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The Effect of Amphetamine on Locomotion Depends on the Motor Device Utilized: The Open Field vs. the Running Wheel

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DELLA MAGGIORE, V. AND M. R. RALPH. *The effect of amphetamine on locomotion depends on the motor device utilized: The open field vs. the running wheel.* PHARMACOL BIOCHEM BEHAV **65**(4) 585–590, 2000.—The effect of amphetamine on the level of locomotion exhibited on two different motor devices was examined in the Golden hamster. Increasing concentrations of the psychostimulant from 4 to 10 mg/kg significantly enhanced locomotor activity in hamsters exposed to an open field. A further increase to 25 mg/kg inhibited ambulatory activity to levels below the control baseline, while augmenting the occurrence of stereotypic behaviors. The activating effect of amphetamine on ambulatory activity was observed regardless of the time of testing (day or night) or lighting condition, with no apparent modulation by the circadian system. On the other hand, home-cage wheel-running activity was maximally inhibited by 10 mg/kg amphetamine, whereas a smaller dosage (1.5 mg/kg) had no effect over the wheel-running activity baseline of saline controls. Although both the running wheel and the open field quantify locomotion, the dissociation obtained shows that they measure different components of it. The results are interpreted within Lyon and Randrup's hypothesis on the actions of amphetamine (16). © 2000 Elsevier Science Inc.

Amphetamine Hamster Wheel running Open field Locomotion Circadian rhythms Light

THE psychostimulant properties of amphetamine have been a subject of study since the 1930s (5). The motor stimulant action of the amine has been described for several mammalian species including different strains of rats, mice, cats, and monkeys (11). In rats exposed to an open field, intraperitoneal (IP) administration of low to medium doses of *d*-amphetamine enhances overall locomotor activity, such as ambulatory activity, vertical rearing, and sporadic sniffing (9). In this species, locomotion increases linearly with the dosage of amphetamine between 0.5 and 2.5 mg/kg (2), beyond which it decreases, probably due to interference produced by the concurrent elicitation of stereotypic behaviors, such as intense licking, biting, and gnawing (6,15,17,25). Converging experimental evidence gathered in the last several decades has implicated the presynaptic dopaminergic terminals within the nucleus accumbens (NA) as the most likely neural substrate mediating the peripheral locomotor effect of amphetamine (1,3,8,14).

In addition to its effect on open field-related behaviors, amphetamine has been shown to stimulate locomotion in a variety of locomotor devices such as the running wheel, the stabilimiter cage, and the photocell cage (15). More recent studies indicate that in situ infusions of amphetamine on the NA enhances both ambulatory activity and wheel running in rats (7,12). These results have, in some cases, led to the assumption that all locomotor devices provide equivalent measures of the level of locomotion, and thus, can be used interchangeably.

In contrast, the effect of other neuropsychological and pharmacological manipulations on locomotion appear to vary remarkably depending on the locomotor device utilized. In rats, both hippocampal and medial-septal lesions increase exploration in an open field but decrease wheel-running activity in the home cage (10,29). Likewise, transient inactivation of the medial septum by infusion of procaine enhances open-field ambulatory activity but attenuates wheel running in hamsters maintained in their home cage or confined to a novel wheel (4). Assuming equal estimation of locomotion by the two devices may, in these cases, lead to a misinterpretation of the data.

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Among the rodents examined for the psychostimulant effect of amphetamine, hamsters have received little attention. Indeed, the only published study carried out in the Golden hamster, reported no effect of *d*-amphetamine (between 5 and 50 mg/kg IP) on the level of ambulatory activity exhibited on an open field (20). Considering the differential effects of medial-septum lesions and procaine on hamster wheel-running and open-field activity, and the fact that both the septum–hippocampal formation and the dopaminergic mesolimbic system project on to the NA, we examined whether the level of locomotion of hamsters treated with *d*-amphetamine can be dissociated upon the experimental motor device utilized. If, as we predict, the running wheel and the open field are not equivalent measures of locomotion, then amphetamine challenge should differentially affect their respective motor outputs.

Considering the close regulation of locomotion by the circadian system (19), we also examined the possibility of daily variations in the action of amphetamine. A putative photic modulation in the response to the drug was also contemplated.

METHOD

Animals

Adult male Golden hamsters (*Mesocricetus auratus*) from our colony (12–13 weeks old) weighing 150–180 g) were housed individually in polypropylene cages containing a 17.5 cm-diameter running wheel, with food and water access ad lib. Temperature in the room was held at 20–24°C. Throughout the study, animals were maintained under a light–dark cycle of 14 h of light and 10 h of darkness (lights on at 1800 h).

Apparatus

Wheel-running activity. Wheel-running activity was collected in 6-min bins throughout the duration of the experiment using Dataquest III system (Mini-Mitter, Sunriver, OR).

Open-field locomotor activity. To assess locomotion, computerized activity-monitoring cages and software (Activity monitor 3.00; Med Associates Inc. St Albans, VT) were used. Activity chambers consisted of clear Plexiglas open-field boxes (17 × 17 inches) with two levels of 16 infrared sensors. Cumulative counts obtained from the total number of infrared beams interruptions were automatically compiled and downloaded every 6 min into an activity monitor data collection program, and processed for two activity measures that were analyzed for the effect of amphetamine, ambulatory, and stereotypic activity.

Procedure

The onset of wheel-running activity for the Golden hamster normally occurs around the offset of light ±20 min. To refer the timing of our pharmacological manipulations to the external light–dark cycle, we defined the offset of light as Zeitgeber time 12 (ZT12). The effect of amphetamine on open-field ambulatory activity and wheel-running activity was assessed during the early night (ZT13), i.e., 1 h after light offset, and during the day (ZT 4), i.e., 8 h before light offset. In all cases, pharmacological manipulations were performed after animals reached 14 days of entrainment (stable phase relationship between wheel-running activity rhythm and the light–dark cycle). Four different groups of hamsters (n = 8–9 per group) were used to assess the following measures.

Experiment 1: Effect of amphetamine on ambulatory activity at ZT 13. Open-field locomotor activity (n = 9) was monitored after IP administration of 1.5, 4, 10, and 25 mg/kg of *d*-amphetamine and saline (0 mg/kg), at ZT13. Each hamster received all amphetamine dosages (five per animal). Injections were given every other day, following a partially counterbalanced order. Previous to the first injection, hamsters were given 15–20 min of adaptation to Plexiglas boxes to reduce the effect of novelty. Ambulatory and stereotypic activity were monitored for 60 min after injection time. Because injections were given during the night cycle, testing was carried out in darkness, under a dim red light.

Experiment 2: Effect of amphetamine on ambulatory activity at ZT 4. A different group of hamsters (n = 8) were tested for the locomotor effect of amphetamine during the daytime. Because it has been reported that light can modify the efficacy of amphetamine, we examined the effect of 10 mg/kg on hamsters tested under light (ZT4L) and dim red light (ZT4D) conditions. All animals were exposed to: saline + light, saline + dark, amphetamine + light, and amphetamine + dark, according to a partially counterbalanced experimental design. Injections were given every other day.

Experiment 3: Effect of amphetamine on wheel running behavior. A different group of hamsters (n = 9) were tested for the effect of amphetamine on wheel-running activity. Hamsters were injected IP with either 0, 1.5, or 10 mg/kg amphetamine at ZT 13. Each animal received all dosages following a partially counterbalanced experimental design. Injections were performed every other day under dim red light, in the animal home cage.

Wheel-running activity from 1 h previous to the manipulation and 1 h after the manipulation was compiled and compared for the effect of the drug.

Drugs

d-Amphetamine was purchased from Sigma Chemicals (St. Louis, MO). Amphetamine was dissolved in physiological saline (0.9% NaCl) and administered via intraperitonal injections. The volume injected varied between 0.15 and 0.18 ml, depending on the weight of the animal.

Data Analysis

The experimental data were analyzed using repeated-measures analysis of variance (ANOVA). The Duncan multiple range test was used for post hoc pairwise comparisons.

The behavioral response to amphetamine plotted in Figs. 1 and 3 appears to follow the course of the underlying biological utilization of the drug, with a low response in the beginning, when the amine enters the general circulation from the peritoneum, a high response in the middle times, when the concentration of the drug at the level of the target is optimal and its elimination little, and a decreasing response by the end of the test, when amphetamine is being metabolized. According to this view, the behavioral data corresponding to the middle time points in the graphs can be considered to be the best representative of the maximal effectiveness of the drug. For this reason post hoc examinations in Experiment 1 and 3, were performed on the data corresponding to the three time points exhibiting the largest difference (for all drug levels) relative to the saline control (times 5, 6, and 7).

Significance was set at $p < 0.05$. All statistical analysis was performed using Statistica package (Stat Soft, Inc; Tulsa, OK).

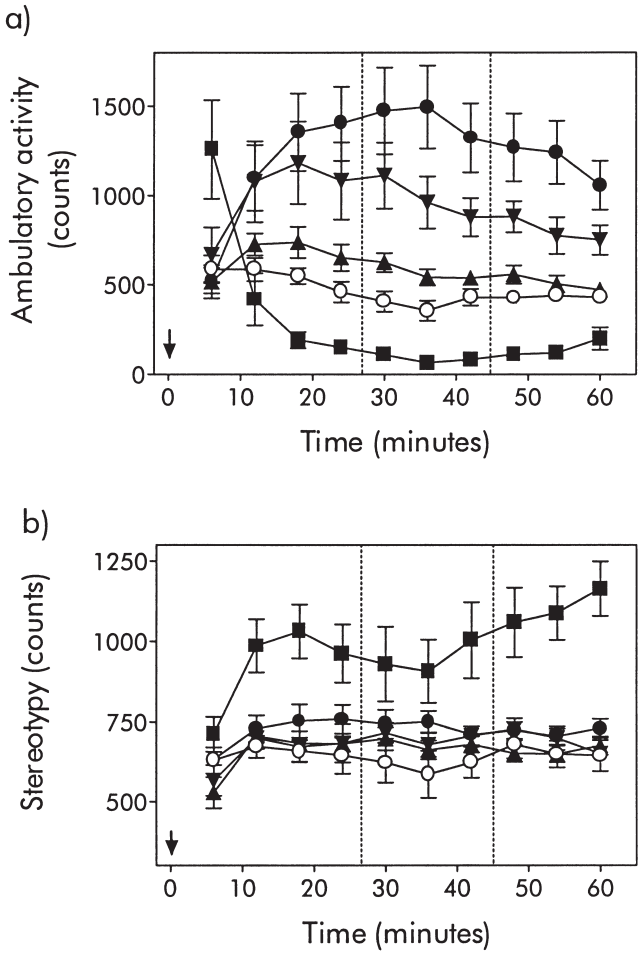

FIG. 1. Time course of open-field locomotion (a) and stereotypy (b) in response to five dosages of amphetamine at (ZT13): 0 mg/kg (○), 1.5 mg/kg (▲), 4 mg/kg (▼), 10 mg/kg (●), and 25 mg/kg (■). Each data point represents the mean ± SEM of ambulatory counts (a) or stereotypy counts (b) accumulated in 6-min bins ($n = 9$). Time of drug administration is indicated by a vertical arrow. Vertical lines within the graph indicate the data points considered for the Duncan's post hoc statistical analysis (statistical significance is specified in the Results section).

RESULTS

Experiment 1

Amphetamine significantly increased open field locomotor activity at ZT13 [two way repeated-measures ANOVA, $F(4,32) = 18.58$, $p < 0.001$ for drug; $F(9,72) = 5.01$, $p < 0.001$ for time; $F(36,288) = 9.07$, $p < 0.001$ for drug × time interaction] (Fig. 1a). All dosages significantly enhanced locomotor activity when compared to each other and to the saline control, except for 1.5 mg/kg (which did not differ from saline) (Duncan's test, 0 vs. 4 mg/kg: $p = 0.001$; 0 vs. 10 mg/kg: $p < 0.001$, 0 vs. 25 mg/kg: $p < 0.05$; 1.5 vs. 4 mg/kg: $p = 0.011$; 4 vs. 10 mg/kg: $p = 0.007$; 10 vs. 25 mg/kg: $p < 0.001$). Dosages between 4 and 10 mg/kg amphetamine, produced high locomotor activation throughout the area of the Plexiglas box, together with increased rearing and exploratory sniffing. Administration of 25 mg/kg amphetamine resulted in an immediate and acute increase in locomotion, which soon declined to activity levels below that of saline controls.

Conversely, the level of stereotypic activity obtained after treatment with 1.5, 4, and 10 mg/kg amphetamine did not differ from saline injections (Fig. 1b), whereas 25 mg/kg amphetamine significantly enhanced it [two-way repeated-measures ANOVA, $p < 0.001$ for drug, $F(4,32) = 20.40$, time, $F(9,72) = 8.96$, and drug × time interaction, $F(36,288) = 2.02$; followed by Duncan's test, 25 vs. 10 mg/kg: $p = 0.004$; 1.5 vs. 10 mg/kg: $p = 0.211$]. Increasing the dosage to 50 mg/kg was lethal, causing death to two out of three animals tested for this purpose. For this reason this dose was not considered in the study. At 25 mg/kg, animals receiving amphetamine typically engaged into stereotypic behavior characterized by intensive sniffing and licking. While engaged in these activities, hamsters tended to walk slowly and, most of the times (seven out of nine animals), backwards.

Experiment 2

Amphetamine significantly increased open-field locomotor activity when administered at ZT 4, regardless of the lighting condition (Fig. 2a and b), [three-way repeated-measures ANOVA, $F(1,7) = 14.31$, $p < 0.01$ for drug; $F(9,63) = 4.09$, $p < 0.001$ for time]. Exposure to darkness during the day (ZT4D) resulted in a pronounced increment compared to the level of ambulatory activity obtained under light conditions (ZT4L), $F(1,7) = 23.55$, $p < 0.005$, for the main effect of light. Besides its effect on the baseline activity levels, the effectiveness of the drug was not modified by the presence or absence of light, $F(1) = p = 0.247$ for light × drug interaction.

The presence of a circadian modulation in the response to amphetamine was also investigated. For this purpose the level of ambulatory activation in response to 10 mg/kg was compared between the group of animals ran at ZT 13 in Experiment 1, and the group of hamsters run under dark conditions at ZT4. No significant difference was found between the increment of ambulatory activity obtained during the daytime vs. that obtained during the nighttime [three-way repeated-measures ANOVA, $F(1,14) = 31.85$, $p < 0.001$ for drug; $F(9,126) = 4.46$, $p < 0.001$ for time; $F(1,14) = 0.239$, $p = 0.632$ for time of day; $F(1,14) = 0.19$, $p = 0.668$ for drug × time of day interaction; $F(9,126) = 8.52$, $p < 0.001$ for drug × time interaction].

Experiment 3

Two different amphetamine dosages were tested for their effect on spontaneous wheel-running activity at ZT13 (Fig. 3). Administration of 1.5 mg/kg amphetamine did not affect the level of wheel-running activity differently from saline injections [two-way repeated-measures ANOVA, $F(2,16) = 54.23$, $p < 0.001$ for drug, $F(9,72) = 6.36$, $p < 0.001$ for time, and $F(18,144) = 5.74$, $p < 0.001$ for drug × time interaction; followed by Duncan's test, 1.5 vs. 0 mg/kg: $p = 0.453$]. However, application of 10 mg/kg amphetamine, the dosage producing the maximum locomotor activation in an open field, completely blocked spontaneous wheel running activity for 40 to 50 min (Duncan's test, 10 vs. 1.5 mg/kg: $p < 0.001$). Besides its effect on wheel running, animals treated with the highest amphetamine dosage exhibited the typical behavioral signs accompanying amphetamine administration, i.e., hyperlocomotion, increased sniffing, and rearing.

DISCUSSION

The effect of *d*-amphetamine on the behavior of the Golden hamster has been previously studied by Peterson and Morin (20). Among the different behavioral categories exam-

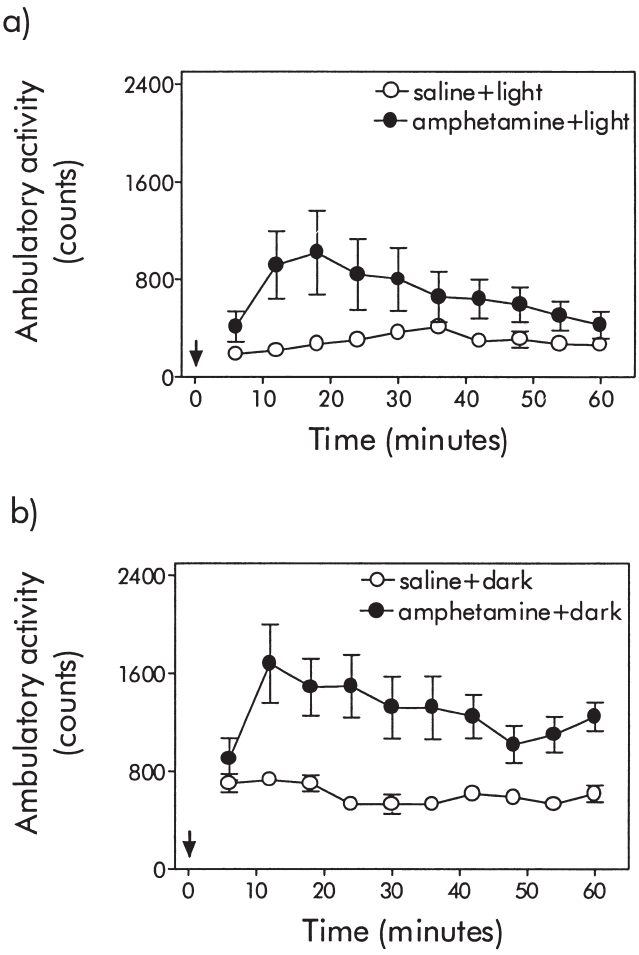

FIG. 2. Time course of open-field ambulatory activity in response to 10 mg/kg amphetamine at ZT4. Shown are the means ± SEM of ambulatory counts accumulated in 6-min bins under light (a) or dark (b) conditions (n = 8). Time of drug administration is indicated by a vertical arrow. Statistical significance is specified in the Results section.

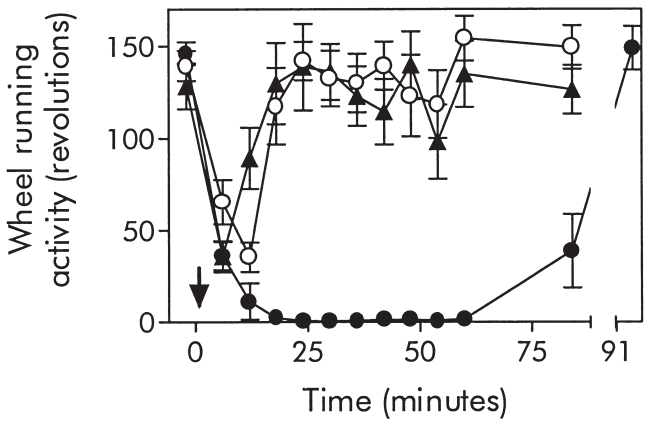

FIG. 3. Time course of wheel-running activity in response to *d*-amphetamine at ZT13. 0 mg/kg (○), 1.5 mg/kg (▲), 10 mg/kg (●). Shown are means ± SEM of wheel-running revolutions accumulated in 6-min bins. Time of drug administration is indicated by a vertical arrow. Statistical significance is specified in the Results section.

ined in an open field, increasing dosages of amphetamine significantly modified the occurrence of rearing, gnawing, and circling behaviors. However, the authors reported no effect on the level of ambulatory activity across the different dosages of amphetamine examined (5 to 50 mg/kg).

In contrast, our results indicate a pronounced effect of *d*-amphetamine on the ambulatory activity of the Golden hamster. The level of locomotion exhibited by animals exposed to an open field, significantly increased at a dose of 4 mg/kg, reaching its maximum at 10 mg/kg amphetamine. Beyond that dose (25 mg/kg amphetamine), ambulatory counts diminished as engagement into stereotypic behaviors (licking, biting, and sniffing) intensified.

Certain studies have shown that the lighting condition in which testing is carried out affects the behavioral response to amphetamine (13,24). We have examined this question by comparing amphetamine-induced ambulatory activity of hamsters exposed to both light (ZT4L) and dark conditions (ZT4D) during the daytime. The results indicate that, although the lighting condition affects baseline locomotion (higher activity levels were found in the dark condition compared to the light condition), it does not modify the effect of amphetamine on locomotion, which was similar for both conditions. Indeed, given that the Golden hamster is a nocturnal species, application of light during the day seems to have an inhibitory action on locomotion.

The existence of a circadian component in the locomotor response to amphetamine was also examined. In the present study, amphetamine treatment enhanced open field locomotion regardless of the time of day, and the lighting condition. However, when the magnitude of the response was compared across time of day it was found that, even though the effect of the drug at ZT13 was more pronounced than at ZT4L, it did not differ from that obtained at ZT4D. In other words, animals tested under dark conditions exhibited a similar response to amphetamine regardless of the time of day.

Daily variations in the response to amphetamine have been previously described at the level of physiology and behavior. However, the outcomes from these studies are quite inconsistent. Higher nocturnal than diurnal susceptibility to amphetamine was described for percentage of mortality (24) and head shaking (28) in rats. Conversely, a recent study (9) reported no circadian differences in the effect of amphetamine on rat locomotor activity elicited by exposure to an open field. Microdialysis assessments of dopamine release from the NA, suggest the presence of a daily rhythm in the release of dopamine with low levels during the daytime and high levels during the nighttime (18,27). Nevertheless, the opposite pattern was encountered in the same rat species for dopamine content (22,23). In addition, another laboratory (19) reported no significant daily variations of dopamine release from the NA.Our results suggest that, rather than reflecting an endogenous circadian modulation, the daily variation in the response to amphetamine results from the acute inhibitory effect of light. It is possible that this modulatory effect of light on baseline locomotion was one of the factors leading to the incongruent circadian literature.

In addition to its general effect on open-field locomotion, we have found that, in the Golden hamster, amphetamine differentially affects ambulatory locomotion and wheel running activity. Administration of 10 mg/kg amphetamine, the dosage producing the maximal locomotor activation in an open field, entirely blocked home-cage wheel-running activity for

at least 40 min (Fig 3). These findings suggest that, depending on the motor device utilized, the susceptibility to amphetamine changes. Therefore, even though ambulatory and wheel-running activity may be considered expressions of locomotion, they are not equivalent measures of it.

In a hypothesis formulated to explain the effect of amphetamine on behavior, Lyon and Randrup (16), and later Lyon and Robbins (15), proposed that increasing dosages of amphetamine enhance perseverative and stereotyped behaviors, leading to higher rates of activity in more limited categories of response. Thus, as the rate of motor activities increases by increasing the dosage of amphetamine, the animal would engage in high rate responses by reducing the number of response categories. For example, under the effect of a moderately high dose of amphetamine, an organism exposed to an open field would increase its response rate by reducing the time spent in categories of behavior that involve relatively more pausing, such as eating and grooming, and instead, engage into vigorous locomotion. Behaviors capable of repetition will therefore become dominant, and their rate will increase with increasing doses of the drug, while behaviors requiring more pausing would be eliminated of the repertoire.

Our data can be interpreted following this model of amphetamine action described above. As perseveration induced by increasing doses of amphetamine augments, engagement into wheel-running activity, which entails more pausing and coordination than ambulatory locomotion, tends to decrease. Therefore, the organism tends to suppress this and other time-consuming behaviors of its repertoire, and instead, engages in repetitive and more simple ambulatory locomotion. Eventually, the motor activation becomes so pronounced and the response rate so high that ambulatory locomotion ceases and is replaced by short response-sequence behaviors such as licking and biting, observed during stereotypy.

Additional evidence supporting this hypothesis comes from a study where a dissociation of the effect of amphetamine is indicated on rat ambulatory activity and exploration of novel stimuli (21). The authors found that, when tested on an open field, 1.5 mg/kg amphetamine stimulated ambulatory activity and decreased exploratory time. However, because the incidence of exploratory bouts was unaffected by the drug, the authors argued that the dissociation obtained was not due to a decrease in the level of motivation towards exploring new stimuli but to the high level of motor activation caused by amphetamine. The latter led the animal to disengage the paused sequences of behavior involved in exploration, and instead, engage in high-rate ambulatory activity.

Nevertheless, we cannot discard the possibility that the observed dissociation induced by *d*-amphetamine may have been due to a decrease in the motivation to run in the wheel. Given the self-reinforcing properties of the psychostimulant and the running wheel (26), it is possible that amphetamine administration during a time when hamsters engage in vigorous wheel-running activity may have substituted for the reinforcing effect of the wheel. In other words, if the rewarding properties of the wheel are signalled by dopamine release, then *d*-amphetamine could have effectively short circuit the reward pathway, reducing the relative dopamine signal—hence the apparent value of the reward. Further investigation assessing the influence of amphetamine on the reinforcing value associated with the wheel is required to test this alternative hypothesis.

We conclude that amphetamine dissociates locomotion, depending on the locomotor device utilized. Using the open field and the running wheel—or any other motor device—indistinguishably, may lead to erroneous interpretation of the experimental data. The extension of this observation into other experimental paradigms may be worth considering when a measure of activity is required.

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