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Memory Processes Governing Amphetamine-induced Psychomotor Sensitization

Stephan G. Anagnostaras, Ph.D., Timothy Schallert, Ph.D., and Terry E. Robinson, Ph.D.

We investigated how, under certain circumstances, the expression of psychomotor sensitization comes to be context-specific. Rats that had previously sustained 6-hydroxydopamine-induced unilateral dopamine depletion received repeated injections of d-amphetamine (AMPH) or saline in group-specific environments, and rotational behavior was measured as an index of psychomotor activation. Following these treatments some groups were given electroconvulsive shock (ECS), when memories of the drug experience were reactivated (and therefore vulnerable to disruption), in order to produce retrograde amnesia. Animals given an AMPH challenge in the environment in which they received drug treatments (Paired) expressed robust sensitization. Animals given an AMPH challenge in a context that was never paired with drug administration (Unpaired) did not express sensitization. A saline challenge in the AMPH paired context produced a conditioned rotational response (CR). ECS had no effect in Control animals, no effect on the expression of sensitization in Paired animals, and no effect on the expression of the CR in Paired animals. However, ECS did affect Unpaired groups: unlike Unpaired animals given sham ECS, Unpaired animals given ECS expressed robust sensitization. Thus, without ECS, the expression of sensitization must have been suppressed in the Unpaired animals (who had the same drug history as Paired animals), and ECS released this otherwise suppressed sensitization. Based on these and other findings, we propose that three memory mechanisms regulate context-specificity of AMPH sensitization: (1) Repeated drug administration induces sensitization of the neural substrate that mediates the unconditional response (UR) to the drug, a form of non-associative *learning; (2) An inhibitory process can block the expression of neural sensitization in contexts where the drug is not expected, a process we speculate may involve a form of inhibitory occasion-setting; (3) An excitatory conditioned response (CR) can amplify the sensitized response in a context where the drug is expected. It is suggested that the ability of drug-associated contexts to modulate the expression of neural sensitization via occasion-setting may combine with the ability of a drug-associated context to produce conditioned responses, together providing powerful associative control over not only behavioral sensitization, but in addicts, over craving and relapse.*

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Behavioral sensitization refers to a progressive and persistent increase in the psychomotor activating and rewarding effects of drugs, which is often seen when drugs of abuse are given repeatedly and intermittently (Segal et al. 1981; Robinson and Becker 1986). There is considerable interest in this phenomenon, both because it is a compelling example of experience-dependent

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plasticity (Robinson and Kolb 1997; Robinson and Becker 1986; Stewart and Badiani 1993; Pierce and Kalivas 1997), and because sensitization-related neuroplasticity in brain reward systems may contribute to addiction (Lett 1989; Piazza et al. 1989; Robinson and Berridge 1993, 2000). However, despite many studies on the neurobiology of sensitization the fundamental nature of the behavioral phenomenon is still poorly understood. By one view, behavioral sensitization is thought solely as the manifestation of cellular plasticity that occurs as a consequence of repeated exposure to drugs of abuse (Kuczenski et al. 1982; Robinson and Becker 1986). In behavioral terms, this neuroadaptationist model views sensitization as a progressive increase in the unconditional response (UR) to a drug, because of drug-induced changes in the neural substrates that mediate the UR. By this strict non-associative view, conditional stimuli (CS), such as contextual stimuli, should have little influence over the induction or expression of sensitization.

There is, however, considerable evidence showing that under some circumstances behavioral sensitization can come under complete contextual control. For example, sensitization is often absent or reduced if animals are tested in an environment where they have not experienced the drug before, even following treatments that produce very robust sensitization (Anagnostaras and Robinson 1996; Stewart and Vezina 1991; Tilson and Rech 1973; Battisti et al. 2000; Carey and Gui 1998). This phenomenon has been called "context-specific sensitization", and supports an *associative* view of sensitization, in which sensitization is considered an example of drug-context conditioning. By this view, when drug administration (the unconditional stimulus; US) is paired with placement into a distinct environmental context (the CS), contextual stimuli acquire the ability to elicit conditional responses (CR), including drug-like psychomotor effects (Pavlov 1927; Post et al. 1981; Stewart 1984; Carey 1986, 1988; Beninger and Hahn 1983; Drew and Glick 1987; Fontana et al. 1993; Tirelli and Terry 1998; Wolgin 2000). By this excitatory conditioning view, behavioral sensitization simply reflects the addition of an increasing CR to the unchanging UR produced by the drug (Tilson and Rech 1973; Hinson and Poulos 1981; Siegel et al. 1987).

However, several findings are problematic for this conditioned excitation model of sensitization. First, the psychomotor CR observed (when saline is given in the context) is small, short-lasting, and does not account for the difference between the sensitized and naïve response to the drug (Anagnostaras and Robinson 1996; Badiani et al. 1995; Beninger and Hahn 1983; Carey 1986). Second, extinction of the CR by exposures to the context without the drug eliminates the CR, but only slightly reduces the sensitized response to an AMPH challenge (Anagnostaras and Robinson 1996; Battisti et al. 2000; see also Stewart and Vezina 1991; Jodogne et al. 1994; Carey and Gui 1998). Third, increasing the interval between exposure to the test context (CS) and drug administration (US) eliminates the development of a CR, but has no effect on the development of sensitization (Crombag et al. 2001). Fourth, sensitization has been observed in contexts never associated with drug administration and in the absence of any evidence of a CR (Vezina and Stewart 1990; Battisti et al. 2000). For example, we found that rats given AMPH in many different contexts, but not in the final test context, express sensitization to the drug in the absence of any CR (Anagnostaras and Robinson 1996). Thus, it seems that excitatory conditioning may contribute to the expression of behavioral sensitization under certain circumstances, but it does not account for the phenomena.

A third view of sensitization incorporates elements of both associative and non-associative models. In this view, repeated drug administration induces neural sensitization non-associatively, which can directly alter the drug UR. Under some circumstances, however, contextual stimuli can gain powerful control over the ability of the sensitized neural substrate to influence behavior (Stewart and Vezina 1988, 1991; Stewart 1992; Anagnostaras and Robinson 1996). We have suggested that contextual stimuli may modulate the expression of sensitization in two ways. First, context may act as an occasion-setter (e.g., Bouton and Schwartzentruber 1986; Rescorla et al. 1985; Holland 1992) to modulate the expression of the sensitized response, and second, context may act as an excitatory CS, generating a moderate CR, which can amplify the drug response in a drug-paired context (Anagnostaras and Robinson 1996). However, in our previous studies we did not provide any evidence indicating whether the occasion-setting mechanism we proposed involves facilitation or inhibition. In order to further explore this issue we searched the literature for a procedure that might disrupt contextual memories.

One procedure known to produce a profound amnesia is electroconvulsive shock (ECS). In classic experiments, Duncan (1949) found that ECS induced a severe retrograde amnesia (RA) of avoidance fear conditioning, when ECS was administered immediately after acquisition (see also Quartermain et al. 1965). In later studies it was found that, although ECS delivered one day after training normally would not disrupt memory, ECS delivered after reactivation (retrieval) of a memory by presentation of a cue that was present during training can produce a potent RA of these "activated" memories (Misanin et al. 1968; see also Mactatus et al. 1979; Judge and Quartermain 1982; Rubin et al. 1969; Robbins and Meyer 1970; Howard et al. 1974). This much neglected phenomenon has received considerable attention recently because of studies showing that the local inhibition of protein synthesis in the amygdala after re-

activation of a fear memory produces a retrograde amnesia (Nader et al. 2000a,b; Miller and Matzel 2000). Indeed, ECS disrupts protein synthesis and this is associated with its ability to produce amnesia (Dunn 1971). Moreover, Rubin et al. (1969) suggested that reactivated, pathologically disturbing memories in psychiatric patients might be highly vulnerable to disruption by ECT. In case studies of their own patients, Rubin et al. used memory activation techniques and immediate application of ECS without anesthesia to suppress later retrieval of the emotional component of these memories. It appears, therefore, that retrieval (and reactivation) of an otherwise stable memory brings it into a labile state subject to disruption. Thus, in the experiment reported here we disrupted contextual memories by delivering ECS when memories of the drug experience were reactivated by context re-exposure and placebo injection (Judge and Quartermain 1982).

We expected that ECS might disrupt any or all of several memory processes involved in modulating AMPH sensitization. ECS could reduce the amount of AMPH sensitization, it could affect the CR, or it could affect the context-specificity of sensitization. We report, however, that ECS produced a remarkably selective effect on only one of these processes, and our data suggest that the context-specific nature of AMPH sensitization is primarily due to an inhibitory process. We speculate that this process involves inhibition by an occasion-setting mechanism.

MATERIALS AND METHODS

Subjects

A total of 102 male Sprague-Dawley rats were purchased from Harlan Sprague Dawley, Inc. (Indianapolis, IN). They weighed 225–275 g at the time of surgery and 350–475 g when behavioral testing began. They were housed in pairs prior to surgery, and individually following surgery, in wire-hanging cages located in an animal colony maintained on a 14:10 light:dark cycle (lights on at 7:00 A.M.). They had unrestricted access to food and water. Prior to surgery all of the animals were allowed to acclimatize to the animal facility for at least one week.

6-Hydroxydopamine (6-OHDA) Lesion Procedure

Prior to behavioral testing all of the animals received a unilateral 6-OHDA lesion of the nigrostriatal pathway using procedures similar to those described previously (Robinson 1984; Schallert and Wilcox 1985; Tillerson et al. 2001). Briefly, animals were given atropine methyl nitrate (0.04 mg/kg, i.p.), anesthetized with sodium pentobarbital (50 mg/kg, i.p., supplemented with methoxyflurane when necessary), and then were given 15 mg/kg of desipramine HCl, i.p. (Breese and Traylor 1971). Thirty to sixty minutes later, a 29-30 g stainless steel cannula was lowered into the medial forebrain bundle where it courses through the posterior lateral hypothalamus (mm from bregma, 3.0 posterior; 1.8 lateral, and 8.3 ventral to the skull surface). This was used to infuse 8 μg of 6-OHDA HBr 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, animals were screened for apomorphine-induced rotation. Each animal 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 #6222, 25 cm lower diameter, 31 cm top diameter, 36 cm high) with Bed-'o'-cobs® (granulated corn cobs) on the floor. The chamber was located in a quiet room. Animals then received an injection of 0.05 mg/kg apomorphine HCl, s.c., in the nape of the neck. Animals 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 animals with greater than a 90–95% unilateral depletion of striatal DA rotate when given this dose of apomorphine (Marshall and Ungerstedt 1977). Overall, 8% of rats that received surgery were not included, either because they did not meet criterion or because of other post-operative complications.

Unless noted otherwise behavior was quantified using the automated computer and photocell-based rotometer system described by McFarlane et al. (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.

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 AMPH-induced rotational behavior in rats with a unilateral 6-OHDA lesion are relatively linear over a wide range of doses (Crombag et al. 1999; Ungerstedt and 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 AMPH-induced locomotor activity is complex, having an inverted U-shaped function over a relatively narrow dose range (Crombag et al. 1999; Kelley et al. 1986; Russell

and 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 and Carey 1992; Leith and Kuczenski 1982; Segal and Mandell 1974). Second, rotational behavior is easily quantifiable and amenable to parametric analysis. 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 large and changes over time (Badiani et al. 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 and Carey 1992; Carey and Gui 1997, 1998).

Apparatus (Test Contexts)

All animals were given AMPH or saline in the following environments: (1) Some animals were pre-treated in rotometers consisting of cylindrical clear plastic flat-bottom buckets (Rubbermaid #6222). Each bucket was located within a 25 cm tall blue laundry basket with wide mesh walls. Bed-o-cobs were placed on the floor and white noise was played continuously. Additionally, animals were attached to a sensor unit fixed over the chamber using a tether described previously (McFarlane et al. 1992). All animals were later tested in this context during the challenge test. (2) Other animals were pre-treated in what we have operationally defined as the Third World. These chambers consisted of clear acrylic Nalgene tubs (41 × 23 × 20 h cm) with wire lids and pine wood-shavings on the floor, and were located in a quiet room, distinct from the rotometer environment. These animals were not tethered. (3) All animals lived in home cages consisting of stainless steel sliding-drawer type cages with a wire mesh front and floor (23 × 20 × 18 h cm). Pine wood-shavings were located below the cages (i.e., not on the floor), and food and water were available at all times. Animals received saline injections after testing in the home cages.

Experimental Design and Protocol

Induction of Sensitization. There were a total of ten groups in this experiment (Table 1), which came from three types of pre-treatment groups: *Control, Paired,* and *Unpaired* groups (see also Anagnostaras and Robinson 1996). Animals in the saline *Control-Rotometer* groups were transported from their home cages in the animal colony, given an i.p. injection of 0.9% saline (0.5 ml/kg), and placed into the rotometers. Animals in the saline *Control-Third World* groups were transported from their home cages and given saline in the Third World environment (see above). Animals in the *Rotometer-Paired* groups were transported to the rotometers, where they received 2.0 mg/kg of d-amphetamine sulfate (weight

Table 1. Treatment groups. Drug pretreatment lasted seven sessions, with each session 3–4 days apart. For each session, rats received either saline or AMPH in the rotometer or Third World environment, followed by saline in the home cage 90 min later. Rats also received three electroconvulsive shock (ECS) or sham treatments after placement in the rotometer or Third World. Each session was 3–4 days apart and consisted of a saline injection, placement in the rotometer or Third World environment, and then 5 min later being given ECS or ear clip sham treatment. Three to four days after the last treatment, all rats were brought to the rotometers for saline and AMPH testing.

	Drug Pretreatment × 7		**ECS / Location × 3**	
	Rotometer	Third World	Rotometer	Third World
Group / subgroup (n)				
Control				
RS (10)	saline	—	sham	—
RE (9)	saline	—	ECS	—
3S (10)	—	saline	—	sham
3E (10)	—	saline	—	ECS
Paired				
RS (10)	AMPH	—	sham	—
RE (10)	AMPH	—	ECS	—
3E (9)	AMPH	—	—	ECS
Unpaired				
3S (12)	—	AMPH	—	sham
3E (11)	—	AMPH	—	ECS
RE (11)	—	AMPH	ECS	—

of the salt; 0.5 ml/kg i.p.). Animals in the *Unpaired* groups were transported from their home cages to the Third World environment, where they received 2.0 mg/kg of AMPH. 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 seven times, once every 3–4 d. During this phase of the experiment, rotational behavior was recorded only from saline *Control-Rotometer* and *Rotometer-Paired* animals, because they were the only groups tested in the automated rotometers.

Electroconvulsive Shock (ECS) Treatment. Three to four days after the last (seventh) treatment with saline or AMPH, rats were given a series of three ECS or sham treatments in group-specific environments (Table 1). For each session, rats were placed into either the *Rotometer* (group "R") or *Third World* (group "3") and given an injection of saline in order to "activate" the memory of drug pre-treatment (Misanin et al. 1968; Judge and Quartermain 1982). Thirty sec later, they were given ECS (E) or Sham (S) treatment while still in the context (see Table 1). ECS consisted of 200-ms, 50-mA AC constant current passed across alligator clips placed on the rats' ears. This was sufficient to induce a moderate tonic-clonic seizure in all rats that lasted about 30 s. Sham treatment was identical, except no current was passed. Rats were returned to their home cages 5 min later at which time they were alert. This treatment was repeated two more times, with each treatment given 3–4 d apart. *Control-Rotometer* groups, which previously received saline in the rotometers, received ECS or sham treatment in the rotometers. *Control-Third World* groups, which previously received saline in the Third World, received ECS or sham treatment in the Third World. *Paired* groups, which previously received AMPH in the rotometers, received ECS in the rotometers or Third World, or sham treatment in the rotometers. *Unpaired* groups, which previously received AMPH in the Third World, received ECS in the rotometers or in the Third World, or sham treatment in the Third World. Thus, the design was relatively complete, although a couple of groups were omitted as they would provide only redundant information about the effects of sham treatment.

Challenge test. The extent to which context produced a CR or influenced the expression of sensitization was determined on a "challenge" test day, which took place 3–4 d after the last ECS treatment day. On the challenge test day, all of the animals in all groups were transported to the rotometers, where they received a saline injection. Rotations were recorded for 15 min, and then all of the rats received an injection of 2.0 mg/kg of AMPH. The rats were then immediately placed back into the rotometers and rotational behavior was recorded for another 90 min. Note that only *Rotometer-Paired* animals had previously received AMPH in this environment.

Statistics

Behavioral data were analyzed using the general multivariate analysis of variance (MANOVA) model. This was followed by appropriate univariate ANOVAs and post-hoc comparisons using the Wald or Fischer's protected least-significant difference (PLSD) tests. Significance was set at $\alpha < 0.05$.

RESULTS

Induction of Sensitization

Figure 1 depicts rotations during the seven pre-treatment sessions for the *Paired* (n = 29) and *Rotometer-Control* groups ($n = 19$). *Paired* animals made substantially more rotations than *Controls* throughout the pre-treatment phase (first session, $F_{1,46} = 32$, $p < .0001$; seventh, $F_{1,46} = 309$, $p < .0001$). Furthermore, *Paired* rats exhibited a nearly 4-fold increase in responding across days (first vs. seventh session; $F_{1,28} = 491$, $p < .0001$) indicating robust sensitization. *Control* rats did not change across test sessions ($F_{1,18} = 0.21$, $p > .6$).

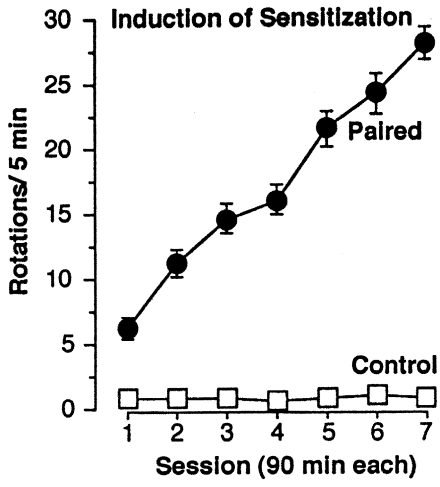

Figure 1. Induction of Sensitization. Rats received either 2 mg/kg AMPH (*Paired*) or saline (*Control*) in the rotometers, followed by saline in the home cage 90 min later for seven sessions, with each session 3–4 d apart. *Unpaired* animals also received AMPH, but in a different, Third World environment and their behavior was not recorded in this phase.

Challenge Test Day

Saline Challenge. After the induction of sensitization, rats received either three ECS or sham treatments (each 3–4 d apart) after a 30-s placement in a group-specific environment. This was followed 3–4 d later by a 15-min saline challenge test in the rotometer test environment, which was novel to some groups but not others (Figure 2, Panel A). There were significant group differences in rotational behavior (ANOVA, $F_{9,92} = 14.5$, $p < .0001$). All *Paired* groups exhibited substantially more rotations in response to a saline injection in the rotometers than all *Control* or *Unpaired* groups (multiple Fisher's PLSD post-hoc comparisons, p values $< .01$). That is, only *Paired* groups showed a conditioned response (CR). *Paired* rats that received sham treatment (RS) exhibited slightly more rotations than those that received ECS in the rotometers (RE, $p = .07$) or in the Third World (3E, $p < .01$). However, this reduction in responding was small, and the CR was left largely intact. ECS did not significantly affect *Control* rats, as they did not differ from one another (p values $> .08$), although there was a trend for those treated with ECS (RE, 3E) to respond less than those that received sham treatment (RS, 3S). *Unpaired* rats were also unaffected by ECS and did not differ significantly neither from one another (p values $> .09$), nor from *Control* rats that received sham treatment (p values $> .2$). Thus, although there was a small effect of ECS in the *Paired* and *Control* groups, ECS did not substantially reduce the CR observed in *Paired* groups, nor did it have a reliable effect in either the *Paired* or *Control* groups (data are summarized in Figure 3, Panel A).

AMPH Challenge. Immediately after the saline test, all rats were given 2 mg/kg AMPH in the rotometers and behavior was recorded for 90 min. The time course of

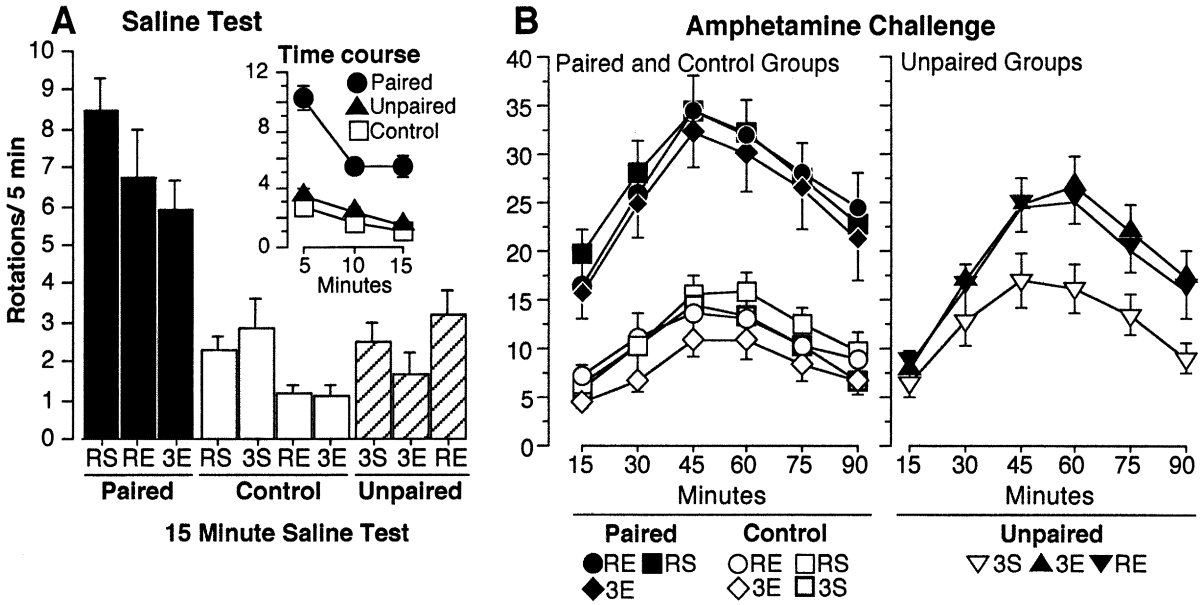

Figure 2. Saline and AMPH challenge tests. All rats received an injection of saline, and then 15 min later an injection of 2 mg/kg AMPH in the rotometers, following induction of sensitization (AMPH or saline treatment) and after ECS or sham treatments to induce retrograde amnesia. Panel A: Saline test. Rats were given an injection of saline and rotations (rotations per 5 min, mean±S.E.M.) were recorded for 15 min. *Paired* animals, which had previously received AMPH in this environment, exhibited a conditional response (CR) to the context and saline, exhibiting more rotations than *Control* rats, which previously received saline, or *Unpaired* rats which previously received the drug in the Third World. *Paired* rats that received ECS (RE, ECS in the rotometers, or 3E in the Third World) exhibited a slightly reduced CR relative to those that received sham treatment (RS). Saline *Control* rats that received ECS (RE, 3E) exhibited a slightly reduced response to saline relative to those that did not receive ECS (RS, 3S). *Unpaired* rats that received ECS (3E, RE) did not differ from those given sham ECS (3S). Thus, ECS left the CR largely intact; it slightly reduced responding in *Paired* and *Control* rats, but did not alter *Unpaired* rats' response. The inset panel illustrates the time course of the saline response in 5-min blocks for the *Paired*, *Unpaired*, and *Control* groups (collapsed). Panel B: AMPH challenge. Rats were given AMPH immediately after the Saline test and tested for 90 min. *Paired* groups (left panel) that received ECS (RE, 3E) did not differ from the sham group (RS), but exhibited greatly sensitized responding relative to *Control* or *Unpaired* rats (right panel). *Control* groups that received ECS (3E, RE) did not differ from the sham groups (RS, 3S). In contrast to *Paired* and *Control* groups, ECS substantially elevated responding to AMPH in *Unpaired* groups whether it was given in the rotometers (RE) or Third World (3E), although their response was somewhat less than in the *Paired* groups (left panel). *Unpaired* animals that received Sham treatment (3S) did not express sensitization, indicating robust context-specificity in this group.

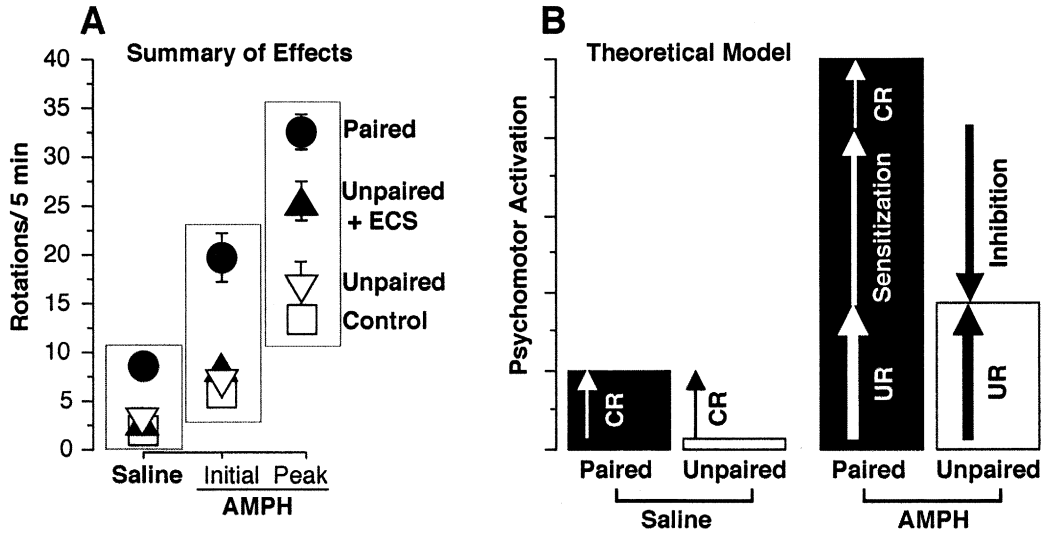

Figure 3. Panel A: Summary of major effects. Saline. *Paired* rats exhibited a large CR to saline; ECS did not affect the CR. AMPH. During the first 15 min, as the drug is taken up, ECS did not affect the response to AMPH. In contrast, during the peak response (30–60 min), ECS revealed a strong sensitization in *Unpaired* rats. Panel B: Model. We suggest that two associative mechanisms contribute to contextual control over the expression of sensitization. By virtue of pairing of the drug with the context in a Pavlovian manner, saline can elicit a drug-like CR under circumstances when the drug would normally be received. Chronic, intermittent AMPH also sensitizes a neural substrate mediating the response to the drug and this is reflected in enhanced psychomotor activation. The excitatory CR observed to saline also contributes to the degree of psychomotor activity when the drug is given, especially shortly after drug administration. The effect of ECS was to reveal sensitization in *Unpaired* rats, in which there was no evidence of a CR. Thus, we suggest that a contextual memory mechanism (inhibition via occasion-setting) inhibits the expression of sensitization in environments where the drug has not been previously experienced.

the behavioral response is depicted in Figure 2, Panel B. There was a significant group × time interaction (MANOVA, $F(45, 460) = 2.3$, $p < .0001$), so selected points of the time course were analyzed rather than the entire time-course. Overall, visual examination of Figure 2, Panel B, suggests that, relative to *Controls*, *Paired* groups exhibited substantially increased responding throughout the test period, whereas *Unpaired* groups seemed to be the source of the interaction. For this reason we analyzed the first 15-min block, which had the lowest response for all groups, as well as the 30–45 and 45–60 min blocks (labeled 45 and 60 in Figure 2, Panel B respectively) where peak responding occurred in the all groups.

Initial Drug Response (0–15 min). There were significant group differences ($F_{9,92} = 11.1$, $p < .0001$; Figure 2, Panel B). *Paired* groups exhibited substantial sensitization, exhibiting significantly more rotations than all *Control* (p values $< .001$) or *Unpaired* groups (p values $< .01$). ECS did not affect *Paired* rats whether it was given in the rotometers (RE) or in the Third World (3E), compared with sham-treated rats (RS; p values $> .05$). No *Control* or *Unpaired* groups differed significantly from each other during this period (p values $> .05$). Thus, only *Paired* rats exhibited sensitized responding during the initial part of the AMPH test session.

Peak Drug Response (30–60 min). Peak responding occurred during the 30–45 min block for *Paired* groups and during the 45–60 min block for *Unpaired* groups. Therefore, we averaged these two blocks to generate comparisons for peak drug responding (Figure 2, Panel B; see also Figure 3, Panel A). During this period, there were significant group differences ($F_{9,92} = 10.6$, $p < .0001$). None of the *Paired* groups differed significantly from one another (p values $> .5$) and all showed a significantly higher peak behavioral response than all *Control* groups (p values $< .0001$). Likewise, none of the *Control* groups differed from one another (p values $> .2$). *Unpaired* groups that received ECS in the Third World (3E) or the rotometers (RE) did not differ from each other ($p > .7$), but importantly, exhibited substantial sensitization relative to the *Unpaired* rats that received sham treatment (3S; p values $< .03$) and relative to all *Control* groups (p values $< .02$). The *Unpaired*-sham (3S) group did not differ from any *Control* groups (p values $> .3$) and was lower than all *Paired* groups (p values $< .001$). Importantly, not all *Unpaired* groups that received ECS differed significantly from all *Paired* groups, although they still exhibited lower numerical responding than all *Paired* groups (significant: PRE vs. U3E, URE; PRS vs. U3E, URE; p values $< .05$; nonsignificant: P3E vs. U3E, URE; p values $> .09$). This indicates

a powerful ability of ECS to reveal sensitization nearly comparable to that seen in *Paired* groups for this time period.

We were surprised that ECS revealed sensitization in *Unpaired* groups regardless of whether it was administered in the Third World (their drug-paired context) or in the rotometers. We had predicted that only placement into the drug-associated context would sufficiently "activate" memories of the drug experience to render them susceptible to disruption by ECS. One possible reason for this is that we may have underestimated the ability of transportation from the colony room and the injection ritual to themselves arouse memory of drug administration, regardless of where the rats were placed. Additional work will be required to determine if this is the case.

In summary: (1) during the saline challenge test only the *Paired* groups exhibited a CR, and ECS had only a weak effect on the magnitude of the CR; (2) ECS had no effect on *Control* or *Unpaired* animals during the saline challenge test; (3) *Paired* animals showed robust sensitization and ECS had no effect on the expression of sensitization in this group; (4) Sensitization was strongly context-specific, because sham-ECS treated *Unpaired* animals did not differ from *Controls*; (5) Most importantly, *Unpaired* animals given ECS did express robust sensitization, as indicated by a large increase in peak drug response. These findings are summarized graphically in Figure 3, Panel A.

DISCUSSION

We hypothesized that ECS delivered when memories of drug administration were re-activated would disrupt the context-specific expression of AMPH sensitization and/or the CR seen in *Paired* animals exposed to the test context (Misanin et al. 1968; Miller et al. 1969; Rubin et al. 1969; Judge and Quartermain 1982; Miller and Matzel 2000; Nader et al. 2000a,b). We were fortunate, because ECS produced a remarkably selective retrograde amnesia in this experiment. As we and others have found before, the expression of AMPH sensitization in the absence of ECS treatment was robust and completely context-specific. On the challenge test day, *Paired* rats exhibited robust sensitization, whereas *Unpaired* rats, which had the same drug history but had received AMPH elsewhere, did not differ from saline pretreated controls (Anagnostaras and Robinson 1996). ECS had no effect on the expression of AMPH sensitization in *Paired* groups or on the drug UR in *Control* groups. However, *Unpaired* groups that received ECS expressed robust sensitization; i.e., only these groups expressed sensitization independent of the treatment context. In contrast, ECS had little effect on the CR produced by a saline injection in the test context in *Paired* animals, nor did it result in the expression of a CR in *Unpaired* groups. Thus, the only effect of ECS was to reveal or "unmask" sensitization in the *Unpaired* groups. These findings have several implications for how behavioral sensitization is conceptualized.

Considering this evidence, our previous work (Anagnostaras and Robinson 1996), and the work of others (Stewart and Vezina 1988 for a review), we propose that three principal memory processes govern the induction and expression of behavioral sensitization (summarized in Figure 3, Panel B). First, the repeated administration of AMPH induces a sensitization of the neural substrate that mediates its psychomotor effects, a form of *non-associative* learning (e.g., Stewart and Vezina 1988; Robinson and Becker 1982, 1986; Kuczenski et al. 1982). Second, during the induction of sensitization an associative inhibitory process can gain control over the sensitized neural substrate, modulating the ability of the sensitized neural substrate to influence behavior (e.g., Anagnostaras and Robinson 1996; Stewart and Vezina 1988; Vezina and Stewart 1990). Third, conditioned excitation, resulting from the Pavlovian pairing of the context and drug, produces a CR to drug-associated cues, and this can add to the sensitized response in the drug-paired context (e.g., Pert et al. 1990; Tilson and Rech 1973). It is important to emphasize that by this view there are **not** *two* forms of sensitization, "context-specific sensitization" and "context-independent sensitization", as is often implied in the literature. There is *one* form, and it is a non-associative form of neuroplasticity manifest behaviorally as an increase in an unconditional drug effect. However, sensitization may or may not be modulated by associative learning, depending on treatment conditions (also see Stewart and Vezina 1988). If it is not modulated, sensitization will appear to be what has been called context-independent, and if it is modulated it will be context-specific. Evidence for each of these processes is discussed below.

Repeated AMPH Sensitizes a Neural Substrate Mediating Psychomotor Activation

There is substantial evidence that repeated exposure to psychostimulant drugs can alter the neural systems that mediate their psychomotor activating effects. The behavioral activating effects of AMPH and cocaine appear to be mediated by their actions on mesotelencephalic and related circuitry, especially dopaminergic projections to the striatum originating in the ventral tegmental area (VTA) and substantia nigra, and glutamate projections originating in the neocortex (Wise and Bozarth 1987; Koob and Bloom 1988; Carlezon and Wise 1996; Vanderschuren and Kalivas 2000; Wolf 1998). Moreover, there are corresponding persistent presynaptic and postsynaptic changes in monoamine and glutamate neurotransmission in the striatum of sensitized animals (for re-

views see Robinson and Becker 1986; Vanderschuren and Kalivas 2000; Robinson and Berridge 2000), which may be related to persistent changes in the morphology of neurons in the nucleus accumbens and prefrontal cortex (Robinson and Kolb 1997, 1999). Many of these sensitization-related neuroadaptations can be observed in the absence of any associative influence. First, neural sensitization is often observed in vitro or in anesthetized animals, where no CS or CR is available. Second, changes in the morphology or neurons are evident even in the absence of any drug challenge. Third, both behavioral sensitization and sensitization-related neuroplasticity have been reported under conditions that do not produce any context conditioning. For example, robust sensitization can be seen under conditions that preclude the development of a CR, such as following habituation to the test environment prior to each drug administration (Crombag et al. 2001) or following treatment in many different environments (Anagnostaras and Robinson 1996; also see Drew and Glick 1988; Martin-Iverson and Fawcett 1996). Indeed, behavioral sensitization and associated changes in dopamine systems are even seen under conditions where AMPH produces no UR (or a CR), notably, following intra-VTA administration (Vezina and Stewart 1990).

These studies all suggest that repeated exposure to psychostimulant drugs induces non-associative changes in neural systems that mediate their psychomotor activating effects, and this is manifest as behavioral or neural sensitization upon re-exposure to the drug. Indeed, as suggested above, it may be misleading to use the terms "context-specific sensitization" and "context-independent sensitization", because this implies that there are two distinct forms of behavioral change due to different neuroplastic processes, and this may not be the case. For example, rats given repeated treatments with AMPH in the test environment (the *Paired* groups here) or given AMPH in a Third World (the *Unpaired* groups here) are treated identically, and as would be expected, when observed in their respective drug treatment environments they both develop psychomotor sensitization (see Figure 5 in Anagnostaras and Robinson 1996). There are no procedural differences between these two groups, therefore they *must* undergo the same process of neural sensitization. But on the challenge test day, if the *Third World* animals are tested in the "*Paired*" environment, they do not express any sensitization. It is unlikely that the sensitization evident in both groups on the last drug treatment day was suddenly reversed on the test day in the *Third World* group. A more parsimonious explanation is that they failed to *express* behavioral sensitization (even though their brains were sensitized) because of powerful contextual control over the sensitized neural substrate.

As put by Stewart and Vezina (1988), "the demonstration that [conditioning] is able to control the manifestation of behavioral sensitization to the extent of completely preventing its expression, illustrates dramatically that the relation between the two is not trivial" (p. 209). The important question, therefore, concerns the nature of contextual control over the expression of sensitization. We propose that neural sensitization is powerfully modulated by (at least) two associative mechanisms. One of these appears to be an inhibitory mechanism that prevents the expression of sensitization in contexts where the drug is not expected (Stewart and Vezina 1988; Vezina and Stewart 1990). The other is the well-established Pavlovian excitatory mechanism that generates a psychomotor CR.

Inhibition by Occasion-setting Controls the Context-specific Expression of Sensitization

The evidence that behavioral sensitization can be completely context-specific necessitates that any theory of sensitization accommodate some associative component. We have proposed (Anagnostaras and Robinson 1996) that an occasion-setting mechanism, acting via conditioned facilitation or inhibition, can gate the expression of the sensitized neural substrate (see also Bouton 1993; Bouton and Schwartzentruber 1991; Rescorla et al. 1985). Occasion-setters are a class of conditional stimuli that do not themselves elicit a CR, but they modulate the ability of other stimuli to elicit responses (see Holland 1985, 1989, 1992; Rescorla 1985). However, in our previous studies we provided no evidence about whether the mechanism was facilitory (enhancing sensitization in the drug-paired context) or inhibitory (preventing expression in the drug-unpaired context). The present results strongly suggest that an inhibitory mechanism is involved. *Unpaired* rats that were treated with ECS expressed sensitization in an environment that had never been paired with drug administration, and, in the absence of a CR. These data are consistent with a conditioned inhibition hypothesis first proposed by Stewart and Vezina (1988, 1991; Stewart 1992). It is interesting to note, however, that in contrast to the studies by Stewart and Vezina (1991), in our experiments the *Unpaired* groups were not *explicitly unpaired*. That is, they were never given saline in the test environment and then drug administration elsewhere. Nonetheless, the effect of ECS indicates that some type of inhibitory mechanism was in place.

The content of the context-drug association that inhibits the expression of sensitization in a context in which the drug was never experienced, and which does not explicitly predict the absence of drug, remains somewhat elusive. Given the present data, ECS seems to have disrupted some form of inhibition, because after ECS, *Unpaired* rats expressed sensitization. However, it seems unlikely our *Unpaired* rats formed an *explicit* negative expectancy of the drug in the rotometers

(the test environment) (there is evidence this can occur, however; see LoLordo and Fairless 1985). Furthermore, it is clear that ECS did not eliminate all memory of the drug-paired context, because ECS failed to disrupt the CR, or to reduce AMPH sensitization exhibited by *Paired* rats in the rotometers (see below). It is also unlikely that ECS produced a confusional state in which rats receiving ECS could no longer effectively discern the drug-paired and unpaired contexts. We observed sensitization to AMPH in *Unpaired* rats receiving ECS, but they did not exhibit the CR to the context and saline, which they would have likely exhibited in the drug-paired context or if they had mistaken the unpaired context for the paired one. Moreover, the evidence that ECS had no effect on the expression of sensitization to AMPH or the CR to the context and saline in *Paired* rats further supports the view that ECS did not affect the animals' ability to recognize contexts per se. Rather, ECS seems to have specifically disrupted an inhibitory mechanism controlling the expression of sensitization to AMPH. We speculate that if rats receive AMPH in only one distinct environment they form an expectation that they will receive the drug only in that environment, and this expectation can serve as an inhibitory occasion-setter in another context. We suggest it was this occasion-setting association that was disrupted by ECS. This association may be present in *Paired* animals as well, but in this case it is not necessary for the expression of the CR or AMPH sensitization. However, when rats are placed in either a novel environment (present experiment) or an environment explicitly unpaired with drug administration (Stewart and Vezina 1991), this association functions as a negative predictor of the drug, and animals fail to express sensitization. Indeed, ECS may have disrupted this association allowing sensitization to be expressed *anywhere*. In the case of animals given AMPH in many environments (the MultiWorld group in Anagnostaras and Robinson 1996), this association may never be formed. This would allow the expression of sensitization without expression of the CR, as was seen in ECS-treated *Unpaired* groups. Nonetheless, further investigation will be necessary to identify the exact nature of this inhibitory mechanism.

Conditioned Excitation Contributes to the Sensitized Behavioral Response

There is considerable evidence that a drug-paired context can elicit a CR that resembles the drug UR, in this case, rotational behavior (Tilson and Rech 1973; Post et al. 1981; Stewart 1984; Carey 1988; Beninger and Hahn 1983; Drew and Glick 1987; Tirelli and Terry 1998; Carey and Gui 1997, 1998; Wolgin 2000; cf. Ahmed et al. 1998; Martin-Iverson and Fawcett 1996). In the present experiment, this response was clearly observed in the *Paired* rats when they were given saline and placed in the drug-associated environment. This CR was largest during the first 5 min after exposure to the test context, and then rapidly diminished in size (see Figure 2, Panel A, inset). Thus, it appears that this CR contributes to the sensitized response particularly in the early part of the test session. Consistent with this, extinction procedures, which eliminate the CR, decrease the sensitized response particularly early in the session (Anagnostaras and Robinson 1996). In the present experiment the effect of ECS in the *Unpaired* groups, which never developed a CR, only emerged 30–45 min after the drug challenge. This suggests the elevated behavioral response in the *Paired* animals seen early after the drug challenge may be primarily due to a CR (compare the time course of *Paired* and *Unpaired* groups in Figure 2, Panel A). However, neither the magnitude nor the time course of the CR is sufficient to account for the difference between the sensitized response in *Paired* animals and the response of drug-naive *Control* animals (see Anagnostaras and Robinson 1996). Furthermore, procedures that eliminate the development of a CR do not eliminate sensitization (Crombag et al. 2001). In conclusion, although the CR produced by excitatory drug-environment conditioning seems to contribute primarily to the early phase of the sensitized response, it accounts for only a small proportion of the overall response. Most of the sensitized response seems to be due to an enhanced drug effect, and this is subject to inhibitory associative control.

It is unclear why excitatory conditioning in the *Paired* groups was left largely intact following ECS and why ECS appeared to selectively impact an inhibitory process. The lack of effect in *Paired* groups was probably not due to a ceiling effect, because rats in the present study peaked at about 35 rotations/5 min, and in a prior study using more treatments and higher doses we have found the ceiling for this response to be greater than 50 rotations/5 min (see Anagnostaras and Robinson 1996). One possible explanation is that inhibitory conditioning is typically weaker and more susceptible to disruption than excitatory conditioning (LoLordo and Fairless 1985), although it remains unclear exactly why this was the case in the present study. Another possibility is that inhibitory conditioning remains susceptible to disruption during reactivation for a longer period of time than excitatory conditioning. It is possible that ECS would have affected excitatory conditioning if given shortly after training (e.g. Miller and Matzel 2000), or with fewer drug-context pairings. Nonetheless, it is remarkable that ECS in the present study and extinction in Anagnostaras and Robinson (1996) doubly-dissociate excitatory conditioning and inhibition. Extinction disrupts the excitatory CR, eliminating the response to saline in *Paired* rats, reduces the response to AMPH during the first 15 min after injection,

but otherwise leaves sensitization largely intact. In contrast, ECS disrupts the context-specificity of sensitization (removing inhibition in the *Unpaired* context), without revealing a CR in *Unpaired* groups, or disrupting the CR in *Paired* groups.

Summary

In summary, the current study provides evidence for at least three distinct memory processes that contribute to sensitization. First, psychostimulant drugs induce neuroplastic changes in neural systems that mediate their psychomotor activating (and incentive motivational) effects. We suggest this neural sensitization is a non-associative form of learning that is manifest behaviorally as an increase in the unconditional drug response. Second, an inhibitory associative process can completely prevent the expression of behavioral sensitization in contexts where the drug is not expected. We suggest this may involve a form of inhibitory occasion-setting, although more work is required to characterize the nature of the inhibitory mechanism (e.g., the extent to which more complicated cognitive processes may be involved). Third, an excitatory associative Pavlovian mechanism generates a CR to drug-associated stimuli (including contexts) and this can amplify the drug response. Given that the expression of sensitization to the incentive motivational effects of drugs may also be greatest in a drug-associated context, research on how these different process interact will be critical in understanding the powerful role that context plays in craving and relapse. Indeed, the ability of drug-associated contexts to both modulate the expression of sensitization via occasion-setting, and to elicit drug-like effects via excitatory conditioning, may combine in the addict to provide very strong associative control over both craving and relapse.

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