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Journal
International Journal of Comparative Psychology, 18(4)

ISSN
0889-3675

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Publication Date
2005-12-31

DOI
10.46867/ijcp.2005.18.04.07

International Journal of Comparative Psychology, 2005, **18**, 298-306.

Inhibition of Successive Positive Contrast in Rats Withdrawn from an Escalating Dose Schedule of D-amphetamine

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Rats in a vehicle treated control condition when shifted from 4% to 32% sucrose displayed successive positive contrast by responding at a significantly higher lick rate in a 5 min trial than rats maintained on 32% sucrose throughout the experiment. In contrast, rats treated with an escalating dose regimen of D-amphetamine (1-10 mg/kg) over a 4 day interval failed to display successive positive contrast. Withdrawal from drug treatment had no effect on lick rate or response latency in rats maintained on 32% sucrose. These data are consistent with many previous reports that withdrawal from a binge-like regimen of psychostimulant drug administration disrupts responding for natural reward stimuli. These findings support the use of psychostimulant withdrawal as a model of drug-induced dysphoria and suggest that incentive contrast is a particularly sensitive measure of these changes in motivation and emotion.

Negative affective states are a cardinal symptom of mood disorders, including unipolar depression, bipolar illness, and dysphoria resulting from psychostimulant drug withdrawal (Markou, Kosten, & Koob, 1998; Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). Accordingly, in order to gain a better understanding of the biological correlates of mood disorders, there is an urgent requirement for animal paradigms that provide objective measures of these dysphoric states (Geyer & Markou, 1995; Willner, 1990). One model of dysphoria in rodents that is gaining increased support utilizes withdrawal from repeated exposure to the psychostimulant drugs cocaine and the amphetamines (Barr et al., 2002; Markou & Koob, 1991; Cryan et al., 2003). Prominent amongst the effects of withdrawal from these drugs are numerous reports of reduced responding for brain-stimulation reward (Cassens et al., 1981; Kokkinidis et al., 1980; Leith & Barrett, 1976; Markou & Koob, 1991). Rats also show reduced motivation to obtain natural rewards, including responding for a sweet sucrose solution on a progressive-ratio schedule (Barr & Phillips, 1999), and access to a sexually-receptive conspecific (Barr et al., 1999). In addition to this amotivational state, rats display increased anxiety during postdrug withdrawal, as measured by increased acoustic startle (Barros & Miczek, 1996), open arm exploration on an elevated-plus maze, and defensive burying (Basso et al., 1999).

Our recent report of increased successive negative contrast in rats withdrawn from a binge-like regime of D-amphetamine provides particularly compelling evidence of a meaningful and sustained change in affect in this model of dysphoria (Barr & Phillips, 2002). Successive negative contrast occurs when the incentive property of a rewarding stimulus is devalued unexpectedly and is observed in many species including rodents, primates and humans (Flaherty, 1982, 1996;

We gratefully acknowledge Dr. S. Ahn for helpful comments and C. White for assistance with the experiments. This research was funded by a grant from the Canadian Institutes of Health Research to AGP. GV was supported by a Fellowship from the UBC Faculty of Graduate Studies. Correspondence concerning this article may be addressed to Anthony G. Phillips, Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver, BC, Canada V6T 2A1 (aphillips@psych.ubc.ca).

Schnorr & Myers, 1967; Specht & Twining, 1999). Several theoretical explanations have been offered to account for successive negative contrast, including the induction of negative affective states such as frustration and disappointment (Amsel, 1958; Crespi, 1942; Flaherty, 1982, 1996). The fact that animals shift to a reward of lesser value than received previously, decrease their running speed as they approach the devalued reward, as well as consume a smaller amount, are also consistent with reduced incentive motivation (Berridge & Robinson, 1998).

A particularly compelling feature of the incentive contrast phenomenon is its bivalent nature. When animals are trained to respond for a reward of a constant value and then unexpectedly receive one of higher incentive value, they often consume greater quantities or run faster in a runway than animals rewarded consistently with the stimulus having greater incentive value (Crespi, 1942; Flaherty, 1996). This elation effect may reflect an elevated mood akin to euphoria consistent with increased incentive motivation. Having shown previously that withdrawal from an escalating dose regiment of D-amphetamine significantly enhanced both the magnitude and duration of successive negative contrast in rats (Barr & Phillips, 2002), we hypothesized that the negative affective state induced by psychostimulant withdrawal would also disrupt the positive affect induced by an unexpected gain in incentive value in the successive positive contrast paradigm. The fact that this effect may occur against a background of increased responding, as a consequence of a shift in sucrose concentration from 4% to 32% would provide important evidence that any changes in responding during drug-withdrawal are not simple performance deficits. Instead, significant results would support the hypothesis that interactions may occur between the negative affective state produced by drug-withdrawal and the emotional correlates of positive or negative incentive contrast. As such, these data may provide further support for the use of incentive contrast procedures to examine the neurobiological and pharmacological correlates of mood disorders as suggested by Flaherty (1996).

Method

Subjects

Thirty-two male Long–Evans rats (Charles River, Quebec), weighing 275–300 g on arrival in the laboratory, were housed individually in a temperature-controlled colony (21°C) under reverse light/dark cycle conditions (lights on at 04:00 h). Training and testing occurred during the dark phase. Water was always available ad libitum in the home cage. All procedures were conducted in accordance with the Canadian Council on Animal Care guidelines and were approved by the UBC Animal Care Committee.

Apparatus

Subjects were trained and tested in four Plexiglas chambers (42×38×38 cm) fitted with wire grid floors. Each test cage was fitted with a lick-activated solenoid valve that provided rats with a drop of sucrose solution each time their tongue contacted the tip of a metal drinking spout, located 4 cm above the chamber floor. The solenoid valve regulated the volume of the drops of sucrose (either 32% or 4% wt/vol) to 0.01 ml. A small light (1.1 W) attached to the roof of the chamber was turned on to designate the start of each training and test session, and was turned off when the session finished; the activation/termination of the valve coincided with light onset/offset. Recording of lick data was computer-controlled, with a sampling frequency of 10 ms (100 Hz).

Drug Administration

The D-amphetamine sulfate (Sigma, Missouri, U.S.A.) escalating-dose regimen used is a recently modified version (Barr & Phillips, 2002) of that described by Leith and Barrett (1976). In this protocol, rats are injected 3 times per day (08:00, 15:00, 22:00 h) for 4 days. For the first three days rats receive a starting dose of 1.0 mg/kg of D-amphetamine which escalated by 1 mg/kg with each subsequent dose. On the fourth day, rats receive three doses of 10 mg/kg. Animals, therefore, receive a total of 12 injections over a 4-day period. The incremental dose regimen is used to minimize the chance of acute toxicity associated with high D-amphetamine doses. Subjects were not exposed to the test chambers at any time during administration of the drug. For the first day of injections, the rats generally displayed elevated locomotor activity and exploratory types of behavior, and thereafter exhibited increasing levels of stereotypy. The D-amphetamine was dissolved in isotonic saline (1 ml/kg), and subjects were weighed each morning before the 08:00 h injection; body weights were also recorded before the five testing session. Control subjects were injected with isotonic saline under the same schedule as rats in the D-amphetamine group.

Procedure

Ten days after their arrival in the colony, rats were placed on a deprived feeding schedule, which maintained their body weight at approximately 85%-90% free-feeding weight, for the duration of the experiment. Rats were weighed and fed daily (about 18 g Rat Diet 5012; PMI Feeds, Delta, British Columbia, Canada) in their home cages. After subjects had attained the desired body weight, they were randomly assigned into two different groups (n = 16 per group), which received either 32% sucrose (unshifted group) or 4% sucrose (shifted group) throughout the experiment. Animals were given access to their respective sucrose solutions for a 5-min period once per day in the testing apparatus. Daily training sessions continued until rats had reached an asymptotic level of consumption of the sucrose solutions (about training day 10). Subsequently, each of the two groups of animals was subdivided into two further groups (n = 8 per group), based upon a rank-ordered division of animals with respect to the number of licks that they exhibited in the final 5-min training session. One group from each of the 32% and 4% sucrose solution exposed animals was then subjected to the 4-day regimen of D-AMPH injections described above, while the remaining groups received injections with the vehicle solution. Following the conclusion of the drug/vehicle treatment, all groups were tested for their consumption (measured as the number of licks) of a 32% sucrose solution for 5 additional days, tested once per day. For the two groups of animals trained with the 4% sucrose solution, the presentation of the 32% solution represented an unexpected increment in the rewarding value of the stimulus.

Data Analysis

All data were initially tested for statistical significance using ANOVA, and where appropriate, further analyzed using the Dunn's or Dunnett's method of multiple comparisons. Statistical analyses were performed using the Systat statistical package.

Results

Prior to the treatment with D-amphetamine or vehicle and the shift from 4% to 32% sucrose, there was a clear difference in lick-rate in the groups responding for 4% sucrose (825 $\pm$ 64; 872 $\pm$ 69) as compared to those responding for 32% sucrose (1410 $\pm$ 69; 1340 $\pm$ 69). A two-way repeated measures ANOVA of lick - rates indicated that there was a significant Group x Time interaction, $F(15, 140) = 5.271$, $p < 0.001$. Post hoc analyses revealed that vehicle-treated rats switched from 4% to 32% sucrose exhibited significantly higher lick rates than those control rats also treated with vehicle and maintained on 32% sucrose. This significant effect persisted throughout all 5 days of postswitch testing. Strikingly, successive positive contrast was completely inhibited in the drug-treated group shifted from 4% to 32% sucrose, for up to 108 h following withdrawal from the escalating-dose

schedule regimen of D-amphetamine. The post hoc analyses of data from the two shifted groups confirmed that the D-amphetamine-treated group exhibited significantly lower levels of sucrose consumption during the 5 post withdrawal trials than the vehicle treated group. Furthermore, withdrawal from drug treatment had no effect on lick rates in the group maintained on 32% sucrose.

Table 1
Latencies to Approach the Drinking Spout, 24 h Before and 12-108 h After Vehicle or D-amphetamine Treatment, Expressed in Seconds. Data are Expressed as Means ± SEM.

Time (h)	32%-32% Veh (s)	4%-32% Veh (s)	2%-32% Drug (s)	4%-32% Drug (s)
-24	5.0 (2.4)	10.8 (2.4) **	6.8 (2.4)	11.7 (2.4)*
12	5.1 (4.5)	4.8 (4.4)	10.0 (4.5)	27.6 (4.5)* †
36	3.8 (1.7)	6.5 (1.7)	5.9 (1.7)	8.0 (1.7)
60	4.1 (0.9)	6.6 (0.9)	5.4 (0.9)	4.5 (0.9)
84	4.6 (1.0)	5.7 (1.1)	6.2 (1.0)	4.8 (1.0)
108	4.6 (1.0)	4.7 (1.0)	5.1 (1.0)	4.1 (1.0)

† Significantly different from 4%-32% Veh ($p < 0.05$)
* Significantly different from 32%-32% Drug ($p < 0.05$)
** Significantly different from 32%-32% Veh ($p < 0.05$)

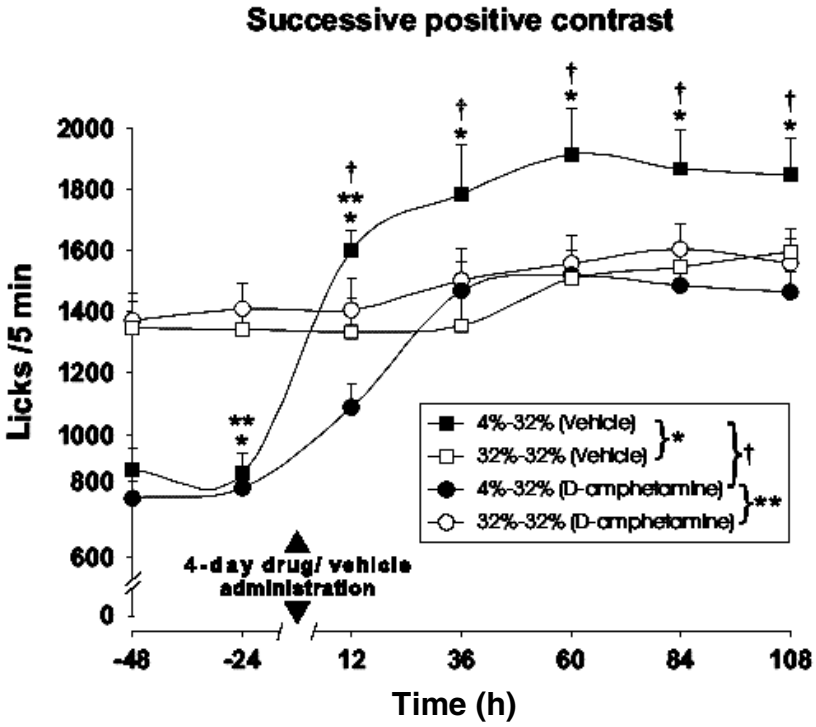

Figure 1. Effects of withdrawal from a 4-day regimen of D-amphetamine, or vehicle on successive positive contrast in rats following an unexpected switch from 4% to 32% sucrose. Sucrose consumption was measured as number of licks per 5 min session. Lick rates are shown from trials conducted 24 and 48 h before drug or vehicle treatment and for 12 to 108 h following withdrawal from drug administration.
*Significantly different from 32%-32% vehicle group, $p < 0.05$.
**Significantly different from 32%-32% D-amphetamine group, $p < 0.05$.
†Significantly different from 4%-32% D-amphetamine group, $p < 0.05$.

In addition to lick rate, latencies to approach the spout dispensing sucrose solution were measured on every trial (see Table 1). A two-way repeated measures ANOVA of latencies indicated that there was a significant Group x Time interaction, $F(18, 168) = 3.418$, $p < 0.001$. Examination of the pre-treatment latencies revealed significantly shorter response latencies in both groups given access to 32% sucrose, relative to 4% sucrose. The other significant finding was a slight increase in latency scores (mean = 27.6 s) in the drug-treated group when tested 12 hr following withdrawal. Importantly, drug-withdrawal had no effect on response latencies at the same time point in the unswitched group maintained on 32% sucrose. Furthermore, response latencies in the switched group subjected to drug-withdrawal decreased to control values on all subsequent trials. A comparison of daily body weight prior to and during treatment with either the escalating dose regimen of D-amphetamine or vehicle revealed small but significant reductions in body mass of 5 g, $F(14, 60) = 3.85$, $p < 0.042$, and 7 g, $F(14, 60) = 9.71$, $p < 0.001$, respectively across the 4-day injection period. (see Table 2).

Table 2
Body Weights Before and After the Vehicle or D-amphetamine Treatment, Expressed in Grams. Data are Expressed as Means ± SEM.

Time (days)	Drug (g)	Vehicle (g)
Pretreatment	330 (2.5)	340 (2.6)
Treatment 1	329 (2.5)	341 (2.8)
Treatment 2	326 (3.7)*	340 (3.8)
Treatment 3	327 (3.6)*	344 (3.6)*
Treatment 4	325 (3.5)*	333 (2.8)*

*Significantly different weight from pretreatment ($p < 0.05$)

Discussion

The present experiment provides a convincing demonstration of the sometimes elusive phenomenon of successive positive contrast in rats, as evidenced by significantly higher rates in vehicle-treated rats switched from 4% to 32% sucrose relative to those maintained on 32% sucrose. This effect was robust and still evident 108 h after the switch in sucrose concentration. Furthermore, successive positive contrast is completely inhibited for an extended period during withdrawal from an escalating-dose regiment of D-amphetamine. Several features of these data are noteworthy. Rats in the shifted condition, which were also experiencing drug withdrawal, increased their lick response rate at the 36 h time point to those maintained by rats in the 32% sucrose unshifted group thereby confirming their capacity for normal consummatory responding. Response latencies, which were significantly longer under the 4% sucrose preshift condition were also reduced following access to 32% sucrose, but did not differ from latencies displayed by rats maintained on 32% sucrose throughout the experiment. Withdrawal from D-amphetamine had no significant effect on sucrose consumption or lick-rate in rats maintained on 32% sucrose throughout the experiment, nor were response latencies affected by drug withdrawal. Although response latencies in the switched group, when measured 12 h following withdrawal, were marginally longer than those maintained on 32% sucrose during withdrawal, it is highly unlikely that this

slight delay in initiation of drinking could account for the nearly 30% difference in lick-rate observed between these two groups. The inhibition of successive positive contrast following D-amphetamine withdrawal parallels the enhancement of successive negative contrast under a comparable state of drug withdrawal (Barr & Phillips, 2002) and together these data provide further support for the use of a withdrawal from binge-like exposure to psychostimulant drugs as a valid model of the negative affective states that define idiopathic and drug-induced depression.

Associative generalization decrements have been postulated to account for the phenomenon of negative contrast (Capaldi, 1971; Flaherty, 1982; Spear & Spitzner, 1966). This hypothesis proposes that a change in either the rewarding environment or the value of the rewarding stimulus results in a reduced association between the two and a commensurate decrease in consumption of the reward. Furthermore, response generalization may be exacerbated in the novel state of withdrawal from D-amphetamine (Grilly, 1975). However, it is highly unlikely that this proposal can explain the disruption of successive negative contrast following withdrawal from D-amphetamine because in our previous study, animals maintained on 4% sucrose during withdrawal did not reduce their consumption of 4% sucrose (Barr & Phillips, 2002). The same situation pertains to the present study, as rats withdrawn from D-amphetamine and given 32% sucrose throughout the experiment also maintained responding at pre-drug levels. The same data also make it unlikely that amphetamine-induced anorexia can explain the absence of successive positive contrast observed in the present study. Previous studies have reported reduced motor activity following amphetamine withdrawal (Paulson et al., 1991; Pulvirenti & Koob, 1993) but again, this cannot explain the present findings, as psychomotor deficits should have affected sucrose consumption in the unshifted group subjected to drug withdrawal.

Many studies have employed treatment with a wide variety of drugs in an attempt to identify the neurochemical correlates of incentive contrast (see Flaherty, 1991), but acute treatment with amphetamine was ineffective in reducing negative contrast. To the best of our knowledge, the effects of either acute or chronic treatment with amphetamine on successive positive contrast have not been studied. Benzodiazapines have been shown to be a particularly effective class of drugs in disrupting successive negative contrast (Flaherty et al., 1986), suggesting an important role for GABA-containing neurons in the inhibition of other neural systems subserving incentive contrast. The role of brain dopamine systems is less clear as treatment with chlorpromazine or the more specific dopamine receptor antagonist haloperidol both failed to disrupt successive negative contrast (Flaherty et al., 1992). Using a different procedure to demonstrate both positive and negative contrast with brain-stimulation reward, we have observed a selective effect of the dopamine receptor antagonist pimozide on positive but not negative contrast, suggesting that dopamine may be particularly important in mediating positive incentive contrast (Phillips & Lepiane, 1986).

In a related study employing the same escalating dose regimen of D-amphetamine, we observed tolerance to the drug-induced increase in dopamine efflux in the Nucleus Accumbens (NAc), measured by brain microdialysis and high-performance liquid chromatography with electrochemical detection (Vacca, Ahn, & Phillips, 2004). Furthermore, this tolerance was maintained for 72 h following withdrawal. In a separate experiment in the same study, rats in a vehicle-

treated group displayed a significant increase in dopamine efflux during both the preparatory and consummatory phases of sucrose intake, whereas rats in the drug-withdrawal group failed to show increased dopamine efflux in the preparatory phase but did show the previously observed increase in dopamine efflux in the NAc during consumption of sucrose (Hajnal & Norgren, 2001). Dopamine efflux in the NAc is also attenuated during successive negative contrast (Genn, Ahn, & Phillips, 2004). Collectively, these findings suggest that the failure to observe successive positive contrast in the present study following withdrawal from D-amphetamine may be directly related to dysfunction of the mesolimbic dopamine pathway.

Currently there is a great deal of interest in the neurobehavioral economics of drug addiction (Bickel, DeGrandpre, & Higgins,1995; Heyman, 2003; Rachlin, 2003), from both the perspective of behavioral economics and the effects of prolonged exposure of psychoactive drugs on assessment of reward value and choice, essential aspects of decision making. The present data provide clear evidence that withdrawal from a binge-like episode of D-amphetamine treatment, which has much in common with the dysphoria experienced by humans in a psychostimulant–withdrawal state, has a profound effect on the relative value of natural rewards. It will be important in future studies to examine the effects of acute treatment with psychostimulants on successive positive contrast to see if they may further distort the relative value of an unexpected gain in reward, thereby biasing choice towards short-term gain represented by stimuli with high incentive value.

As Flaherty noted in the epilogue of his important synthesis of research on the effects of reward magnitude on animal behavior entitled *Incentive relativity,* successive negative contrast "provides a model for the characterization of the neurobiology and psychopharmacology of disappointment" (Flaherty, 1996, p. 173). To this, we would add that both successive negative *and* positive contrast may provide measures of affect that are specifically disturbed in mood disorders such as anxiety and depression and as such have much to offer in studying basic processes related to these disorders. Later in the epilogue, he also notes that anticipatory contrast may enhance our understanding of drug addiction (Flaherty, 1996, p. 174). The present data certainly support this conjecture and further emphasize the relevance of incentive contrast to many of the most current topics in behavioral neuroscience and psychopharmacology.

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Received March 24, 2005.
Revision received May 18, 2005.
Accepted May 19, 2005.