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Amphetamine-Elicited Perseverative and Rotational Behavior: Evaluation of Directional Preference

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KOKKINIDIS, L *Amphetamine-elicited perseverative and rotational behavior Evaluation of directional preference* PHARMACOL BIOCHEM BEHAV **26**(3) 527–532, 1987 —Four experiments examined the effects of d-amphetamine on lateralized direction preference, circling behavior, and perseveration The nature as well as the magnitude of the behavioral response to amphetamine was dependent upon the testing situation Whereas 5 0–10 0 mg/kg of the drug induced a robust circling behavior in a circular alleyway, it required 10 0 mg/kg of amphetamine to produce a significant turn preference in an open field exploratory situation In a symmetrical Y-maze, mice displayed spontaneous alternation behavior characterized by an exploratory pattern involving different arm sequences After amphetamine administration, spontaneous alternation was reduced and pronounced perseverative patterns of exploration were evident at dose levels similar to those that induced rotational behavior Directional preferences could not account for the exploratory patterns in the Y-maze of animals in the undrugged state, or under the influence of amphetamine regardless of dose Since lateralized motor asymmetries after amphetamine were limited by the behavioral context in which the effects of the drug were evaluated, it was argued that rotational behavior cannot be considered to be a simple mechanistic behavior Rather, in addition to the expression of a side preference, it involves a drug-induced perseverative tendency On the basis of these data, it was suggested that evaluation of the direction of turning in an open field is a less biased measure of spatial preference following amphetamine administration It was further argued that perseverative behavior is a prepotent response to amphetamine and the possibility of lateralized attentional asymmetries was discussed

d-Amphetamine Rotational behavior Perseveration Stimulus factors Lateralized asymmetries

SEVERAL factors come into play in the decision making of an animal faced with making a choice in even an ostensibly simple experimental paradigm In addition to the stimulus aspects of the situation, lateralized motor function plays an important role in the final behavioral outcome Glick and his associates have demonstrated that rats exhibit a natural turning bias which is related to striatal tissue with the highest dopamine content contralateral to the side of the motor/spatial asymmetry [7] Recent data suggest that lateralized motor function occurs primarily among females and is not prominent in the male rat population [3], and even among females there appears to be a variation both in the strength and in the directionality of spatial asymmetry For example, Dark *et al* [3] found that approximately fifty percent of female subjects tested demonstrated a turn preference and a higher dopamine content in the striatum opposite to the turning bias, whereas the remaining half did not display a significant motor asymmetry and had more dopamine in the ipsilateral side.

The finding however, that systemic amphetamine administration produces a rotational bias in a number of species including mice, rats and cats [8–10], has provided considerable support for the ubiquity of a functional motor asymmetry in normal animals. Moreover rotational behavior after amphetamine treatment is observed regardless of sex although the bias is stronger in female rats [25] Once again the drug-induced spatial preference was related to a functional asymmetry of dopamine activity in the striatum of the two hemispheres. The correlation between turning behavior and contralateral dopamine activity, however, was only observed in female rats and drug-induced rotational behavior in male rats did not correlate with contralateral striatal dopamine content [25].

Considering the variety of effects of amphetamine on behavior it was argued that in addition to a side preference, rotational behavior after amphetamine treatment involved the effects of the drug on perseverative processes [16,17]. For example, when mice or rats are placed in a symmetrical Y-maze they tend to visit the least recently visited arm, i.e , spontaneous alternation [12, 14, 21]. That is they tend to make 3 different arm response sequences, and in so doing, it follows that animals make more unidirectional (i.e., either right or left) turns After amphetamine treatment, however, spontaneous alternation is not increased as would be expected if the drug facilitated an already existing side preference. Rather, animals exposed to the drug demonstrate a fairly continuous response pattern utilizing two compartments of the maze only [14,21] Although not objectively quantified, animals that show perseverative behavior in the Y-maze after amphetamine treatment must necessarily make left-right turns, an outcome that apparently is opposite to that observed in a rotometer on circular alleyway [12,16]

The perseverative effects of amphetamine on behavior are not related to the motor consequences of the drug, but rather involve deficits in attentional mechanisms [12,18], characterized by the inability of animals to inhibit responding to previously sampled stimuli [18,19], as well as increased responding to unrewarded stimuli [24]

In order to better understand the relationship between amphetamine-induced spatial asymmetry and perseverative behavior, the present study was designed to systematically investigate the effects of several doses of amphetamine on turning behavior in four experimental paradigms that varied in stimulus complexity Comparing changes in directionality in drugged and undrugged animals, in different behavioral situations, may shed some light on factors (e.g , stimulus, motor) involved in amphetamine-induced rotational behavior

In the first experiment the effects of amphetamine were assessed in a circular alleyway, an apparatus that previously has been demonstrated to promote rotational behavior. A second experiment evaluated the number of amphetamine induced left and right turns in an open field situation where behavior is not channelled in one of two directions, as is the case with either a rotometer or circular alleyway A third experiment assessed the patterns of exploratory behavior in a symmetrical Y-maze (spontaneous alternation), and the final experiment evaluated the effects of amphetamine in a symmetrical Y-maze, but instead of determining the sequence of arm entries, the number of left and right turns made within each arm and at the choice point were recorded In this way the pattern of exploration in the Y-maze could be assessed in relation to the actual directionality of the response sequences

METHOD

Subjects

One hundred and ninety-two Swiss male mice between 50 and 65 days of age served as subjects. Mice were obtained from the Animal Resources Centre at the University of Saskatchewan and were housed in groups of 3–5 in polypropylene cages Subjects were permitted free access to food and water and were acclimatized to the laboratory for seven days prior to behavioral testing. Animals were housed under a regular 12-hr light/dark cycle and testing was carried out during the light portion of the cycle

Apparatus

The apparatus used in Experiment 1 consisted of an opaque plastic circular alleyway 6 0 cm wide. The alleyway was divided into four quadrants of equal size and had an outside circumference of 69.0 cm. In Experiment 2 mice were tested in an open field which consisted of an opaque plastic box 28 0 cm long, 17.5 cm wide, and 12.0 cm high and the open field was covered with a clear Plexiglas roof. The symmetrical Y-maze in Experiments 3 and 4 consisted of black Plexiglas arms 9.0 cm long, 6.0 cm wide and 7.0 cm high and a black Plexiglas floor The roof of each compartment was clear Plexiglas

Procedure

Mice in each experiment (N=48) were randomly assigned to one of 6 groups (N=8 per group), and injected intraperitoneally with either saline or 1 0, 3.0, 5 0, 7 0 or 10.0 mg/kg of d-amphetamine sulfate After drug injection animals were

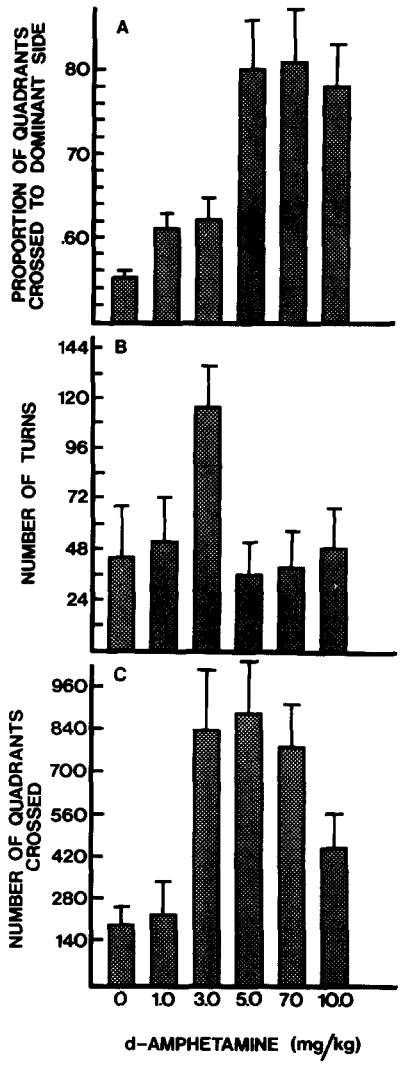

FIG 1 Mean (±S E M) proportion of quadrants crossed to dominant side, mean (±S E M) number of direction changes, and mean (±S E M) total quadrants crossed during a 15 minute test session in a circular alleyway after saline and d-amphetamine The 5 0, 7 0 and 10 0 mg/kg doses induced significant circling behavior (Panel A), 3 0 mg/kg of amphetamine increased the number of turns (Panel B), 3 0, 5 0 and 7 0 mg/kg increased locomotor activity (Panel C)

placed in a holding cage for 10 minutes and then were tested in the circular alleyway (Experiment 1), the open field (Experiment 2) or the Y-maze (Experiments 3 and 4)

In the circular alleyway the number of quadrants crossed in both directions as well as the number of direction changes were recorded for 15 minutes The proportion of rotations was calculated by dividing the number of quadrants crossed to the dominant side by the total number of quadrants crossed The direction towards which more turns were made was considered dominant The mean proportion of individual rotations was analyzed through analysis of variance and Newman-Keuls multiple comparisons Separate analyses of variance were carried out on the total number of turns, as well as on the total number of quadrants crossed

In the open field the number of left and right turns as well as the number of direction changes made during exploration

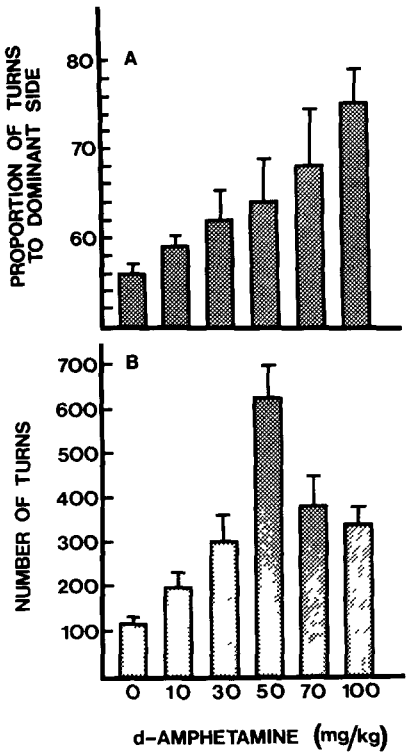

FIG 2 Mean (±S E M) proportion of direction turns to dominant side, and mean (±S E M) number of total turns during a 15 minute test session in an open field after saline and d-amphetamine The 10 0 mg/kg dose was significant in inducing a turn preference (Panel A), the 3 0, 5 0, 7 0 and 10 0 mg/kg doses increased the number of turns (Panel B)

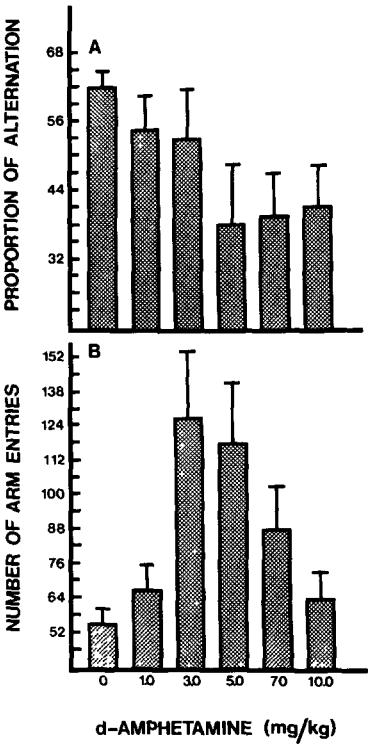

FIG 3 Mean (±S E M) proportion of individual spontaneous alternation, and mean (±S E M) number of arm entries during a 15 minute test session in a symmetrical Y-maze after saline and d-amphetamine 5 0, 7 0 and 10 0 mg/kg of d-amphetamine produced significant perseverative behavior (Panel A), 3 0, 5 0 and 7 0 mg/kg of the drug significantly increased locomotor activity (Panel B)

of the open field were recorded for 15 minutes The proportion of turn preference was determined by dividing the total number of turns into the number of turns made to the dominant side. Once again the direction towards which more turns were made was considered dominant. The mean proportion of individual turn preferences scores as well as the total number of turns were analyzed through analysis of variance

In Experiment 3, subjects were placed in one arm of the Y-maze and were allowed to explore the maze freely for 15 min A response sequence in which animals entered the arm least recently visited (e g., arm 1-arm 2-arm 3) was considered as an alternation response. In the case where animals returned to the most recently visited compartment their response pattern was recorded as a non-alternation (e.g , arm 1-arm 2-arm 1) The proportion of alternation was computed by dividing the number of alternation response sequences by the total number of response sequences (i e , alternations + non-alternations) The proportion of individual alternation scores and the total number of arm entries were analyzed by analysis of variance Since spontaneous alternation is defined as alternation behavior which significantly exceeds chance levels, and perseveration is defined as alternation behavior which is significantly below chance [12,13], χ^2 analysis of the total group alternation and non-alternation data was conducted

In Experiment 4 animals were placed in one arm of the Y-maze and the number of left and right turns made at both the choice point and in each arm were recorded In addition the number of direction changes were recorded over the 15 minute test session Turn preference was determined by dividing the number of turns to the dominant side by the total number of turns. The dominant side was considered to be the direction in which animals showed the largest bias The mean proportion of individual turn preference scores and the total number of turns were analyzed through analysis of variance

RESULTS

Figure 1 (Panel A) shows the mean individual rotational behavior in a circular alleyway after injection of saline, 1.0, 3 0, 5 0, 7.0 and 10 0 mg/kg of d-amphetamine. One-way analysis of variance of these data yielded a significant effect for dose, $F(5,42)=7\ 38$, $p<0\ 01$. As is evident in Fig. 1 (Panel A), systemic amphetamine administration produced a pronounced circling response. Whereas 1.0 and 3.0 mg/kg of the drug did not induce significant circling behavior, animals treated with 5 0, 7.0 and 10.0 mg/kg displayed a strong spatial bias relative to control animals

Amphetamine treatment also increased the total number of turns, $F(5,42)=2.93$, $p<0\ 05$, as well as the total number of quadrants crossed, $F(5,42)=6.83$, $p<0\ 01$ Evaluation of the dose response curve of amphetamine revealed that the drug did not produce congruent effects on these behaviors. In the case of the number of turns made during the test

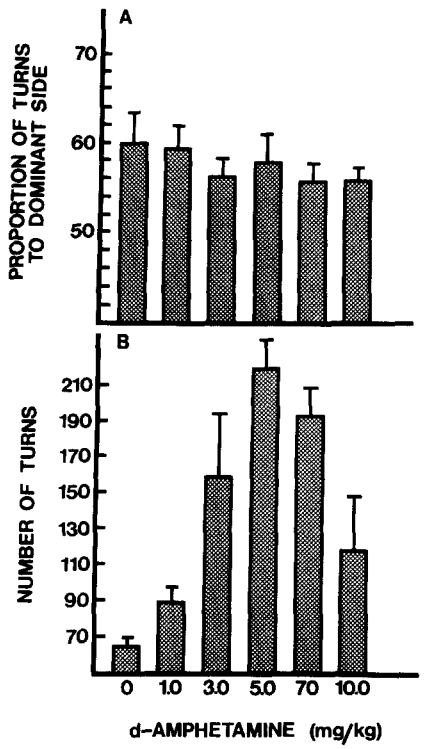

FIG 4 Mean (±S E M) proportion of turns to dominant side, the mean (±S E M) number of turns in a symmetrical Y-maze during a 15 minute test session after saline and d-amphetamine No significant effects were evident with respect to a turn preference in the Y-maze (panel A), 3 0, 5 0 and 7 0 mg/kg of d-amphetamine significantly increased the total number of turns (Panel B)

session only 3.0 mg/kg of amphetamine significantly increased the total number of turns relative to the remaining groups (Fig 1, Panel B), whereas the higher doses of the drug substantially increased the total number of quadrants crossed (Fig 1, Panel C) Thus, animals injected with 5.0, 7 0 and 10.0 mg/kg of amphetamine displayed increased motor output with no concomitant increase in the total number of turns during the test sessions resulting in a net rotational bias to a preferred side.

Figure 2 depicts turn preference in the open field task (Panel A) and the number of turns made during the test session (Panel B). Analysis of variance of the proportion of mean individual turns to the dominant side resulted in a significant dose effect, $F(5,42)=3\ 38$, $p<0\ 05$. As is evident in Fig. 2 (Panel A) the proportion of turns increased monotonically as a function of dose Although amphetamine produced a dose-dependent increase in turn preference, Newman Keuls multiple comparisons ($\alpha=0.05$) revealed that only the highest dose of the drug (10.0 mg/kg) induced a significant turn bias in the open field task Side preference after the 7 0 mg/kg dose was only marginally significant ($p<0\ 10$)

Amphetamine also facilitated the total number of turns made in the open field. $F(5,42)=12.27$, $p<0\ 01$ Increased number of turns was observed after 3.0–10.0 mg/kg of the drug with the 5.0 mg/kg dose being the most effective in this respect. Comparing the dose response curves in Fig. 2, it becomes apparent that there is no relationship between the motor activating effects of the drug (total number of turns) and the drug-induced turn preference Whereas 5 0 mg/kg produced the greatest motor stimulation it did not induce a significant turn preference

The mean alternation responses and arm entries are depicted in Fig. 3 (Panels A and B). Analysis of variance revealed a significant drug effect with respect to the alternation data, $F(5,42)=5.23$, $p<0\ 01$. The 5.0, 7 0 and 10 0 mg/kg doses of the drug significantly reduced spontaneous alternation behavior χ^2 analysis of the total group alternation scores indicated that whereas control animals alternated significantly above chance levels, $\chi^2(1)=10\ 92$, $p<0\ 01$, animals treated with the three highest doses of the drug alternated significantly below chance levels, $\chi^2(1)=38\ 7$, 19 7 and 24 8, p's$<0\ 01$, for the 5 0, 7 0 and 10.0 mg/kg doses, respectively. Thus, whereas saline treated animals displayed significantly more different arm response sequences, animals injected with amphetamine did not show an alternation tendency in the exploration of the maze, but rather made significantly more non-alternation sequences (perseverative behavior)

With respect to the number of arm entries, amphetamine significantly increased locomotor activity, $F(5,42)=4\ 48$, $p<0\ 01$ The 3 0 and 5 0 mg/kg doses of the drug were most effective in this respect There appears to be no relationship between drug-induced locomotor activation and perseveration For example, whereas 3 0 mg/kg of amphetamine was the most potent in increasing the number of arms entered, it did not result in perseverative behavior

The mean perference and number of turns made in the exploration of the Y-maze are shown in Fig 4 (Panels A and B) Analysis of variance revealed no significant drug effects on turn preference, $F(5,42)=0\ 556$, $p>0\ 70$ As can be seen in Fig 4 (Panel A), mice injected with amphetamine did not show a significant turn bias in the Y-maze exploration task as compared to controls regardless of dose A turn bias was not evident despite the observation that amphetamine significantly increased activity levels, $F(5,42)=9\ 33$, $p<0\ 01$ Multiple comparisons revealed that the 3 0, 5 0 and 7 0 mg/kg doses significantly increased the total number of turns made during the test session

It should be pointed out that although amphetamine animals did not differ from controls with respect to a turn preference in the Y-maze, a turn preference was evident in control animals and after some doses of amphetamine Specifically, undrugged mice that showed significant spontaneous alternation also displayed a turn bias, $\chi^2(1)=6\ 7$, $p<0.01$ (χ^2 analysis of the total group left/right turns) Amphetamine treated mice which did not exhibit spontaneous alternation, but rather displayed perseverative behavior, also had a side preference after some doses, $\chi^2(1)=25\ 6$, 19 2, $p<0\ 01$, for the 1 0 and 5 0 mg/kg doses, and $\chi^2(1)=0$, 2 3 and 1.6, $p>0\ 05$, for the 3 0, 7 0 and 10 0 mg/kg doses, respectively These findings indicate that the turn preference observed after saline and some doses of amphetamine significantly exceeded chance levels Given that the side preference was not consistently observed after all doses of the drug, it is likely that the different patterns of exploratory behavior in the Y-maze after saline and amphetamine treatment are not related to the systematic turning to a preferred side

DISCUSSION

A behavioral evaluation of the effects of amphetamine on directionality finds that the manifestation of a drug-induced

turn preference, as well as the magnitude of the effect is dependent upon the testing situation in which the drug is evaluated Consistent with numerous reports systemic administration of d-amphetamine produced circling behavior [7–10]. In the circular alleyway, where animals can express the behavioral arousing effects of the stimulant in one of two directions, amphetamine produced a substantial rotational response to a preferred direction Moreover, comparable circling was observed after the three highest doses of the drug (5 0, 7.0 and 10.0 mg/kg) A significant turn preference was also evident when animals were tested in the open-field task, however, the dose response curve for amphetamine was not similar to that seen when animals were tested in the circular alleyway. Only the highest dose (10.0 mg/kg) elicited a significant turn bias and the directionality preference was not as strong as that observed in the alleyway in terms of maximal effect

When the effects of amphetamine were considered in the symmetrical Y-maze task, considerable variation in behavior was evident relative to the other testing situations. As previously demonstrated in both rats and mice, amphetamine attenuated spontaneous alternation behavior and induced a pronounced perseverative response [14, 15, 21]. Thus, whereas undrugged animals made a significantly higher proportion of different arm response sequences (alternation) during the test session, animals tested after receiving amphetamine displayed repetitive responding to only two arms of the apparatus (perseveration) Interestingly, the diverse pattern of exploration of the maze after saline and amphetamine treatment was not accompanied by significant changes in directionality That is, evaluation of turning both within each arm and the choice points, revealed that after amphetamine administration behavior was comparable to that of control animals. The absence of a difference between saline and amphetamine treated animals suggests that neither spontaneous alternation in naive undrugged animals, nor perseveration typically seen after amphetamine treatment involves exploration of the maze on the basis of a directionality bias

It has been demonstrated that in addition to perseveration, amphetamine facilitates switching behavior in operant situations, at doses that are generally lower than those necessary to induce perseveration [5]. Consistent with these findings, switching of turns was observed after lower doses of amphetamine than were required to elicit circling or perseverative behavior For example, whereas rotational behavior was observed in the circular alleyway after 5 0–10 0 mg/kg of the drug, only the 3.0 mg/kg dose of the drug increased direction changes. Similarly, in the open field task an increased turn bias was evident after 10.0 mg/kg of amphetamine, and switching was maximal at the 5 0 mg/kg dose. In the Y-maze, perseverative behavior was observed after 5 0–10 0 mg/kg, whereas increased switching was evident after 3.0–7 0 mg/kg. These data indicate that the dominant type of behavior after systemic amphetamine treatment is dependent upon dose, and argue against recent suggestions that perseverative behavior may be related to the direction of turning [21] The observation that amphetamine treated animals did not differ from controls with respect to a turn preference in the Y-maze, regardless of dose, is consistent with this position

A strong relationship exists between the behavioral effects of amphetamine and the environmental stimuli of the testing situation Under conditions where the orientation response is limited to a choice between one of two directions, a robust circling response is observed after systemic amphetamine injection. When the choice involves the exploration of a symmetrical Y-maze, however, significant perseverative behavior emerges in the absence of a directionality bias. Comparison of the dose response curves in these tasks, demonstrates a marked similarity between the dose effects of amphetamine on circling and perseverative behavior This observation, coupled with recent reports that amphetamine administration results in perseverative head dipping [13], perseverative patterns of locomotion [26], and operant behavior [23], suggests that one of the primary behavioral effects of amphetamine is the perseveration of response sequences, the expression of which is dependent upon the stimulus complex of the testing situation.

Considerable evidence suggests that manipulation of the stimulus array of the testing situation can influence the behavioral response to amphetamine. For example, repeated exposure to the Y-maze increased the perseverative effects of the drug [21], and repeated testing in a rotometer increased drug-induced rotational behavior after low doses of the drug, which ordinarily do not induce circling [4] Allowing animals to habituate or adapt to the environment reduces prepotent exploratory tendencies, and maximizes drug-induced perseveration [14,15], and rotational behavior [17] Alternatively, increasing the exploratory value of the testing environment decreased the perseverative effects of amphetamine [2, 15, 18] More recently, it was demonstrated that sex differences in the effects of amphetamine on schedule-controlled behavior, were dependent upon the environmental contingencies maintaining the behavior [11]. This is not to imply that amphetamine does not elicit a directionality bias To the contrary the results of this study confirm previous reports that the drug does indeed produce a turn preference The preference, however, is dependent upon the stimulus constraints of the apparatus.

Although systemic amphetamine administration induces a spatial orientation preference in normal animals, it is clear that the magnitude of the preference as measured in a rotometer or circular alleyway may not adequately reflect the strength of the turning bias Since performance in these tasks involved locomotion in a preferred direction, quantifying this behavior in terms of number of rotations or quarter rotations, may not be a good indication of the magnitude of the side preference, but rather is an index of a perseverative running response. In this respect it would appear that behavior in an open field might be better suited as a less biased measure of laterality. In any event, it is clear from the results of this study that rotational behavior is indeed complex, and dependent upon a number of factors other than hemispheric imbalances of striatal dopamine After all, male rats and mice consistently show high and robust levels of circling after simulant drugs [4, 22, 25], that is not related to a hemispheric dopamine asymmetry [25] Thus, it is not surprising to find that postural asymmetry which reflects an imbalance within nigrostriatal dopamine activity, did not correlate with amphetamine-induced rotational behavior [20] Similarly lateralized taxis for edges was not related to apomorphine-induced circling, and laterization for postural support after apomorphine was not predictive of rotational behavior [22].

If we accept that lateralized spatial preference in intact animals after amphetamine involves a drug-induced side preference (as demonstrated in the open field), and perseveration (as observed in the circular alleyway and Y-maze), then the results of this study have important implications for the interpretation of data involving rotational behavior in a

rotometer or circular alleyway For example, the circling response to stimulant drugs is greater in females than males suggesting differences in lateralized functional brain asymmetries between the sexes [6,25] Since perseverative behavior is a prepotent behavioral response to amphetamine that has been demonstrated in a wide variety of paradigms varying in complexity, and the perseverative response to the drug is independent of motor habits or side preferences, it is interesting to speculate whether sex differences would be evident in perseverative behavior in tasks other than the circular alleyway or rotometer. This would not be surprising when it is considered that after amphetamine treatment females developed greater increases in both stereotypic behavior and locomotor activity relative to male rats [1,27]

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