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# Similar Effects of $D_1/D_2$ Receptor Blockade on Feeding and Locomotor Behavior

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PITTS, S. M. AND J. C. HORVITZ. *Similar effects of $D_1/D_2$ receptor blockade on feeding and locomotor behavior*. PHARMACOL BIOCHEM BEHAV **65**(3) 433–438, 2000.—Recent evidence suggests an important relationship between dopamine (DA) modulation of feeding and locomotor activity. To investigate this relationship, the free-feeding and locomotor behavior of rats under the influence of $D_1/D_2$ antagonist *cis*-flupenthixol was examined. DA antagonists are known to produce within-session declines in reinforced behavior, with behavioral suppression occurring only after a number of normal responses have been emitted. In the present study, *cis*-flupenthixol (0.30 mg/kg ) produced a within-session decrement in both free-feeding behavior and in locomotor/exploratory activity of animals in an environment that had never been paired with food. In addition to producing similar patterns of disruption in feeding and locomotion, the drug also produced a similar magnitude of suppression in the two behaviors. The results show that disruption of DA activity suppresses locomotor/exploratory activity in a manner that closely mirrors neuroleptic suppression of feeding. Although neuroleptic-induced suppression of locomotion and feeding are traditionally presumed to reflect an attenuation of DA motor and reward functions, respectively, the present results suggest that DA plays a similar role in the modulation of these two behaviors. © 2000 Elsevier Science Inc.

Feeding Locomotion *cis*-Flupenthixol Neuroleptic Dopamine Reinforcement Sensory Exploratory Within-session antagonist

DISRUPTIONS in brain dopamine (DA) transmission suppress feeding (5,28,29,31) and locomotion (2,13,17). It has been suggested that DA antagonists reduce feeding by disrupting a DA reward signal necessary for the maintenance of consummatory behavior (10,28,29,36). An additional function of DA may be to facilitate motor responses to sensory events (19,20), and disruptions in this function may be manifest as locomotor or exploratory suppression. It is possible, then, that neuroleptic-induced reductions in feeding and locomotion reflect distinct disruptions in reward and motor processes, respectively.

However, a close relationship exists between DA's involvement in locomotion and feeding behavior. For example, elevations in accumbens DA release during feeding (7,21, 25,34) are most likely to be seen under feeding regimens that are accompanied by large elevations in general behavioral or exploratory activity (21). In the absence of locomotor elevations, feeding is not accompanied by elevations in DA release (21). White (33) has argued that feeding reductions observed in DA-depleted or neuroleptic-treated animals reflect an impairment in a DA sensory-motor function, or an increased threshold for sensory inputs to elicit appropriate motor responses. If true, DA antagonist-induced reductions in both feeding and exploratory locomotor activity may reflect a common impairment in the animal's behavioral responsiveness to incoming sensory stimuli. Recent electrophysiological data have shown that DA neurons within the ventral tegmental area (VTA) and substantia nigra (SN) respond to a wide range of salient environmental stimuli, including unexpected food presentation (18,22,23), novel events (18), and salient auditory and visual stimuli without conditioned appetitive properties (14,30). DA activity is, therefore, likely to be elevated by salient stimuli, including the orosensory stimuli associated with feeding, and one of the functions of this DA elevation may be to facilitate behavioral outputs as distinct as feeding and locomotion.

Although these data suggest that DA may play a similar role in the expression of locomotor and feeding behaviors, DA disruptions are known to produce specific *patterns* of disruption in feeding, and other food-motivated behaviors. Hungry animals under the influence of DA antagonist drugs show within-session declines in feeding (36) and operant respond-

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ing for food (4,35). Animals under the influence of these drugs show normal behavior at the onset of the session, and reductions in behavior only after a number of normal responses have been emitted. It is, therefore, important to determine (a) whether $D_1/D_2$ receptor blockade produces within-session decrements in nondeprived animals freely consuming a palatable food, and (b) whether a similar within-session decrement is seen in locomotor behavior. The underlying question is whether disruption of DA activity suppresses locomotor/exploratory activity in a manner that closely mirrors the suppression seen in feeding behavior.

## METHOD

### *Subjects*

Male Sprague–Dawley rats (Charles River, Kinsington, NY), weighing 516 ± 156 (SD) g at the start of drug testing, were housed in standard Plexiglas cages (16.5 × 8 × 8″, Allentown), and were maintained within a temperature-controlled 23°C 12 L:12 D vivarium environment (lights on at 0800 h). All weighing, handling, and experimental sessions were performed during the light phase of the cycle. Purina 5012 Rat Diet (St. Louis, MO) and water were available ad lib.

### *Apparatus*

All experiments were conducted in test chambers (10 × 11.5 × 11.5″) housed within isolation cubicles for sound and light attenuation. Two of the test chamber walls were Plexiglas; the other two were metal. A house light was centered horizontally at the top of one of the metal walls. The bottom center of this wall contained a food trough (1.5 × 1.25 × 2″) 1 inch above the chamber floor, where animals found individual 45-mg food pellets (Bioserve F00021 rat pellets, Frenchtown, NJ). An infrared photobeam-emitter and -detector were located on the sides of the trough. The beam was interrupted by the presence of a pellet in the trough, allowing the detection of each pellet removal (2-s resolution) during feeding sessions. Locomotor activity (0.05-s resolution) was recorded with an activity monitor that detected the movement of infrared body heat across small compartments of a ceiling-mounted lens. Test chambers and associated devices were purchased from Coulbourn Instruments, L.L.C. (Allentown, PA), and were interfaced with a Dell Pentium computer running Coulbourn L2T2 data acquisition software.

### *Systemic Drug Injections*

$D_1/D_2$ receptor blocker *cis*(x)-flupenthixol (0.15 and 0.30 mg/kg; RBI, Natick, MA) was dissolved in isotonic saline. The high dose of 0.30 mg/kg *cis*-flupenthixol has previously been shown to attenuate rates of food-reinforced operant lever pressing (6). Intraperitoneal (IP) injections of *cis*-flupenthixol or its vehicle were delivered in a volume of 1 ml/kg of body weight. Animals received each dose in a counterbalanced order, with at least two drug-free sessions separating drug test sessions. All IP injections were administered 60 min prior to the onset of drug test sessions, with the exception of those for the 40-min preinjection control group.

### *Central Drug Infusions*

Rats in the *feeding and locomotion* group were implanted with bilateral guide cannulae (22 gauge) aimed above the nucleus accumbens (AP +1.7, ML +1.5, DV −4.3 relative to bregma) (24), because an original aim of the study was to examine the effects of intraaccumbens *cis*-flu on feeding and locomotion. On intraaccumbens *cis*-flu test days, bilateral injection cannulae (28 gauge) were lowered 2.5 mm beyond the guide cannulae. *cis*-Flu (0, 5, or 10 μg) was delivered in a volume of 0.5 μl of saline over a 1.5-min infusion interval, with an additional minute allowed for diffusion. A microdrive pump (Razel) controlled infusion rates, and was connected to the injection cannulae via PE-20 tubing. For animals in the *feeding and locomotion* group, these intraaccumbens infusions were included in the counterbalanced drug regimen described above, with each animal receiving each central dose 5 min before behavioral testing. Intraaccumbens infusions of *cis*-flu, however, failed to influence either locomotor or feeding behavior. On the basis of these negative results, the effectiveness of the central drug injections could not be demonstrated, and strong inferences on the basis of these results could not be drawn. The study, therefore, focuses on the results of systemic *cis*-flu administration, with the results of the central infusions discussed only briefly in the Discussion section.

### *Experimental Procedure*

*Feeding and locomotion group.* During each 1-h session, animals were permitted to freely consume individual food pellets from a food trough, with the removal of each pellet triggering the delivery of the next. The computer recorded the time of each pellet removal and locomotor count throughout the sessions. To minimize variability in total pellet consumption, a baseline criterion required each animal ($n = 8$) to show less than 15% variation in total pellets consumed for 3 consecutive days. Failing to achieve this criterion, animals received at least 120 baseline feeding sessions in the experimental chambers, making feeding in the test chamber a routine behavior, similar to home-cage feeding.

*Locomotion-alone group.* For each of these sessions, naive rats ($n = 6$) were placed in the experimental chambers for 1 h while spontaneous locomotor activity was recorded. These animals never received food in the test chambers. Under the repeated dosing design used in the present study, it was important to maintain stable levels of baseline and test day locomotor activity over repeated test sessions. The following testing cycle was employed to minimize the effects of habituation on baseline and test day activity levels: three daily nondrug locomotor sessions, one drug test locomotor session, an additional nondrug locomotor session, a 3-day period during which animals remained in their home cages. This regimen was repeated for three cycles (i.e., three drug injections), but the drug tests for the second and third cycles were preceded by two (rather than three) nondrug locomotor sessions. Under this regimen, baseline locomotor activity levels on the day before and after drug testing remained relatively constant throughout the experiment.

*40-Min preinjection group.* Pilot data showed that following the 60-min preinjection interval employed in the *feeding and locomotion* and *locomotion-alone* groups, 0.30 mg/kg *cis*-flupenthixol suppressed locomotor behavior only after the first several minutes of the session. To ensure that such a delay in behavioral suppression was not merely a function of postinjection time, i.e., drug absorption, an additional group of naive animals ($n = 6$) received vehicle or 0.30 mg/kg of *cis*-flupenthixol 40-min prior to the onset of the 1-h locomotor test session.

### *Data Analysis*

Baseline levels for pellet consumption and locomotor activity were defined as the mean of the measure obtained 1 day

before and after drug test sessions to ensure that drug effects assessed under the repeated dosing regimen were not influenced by variations in baseline performance over time. Total pellets consumed and total locomotor counts during drug test sessions were expressed as a percentage of the baseline measure, and were subjected to repeated measures one-way analyses of variance (ANOVA). Paired samples Student's *t*-tests (with overall alpha set to 0.05) were used to compare feeding and locomotor behavior under specific drug doses to that under vehicle control conditions. To determine the time point during the test session during which *cis*-flupenthixol effects on feeding and locomotion first emerged, paired-sample *t*-tests were conducted on data at consecutive 1-min intervals, comparing *cis*-flupenthixol to vehicle. The onset of *cis*-flupenthixol behavioral suppression was defined as the first point at which *cis*-flupenthixol and vehicle data differed at the $p < 0.05$ level for two consecutive 1-min time bins.

## RESULTS

*cis*-Flupenthixol produced a similar suppression of feeding and locomotion, with the high (0.30 mg/kg) dose of *cis*-flupenthixol reducing both pellet consumption and locomotor activity in the *feeding and locomotion* group to approximately 30% of baseline levels (see Fig. 1). Locomotor suppression was similar regardless of whether the locomotion was measured during feeding sessions (*feeding and locomotion* group) or in a neutral environment in the absence of food (*locomotion-alone* group). *cis*-Flupenthixol produced a reduction in total pellets consumed, $F(2, 14) = 14.59$, $p < 0.001$, total locomotor counts during feeding sessions, $F(2, 14) = 8.25$, $p < 0.01$, and total locomotor counts in the neutral environment, $F(2, 10) = 13.67$, $p = 0.001$. The 0.30 *cis*-flupenthixol dose suppressed feeding, $t(7) = 7.66$, $p = 0.0001$, locomotor behavior in the presence of food, $t(7) = 3.98$, $p < 0.01$, and locomotor behavior in the absence of food, $t(7) = 4.53$, $p < 0.01$. Although 0.15 mg/kg *cis*-flupenthixol failed to produce significant suppression in any of the three behavioral measures, there was a trend toward locomotion suppression under this dose.

In the *feeding and locomotion* group, feeding and locomotion were measured simultaneously, allowing the effect of the neuroleptic to be assessed for these two measures within each individual animal. Pearson correlation of total pellet consumption and motor counts occurring within a session revealed no correlation following administration of either vehicle ($r = 0.38$, $p = 0.35$) or 0.15 mg/kg *cis*-flupenthixol ($r = 0.21$, $p = 0.61$). However, for animals under the influence of 0.30 mg/kg *cis*-flupenthixol, a strong correlation existed between feeding and locomotor activity ($r = 0.89$, $p < 0.005$). Under the high dose of the drug, the magnitude of motor suppression was a strong predictor of feeding suppression in the same animal (see Fig. 2).

Within-session decrements in food-reinforced operant behavior and free-feeding following administration of DA antagonists are often taken as evidence for a drug-induced reward deficit (4,35,36). The normal responding seen in neuroleptic-treated animals at the onset of a test session demonstrates that the animal is motorically capable of performing the response. Response deficits that emerge later in the session are interpreted to reflect an attenuation of the reward value of the reinforcer. It was, therefore, of interest to determine (a) whether a neuroleptic-induced within-session decrement in responding would be observed in the present free-feeding tests; and (b) whether a similar within-session decrement would be seen in behavior, such as locomotion, that is not directed toward an explicit reinforcer. Figure 3 depicts the pattern of feeding for the *feeding and locomotion* group (Fig. 3A) and the pattern of motor behavior for the *locomotion-alone* group (Fig. 3B) under each drug condition. As can be seen, the response patterns for feeding and locomotion are remarkably similar. Neuroleptic-induced within-session decrements are observed in both cases. Animals under the influence of *cis*-flupenthixol show normal response rates early in the session, but as the session progresses, decrements in responding are observed. Compared to vehicle con-

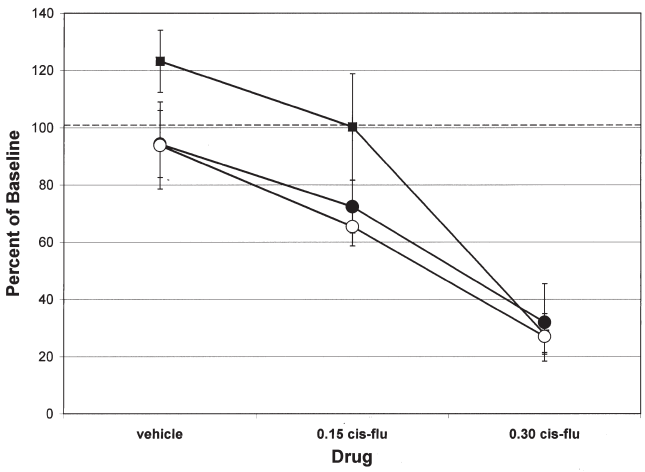


FIG. 1. Mean (±SEM) total pellet consumed (filled squares), locomotor activity counts during feeding sessions (filled circles), and locomotor activity counts in a nonappetitive environment (open circles) for animals under the influence of vehicle or *cis*-flupenthixol (0.15 or 0.30 mg/kg). Data are expressed as a percent of baseline values for each behavior.

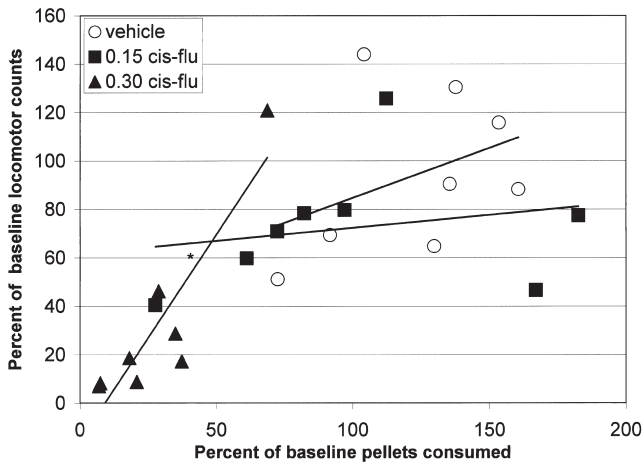


FIG. 2. Total locomotor counts are plotted against corresponding total pellets consumed during the feeding and locomotion sessions, for each rat ($n = 8$). Data are expressed as a percent of baseline value for each behavior. Total pellets consumed and locomotor activity counts were correlated under 0.30 mg/kg *cis*-flupenthixol (*$p < 0.005$), but were not correlated under vehicle or the low dose of *cis*-flupenthixol. Lines represent a best fit of data for each drug condition.

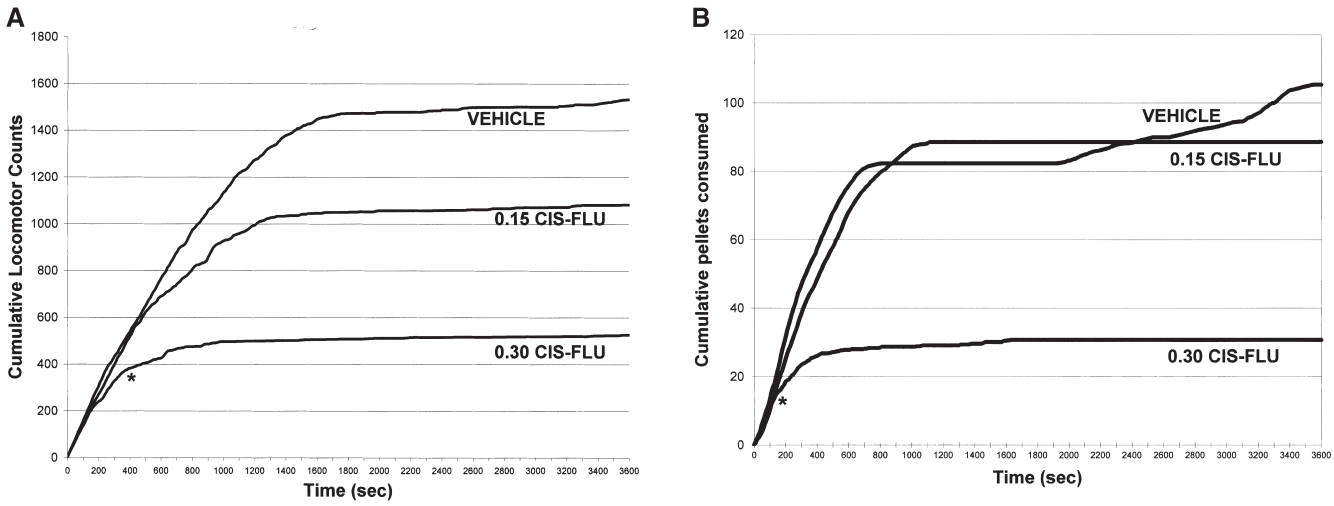


FIG. 3. (A) Mean cumulative pellets consumed during 1-h feeding sessions following administration of vehicle, 0.15, or 0.30 mg/kg of *cis*-flupenthixol. Asterisk indicates the first of two consecutive 1-min bins for which *cis* 0.30 and vehicle values differed significantly ($p < 0.05$). (B) Mean cumulative activity counts during 1 hr locomotion-alone sessions following administration of vehicle, 0.15, or 0.30 mg/kg of *cis*-flupenthixol. Asterisk indicates the first of two consecutive 1-min bins for which *cis* 0.30 and vehicle values differed significantly ($p < 0.05$).

trols, *cis*-flupenthixol (0.30 mg/kg) did not cause deficits in pellet consumption until minute 2, $t(7) = 3.15$, $p < 0.05$, or locomotor deficits until minute 5, $t(7) = 4.43$, $p < 0.05$; *feeding and locomotion* group; and minute 8, $t(5) = 6.93$, $p < 0.01$; *locomotion-alone* group.

The delayed appearance of the locomotor suppression seen in these animals, tested 60 min after drug injection, cannot be due to drug absorption factors, for animals in the 40-min preinjection group, tested 40 min after administration of *cis*-flupenthixol (0.30 mg/kg) showed significant behavioral suppression 12 min into their session, $t(5) = 3.19$, $p < 0.05$, that is, 52 min after drug injection, well before the onset of the 60-min preinjection session.

## DISCUSSION

$D_1/D_2$ DA antagonist *cis*-flupenthixol produced similar effects on feeding and locomotor/exploratory behavior. First, the magnitude of behavioral suppression observed under the high dose of *cis*-flupenthixol, relative to nondrug baseline performance, was nearly identical for feeding and locomotor behavior. Second, the magnitude of neuroleptic-induced feeding suppression within a given animal was strongly correlated with the neuroleptic-induced locomotor suppression observed in that animal during the same session. Third, and most striking, the progressive within-session decline in feeding behavior produced by neuroleptic treatment, generally presumed to reflect an extinction-like reduction in appetitive behavior due to reinforcement attenuation (4,35,36), was also observed in locomotor behavior. Compared to vehicle controls, animals under the influence of the DA antagonist showed normal feeding behavior early in the session, and progressive reductions in behavior over time. Similarly, animals under the influence of the neuroleptic show normal locomotor behavior early in the session, and progressive decrements in locomotion over time compared to vehicle controls. The normal levels of behavioral activity observed at the onset of the session were not due to low levels of drug absorption at the onset of the session, 60 min postinjection, because animals in the 40-min preinjection control group showed behavioral suppression 12 min after the onset of the test session, i.e., 52 min after drug injection, well before the onset of the 60-min preinjection sessions (*feeding and locomotor* and *locomotor-alone* groups).

Although neuroleptic-induced suppression of locomotion (2,13,17) and feeding (5,28,29,31,36) are traditionally presumed to reflect an attenuation of DA motor and reward functions, respectively, the present results suggest instead that DA may play a similar role in the expression of these two behaviors. The fact that DA disruption produced a similar within-session decrement in feeding and locomotor behavior may be explained in two very different ways. According to the first explanation, the neuroleptic-induced within-session decrements in feeding and locomotion both result from reinforcement attenuation. The progressive reductions in consummatory behavior seen under neuroleptic conditions reflect the loss of the response-maintaining or "rewarding" properties of the food pellets. A similar explanation may be offered for the within-session reductions in locomotor activity. The locomotor activity observed here is best described as exploratory, for even in the absence of the drug, locomotor behavior diminishes after animals have explored and habituated to environmental stimuli. The progressive reduction in exploratory behavior seen under neuroleptic conditions beyond that observed in vehicle controls, then, would reflect an attenuation of the incentive properties of novel environmental stimuli in the test chamber. According to this view, DA is involved in reinforcement, but is *not* involved in the initial motivational properties of the incentive stimuli (13), because at the onset of the session, the incentive stimuli are capable of eliciting normal levels of both feeding and locomotor activity, despite neuroleptic challenge. Against this view, dopamine antagonists have been shown to produce deficits, including within-session decrements, in consumatory behavior that reflect an impairment in motoric or sensory-motoric function rather than reward processes (8,27). Further, single-unit data show that midbrain DA neurons are activated, not only by reward stimuli (18,22), but also by salient nonreward sensory events (14,30). This casts doubt upon the notion that DA neurons

signal reward value. Therefore, while the presently observed within-session decrements in feeding and locomotion might reflect neuroleptic-induced reinforcement attenuation, there is reason to doubt this account of the findings.

A very different explanation for the within-session declines in feeding and locomotion may be offered. At the onset of the session the animal is exposed to stimuli that strongly elevate DA release. It is known that DA activity is elevated by stress (1,15,16,32,37), novelty (18,26), salient sensory stimuli (11,14), and unpredictable food delivery (22). During the early minutes of the feeding sessions, DA is therefore likely to be elevated by the stress of recent handling, the change of environmental stimuli from the home cage to the test chamber, and consumption of the initial food pellets. This early surge in DA activity produces a concentration of synaptic DA that is high enough to compete with the antagonist drug for postsynaptic receptor sites, and to permit normal behavioral outflow. Neuroleptic-induced behavioral suppression occurs only later in the session, when environmental stimuli are less novel, less salient. At this point, synaptic concentrations of DA are no longer high enough to compete with the antagonist drug for postsynaptic receptor sites. As a result, DA transmission is reduced and normal behavioral outflow is no longer possible. The same explanation can account for the neuroleptic within-session decrements in locomotion. Fowler (9) proposed a similar explanation to account for neuroleptic within-session response decrements.

Although this study focused upon the effect of systemic *cis*-flu administration on feeding and locomotor activity, animals in the *feeding and locomotion* group also received central infusions of the drug to the nucleus accumbens. These infusions produced no detectable effect upon feeding or locomotion. In the absence of any positive effects of intra-accumbens infusions, the effectiveness of the central drug injections could not be demonstrated, and therefore, inferences were not drawn on the basis of these results. One might ask, however, whether the cannulation and accumbens infusions in this group might have in some way influenced the observed results of systemic *cis*-flu administration. The major finding of this study was that systemic *cis*-flu produced a nearly identical pattern of change (i.e., within-session declines) and magnitude of change (similar suppression) in locomotion and feeding behavior in the *feeding and locomotion* group, the *locomotion-alone* group, and the *40-min preinjection* groups. Neither cannulation nor central infusions in the former group can account for this pattern of results.

DA disruption within the dorsal striatum reduces food consumption (3), but does not affect locomotor activity (12). In contrast, disruption of DA within the nucleus accumbens suppresses locomotor/exploratory activity (12,17), but does not reduce free feeding (3,17). It is, therefore, likely that expression of feeding and locomotion is modulated within distinct striatal target sites, and that DA plays a similar modulatory role at these sites. It will be important to determine whether the within-session decrements in feeding and locomotion observed in the present study are seen following local neuroleptic administration within the striatum and accumbens, respectively. It will also be of interest to determine whether these parallel effects on the two behaviors are seen following selective $D_1$ vs. $D_2$ receptor blockade. Regardless of whether the presently observed within-session decrements in feeding and locomotion are due to (a) reinforcement attenuation, or (b) a stress- and stimulus salience-induced elevation in synaptic DA release at the beginning of the test session that temporarily overcomes neuroleptic challenge, DA disruption is shown here to affect the expression of behavioral output in a similar manner across behavioral domains as varied as feeding and locomotion.

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