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The Description of Rat Drug-Induced Behavior: Kinematics Versus Response Categories

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ADANI, N , N. KIRYATI AND I GOLANI *The description of rat drug-induced behavior. Kinematics versus response categories.* NEUROSCI BIOBEHAV REV **15**(4) 455–460, 1991 —The study of rat drug-induced locomotor behavior is largely based on the assumption that behavior consists of a sequence of response categories performed by the whole animal one at a time By analysing this behavior under (+)-amphetamine (5 mg/kg), we illustrate how even a precise definition of such categories may not be sufficient for the establishment of behavioral variables that have a "physiological reality " We describe the changes of relation between the parts of the rat's body in reference to selected coordinate systems, and show that a great variety of locomotor patterns observed under amphetamine can be reduced to as few as 3 descriptive component-variables These continuous and relatively independent variables, which behave predictably in the course of drug action, operate simultaneously Variations in their relative timing of onset and termination account for the apparent variability in observed behavior The economy and generality of a description based on these variables suggest the existence of corresponding central mechanisms of control

Amphetamine Apomorphine Locomotor behavior Stepping Stereotypies Stereotyped behavior Open-field behavior Behavioral assessment of drug action

THE study of rat drug-induced locomotor behavior is largely based on the assumption that behavior consists of a sequence of response categories performed by the whole animal one at a time. Behavior is commonly classified either in rather general terms such as locomotion and stereotypy, or in terms of discrete categories such as rearing, circling, side-to-side head movements, pivoting, and sniffing (4, 5, 13, 14). Another option, addressed in the present paper, is to describe whole animal movement in terms of the relations and changes of relation between the parts of the body, in reference to selected coordinate systems across time. A coordinate system that reveals an organized pattern of movement shared by all examined animals might be a coordinate system actually used by the animal itself Unlike the situation in physiology, where the identity of the controlled quantities is often preestablished at the onset of a study (e.g., neurotransmitter levels, neuron firing rates), we mostly don't know what the controlled quantities of spontaneous behavior are.

The aim of the approach illustrated here is to look for coordinate systems which yield representations of whole-animal movement which both correspond as closely as possible to the morphology of movement and provide kinematic quantities which are presumably controlled by the brain. Kinematics deals with the (geometrical) form of movements without reference to the forces involved. A controlled kinematic quantity is an aspect of movement which is maintained at a given value (or transformed according to a prescribed rule) across situations. For instance, if during the swing phase of a stepping foreleg, the forepaw of a rat establishes a particular geometrical relationship with the head, and this relationship is then maintained as a result of the simultaneous movements of the head on the torso, and of the foreleg on the torso, this relationship may be described as a kinematic quantity which is presumably controlled. The isolation of such an invariant quantity (e.g., right forepaw opposes right corner of mouth at a particular distance from it) thus reduces the apparent variability of behavior (i.e., it accounts in this example for the variable movements of the head and the foreleg). It also suggests that the measured quantity is controlled and that the organism contains a control system controlling that quantity (16). A description based on presumably controlled quantities is therefore both economical and general. On the other hand, an economical description which does not sacrifice the close correspondence to the morphology of movement and is also general, can serve as a proper candidate for a specification of the kinematic quantities actually controlled by the brain.

Several examples of presumably controlled kinematic quantities and the coordinate systems that reveal them are illustrated in the present paper, in the analysis of (+)-amphetamine (5 mg/kg, SC)-induced rat open-field behavior.

DESCRIPTIVE METHOD

The coordinate systems used in the present report are part of the Eshkol-Wachman Movement Notation (EW) (8,9). A detailed exposition of their use in the analysis of vertebrate behavior is given elsewhere (7, 12, 19). In the present study, the rat's trunk is divided into 3 parts: lower torso, upper torso, and head (Fig. 1). The movements of a part of the trunk is described in relation to a spherical coordinate system centered at that part's caudal end. Each of the parts of the trunk has its own coordinate system. Since the present study examines rat amphetamine-induced behavior at a stage when vertical movements (e.g., head raising, rearing) have been practically eliminated from the rat's

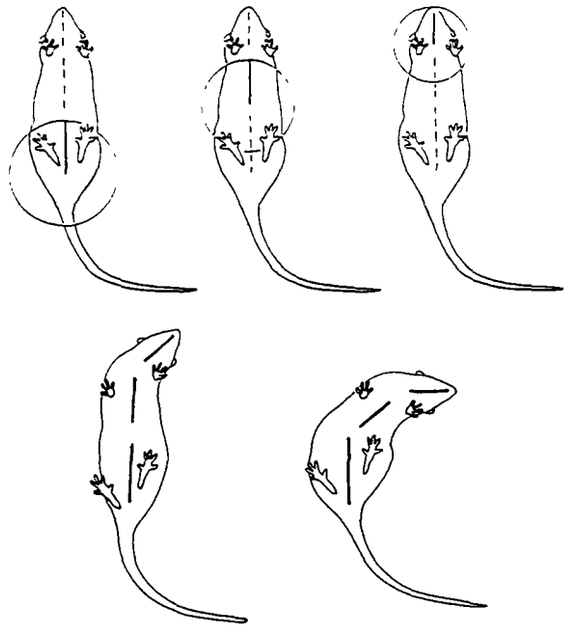

FIG 1 Representation of horizontal movements Thick lines represent the longitudinal axes of the parts of the trunk—lower torso, upper torso, and head Top horizontal row each part of the trunk has its own horizontal circle which is schematically attached to its caudal end Posture in upper row illustrates initial position for movements whose final position is illustrated in lower row Lower row left head movement, right upper torso movement and head movement.

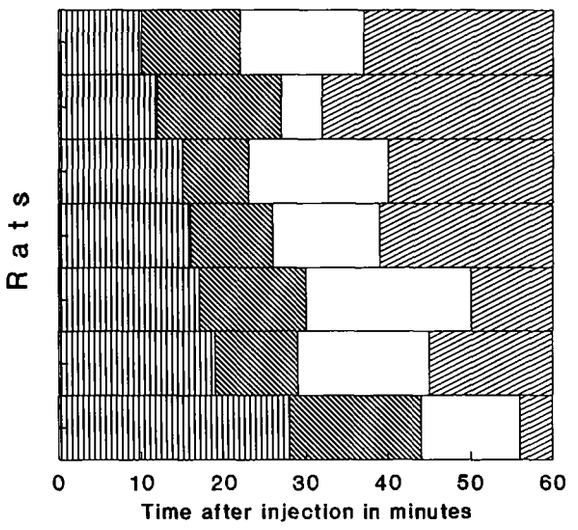

FIG. 2 Partitioning of the 1-hour sessions of rat locomotor behavior under 5 mg/kg amphetamine into 4 successive morphological stages Note that the same stages appear in all of the rats in the same order

repertoire, the rat was video recorded from a ventral view which provided maximal information on horizontal trunk movements and stepping. Trunk movements were described in relation to horizontal circular coordinate systems which represent the equatorial plane of the EW sphere A movement is defined as a change of relation between a part of the trunk and its adjacent caudal part.

Forward progression is defined as locomotion involving forward stepping of hindlegs. The method of description of the direction of foreleg stepping in relation to the contralateral foot or in relation to the head's surface [relationship of "opposition" in EW (19)] is provided in the Results section.

The method of filming and of data acquisition is described in (7) Data were collected from video records, using stop-frame analysis. Statistical methods are described in (1,2) Results are given in percentage points (standard errors in parentheses).

LOCOMOTOR BEHAVIOR UNDER AMPHETAMINE THE ORGANIZATION OF MOVEMENT IN BODY-RELATED SPACE

The following analysis of trunk movements includes two parts In the first part, rat amphetamine (AMPH)-induced behavior across the 1-hour session is partitioned into successive stages In the second part, the borderlines between these stages are used as "landmarks," to guide the reader in the partitioning of behavior into spatial component-variables whose superposition on each other generates the composite behavior of all the examined animals across time

A partitioning of rat AMPH-induced behavior into successive stages determined by time is not useful, because changes in behavior occur across rats at variable times after the onset of drug action. In contrast, partitioning into successive stages determined by behavioral criteria provides a structure shared by all rats As shown in Fig. 2 the behavior of each of the AMPH-treated rats could be partitioned into 4 successive stages.

Stage 1. Characterized by an alternation between periods of continuous movement and periods of complete arrest of all the parts of the body (for at least 1 s). During this stage the rats alternate between horizontal, forward, and vertical movements.

Stage 2. Characterized by long bouts of forward progression which dominate the rat's behavior. Starts immediately after last arrest and ends at onset of rhythmic horizontal (lateral, side-to-side) movements

Stage 3 Characterized by forward progression with simultaneous rhythmic side-to-side movements of the parts of the trunk. Starts with onset of continuous rhythmic side-to-side horizontal movements and ends with termination of forward progression.

Stage 4: Characterized by absence of forward and presence of sideways and backward stepping of hindlegs. Starts with termination of forward progression. Consists of rhythmic horizontal movements

While the duration of each of the stages is highly variable across rats, the stages and their order of appearance are common to all (Fig 2).

SPATIOTEMPORAL ORGANIZATION OF TRUNK MOVEMENTS

In the course of the session there is first an exaggeration and a subsequent elimination of vertical movements, then an exaggeration and a subsequent elimination of forward movements, and finally an exaggeration of horizontal movements (1,6). In what follows we will focus on the transition from forward to horizontal movement. This transition takes place during the last 3 stages represented in Fig. 2.

During the stage of exaggerated forward progression (2nd stage, Fig 2) the rat mostly progresses along straight paths (Fig 3I). Horizontal movements of the anterior parts of the trunk are performed only during staying in place or during turning in place in a new direction. Toward the end of this stage the rat's head

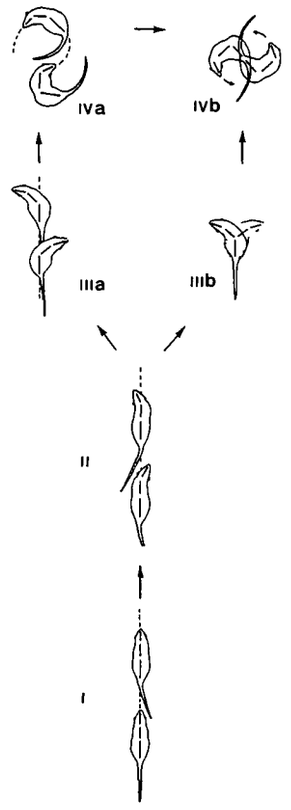

FIG 3 A schematic illustration of the superposition of rhythmic horizontal trunk movements on pure forward progression under 5 mg/kg amphetamine Uninterrupted lines represent the parts of the trunk Interrupted lines represent the path traced in the environment during progression. Roman numerals designate the composite locomotor patterns observed, and their order of performance in the course of drug action. In the sequence illustrated in (a), forward progression is eliminated after the onset of horizontal lower torso movements In (b), before the onset of forward progression Note that both sequences end in IVb

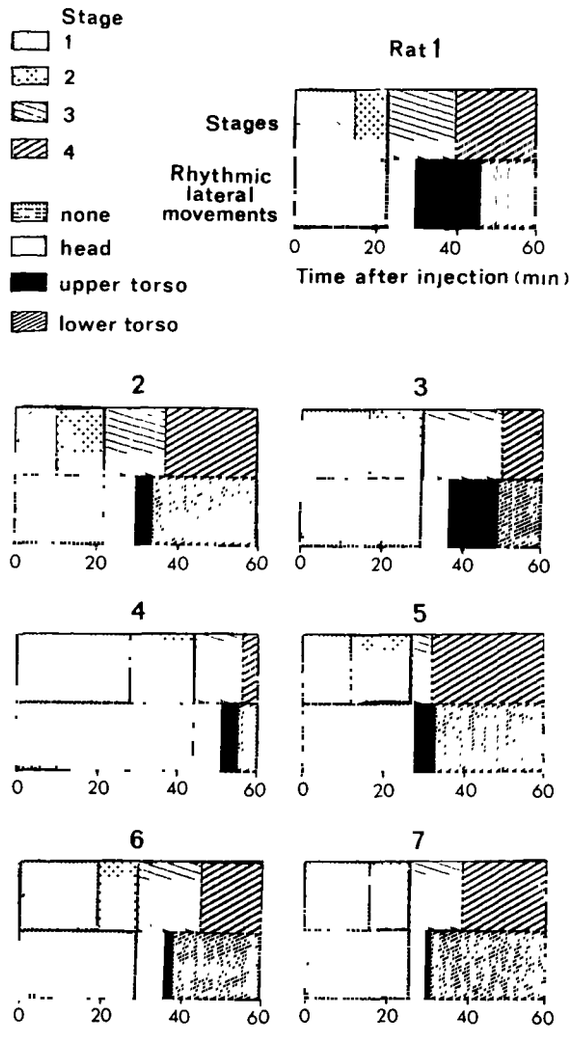

FIG. 4 Timing of onset of rhythmic horizontal head, upper torso, and lower torso movements in relation to the 4 stages defined in Fig 2, in individual rats Upper horizontal row repeats the partitioning presented in Fig 2 Lower row represents timing of onset of rhythmic horizontal movements in the course of the hour Note timing of end of forward progression (end of stage 3, upper row), in relation to onset of lower torso movements (beginning of stage 3, lower row)

starts to perform sporadic horizontal movements on the upper torso, also during forward progression. These movements increase in frequency until they become rhythmic and continuous. The time of onset of continuous rhythmic movements is defined as the onset of stage 3. In the course of stages 3 and 4 the rhythmic horizontal movements increase in amplitude, gradually recruiting the parts of the trunk in a cephalocaudal order. Horizontal head movements first set in without recruiting the upper torso (Fig. 3II). Upper torso horizontal movements are then recruited by the head movements, without recruiting the lower torso (Fig. 3III). Finally, the lower torso is recruited as well (Fig 3IV). The caudal parts of the trunk are constrained during stages II–III from performing horizontal movements during progression from one place of stopping to another. While the anterior part(s) performs side to side movements, the hind part(s) traces a straight path in the environment.

In some rats (rats 1, 5), forward progression is eliminated before side-to-side horizontal lower torso movements set in (Fig. 4). Such rats first perform side-to-side upper torso and head movements while staying in place (Fig. 3IIIb), and then pivot in alternating directions in place (Fig. 3IVb). In other rats (rats 2, 3, 4, 6, 7), forward progression is eliminated after the onset of horizontal lower torso movements (Fig 4). Such rats first show superposition of whole body horizontal movement on forward progression, i e., progression along curved paths (Fig. 3IVa), and only then pivoting in place (Fig. 3IVb).

A representation of AMPH-induced behavior in terms of whole-animal-one-category-at-a-time sequences would suggest that different rats behave differently under this drug. While some rats show the sequence of composite patterns of locomotion illustrated in Fig. 3IIIb and IVb, others show the sequence illustrated in IIIa, IVa, and IVb. In contrast, a representation of the same behavior in terms of only 2 continuous kinematic quantities (component-variables) reveals that all rats show the same behavior, the two different sequences merely reflect the different timing of elimination of forward progression in relation to the onset

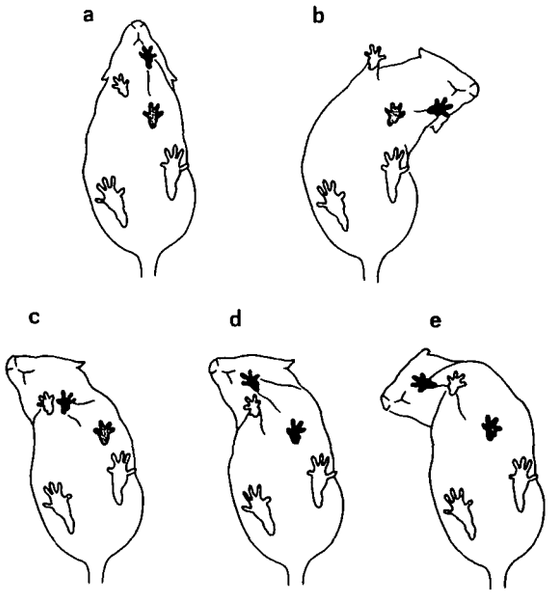

FIG 5. Types of foreleg stepping observed in rats. Figure illustrates bottom view of rat. Grey paw represents paw location just before stepping, and black paw represents paw location at the moment of landing. Note relationship between paws at the time of landing (a) forward step, (b) open step, (c) regular closing step, (d) forepaw crossing step, (e) forearm crossing step

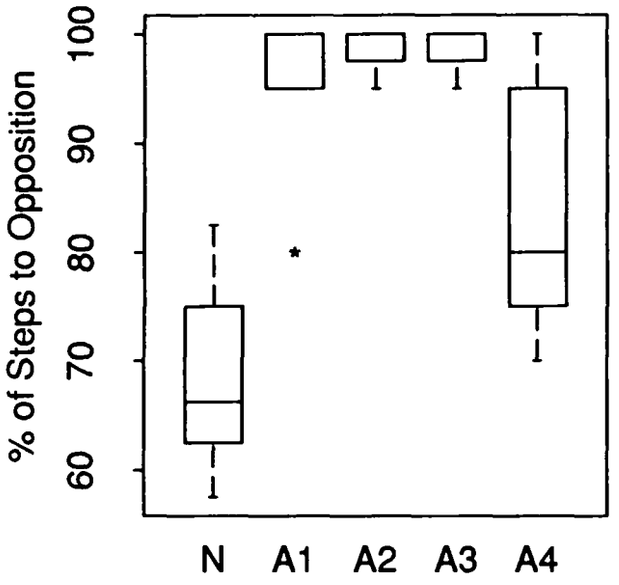

FIG 6. Side-by-side boxplot displays show the distribution of the average percentages of foreleg steps to opposition-with-head, in individual normal (N) and AMPH-treated rats during the 4 stages (A1–A4) of drug action. The boxplot displays graphically numerical summaries of groups of observations The box is plotted by drawing its bottom and top at the 25% and 75% percentiles respectively, the box is cut by a line in the median, two whiskers extend from the box to the furthest observations that are still no more than two box lengths away from the sides of the box, observations outside this range are plotted individually Each data point in the normal group represents the average percentage of a total of 40 steps, collected in 5-min intervals, 10 steps per interval, in the session of 1 normal rat, n = 7 Each data point in each stage of the AMPH-treated rats represents the average percentage of a total of 20 successive steps collected from the middle of each stage of drug action, in the session of 1 drugged rat; n = 7 The boxplot displays show a large increase in the percentage of steps to opposition (compared to normal) during the first 3 stages, and a decrease in the 4th stage

of lower torso horizontal movements. A continuous decrease in amplitude in one kinematic variable (forward progression) and a concomitant increase in another (horizontal movement) thus generate all the composite patterns of locomotion observed from the second stage of drug action and on, in all rats.

The same kinematic variables are subjected to similar (but not identical) transformations under the influence of the direct dopamine agonist apomorphine (APO) (18), and to the opposite transformations, in recovery from brain damage (12) and in ontogeny (7). The universal applicability of these spatial variables and transformations suggests that they represent distinct, presumably controlled, kinematic quantities. It might be possible, therefore, to reduce them smoothly to corresponding neurophysiological control mechanisms

RELATIONSHIP BETWEEN TRUNK MOVEMENTS AND FORELEG-STEPPING PATTERNS

In the following section we illustrate how even the use of clearly and precisely defined categories of movement might not be sufficient if one looks for controlled kinematic quantities which are influenced by a specific drug.

Figure 5 illustrates five types of foreleg steps observed in rats. The type of a step is defined in terms of the relationship observed between the two forepaws during landing of a stepping leg. In (a), the stepping leg landed forward and ahead of the contralateral foreleg (forward step). In (b), the forepaw stepped away from the contralateral forepaw and landed sideways and away from it (open step). (c), (d), and (e) illustrate closing steps In all of them, the stepping leg stepped toward the contralateral paw, landing, in (c), near and besides the contralateral paw (regular-closing step), in (d), ahead and across the contralateral paw (forepaw-crossing step), and in (e), ahead and across with forearm crossing (forearm-crossing step).

A study entitled "Evidence that apomorphine and (+)-amphetamine produce different types of circling in rats" compared stepping patterns under the two drugs (3). It has been shown that under AMPH rats often perform forearm-crossing steps, whereas under APO they perform regular-closing steps and less frequently, forepaw-crossing steps, but hardly ever a forearm-crossing step. This has been used to argue that the two drugs produce their drug-specific circling via different substrates in the brain, which in turn influence different parts of the body. The classification of foreleg stepping thus proved useful in demonstrating a clear-cut difference in the form of stepping under the two drugs. But does it reflect a physiological reality, in the sense that there should be particulate neurophysiological mechanisms or processes which correspond on a one to one basis to the various types of stepping? This question is examined in the next few paragraphs.

In the above described analysis, the stepping of one foreleg was described in relation to a coordinate system schematically centered at the contralateral forepaw. Another option available in EW is to describe stepping in relation to a coordinate system schematically attached to the surface of the animal's own body. When stepping is described in relation to such a coordinate system attached to the surface of the rat's head, it immediately be-

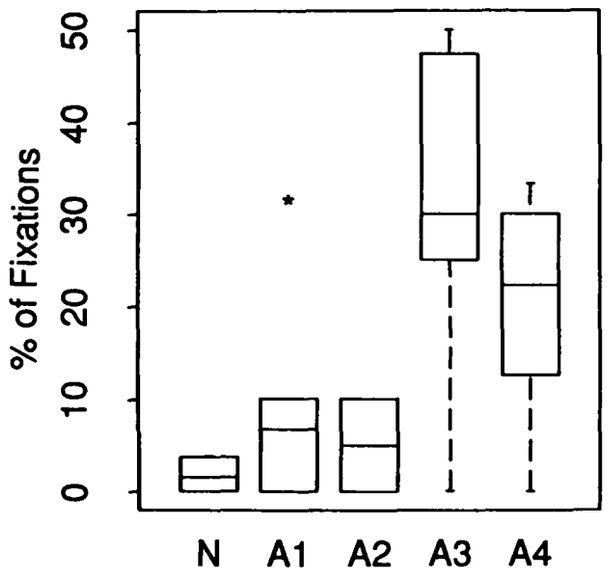

FIG 7 Side-by-side boxplot displays show the distribution of the average percentages of steps to opposition including active maintenance (fixation) of opposition in normal, and in AMPH-treated rats, during the 4 stages of drug action. Each data point represents the average percentage of steps including a fixation, out of the total number of steps to opposition collected in each of the samples described in the legend for Fig 6 (Normal rats· n=7, sample of 40 steps per rat, AMPH rats: n=7, sample of 20 steps per stage per rat). Note the large increase in the percentage of steps including a fixation during the 3rd stage of AMPH action, compared to the normal

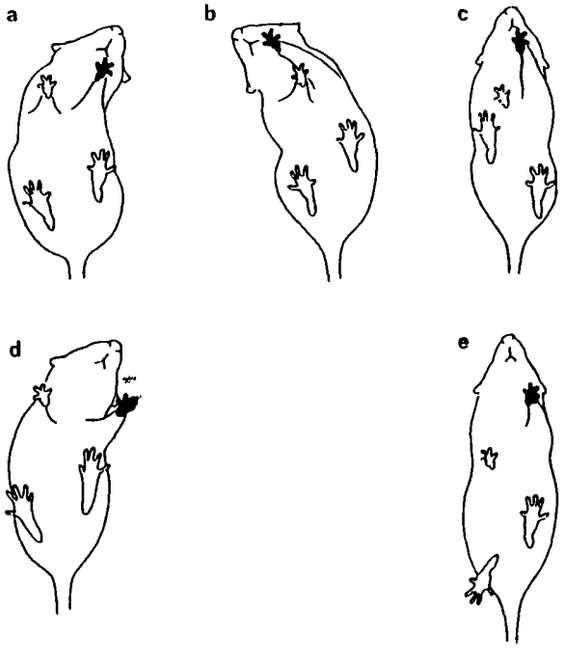

FIG. 8. Relationship between forepaw and head at the moment of landing of the paw Upper horizontal row under amphetamine, Lower row under apomorphine Dark paw indicates paw location at moment of landing. Under amphetamine paw always lands in opposition to same topographical position on head surface (when viewed from below, between mouth and ear) This generates open (a), forearm crossing (b), and forward (c) steps Under apomorphine, during turning, inside paw (in relation to turning direction) typically lands outside contours of head (lower left) During forward progression forepaw lands inside head contours (lower right).

comes evident that under AMPH the forelegs almost always land in opposition to a particular location on the ventral surface of the rat's head (along midsagittal plane of head, on the ipsilateral side of the stepping leg, between mouth and ear). As shown in Fig. 6, this relationship is established in almost all of the steps during the first 3 stages of drug action [mean during 1st stage—96.4% (2.8%), 2nd—98.6% (0.9%), 3rd—98.6% (0.9%)] with a decrease during the fourth stage. Normal rats establish this relationship in only 68.3% (3.7%) of the steps, and often land in opposition to other body surfaces: the neck, the midsagittal plane of the head, and outside and beside the head contours.

Under amphetamine, the particular paw-to-head opposition is achieved during the swing phase of the stepping leg. During the first and second stages of AMPH action (as defined in Fig. 2), the foot lands as soon as it achieves this relationship. Starting with the onset of rhythmic side-to-side head movements (stage 3), however, this relationship may be first achieved and then maintained actively through coordinated movements of head, upper arm, and lower arm, until the time of landing. Such active maintenance of paw-to-head opposition, termed fixation of opposition in EW, is common during the third stage of AMPH action [mean—29.6% (6 3)] and rare in normal rats [1.8% (0.8%)] (Fig. 7).

The larger the amplitude of head movement becomes, the longer the period of active maintenance of the paw-to-head opposition. If the head is positioned in the midsagittal plane of the upper torso during landing, a forward step ensues (Fig. 8c); if the head is positioned in the ipsilateral hemisphere of the stepping leg, an open step follows (Fig. 8a); and if the head is positioned in the contralateral hemisphere of the stepping leg at the moment of landing, a crossing step ensues (Fig. 8b). During the third stage of drug action, for instance, rats perform an average of 35% (2.8%) forward, 26% (2 6%) open, 3.5% (1.1%) regular closing, 22% (2.4%) paw crossing, and 13.6 (2%) forearm crossing steps. These steps [92.8% (1.5%)], however, are steps to opposition with head (based on 40 successive steps sampled from middle of third stage in each of 7 rats). In other words, a variety of step types are employed, in what appears to be a random order, so as to achieve an invariant opposition of the paw with the head (which performs all the while relatively regular side-to-side movements). This state of affairs can be best represented by the more economical description of stepping to opposition with the head. Furthermore, the actively maintained invariance of opposition suggests control, i.e., an internal organization that acts so as to achieve and maintain a preselected perceptual state (16). The answer to the question posed earlier—is there a physiological reality to step types—is, therefore, that a representation in terms of steps-to-opposition with head is more likely to have a physiological reality than a representation in terms of a variety of step types performed in no apparent order. The large forearm-crossing steps observed under AMPH and reported in (3) thus seem to be a mere by-product of the large amplitude lateral head movements. These large amplitude movements highlight an endogenous perceptual reference which is not as conspicuous during the earlier 2 stages of AMPH action, when forward locomotion is not accompanied by rhythmic lat-

eral head movement (Fig. 7).

In contrast, during turning under APO, the inside foreleg, i.e., the foreleg which is ipsilateral to the direction of turning, typically lands outside of the head contours (unpublished results; Fig. 8d). Thus, whereas under AMPH the forelegs always perform catching up steps with the head, under APO they perform both catching up (Fig. 8e), and reaching out steps.

Finally, in (3), the different foreleg stepping patterns were used as evidence that the two drugs produce in rats different types of circling. But is "circling" under amphetamine a morphogenetic unit in its own right or is it a by-product of the superposition of more fundamental component variables? Examination of the literature shows that the behaviors lumped together under the category "AMPH-induced circling" are comprised of unidirectional progression along the edge of the testing environment, turning in circles, and pivoting in place (11,13). This category might therefore provide a useful measure of drug-induced laterality. From a morphological point of view, however, it lumps together pure forward progression, pure lower torso horizontal movement (pivoting), and progression along curved paths (turning in circles). The last behavior is itself a composite locomotor pattern generated by the superposition of forward progression and lateral lower torso movement Under amphetamine, progression along curved paths is observed only in rats whose forward progression has been eliminated after the onset of lateral lower torso movements (Fig. 3IVa, Fig 4). It is observed, if at all, at a late stage of amphetamine's action. Thus, if the term circling is to be interpreted *sensu strictu* as progression along curved paths, then under AMPH genuine circling is a mere by-product of the superposition, observed in some of the rats, of two component-variables Also under APO (1.25 mg/kg SC) circling is generated by a superposition of horizontal whole-trunk movements on forward progression (18), but there, it appears at an early stage of drug action, at a time when all rats possess these two component-variables. Therefore, under APO it is generated in all rats.

CONCLUSION

The use of ad hoc response categories such as "enhanced locomotion," "stereotypy," and "circling" is a useful first approximation description of drug action, but it obscures fundamental structural differences between the behavioral effects of different drugs. The use of precisely defined categories such as, e.g., forward, closing, and crossing steps, may reveal differences in drug effects, but it may also obscure the organizing principles of behavior. In contrast, when rat drug-induced behavior is described in terms of established kinematic quantities—variability disappears at a given level, without being ignored at another level. Furthermore, the observer becomes sensitized to the variety of composite patterns performed at this other level. Kinematic regularity suggests some form of control, i.e., a correspondence with a neurophysiological mechanism designed to achieve and maintain it. In particular, invariant kinematic quantities indicate that there should be corresponding control systems that act to achieve and maintain them. A description based on kinematics is therefore more relevant to the assessment of brain-behavior relations than a description based on ad hoc discrete response categories.

ACKNOWLEDGEMENT

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