization. That is, it is possible that rats in this group generalized between the treatment and test environments, and context did serve as an excitatory CS, accounting for their moderate degree of

sensitization. If this were true, however, one would expect the multiple-worlds group to have shown a significant CR following an injection of saline in the test environment (as did rotometer paired rats), and they did not. Furthermore, following extinction, the multiple-worlds group did not show a decrease in amphetamine-induced rotation, as did rotometer paired rats, suggesting there was no extinction of an excitatory CS (data not shown). Thus, in the multiple-worlds group sensitization was expressed in the absence of any evidence for a CR.

The absence of a CR is not strong evidence against an excitatory CS model, however, because apparatus cues alone may not have been sufficient to generate a robust CR, as suggested by Pert et al. (1990). In sensitization experiments there are a number of stimuli, in addition to apparatus cues, that predict drug administration and could potentially serve as excitatory CSs, including the injection ritual (e.g., handling and needle jab) and the interoceptive cues produced by the drug itself. Pert et al. argued that all of these stimuli (apparatus cues, the injection ritual, and interoceptive drug cues) "should be capable of eliciting the conditioned response to some extent depending on their relative saliency" (p. 216) and that the most robust conditioned reactions may only be present in response to the entire configuration of drug-associated stimuli. This argument could also be used to explain why extinction procedures were not effective in eliminating the expression of context-specific sensitization in the present study. Simple exposure to the drug-paired context (and saline injection) would not extinguish the potential CR to the interoceptive drug cues.

Although it may be true that the injection ritual and the interoceptive cues produced by drugs can serve as CSs, they were not sufficient to either generate a CR or support the expression of sensitization under the conditions of this study. This point is best illustrated by consideration of the third-world group. In this group there were a number of cues besides the test chamber that reliably predicted the drug. These included transport from the animal colony to a novel apparatus, the injection procedure (handling and needle jab), as well as the interoceptive cues of the drug. Furthermore, these rats never underwent inhibitory conditioning in the test apparatus (i.e., the rotometer) because they were never exposed to that environment in the absence of the drug (as was the rotometer unpaired group). If the injection ritual or interoceptive cues associated with the drug played an important role in establishing a CR or promoting the expression of sensitization, one might expect that presentation of these cues alone would be sufficient to have some influence on the behavioral response. But when given amphetamine on the challenge test day (and thus experiencing its interoceptive effects), these rats behaved the same as saline-pretreated controls; only the rotometer paired group showed a CR on the saline challenge test day. Although this does not establish that the injection ritual or interoceptive cues play no role in context-specific sensitization, it does suggest they are not in themselves sufficient to influence this behavioral response or to produce a CR. Of course, one could still argue that these cues are effective only when they are combined with contextual stimuli to form a configural

CS (Fontana et al., 1993; Pert et al., 1990). On the other hand, it is also possible that contextual stimuli are unique in their ability to gain control over drug responses.

Another difficulty for a simple excitatory CS model concerns the magnitude of the CR. In the present experiments the magnitude of the CR was estimated by the response to saline given in the test context, and this was quite small relative to the magnitude of the sensitized response to amphetamine. For example, the average CR was about 2–4 rotations per 5 min above control, whereas following sensitization the average difference in amphetamine response between rotometer paired and saline control or rotometer unpaired groups was approximately 10–25 rotations per 5 min. Even the maximal CR (i.e., the maximal rate of rotation for any 5-min interval during the saline challenge test) does not account for the minimal difference between the saline control group and the rotometer paired group on the amphetamine challenge test day (data not shown). That is, the sum of the CR (the response to the saline challenge) and UR (the response to the first injection of amphetamine) is much smaller than the magnitude of the sensitized response (also see Badiani, Browman, & Robinson, 1995; Beninger & Hahn, 1983; Carey, 1986). It is always possible that the saline challenge test greatly underestimates the magnitude of the CR, because, as mentioned earlier, it does not reproduce the "entire stimulus complex," including interoceptive drug cues (Pert et al., 1990). Interoceptive drug cues also could be evoked to explain why sensitization was still expressed and was still context specific following extinction training, as found here and as has been reported by others (Drew & Glick, 1988). This could be due to renewal or reinstatement of the CR by drug cues, phenomena that have been well documented in the learning literature (Bouton, 1993; Bouton & Swartzentruber, 1991). Alternatively, it is also possible that the saline challenge test overestimates the contribution of the CR to the sensitized response. The CR lasted for only a brief period of time, no more than 15–30 min (data not shown), but the rotometer paired and rotometer unpaired groups differed maximally during the period of peak drug effect, 40–60 min after drug administration, when there was little evidence for a CR.

On the other hand, one could argue that a more valid estimate of the magnitude of the CR is obtained during the amphetamine challenge test, for the reasons discussed earlier (e.g., this better recreates the "entire stimulus complex"). Thus, the response to the first injection of amphetamine, or the response of saline control rats during the amphetamine challenge test, represents the UR, and the difference between the UR and the "sensitized" response of the rotometer paired group represents the magnitude of the CR. This approach raises, however, another problem related to the magnitude of the CR. If this were true in the present experiment, the magnitude of the CR would be three to four times greater than the magnitude of the UR, because on the amphetamine challenge test day the response of the rotometer paired group was three to four times greater than the response of the saline control group. Given that the UR and CR assume the same response form, this seems to violate

one of the general assumptions of many conditioning models, that the strength of the US dictates the maximal strength of the CR (e.g., Rescorla & Wagner, 1972). That is, CRs are usually not many times greater than URs.

Although an excitatory CS model could potentially account for some of the data reported here, the discussion thus far has emphasized that there are a number of problems with this account. Furthermore, a strictly associative view does not explain all examples of sensitization, and it may be possible to dissociate the expression or development of a CR from sensitization both behaviorally (Damianopoulos & Carey, 1992; Drew & Glick, 1987, 1988; Martin-Iverson & Fawcett, 1996; Mazurski & Beninger, 1987; Stewart & Vezina, 1988) and biochemically (Beninger & Hahn, 1983; Carey, 1990; DiLullo & Martin-Iverson, 1991; Hiroi & White, 1989; Weiss et al., 1989). Perhaps the strongest evidence that sensitization is not just the addition of a CR to a drug-induced UR comes from reports of completely context-independent sensitization. For example, the injection of amphetamine locally into the ventral tegmental area (VTA) induces sensitization to a subsequent systemic challenge injection of amphetamine, cocaine, or morphine (Kalivas & Weber, 1988; Vezina & Stewart, 1990), but intra-VTA injections of amphetamine do not result in the development of a CR and sensitization is context independent (Stewart, 1992; Vezina & Stewart, 1990). Furthermore, neural sensitization has been described under conditions that preclude the influence of contextual stimuli on the expression of the sensitized response. For example, stimulated DA release is enhanced in striatal tissue slices removed from rats previously sensitized to amphetamine in their home cage (Castañeda, Becker, & Robinson, 1988; Robinson & Becker, 1982). Also, electrophysiological evidence of neural sensitization has been reported following the local application of DA agonists in anesthetized animals (Henry & White, 1991, 1995). These neurobiological experiments strongly suggest that exposure to psychostimulants can sensitize a neural system, the mesostriatal DA system, and that neural sensitization can be manifest in the absence of any conditional stimuli predictive of drug administration. Nonetheless, in many studies of behavioral sensitization, there is probably at least some portion of the "sensitized" response that is due to simple excitatory conditioning. Our data suggest, however, that the contribution of conditioned excitation to the expression of amphetamine sensitization is relatively small.

Inhibitory Conditioning Model

We refer to a second view of how associative learning may contribute to the expression of sensitization as the *inhibitory conditioning model*. This view arose from experiments by Stewart and Vezina (1988, 1991) on the effects of an extinction procedure on the expression of locomotor sensitization. They reported that locomotor sensitization to amphetamine was context specific; that is, paired (CS^+) but not unpaired (CS^-) animals showed a sensitized response to the initial amphetamine challenge. Following extinction

training, however, unpaired animals (CS^-) came to show a sensitized response to amphetamine (cf. Ahmed et al., 1993). Jodogne et al. (1994) reported similar findings for unpaired "low responders" (cf. Ahmed et al., 1993), whereas they found that paired "high responders" showed a decreased response during a postextinction amphetamine challenge test, similar to that reported here. In interpreting their results, Stewart and Vezina (1991) concluded that "sensitization to the locomotor effects of amphetamine had developed in group Unpaired, but that prior to extinction its expression was inhibited in the environment explicitly unpaired with amphetamine" (p. 69).

This is an example of a model that incorporates elements of both associative and nonassociative views of sensitization (Stewart & Vezina, 1988). Sensitization itself is considered a nonassociative process characterized by a progressive increase in a UR to the drug, presumably due to drug-induced adaptations in a specific neural substrate. The role of contextual stimuli is to inhibit the expression of this sensitized neural substrate in unpaired (CS^-) animals. Specifically, by an inhibitory conditioning view, sensitization is not expressed in unpaired animals because the negative contingency (inhibitory conditioning) produced by explicitly unpairing the context (CS) and drug (US) results in contextual stimuli actively inhibiting the sensitized UR, that is, acting as an inhibitory CS (CS^-). According to Stewart and Vezina (1988, 1991), extinction training diminishes the effects of the inhibitory CS, resulting in the subsequent expression of the sensitized response.

There are a number of reasons why an inhibitory conditioning model cannot explain the data reported here. First, it was not necessary to explicitly unpair the test environment with drug administration (as with the rotometer unpaired group) to obtain context-specific sensitization. It did not matter, for example, whether rats received drug injections in their home cage (as in the rotometer unpaired [R^-H^+] or home group [H^+H^-]) or in a novel third environment (third-world group [3^+H^-]). The expression of sensitization was completely context specific in all cases. This establishes that it is not necessary for contextual stimuli to explicitly predict the absence of the drug for the expression of sensitization to be context specific. Indeed, the negative contingency programmed between the rotometer environment and amphetamine for rotometer unpaired rats seems to have had no measurable effect; these rats did not differ from saline controls or from the third-world group. These data are not consistent with the idea that context-specific sensitization is due to inhibitory conditioning to an explicitly unpaired context.

Second, in the present study, sensitization remained entirely context specific following extinction training. During the postextinction challenge test, the rotometer paired group still made significantly more rotations than the saline control group and the rotometer unpaired group, which did not differ from one another. That is, following extinction, rotometer unpaired rats still did not express sensitization in the rotometer environment. It is possible that a sensitized response would have emerged if more extinction trials had

been given, and this may have been required because the strength of contextual control was greater under the conditions of this study than that of Stewart and Vezina (1991). Hinson and Poulos (1981) reported, for example, that 36 extinction trials abolished environment-dependent sensitization (although in this report one cannot tell if the paired group went down or the unpaired group went up). On the other hand, others also have failed to find enhanced responding in unpaired groups after extinction training (e.g., Ahmed et al., 1993; Drew & Glick, 1988). Indeed, it has been reported that extinction is generally not effective in abolishing inhibitory conditioning (Zimmer-Hart & Rescorla, 1974; for a review of procedures that are effective in reducing conditioned inhibition, see Fowler, Kleiman, & Lysle, 1985; Fowler, Lysle, & DeVito, 1991). In some studies, extinction training has even been found to enhance conditioned inhibition (e.g., DeVito & Fowler, 1987). These observations are, of course, not consistent with the evidence cited in support of the inhibitory conditioning view.

Third, it is generally agreed that there are two tests that should be satisfied before evoking conditioned inhibition: summation and retardation (Rescorla, 1969a, 1969b). *Summation* refers to the ability of an inhibitory CS to reduce the response to another stimulus (CS or US). In sensitization experiments, evidence of summation may be sought during the saline challenge test for a CR. In the present experiment, if the rotometer environment served as a conditioned inhibitor, one might expect that rotometer unpaired rats would show a suppression in behavior when exposed to the conditioned context, in comparison with controls, and they did not. *Retardation* refers to a decreased rate of acquisition of a CR if an inhibitory CS is subsequently used as an excitatory CS. In unpublished experiments, however, we found no evidence for retardation of sensitization in rotometer unpaired animals subsequently given repeated injections of amphetamine in the test environment, compared with saline control animals. Although these tests for summation and retardation may not be conclusive, the criteria for conditioned inhibition have not, to our knowledge, been met in the literature. We suggest, therefore, that the available evidence does not support the hypothesis that context-specific sensitization is due to conditioned inhibition.

We should qualify this, however, because there may be other procedures different from those used here that can produce conditioned inhibition in drug sensitization studies. In conditioned inhibition studies, procedural differences often yield different kinds of learning (Holland, 1985), and we have not examined any other conditioned inhibition procedures. Also, we have discussed the concept of conditioned inhibition as if it is the opposite of conditioned excitation, ignoring the debate in the animal-learning field regarding the nature of conditioned inhibition. It has been argued, for example, that conditioned inhibition is not the opposite of conditioned excitation, but rather the opposite of a different kind of learning effect, a type of occasion setting known as *conditioned facilitation* (Rescorla, 1992; cf. Holland, 1989b).

Occasion-Setting Model

Given the limitations of both the excitatory and inhibitory conditioning models discussed above in explaining the data reported here, we need to consider the possibility that the primary role of context in the expression of sensitization is neither as a traditional excitatory CS nor as a traditional inhibitory CS. If this is true, however, why was the expression of sensitization completely context specific; that is, by what mechanism does context modulate the expression of sensitization? A clue comes from the suggestion by some learning theorists (Bouton, 1993; Bouton & Swartzentruber, 1986; Holland, 1992; Rescorla, Durlach, & Grau, 1985) that in conditioning experiments context frequently acts, not as a traditional CS (CS⁺ or CS⁻), but as what Holland (1986, 1992) called an *occasion setter* and Rescorla (1985, 1992) called a *modulator* (facilitator or inhibitor). We suggest below that a drug-paired context also may modulate the expression of sensitization by an action as an occasion setter.

The occasion-setting model is derived from recent developments in learning theory, which suggest that Pavlovian conditioning often involves much more than just the process by which a stimulus acquires the ability to elicit the response originally produced by another stimulus (Rescorla, 1988; Turkkan, 1989). Pavlovian learning is now thought to involve not only stimuli acquiring the ability to act as traditional CSs, but the ability to modulate responses to other stimuli. This latter type of stimulus is what is called an occasion setter or modulator. It is important to emphasize that occasion setters are fundamentally different from excitatory CSs. The circumstances that produce occasion setters and those that reduce their power are different from those that produce and reduce simple excitatory CSs (Rescorla, 1985). For example, the temporal relationship between a cue and the US is particularly important in determining whether a stimulus will come to act as an occasion setter or as a conditioned excitor (Holland, 1986), and the nature of the temporal relationship between contextual stimuli and more discrete USs may be ideal for promoting occasion setting (Bouton, 1993; Bouton & Swartzentruber, 1986; Holland, 1992; Rescorla et al., 1985). The function of occasion setters in behavior seems to be to modulate the excitatory strength of other stimuli (Rescorla, 1985), and there is considerable independence of a cue's occasion-setting properties and its ability to elicit behavior (conditioned excitor properties; Holland, 1992). For example, the ability of a cue to elicit an excitatory CR is readily diminished by extinction training, whereas the ability of a cue to gate the properties of other stimuli (to act as an occasion setter) is not readily diminished by traditional extinction procedures (Holland 1992; Rescorla, 1992).

Thinking about context as an occasion setter, rather than as a traditional CS, makes sense of many of the findings reported here. First, it explains why sensitization was completely context specific, even though contextual stimuli did not produce a large enough CR to account for sensitization. According to an occasion-setting model, the expression of sensitization will be context specific when the contingen-

cies are arranged so that a specific context reliably predicts drug administration, because this will result in context acquiring the ability to "set the occasion" for the sensitized response. That is, the associatively paired context will come to enable the sensitized response. When presented alone, however, occasion setters may not evoke a CR (Holland, 1992; Rescorla, 1985), and this may be why context was able to exert powerful modulatory effects on the sensitized response without producing a large CR. The small CR reported here presumably represents a separate action of context, an action as a simple excitatory CS, not as a modulator. The ability of context to acquire both simple excitatory CS properties and at the same time modulatory properties is consistent with previous descriptions of occasion setters. It has been reported that the ability of a stimulus to develop an association with a US (to become an excitatory CS) can develop independently of its ability to modulate the response to other stimuli (i.e., to act as an occasion setter; Bouton & Swartzentruber, 1986; Holland, 1992; Rescorla, 1985), and thus, the drug-paired context could serve simultaneously as an excitatory CS and as an occasion setter.

Second, the independence of the excitatory CS and occasion-setting properties of contextual stimuli can explain the effects of extinction reported here. Extinction procedures abolished the effect of context as an excitatory CS (the small CR seen on the saline challenge test day extinguished), but during the postextinction amphetamine challenge test the expression of sensitization was still completely context specific. This is consistent with previous observations that although extinction procedures diminish the action of excitatory CSs they are relatively ineffective in influencing the modulatory actions of occasion setters (e.g., Holland, 1989a; Rescorla, 1985; Ross, 1983). The small decrease in rotational behavior between the pre- and postextinction amphetamine challenge tests in rotometer paired animals may reflect the loss of the contribution of excitatory conditioning to the sensitized response.

Third, in the present experiments, sensitization was context specific even in those groups for which the test environment did not explicitly predict the absence of the drug (e.g., the third-world and home groups). This could be explained if context did not act as a CS⁻, but if whatever environment the rats received their drug treatments in developed "feature-positive" occasion-setting properties. Thus, the third-world and home groups showed sensitization when observed in their respective drug treatment environments, but outside of that context (in the test environment), they did not express sensitization because the test environment failed to "set the occasion" (i.e., failed to enable the sensitized response).

Fourth, the multiple-worlds group did express sensitization in the test environment, albeit less robust sensitization than the rotometer paired group. This could be explained in a couple of ways. First, it is possible that in this group no specific environment developed occasion-setting properties because none were reliably associated with drug administration. The sensitized response seen in the test environment could be, therefore, context-independent sensitization caused by nonassociative sensitization of the neural substrate that

mediates the UR to the drug (rotational behavior in this case). The expression of sensitization was "released" from contextual control because the contingencies required for context to develop occasion-setting properties (or excitatory CS properties for that matter) were not present. Alternatively, in the multiple-worlds group contextual information may have been ambiguous, because the rats were exposed to the drug in many different environments. This may have forced the rats to rely on other occasion-setting cues that allowed for the activation (or partial activation) of an occasion-setting mechanism related to expectation of the drug, such as exposure to any novel environment. This expectation was not sufficient to generate an excitatory CR, and this may explain why the sensitized response in this group was smaller than in the rotometer paired group; that is, the smaller response reflects the loss of the contribution of an excitatory CR.

Although there was no evidence for this in the present experiments, it is possible that under some conditions "feature-negative" occasion setting could play a role in the expression of sensitization. In such a case, cues that reliably predict the absence of the drug might attenuate the expression of sensitization. Rescorla (1992) suggested that feature-negative occasion setting is principally the same as conditioned inhibition, and as discussed earlier, different conditioned inhibition procedures from those used here might produce evidence for this kind of occasion setting (e.g., Holland, 1985). However, in the present experiments we suggest that the drug-paired context acquired feature-positive occasion-setting properties, which enabled the sensitized amphetamine response.

To conclude, we propose that the available evidence suggests that amphetamine sensitization is best characterized as a phenomenon that incorporates elements of both nonassociative and associative processes (also see Pert et al., 1990; Stewart & Vezina, 1988). The repeated intermittent administration of amphetamine produces progressive neuroplastic adaptations in a neural substrate that mediates the psychomotor stimulant (and incentive motivational) effects of the drug, which renders the neural substrate hypersensitive (sensitized) to activating stimuli. Thus, neural sensitization appears to be a nonassociative process, which can be manifest behaviorally as a progressive increase in particular drug effects (although it is important to note that even the rate and extent of sensitization can be influenced by environmental factors, e.g., Badiani, Anagnostaras, & Robinson, 1995; Badiani, Browman, & Robinson, 1995; Badiani, Morano, Akil, & Robinson, 1995). One neural substrate that is sensitized by amphetamine is the mesostriatal DA system (Kalivas & Stewart, 1991; Robinson & Becker, 1986).

Whether neural sensitization is expressed at any particular place or time, however, is determined largely by CSs (especially contextual stimuli) that have been associatively paired with drug administration (an associative process). It is not known how environmental stimuli gain control over the sensitized neural substrate, but there are many possibilities, and it has been suggested previously that this may occur independently of the ability of CSs to elicit a CR (e.g.,

Badiani, Browman, & Robinson, 1995; Stewart & Vezina, 1988). Thus, in considering the neural mechanisms by which associative factors modulate the expression of sensitization, it will be important to take into account the evidence presented here that the role of contextual stimuli may be twofold. First, contextual stimuli may act to "set the occasion" or "enable" the sensitized response in the same sense that occasion setters are proposed to modulate other responses (Holland, 1992; Rescorla, 1985). Second, contextual stimuli may also acquire simple excitatory CS properties, producing a CR that adds to the UR produced by the drug. We suggest, however, that the action of context as an occasion setter may have a greater influence on the expression of sensitization than its action as an excitatory CS. Of course, this application of occasion setting is somewhat novel because previous examples from the animal-learning literature have focused on the ability of occasion setters to modulate CRs (Holland, 1992; Rescorla, 1985). We hypothesize, however, that contextual stimuli that have been paired with drug administration may also acquire the ability to modulate the UR to a drug, especially under conditions in which the UR changes with repeated drug experience (i.e., during sensitization). It is not known how this occurs, but as has been suggested for modulation of CRs, occasion setters could act to amplify the representation of the US (Holland, 1992; Rescorla, 1985) or to enable the production of the sensitized UR.

In closing, we propose that the interactions between neural sensitization and associative learning discussed here may be especially important in the development of addictive behavior. An interaction between sensitization of a neural substrate that mediates the incentive motivational effects of drugs of abuse and associative learning may be responsible for the pathological focus on drug-associated stimuli and mental representations of drug taking in addicts, and in the critical role that context plays in precipitating relapse (Berridge & Robinson, 1995; Robinson & Berridge, 1993).

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