

THE MORPHOGENESIS OF STEREOTYPED BEHAVIOR INDUCED BY THE DOPAMINE RECEPTOR AGONIST APOMORPHINE IN THE LABORATORY RAT

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Abstract—The seemingly unrelated stereotyped locomotor “acts” reported in the literature to be produced by apomorphine in rats are shown to be composites, whose form and sequence are determined by the particular values of a few component variables which form a common denominator in each of the behaviors. Three variables, continuous snout contact, forward progression and turning, account for much of the behavior. In the course of the drug’s action these emerge in succession and vary in amount, the latter two successively reaching a peak and subsiding. The interaction between forward progression and turning yields in sequence, forward walking, circling, revolving, tight pivoting and finally side-to-side movements of the forequarters around the relatively stationary hindquarters. Later behaviors in this list are gradually incorporated into the sequence as earlier ones are eliminated. The course of change in forward progression and turning is also reflected in changes in the sequence and in the direction of stepping of each of the four legs.

The order in which the behavior unfolds under the drug is opposite to that manifested in ontogeny and in recovery from lateral hypothalamic damage, suggesting that at the particular high dose used, apomorphine is acting not only to activate the behavior but also to shut it down.

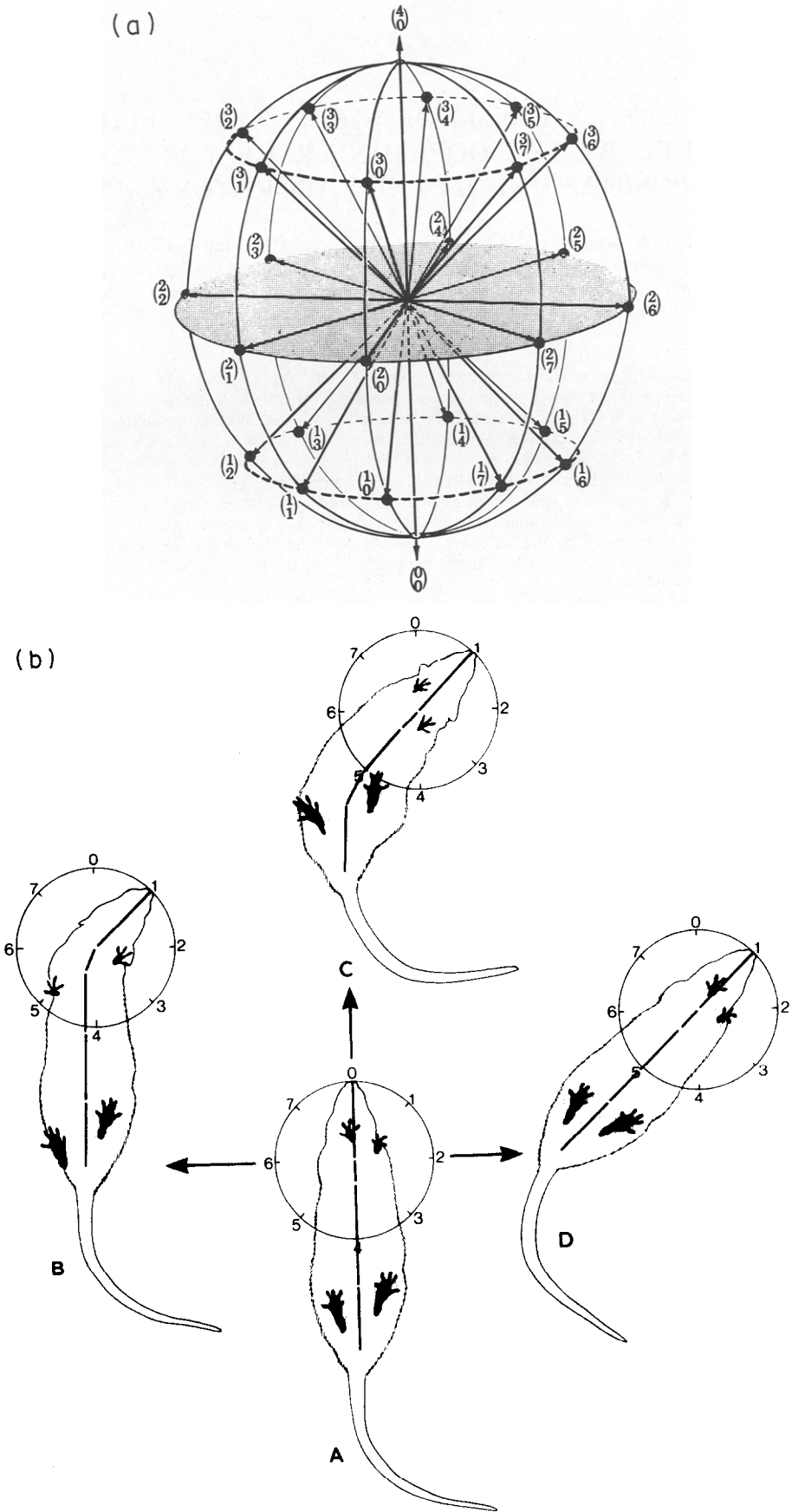
Apomorphine- and amphetamine-induced behavior is usually described in terms of seemingly disconnected fragmentary acts, such as sniffing, licking or biting,⁵ chewing,^{2,19} verticalization,⁴¹ rearing,⁶ head-down,¹³ repetitive head and limb movements,³⁴ head-bobbing,³³ side-to-side head movements,^{38,42} checking,²⁹ forward locomotion, circling^{20,21} and rotating.³² By using the Eshkol-Wachman Movement Notation^{10,11} to analyse apomorphine-induced behavior in rats, in this study we attempt to isolate a few common component variables whose interaction might explain the structure and the sequence of appearance of several of the apparently unrelated acts described by earlier workers. Such factors may relate more meaningfully than behavioral “acts” to corresponding neurochemical systems that may be activated by the drug.

EXPERIMENTAL PROCEDURES

In our previous studies on ontogeny and neurological recovery,^{15,16} it was demonstrated that exploratory locomotion in an open field is based upon specific components of movement. To reveal those components it was necessary to observe the rat in as simple an environment as possible. In the study of drug-induced stereotypies as well, the structure of the environment can potentiate different components of the behavior.^{3,4,8,22,23,26,30} To minimize such environmental molding, particularly with respect to rearing with snout contact along walls,³⁷ nose-poking and biting, and to

allow the animal to display more clearly the paths of locomotion induced by the drug, the following procedure was employed. Immediately after a s.c. neck injection of 1.25 mg/kg apomorphine hydrochloride dissolved in a solution made up of 0.9% saline and 0.1% ascorbic acid, each male rat was placed individually on the surface of a flat glass table (100 × 140 and 150 cm high). Thirteen naive Wistar male albino rats (Dept. of Animal Breeding, Weizmann Institute of Science, Rehovot, Israel) weighing 300–350 g were used. Seven of them were injected with apomorphine and six were used as controls. Two other rats that were used (rats E1 and E2) were male albino Sprague-Dawley rats (Canadian Breeding Farms) and weighed 490 and 570 g, respectively. The animals were grouped and housed with free food and water in a colony room with lights on from 05:00 to 19:00 h. and were tested during the light portion of the cycle. Each rat was experimentally naive and was tested once. The table on which the rats were tested was situated in the middle of the room away from any walls and had no objects on it. A large mirror was placed underneath the table tilted at 45° to it to allow filming and videotaping of a bottom view of the animal. This view allows an accurate evaluation of the horizontal orientation of the pelvis, torso, head and neck, and the direction of stepping of all four legs. To provide sufficient illumination for filming, photographic lights were used (room lights were adequate for videotaping). The kind of lighting used made no observable difference in the behavior induced by the drug. The film was taken at 24 or 16 frames/s. At various times after placing the rat in the open field, its behavior was filmed for 20–240 s. The filming was initiated when there was an observable change in the rat’s behavior. When recorded on videotape, the rat’s behavior was monitored continuously from the moment it was placed in the open field until the end of the session. Films of three rats were analysed frame by frame using Eshkol-Wachman Movement Notation. Six control rats were also studied using the same procedure (four on film, two on videotape). After this analysis was completed, 50 additional rats, also injected with apomorphine, were observed in order to verify the regularities isolated by

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movement notation analysis. Additional, less systematic, observations were made in other environments. The changes that rearing-along-walls undergoes under the drug were studied in a small enclosure of high smooth Plexiglas walls (10 × 13 × 35 cm). The effect of nose-poking and biting on the paths traced by the animal during drug-induced exploration were studied by placing the animal on a large (140 × 60 cm) wire mesh.

Descriptive method

Eshkol-Wachman Movement Notation* is designed to express the relations and changes of relation between the parts of the body, and information which can be derived from these. A part of the body is any limb which either lies between two joints or has a joint and a free extremity (in Eshkol-Wachman Movement Notation the word limb applies not only to the appendages but to any part of the body). The vertebrate's limbs are imagined as straight lines (axes); in the analysis of movement, we treat the body as a system of articulated axes. A horizontally ruled page represents the body (see Fig. 6). The spaces between the lines are assigned to the parts of the body (limbs) whose movements are to be represented. Vertical lines divide the manuscript system into columns denoting units of time and the symbols are written in order, from left to right. The system of reference used in Eshkol-Wachman Movement Notation is a sphere: the movements of a single axis of constant length free to move about one (fixed) end will all be enclosed in a sphere. Every limb in the body can be regarded as such an axis. Typically the curves described on the surface of the sphere will be circles or parts of circles, of various sizes and orientations. In order to define these curves, co-ordinates are ascribed to the sphere (Fig. 1a). The equatorial plane of the sphere of movement parallel to the ground is called the horizontal plane. One direction on it is selected as the starting position for all measurements, and called "absolute zero" (0). Other positions on the horizontal plane are defined in relation to this absolute zero. An easily perceptible unit of measurement is chosen, for example $1 = 45^\circ$. By measuring off intervals of 45° , eight positions are obtained on the horizontal plane (see Fig. 1a). These are numbered in the clockwise direction. The unit of measurement being used may be further divided into a half unit (+), one third unit (÷) or two thirds of a unit (\neq).

Vertical planes are perpendicular to the horizontal plane, and are identifiable inasmuch as they intersect with posi-

tions which result from the division of the horizontal plane. Each vertical plane is divided according to the same scale as the horizontal plane. The network of co-ordinates dividing the surface of the sphere is thus constructed (like the geographical globe) from an intersecting net of "lines of longitude" (vertical circles) and "lines of latitude" (horizontal circles), the intersections of which are the points of the co-ordinate network.

Any position of the moving axis (pivoting at the centre of its own, individual sphere of movement) can now be defined by stating (i) the horizontal component, the number designating the plane on which it lies; and (ii) the vertical component, a number indicating its degree on this vertical plane. The two numbers are written in parentheses, the vertical component above, and the horizontal component below; for example ($\hat{6}$) (see Fig. 1a).

The positions and movements of each part (limb) of the body are related to a system of reference centred upon the joint about which the part moves. These individual systems of reference are parallel to one another at all times.

There are three types of movement: rotatory, in which the axis of the limb coincides with the axis of movement; plane movement, in which the angle between these axes is 90° ; and conical movement, in which the angle is between 0 and 90° .

The limbs of the moving body are characterized as active or carried. An actively moving limb is called "heavy", its movements change the location and modify the paths of movement of any "lighter" limb which it carries. The centre of each individual sphere is made to coincide with the articulation of the limb with its heavy neighbour, so that the position is established as the line from the joint "outwards". In walking in quadrupeds, we consider the pelvis as the heaviest limb of the trunk, the chest as lighter, and the head as the lightest limb. The position of these limbs are therefore established in a cephalad direction. Each limb's movement is written as though in isolation, in relation to an immobile heavy neighbouring limb. But the path of this movement will actually be modified as a result of the fact that its heavy neighbour moves as well.

The orientation of the body as a whole in relation to the absolute horizontal plane is described in the lowest horizontal space on the manuscript page labelled Front. When the pelvis, chest and head combine in lateral horizontal movement (the lighter limbs either moving actively or being carried) and the result is a turn of the whole body, this may be written as a rotatory movement in the Front space. Walking in a circle may also be notated in the Front space (see Fig. 6).

In "bodywise" writing, the movement of a limb is notated in relation only to the adjacent heavy limb, whatever the

*The description of the notation is mostly based on excerpts from Eshkol (1978).¹⁰

Fig. 1(a). The Eshkol-Wachman Movement Notation Sphere. (b) Bottom views of a rat as observed through a glass floor in a 45° -tilted mirror with superimposed longitudinal axes (straight lines) of the pelvis, lower torso, chest, neck and head. In the example, (A) represents the initial position of the rat, in which all its trunk segments, including the head, are aligned in the same horizontal direction of absolute zero (0). In the represented transitions from (A) to (B), (A) to (C) and (A) to (D), the rat always displaces its head angularly clockwise for one amount of movement ($1 = 45^\circ$), in relation to the absolute frame of reference but achieves this using different combinations of movements. The individual horizontal plane of the head is centered upon the joint between the neck and the head, so that the head's direction is read from this joint to the coordinate on which it lies. The direction of all the other trunk segments is also read from their caudal joint, rostrally. The co-ordinates on the horizontal plane are parallel to one another at all times. Even when the head is carried by the movement of another part, its system of reference is considered to be moving together with it. In the transition from (A) to (B), a horizontal angular displacement of one amount is accomplished through a combination of movements of the neck on the chest and of the head on the neck, in the same direction. In the transition from (A) to (C), the same angular displacement of one amount clockwise is accomplished through a combination of movements of the lower torso on the pelvis and of the chest on the lower torso in the same direction; the neck and the head are merely carried along. In the transition from (A) to (D), the same angular displacement of the head of one amount clockwise is obtained through a clockwise movement of the pelvis which carries along all the more rostral segments including the head to absolute position (1).

position of the latter. Whatever the position of the heavy limb, it now serves as zero position (bodywise). For example, the direction of stepping of a hindleg is notated in the present study in relation to the direction of the axis of the pelvis.

In the present study, in order to summarize the effect of the active movements of all the segments of the trunk, including the head, on the head's change of position in the horizontal plane, we notated the head's lateral angular displacement separately, regardless of whether it moved actively or was carried on the more caudal, heavier limbs (Fig. 1b). This aspect was notated in addition to the notation of the movements of the pelvis, chest and head, and is therefore, in a sense, redundant.

Finally, we notated the direction of individual steps of all four legs. Because the rats were filmed from below, the direction of a step was determined by assessing the angle between the longitudinal axis of the chest or pelvis and the imaginary line traced by the fore and hind paw, respectively, during their swing phase. This variable yields "bodywise" directions: forward ([0]S), diagonally forward ([1]S; [7]S), sideways ([2]S; [6]S) and backward steps ([4]S). A step was notated as such whenever it involved release of foot-contact, a shift of weight in the direction of stepping and re-establishment of contact. The shift of weight was inferred from the movements of the trunk segments.

The presence and absence of "loose" sliding contact of the snout with the glass floor was recorded continuously throughout the observation period. Release of snout contact, face grooming and then body grooming determined the end of the observation period, because after their occurrence the animal settled down and became quiet.

RESULTS

When placed for the first time in an open field away from walls, a normal rat explores the new environment for a few minutes at most (range, 100–160 s; $n = 6$), then settles down, grooms its face and body (Table 1, latency to groom) and remains stationary for some time (range, 3–60 min; $n = 6$). Five of the six control rats showed only one such activity-arrest cycle, remaining stationary for the rest of the hour. The sixth rat exhibited two such cycles with a 3-min stationary period between them and then finally also settled down for the remainder of the hour. In contrast, apomorphine-treated rats were active incessantly for at least an hour before they finally groomed and settled down (Table 1, latency to groom).

For the first 2 min or so after an injection of

apomorphine, the rat behaves much the same as normal, pivoting around its hindquarters, walking forward a few steps at a time, rearing and pausing. Then its behavior changes markedly. Loose sliding snout contact with the ground is established and not released, often for periods as long as 1 h (Table 1, duration of snout contact; for dose-response data see Ref. 37). Head raising and rearing, which involve release of snout contact with surfaces, are abolished. From now on, until the effect of the drug appears to wear off, whatever the animal does, be it walking, gnawing, licking or sniffing, involves the maintenance of snout contact. Concomitantly, the behavior undergoes the following transformations. In brief, during the early action of the drug forward walking predominates, to the virtually complete exclusion of movement along other dimensions. The effect is so powerful that some animals do not stop or change direction as a normal animal would, but instead continue on over the edge following the surface with their snout and attempting to maintain snout contact even with the underside of the table, before falling to the ground. Later lateral movement appears, involving sideways angular displacement away from the midline longitudinal axis of the body. As lateral movement increases in amplitude, the forward movement diminishes and ultimately disappears. At this time the rat pivots in place around one hindleg. Eventually even lateral movement diminishes and the rat's hindquarters become relatively immobile. In the course of this process the area covered by the moving animal first reaches a peak encompassing the whole field and then subsides to include only the area around the relatively immobile rat. After an hour or so, as the effect of the drug presumably starts to wear off, forward progression gradually reappears with its associated stepping patterns and the area covered by the moving animal gradually expands. In what follows the changes in each of these variables will be described in detail.

Forward progression

The amount of forward progression, as measured by the number of forward steps/15 s interval taken by

Table 1. Latency to groom and duration of snout contact during exploratory activity of normal and apomorphine-injected rats

Rat	Control		Rat	Apomorphine (1.25 mg/kg)	
	Latency to groom (s)	Duration of snout contact (s)		Latency to groom (s)	Duration of snout contact (s)
N2	160	43	B3	> 3600	3600
N3	150	70	A1	> 3600	3480
N4	100	70	A2	> 3600	2760
N5	120	60	D4	> 3600	3660
D2	150	—	D5	> 4800	4140
D3	160	—	D1	> 3600	3480
			B1	> 4800	4500
			E1	> 4200	3910
			E2	> 4800	3830
Mean	137			> 3940	3660

—, data not obtained.

LONGITUDINAL AND LATERAL MOVEMENTS

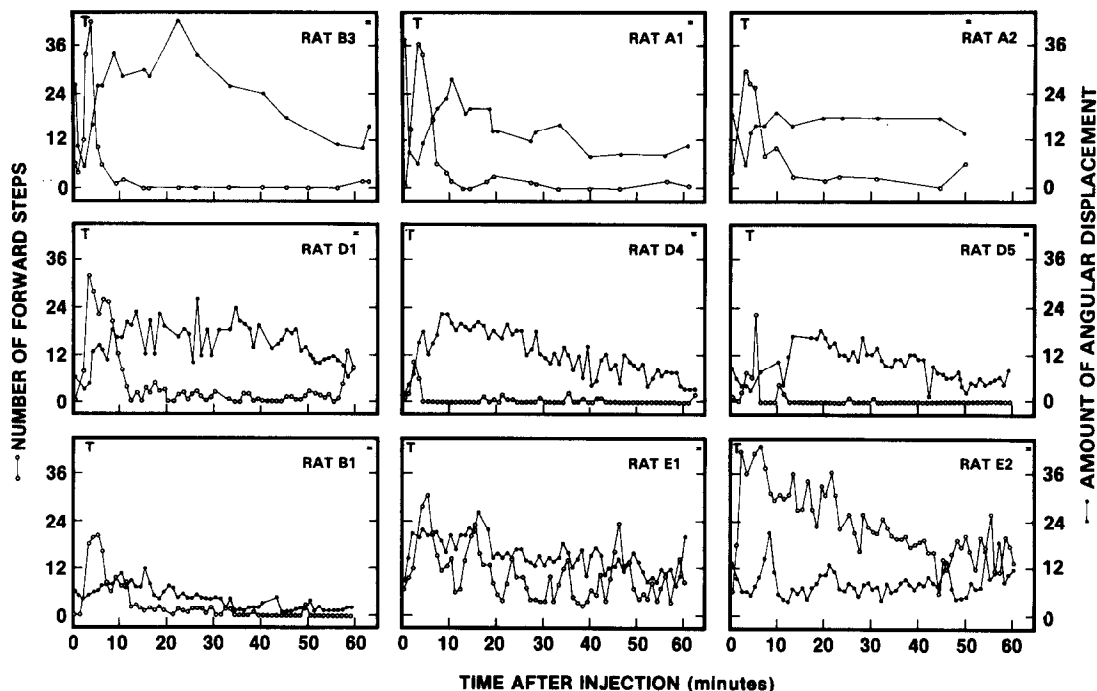


Fig. 2. Time course of forward progression and of lateral angular displacement of the head in individual rats injected with 1.25 mg/kg of apomorphine. Forward progression was measured in terms of forward steps. Lateral angular displacement was measured in units of 45° ($1 = 45^\circ$). For animals B3, A1 and A2 (top row) only selected portions of their behavior were filmed and then notated. Data were obtained from these notation scores; each graph point corresponds to 15 s of activity. For the remaining rats data were obtained from continuous video records of the rat's behavior; these graphs provide a complete summary of the animals' activity. For each component every data point represents the value in the minute interval at the indicated time—the score was divided by four to correspond to the 15 s intervals employed for the animals in the top row. In this and in all subsequent graphs, the position of the sign "T" indicates the time at which uninterrupted snout contact was established, and the position of the sign "=", the time at which snout contact was released. If snout contact was released after 65 min, the release sign (=) was positioned at the extreme right of the graph.

the animal's hindlegs (steps "to opposition" excluded), increases rapidly to a high level within the first few minutes and then decreases to an extremely low level, or is completely eliminated for most of the observation period (Fig. 2).

The total distance per time interval traversed during forward progression is a function of the frequency and the length of the individual paths of forward progression per time interval. Therefore another measure of the change in the amount of forward progression can be the length of the individual forward paths. To reveal the overall change along this variable, only the maximal individual path in each time interval was plotted (see Fig. 3, top panels); the initial rise and subsequent elimination of forward progression is also characterized in the amplitude of such maximal individual forward paths.

It should be noted that during forward progression the rat may occasionally veer off the straight path by as much as half an amount of movement ($45/2^\circ$). Veering during forward progression can be initiated by small lateral movements of the forequarters and

subsequent alignment of the hindquarters, or by small lateral bending of the torso followed by alignment of the forequarters with the new orientation of the hindquarters in the environment. Also large amplitudes of lateral angular displacement are observed at the corners and edges of the table. The straight paths are not a side effect of walking along the edges, appearing also as the animal crosses the open field. In some animals, diagonal forward progression, consisting of the maintenance of a fixed orientation of the rat's longitudinal axis, while at the same time progressing both sideways and forward, is observed at this stage. This form of progression is occasionally seen along the table's edge but may also occur in the open field.

Lateral angular displacement

As soon as continuous snout contact with the floor is established, large lateral angular displacements of the head (more than half an amount of movement) disappear for a brief period, leaving—when uninterrupted by corners and edges—only pure forward

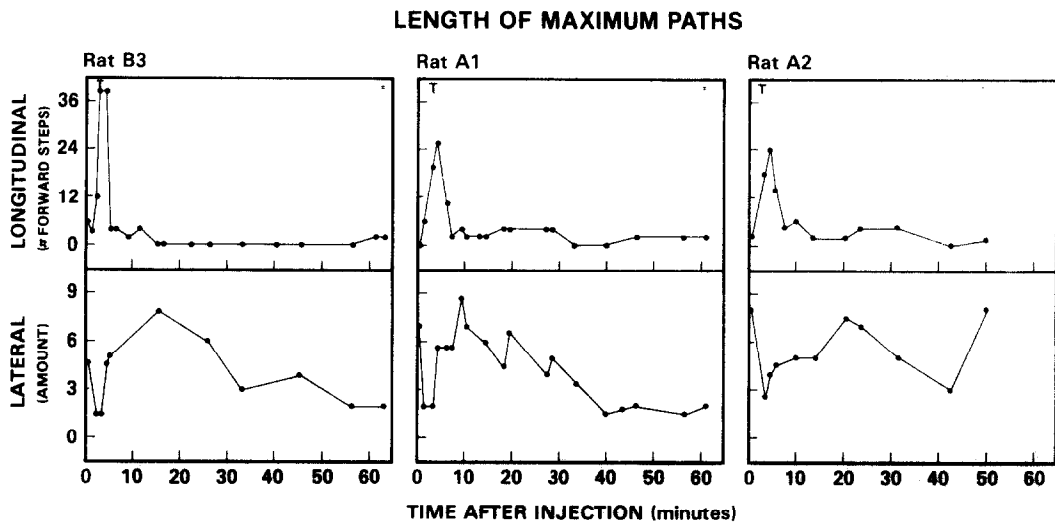


Fig. 3. Growth and decline in the size of maximal individual paths of forward progression and of lateral angular displacements performed during successive 15 s intervals during the course of apomorphine's action. The size of an individual forward path is expressed in terms of the number of consecutive forward hindleg steps the animal takes before it stops; the size of an individual angular displacement ($1 = 45^\circ$) is measured from the moment the head starts to turn until it stops or reverses the direction of turning.

progression. Next, lateral angular displacements reappear, rapidly increasing in their total amount, reaching an exaggerated maximum and finally gradually decreasing (Fig. 2). The amplitude of maximal individual lateral angular displacements similarly first increases to an exaggerated level, up to 415° at a time and then gradually decreases to about 90° at a time, during the last phase of the observation period (Fig. 3, lower panels).

The interaction between forward progression and lateral angular displacement (turning)

The interaction between the variables of forward progression and lateral angular displacement yields the variety of patterns of locomotion observed under apomorphine on a smooth horizontal surface. Before the emergence of lateral angular displacement, only straight forward paths are seen (Fig. 4, top row). Then the rat starts to walk along curved forward paths. With time, the amplitude of angular displacement grows, and concurrently, forward walking gradually diminishes, often being totally eliminated. The interaction between the variables of forward progression and lateral movement, as forward progression shrinks and the ratio between the two decreases, yields ever-tighter circling (Fig. 4, second row), then revolving (Fig. 4, third row) and ultimately, pivoting (Fig. 4, bottom row). The latter pattern involves movement only along the lateral dimensions. Finally, as the laterals also decrease in amplitude, the hindquarters become relatively immobile, and the forequarters engage in small lateral as well as "minimal" lateral, forward and backward movements.

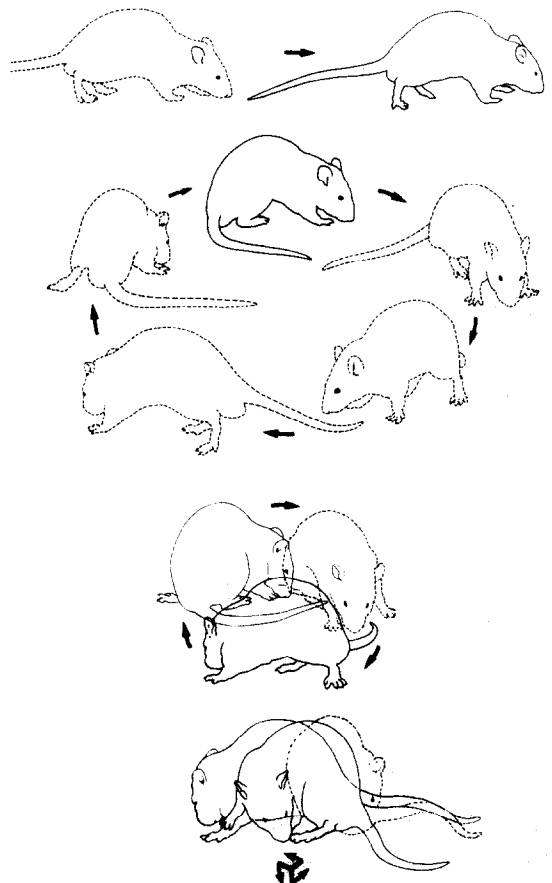


Fig. 4. A schematic illustration of four successive composite stereotypies generated in the course of action of apomorphine. From top to bottom: forward walking, circling, revolving and pivoting. It should be noted that during "circling" the animals typically locomote along circular paths without completing 360° before changing direction.

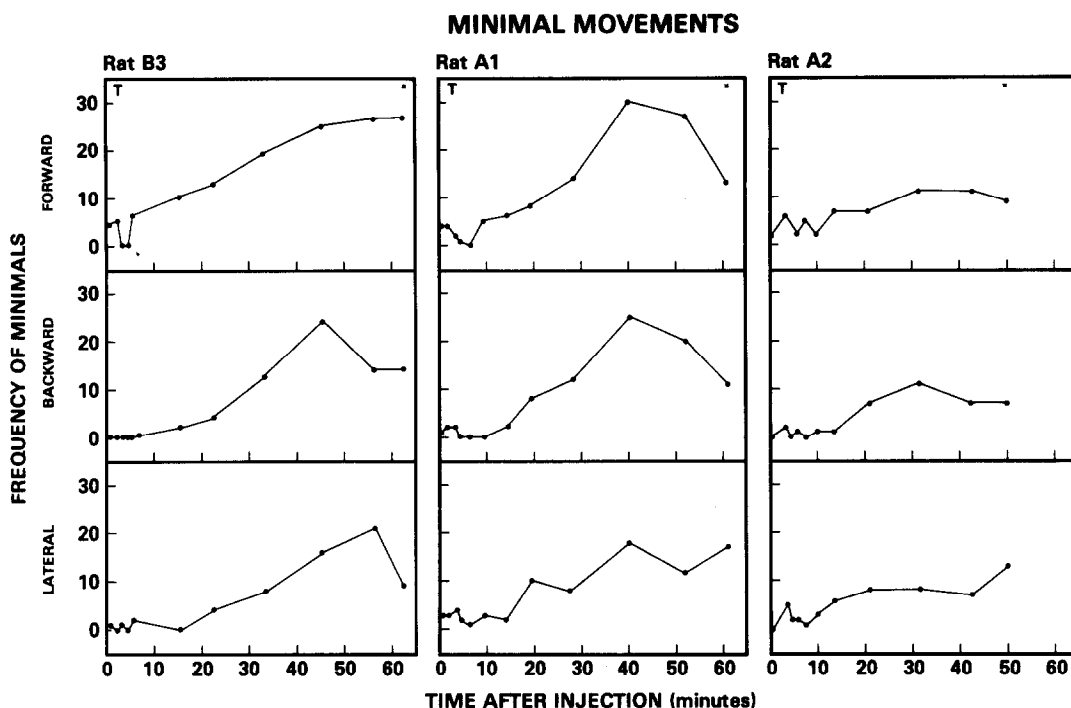


Fig. 5. Incidence of small amplitude head scans ("minimals") in successive 15 s intervals during the course of apomorphine's action.

"Minimal" forward, backward and lateral head scans

As soon as snout contact is established at the beginning of the drug's action and the animal engages in forward progression, it performs few, if any, extremely small lateral, forward or backward scanning movements with its head and neck. These movements, which are smaller than $45^\circ/3$ in the lateral, and half a step length forward or backward, were recorded as "minimal" movements. The frequency of these minimals increases gradually, reaching their peak and occurring in pure form towards the end of the drug's action (Fig. 5). Before that time they may also be superimposed on the larger amplitude movements of forward progression and lateral angular displacement.

Their distinct size and the fact that their specific frequency distribution during the course of the drug's action is different from that of both forward progression and lateral displacement suggests that they represent a separate behavioural subsystem. These short, saccadic head movements which involve loose sliding snout contact predominate during the phase of relative immobility of the hindquarters. Their incessant performance at that time gives the impression of a detailed tactile and/or olfactory (sniffing) investigation of very small areas around the animal's forequarters.

Stepping

The course of change along the longitudinal and lateral variables is also reflected in the patterns of stepping. These patterns provide a fine-grain description that (1) yields distinct signposts which delimit

specific phases in the course of the interaction of forward progression and turning; (2) can discriminate between different forms of locomotion that might otherwise appear similar. For instance revolving, which involves little forward progression, may easily be confused with pivoting, which involves none. The direction of stepping clearly distinguishes between them—forward stepping of the hindlegs is still present in revolving, whereas pivoting involves only backward stepping. In a rotometer, which measures only circling, these two forms may be confused though they represent distinct stages in the course of the drug's action; and (3) may highlight aspects of normal stepping which might not be readily discerned in an undrugged animal. By limiting behavior to one or a few repetitive patterns at each stage of its action, the drug isolates each particular pattern from the myriad of others which may obscure it.

In brief, with diminishing forward progression and increasing lateral angular displacement, the hindleg contralateral to the direction of turning (outside hindleg) is increasingly used as the axis of pivoting and support rather than for stepping; the ipsilateral (inside) hindleg shifts from forward to sideways to backward stepping. Concomitantly, the forelegs shift from forward to sideways stepping. The diagonal stepping sequence typical of normal forward locomotion,¹⁴ is preserved throughout most of the course of the drug's action in circling, revolving and even pivoting, when the outside hindleg ceases to step, in the sequence of stepping of the other three legs. It disappears only in the final stage when both hindlegs become stationary (Fig. 6 I–VI). As the weight is

Fig. 6. Six examples representative of the changes in behavior during the course of action of apomorphine written in Eshkol-Wachman Movement Notation. Notation was made from film of rat B3 taken at 24 frames/s. Numerals on top indicate frame number on film and each column represents a time unit (TU) of 2 frames. The score is read from left to right and from bottom to top. The initial position is closed by a double bar line. Vertical bar lines indicate start or end of a movement. Each row is allocated for a limb, from bottom to top: R.H., right hindleg; L.F., left frontleg; L.H., left hindleg; and R.F., right frontleg, pelvis, chest and head. The orientation of the whole body in the horizontal plane is noted in the bottom row, Front. The Head's angular displacement is described by Hd. Ang. Disp. The following is the vocabulary used in these scores:

(a) k: is an abbreviation for "key signature". A key signature provides an overall specification which applies to the whole notation score. Here key signatures specify two kinds of steps: in scores I, II, III ([0]S) indicates forward steps and in scores IV, V, VI, (S) indicates steps without specifying direction. Use of these key signatures makes it unnecessary to write these symbols inside the scores.

(b) →, ←: symbolize movement in the horizontal plane clockwise and counterclockwise, respectively. Amount of movement is written above the arrow.

(c) ⊙, ⊖: symbolize rotational movements clockwise and counterclockwise, respectively. Amount of movement is written inside a symbol or below it.

(d) Circular paths: in the Front space in, e.g. score II, ⊖^[6] stands for a circular path that is defined by stating the rotational state (the side of the animal's body surface) facing the center of the circle, in this case, rotational state [6] (left side of the body). The number adjacent to the rotational state defines the amount of movement. The direction of the arrow expresses whether the circle is performed clockwise or counterclockwise.

(e) ⊥ : contact with the ground. (h) ⊥ : contact between parts of the body.

(f) = : release of contact. (i) ⊥ : loose contact.

(g) ⊥ : contact with the ground without weight. (j) ⊥ : rotating loose contact.

(k) ⊔, ⊕, ⊖, ⊗ : symbols for opposition. Here the oppositions are between symmetrical legs.

(l) () : signifies that the information within the parentheses is read in the absolute frame of reference. When two numerals are inserted within the parentheses, the lower describes the horizontal and the higher, the vertical coordinate. One numeral describes the orientation in the horizontal plane.

(m) [] : signifies that the information within the square brackets is read bodywise.

(n) (·) : the extreme point of a limb.

(o) ≠, #, +: two thirds, one half and one third of a unit respectively. For example, if one unit = 45° then ≠ = 30°.

(p) m, M: minimal and maximal movements respectively.

(q) f: fixation.

(r) x: arching.

I TU=2frames

Frame	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38
Hd. Ang. Disp																
Head	(⊙)															
Chest	(⊙)															
Pelvis	(⊙)															
R. F.	⊥	=		⊥			=		⊥			=	⊥			
L. H.	⊥			=		⊥			=	⊥			=	⊥		
L. F.	⊥				=	⊥			=	⊥			=	⊥		
R. H.	=		⊥			=		⊥			=		⊥			
Front	(⊙)															

II TU=2frames

Frame	27	45	6	8	50	2	4	6	8	60	2	4	6	8	70	2	4	6	
Hd. Ang. Disp			*							←	+								
Head	(⊙)																		
Chest	(⊙)					≠		(⊙)											
Pelvis	(⊙)			2															
R. F.	⊥	=	⊥					=	⊥			=	⊥						
L. H.	⊥			=		⊥			=	⊥			=	⊥					
L. F.	⊥				=	⊥			=	⊥			=	⊥					
R. H.	=	⊥				=		⊥			=		⊥						
Front	(⊙)		←	2															

III TU=2frames

Frame	3217	8	20	2	4	6	8	30	2	4	6	8	40	2	4	6	8
Hd. Ang. Disp		2+															
Head	(6#)	←															
Chest	(6#)																
Pelvis	(6#)	←															
K:(125)	R. F.	=	T					=	T				=	T			
	L. H.	T		=	T					=	T				=	T	
	L. F.	T			=	T				=	T					=	T
	R. H.	T				=	T					=	T				=
Front	(6#)	←	(6)2														

IV TU=2frames

Frame	4272	5	5	7	5	9	5	5	7	9	9	5	5	7	5	30	5	
Hd. Ang. Disp		2#																
Head	(6)																	
Chest	(6#)													←				
Pelvis	(6#)	←	1#													←	3	
K:(5)	R. F.	T		=	4	T				[0]	T					=	4	T
	L. H.	T				[7]	T			[7]	T							
	L. F.	=	[7]	T			[7]	T							[7]	T		
	R. H.	T		[7]			[0]	T			T							
Front	(6#)	2#																

V TU=2frames

Frame	5272	2	90	2	4	6	8	9000	2	4	6	8	10	2	4	6	8
Hd. Ang. Disp	(5)	←	3														
Head	(5)																
Chest	(6)		←	#													
Pelvis	(6#)	←	2#														
K:(5)	R. F.	T	[0]	T			[0]	T			[6]	T				[6]	T
	L. H.	T		[4]	T			[4]	T			[4]	T			[4]	T
	L. F.	T			[6]	T			[6]	T						[6]	T
	R. H.	T			[6]												
Front	(6#)	2#															

VI TU=2frames

Frame	4445	4	4	8	50	2	4	4	8	60	2	4	6	8	70	2	4
Hd. Ang. Disp										(3)							(4)
Head	(8)	(2)1								T	=						
Chest	(5)		2	→											1	→	
Pelvis	(3#)	0								#	↓						
K:(5)	R. F.	T			[3]	T			[4]	T				[2]	T		
	L. H.	T															
	L. F.	T			[2]	T											
	R. H.	T								T	[4]	T					
Front	(0)	2	#														

shifted backward during the course of the drug's action, the hindlegs step less frequently and the foreleg steps involving shift of weight are replaced by almost weightless stepping gestures which consist of repetitive release and re-establishment of forepaw contact with the ground, and by stepping in place (which involves a shift of weight to the other foreleg).

Although the overall trend toward relative immobility is clear during the action of the drug, it always involves brief periods of reversal. For instance after having begun tight circling, larger circles briefly reappear before being totally eliminated. Similarly, after the disappearance of forward stepping with the outside hindleg, yielding pivoting, the outside hindleg will temporarily step forward, again yielding revolving, before the final disappearance of such steps. The first and the last occurrence of a specific stepping pattern may therefore be used as signposts for the start and end of each qualitative behavioral process during the course of the drug's action.

Hindleg stepping. During pure forward progression both hindlegs step forward, each leg landing ahead of the other at the end of its swing phase ([0]S). The hindlegs step in sequence with the forelegs, yielding the normal diagonal pattern. Then the steps become smaller, involving a digitigrade rather than a plantigrade gait. With the emergence of lateral angular displacement and the decrease in forward progression, the size and direction of stepping changes, depending on whether the step is on the inside or the outside of the turn.

Outside hindleg

As the ratio of forward progression to lateral angular displacement decreases, release of contact of the outside hindleg is delayed and its support phase lengthens as the rat successively incorporates the following types of step: (1) short steps forward, still landing ahead of the other hindleg, while maintaining the stepping sequence in relation to the other three legs (Fig. 6II); (2) smaller steps "to opposition" landing in parallel or immediately in front of the other hindleg at trunk's width ([0]S \square), still in the proper diagonal sequence (Fig. 6III); (3) as in (2), but landing in the immediate proximity of the inside hindleg, almost touching it ([0]S \square); and (4) every so often missing a step altogether in relation to the other three legs, as the outside hindleg begins to be used as the axis of pivoting ($f_i(\cdot)$). At first, all three patterns become interspersed; then as the amplitude of forward progression diminishes, patterns (1), (2) and (3) disappear successively, as the outside hindleg is increasingly used as the point of support, rotating in place during pivoting (Fig. 6V). Forward stepping with the outside leg does not reappear until the end of the observation period, as the drug effect presumably wears off and forward walking re-emerges in increasing amplitudes. The last forward step of the outside hindleg during the course of the drug's action marks the end of forward progression. In many

instances, however, the decrease in forward stepping is not so pronounced and some forward stepping of the outside hindleg may be seen intermittently throughout the course of the drug's action.

Inside hindleg

The transformation from pure forward walking to pivoting in place is reflected in three concurrent processes in the stepping pattern of the inside hindleg. (1) The direction of individual steps changes from forward ([0]S) (Fig. 6II, III) to sideways ([1]S; [7]S; [2]S; [6]S) (Fig. 6IV) to backward ([4]S) (Fig. 6V). In the beginning, all hindleg steps are directed forward, and at the end, backward. Between these two extremes, all three patterns gradually become interspersed, increasing in frequency from forward to sideways to backward. (2) As the outside hindleg gradually ceases to step, being used more and more for pivoting, the inside hindleg becomes partly uncoupled from the stepping of the other legs and may take more than one step at a time. Some of these backward steps are elicited by touch when, during pivoting with the body greatly arched and bent laterally, the rat's snout bumps into the hindpaw, often licking and sometimes chewing at it. (3) As the turning becomes tighter, the inside hindleg becomes more and more plantigrade.

Coupling between hindlegs

As long as the rat walks forward and all four legs are co-ordinated in normal size steps in a diagonal sequence, the animal has a wide base of support. As the turning becomes tighter the nature of the coupling changes: the pelvis rotates on the supporting hindlegs, causing the outside hindleg to lag behind. It then performs a step "to opposition", landing alongside, and sometimes actually treading on, the toes of the inside hindleg. The resultant narrow base of support is then widened by a quick sideways step of the inside hindleg. This quick two-step pattern disappears as weight is shifted backward and the outside hindleg becomes the base of support in pivoting, leaving the inside hindleg free to step backward independently. It should be noted that the quick two-step pattern may also be seen during the early period of pure forward progression, during tight turning in corners and along the cliff.

Foreleg stepping. Throughout the drug's action foreleg steps decrease in size so that the normal steps seen initially in forward progression are gradually replaced by smaller ones, or even steps in place, as very small forward and backward "minimal" progressions emerge. The rat starts with the highly co-ordinated diagonal stepping pattern seen in forward walking and then with the onset of turning, it steps sideways with the inside foreleg ([2]S; [6]S), and performs sideways steps ("to opposition") with the outside foreleg. In these steps to opposition, the outside foreleg may land in parallel, at trunk's width ([2]S \square), or closer to the inside foreleg ([2]S \square), or

land in front ($[2]S\overline{4}^*$) or cross over in front ($[2]S'\overline{4}^*$) of the inside foreleg (Fig. 6V). Finally, as it shifts its weight backward onto its hindquarters and arches dorsally, it frees its forelegs to tap almost weightlessly sometimes up to four times in a row with the same foreleg. At this time the forelegs sometimes step backward whereas the rat's snout is pushed minimally forward, and vice versa (Fig. 6VI).

Foreleg-to-hindleg stepping ratio. In the first few minutes as the drug starts to take effect, the ratio of foreleg to hindleg stepping (as reflected in the number of contact releases of the feet) is 1:1 (Fig. 7, top panels). As the animal shifts to circling, revolving, pivoting and relative arrest of hindquarters, the ratio gradually increases to as much as 5:1, involving five releases of contact of a foreleg to one of a hindleg. In contrast to the hindlegs, which show a reduction in the absolute number of steps, the frequency of foreleg releases of contact remains the same throughout. The constant frequency of foreleg releases of contact is a result of the replacement of actual steps involving shift of weight by small steps in place and almost weightless step gestures when the rat shifts its weight backward onto its hindquarters and then taps lightly with its forelegs (Fig. 6VI). Towards the end of the drug's action, many steps seem to be elicited by touch, as the rat's snout contacts a forefoot. At

this time, the animal shifts erratically from one direction of stepping to another, thus giving the impression of haste.

Individual differences

Not all animals show the behavioral sequence in its full-blown form unfolding during the course of the drug's action. Some animals do not show pure forward locomotion and begin to circle as soon as they establish continuous snout contact (e.g. animal D4, Fig. 2). In some, forward locomotion, although gradually decreasing from its peak, may not disappear completely, being seen sporadically and involving few steps at a time, between bouts of pivoting (e.g. animal D1, Fig. 2). Still others continue to walk forward throughout the course of action of the drug (e.g. animal E2, Fig. 2). In such animals, however, the tie of the behavior to a specific route in the environment is preserved, as they continuously progress by a fixed route along the table's edges. Finally, pure pivoting may not be seen. Nevertheless, these qualitative variations in behavior do not violate the basic regularity we have described between forward locomotion and turning, in the sense that (1) all animals show a decreasing ratio between these two variables in the course of drug action and (2) various animals may begin at a later stage in the full-blown sequence or

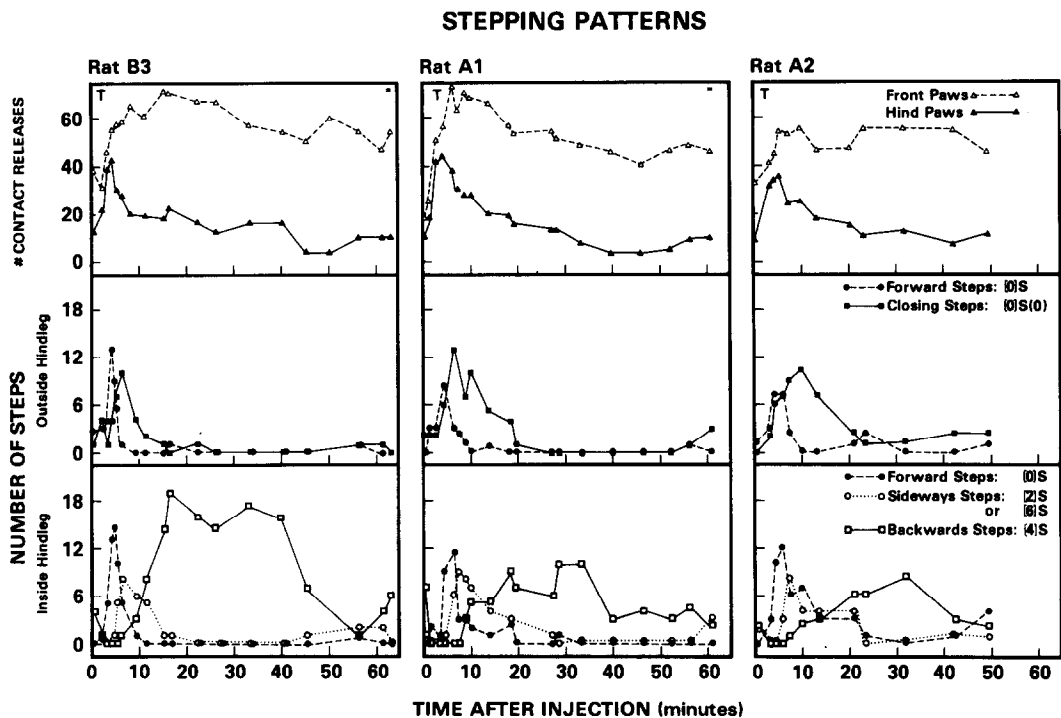


Fig. 7. Ratio between level of activity in fore- and hindlegs (top row) and the direction of individual steps taken by the hindlegs (middle and bottom rows) during the course of apomorphine's action. Top row: each point represents the number of times the rat lifted its paws off the floor in 15 s ("# of contact releases"), regardless of direction of the ensuing step. Middle row: frequency of forward steps and of steps "to opposition" (closing steps) taken in 15 s intervals by the outside (contralateral) hindleg during turning. Bottom row: frequency of forward, sideways and backward steps, taken in 15 s intervals by the inside (ipsilateral) hindleg during turning.

SHRINKAGE OF EXPLORATORY SPACE

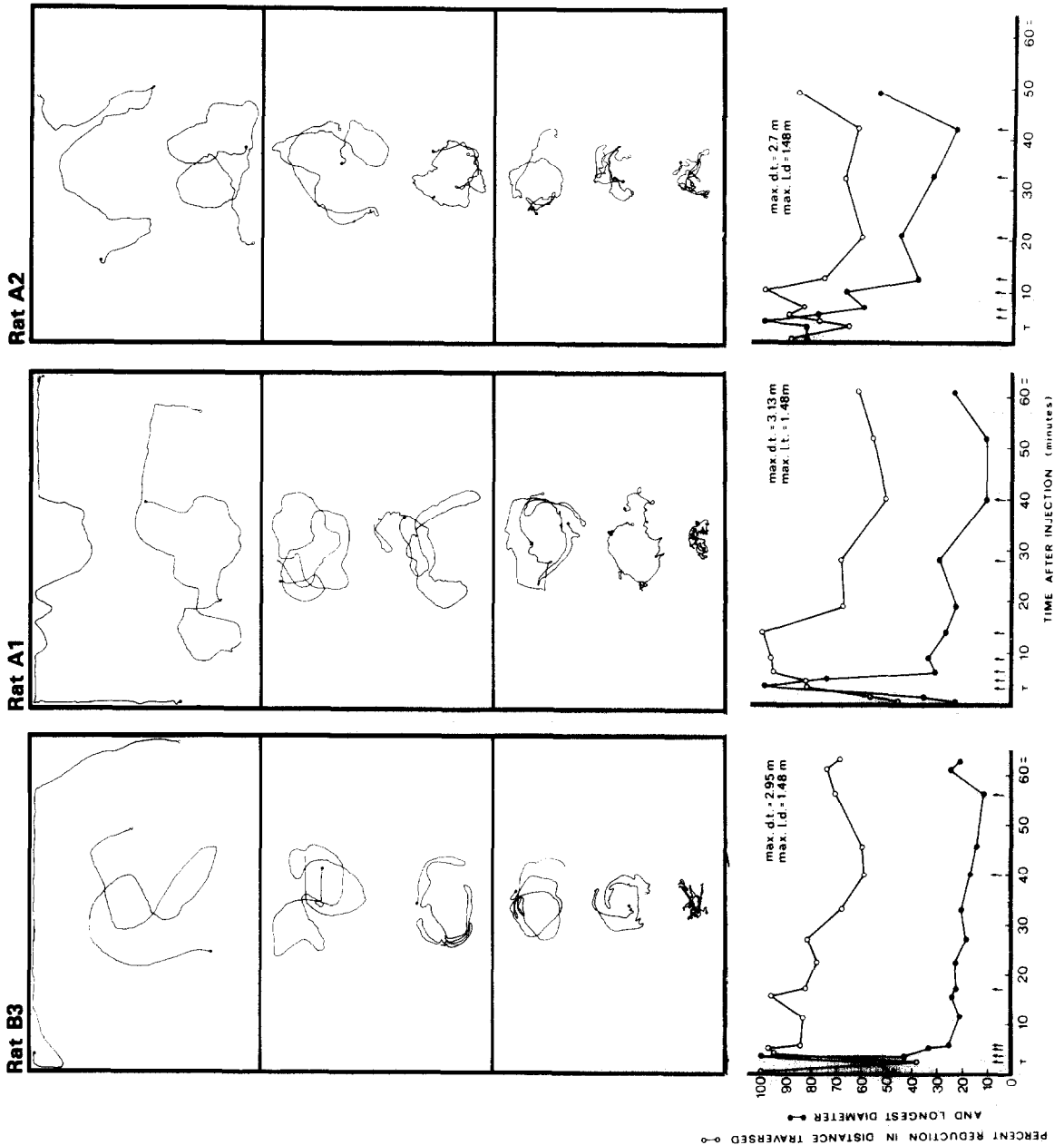


Fig. 8. Seven representative paths traced by the snout of each of three rats exploring the open field in successive 15 s intervals during the course of apomorphine's action. Snout paths were drawn from film records. Rectangles and traces are a scaled representation of the open field and the paths traversed by the rat's snout (two separate paths are shown in the top rectangle, two in the middle, and three in the bottom one). The beginning of the path is indicated by an open circle (○) and the end by a filled circle (●). For the purpose of this illustration, the paths were positioned along the vertical midline of the open field, regardless of their actual physical location. Each arrow on the bottom graph indicates the time during the course of action of the drug at which such a path was exhibited. The seven paths from top to bottom correspond to the seven arrows on the graph, from the beginning of the drug's action to its end. The length of each path (distance traversed, d.t.) was measured from tracings using an image analyser. The largest diameter (l.d.) of the path was determined by fitting the longest possible line between two extreme edges of the path. Whereas distance traversed measures path length, longest diameter is an indication of the range of the environment explored by the rat.

end at an earlier stage, but the order of incorporation of new behaviors and the order of elimination of old ones is always the same.

In an open field with a wire mesh floor, apomorphine typically elicited biting and licking in addition to its effects on forward progression and turning. Such mouthing stereotypies were virtually eliminated in most animals by the smooth glass floor. However, in another strain of Wistar rats that we have examined³⁷ biting and licking predominated to such an extent that such animals even bit and licked at the smooth glass surface, partially obscuring and limiting apomorphine's effects on progression and turning.

The range and density of exploratory paths

The path traced by the rat's snout in the environment may be regarded as the sum total of the kinematic variables that have been described above, revealing how much of the environment is explored and in what fashion. The same path length may densely cover a limited area, reflecting its detailed repetitive examination (Fig. 8, bottom example) or merely encircle a larger one (Fig. 8, second example from top), suggesting a one-time examination of ever-new locations. Figure 8 presents in each of three rats, seven examples of the paths traced by the rat's snout on the glass floor during 15-s intervals sampled successively in the course of the drug's action. In the first example the range covered, expressed by the length of the straight line connecting the two most extreme points on the path, is constrained by the edges of the table. Because at this stage the rat typically progresses along a straight path, had it not been for the table edges, there would have been no distinction between range and path length. In each successive example, the range covered by the rat's snout becomes progressively smaller and more condensed until the path ultimately densely covers an area, the diameter of which is smaller than the rat's body length. The percent reduction in the length of the path traversed by the rat's snout during successive equal intervals and the percent reduction in the maximal diameter of the respective ranges covered by the snout are represented in the graphs (Fig. 8, lower panels). While the path's maximal length is reduced in the course of the drug's action by some 30–50%, the diameter of the range decreases from its maximum by some 75–90%. Since the initial range is limited by the size of the table, the actual reduction is even greater.

In summary, a reduction in range diameter, while the path length remains relatively high, yields exploration of ever smaller ranges, repetitively and in increasing detail.

DISCUSSION

In earlier work on the akinesia produced by extensive bilateral lateral hypothalamic damage,¹⁵ involving the ascending dopaminergic systems,^{24,39} it

was shown that at a certain stage of recovery, rats performed highly stereotyped, purposeless, locomotor acts, so repetitive that they became trapped in corners and other partial enclosures. By analysing the recovery of movement from complete akinesia through relatively normal exploratory locomotion, our group isolated three component variables of movement, growing continuously in amplitude and appearing successively: lateral movement first, forward next and vertical (along surfaces and then in the air) last. The stereotypies performed at a particular stage of recovery were seen to result, on the one hand, from the interaction of those variables that had recovered to a certain amplitude, and on the other hand, from the absence or insufficient amplitude of the remaining variables. A similar interaction of variables of movement was seen in developing normal intact rats, in the course of their transition from immobility to exploratory locomotion in an open field.^{7,16}

Since dopaminergic drugs probably affect the systems involved in the recovery of exploratory locomotion after lateral hypothalamic damage,^{25,31} we wanted to determine whether similar components of movement account for the stereotyped exploratory locomotion produced in rats by apomorphine. To see components of movement more clearly it is necessary to start with a simple environment and only later introduce more complex features (such as wall, holes, wire mesh, etc.). The methodology employed in the present study involves (1) simplification of the environment (the rats were observed on a large smooth horizontal surface); (2) observation of the drug's effects throughout the course of its action, not merely at its peak; and (3) use of the Eshkol–Wachman Movement Notation to allow the simultaneous recording of snout contact, turning and the order and direction of stepping. Through the use of these procedures, three component variables of movement were isolated, whose interaction explains the structure and the sequence of appearance of several of the otherwise seemingly unrelated locomotor stereotypies that are performed in the course of the drug's action. These stereotypies are shown to be composites, generated by particular amplitudes of the variables.

As the drug starts to take effect, rearing in the air is eliminated and forward progression sets in, with snout contact being established and maintained throughout all subsequent behavior.³⁷ For a brief period pure forward walking is observed. Then turning sets in and grows in amplitude while forward progression diminishes. As the ratio between forward progression and turning decreases, forward walking changes first into circling and then into revolving. When forward progression is eliminated pivoting is seen. Then as weight is shifted backward and lateral angular displacement diminishes and the hindlegs become relatively immobile, side-to-side movements of the head and forequarters are mostly seen. Minimal forward, backward and lateral head movements

increase in frequency, finally yielding what appears to be a detailed tactile and/or olfactory examination of the surface. The stepping patterns associated with each composite stereotypy (walking, circling, revolving, pivoting, side-to-side forequarter movement) reveal the ratio between forward progression and lateral angular displacement and allow a detailed mapping of the gradual transition from one stereotypy into the next. These stepping patterns might be useful in a rotometer⁴⁰ for instance, in the distinction between circling, revolving and pivoting which involve different ratios of lateral angular displacement to forward progression.

Other component variables of movement not analysed systematically in this study also appear to play a role. In some animals under apomorphine, shortly after the drug is injected, exaggerated rearing involving upward pointing of the head in the air is seen, but only briefly before snout contact is established. In the course of the drug's action the head is progressively tilted ventrally, until it ultimately points downward or even backward. Extension of the hind-legs, dorsal arching of the torso and lateral bending of the trunk all seem to increase during the course of action of apomorphine to an exaggerated maximum and then subside. These components should also be considered in further analyses of the action of dopaminergic stimulants such as apomorphine and amphetamine.

The process outlined above is both coupled to and modulated by the environment: cliffs and corners guide the animal's movements along their contours, walls elicit upward scans and edges evoke mouthing, which in turn temporarily interrupts the flow of forward progression and angular displacement. Despite these interruptions, a transition from forward progression to pure, or almost pure, turning was discerned in all the examined environments.

For instance, when placed in a small enclosure with high smooth Plexiglas walls, the rat mostly rears and climbs with snout contact along the walls, thus still maintaining bodywise forward progression.³⁷ When lateral angular displacement of the head sets in, even in this vertical position, the rat superimposes a rotation of its forequarters on its vertical position. In extreme form such rotation, if not accompanied by postural adjustments of the hindquarters, may cause the rat to fall to the side. On a wire mesh floor, where the predominant activity may be nose-poking and biting, the path of the animal's progress on the floor, albeit much slowed down and diminished, still reveals the gradually changing relationship between forward progression and lateral angular displacement.

Concluding remarks

Since apomorphine is known to be a dopaminergic agonist, one might expect that the course of its action on movement would parallel the course of neurological recovery of movement after damage to the dopaminergic system. This is indeed what happens

in rats made akinetic by previous treatment with 6-OHDA. In such animals, low doses (0.05–0.20 mg/kg) of apomorphine produce a sequence of movement closely resembling the "warm-up" seen in spontaneous recovery from lateral hypothalamic damage.^{15,25} Therefore our results, demonstrating a sequence opposite to that seen in recovery (see Table 2), presumably reflect not an activation, but rather a shut-down of movement.

Current evidence^{17,35} suggests that apomorphine can shut down the dopaminergic system by an action in low doses on autoreceptors of the cells of the substantia nigra. But our effects must be postsynaptic because of the high dose (1.2 mg/kg) involved and because of the high degree of behavioral activity induced. Is there evidence for a postsynaptic neurophysiological mechanism that could account for the production of behavioral "warm-up" in low doses and behavioral "shut-down" in high doses? In animals whose nigrostriatal dopaminergic function has been damaged by 6-OHDA, the spontaneous level of firing in postsynaptic (caudate) cells is higher than normal.¹ Akinesia, the inhibition of movement, is therefore correlated with a higher than normal level of firing bilaterally in the caudate. At relatively low doses, dopaminergic agonists decrease the firing of caudate cells,^{28,35} such low doses in animals made akinetic by 6-OHDA generate movement in the "warm-up" sequence,²⁵ presumably correlated with a decrease in caudate firing rate. Rebec *et al.*²⁸ have shown that amphetamine, a presynaptic dopaminergic agonist, has a biphasic action on neostriatal (postsynaptic) cells: low doses (1.0 mg/kg), which are known to generate increased locomotion, do so by inhibiting neostriatal firing, but high doses (7.5 mg/kg), produce an opposite effect—an increase of caudate firing, which should presumably correspond to a "shut-down" of locomotion. If apomorphine acts in an analogous manner, then their results could be a postsynaptic electrophysiological demonstration of a "shut-down" corresponding to our behavioral results. In other words, a gradual increase in caudate firing as a function of dopaminergic agonist dose should be closely and continuously correlated with the "shut-down" in locomotion described here.

Ellinwood⁹ points out that in human amphetamine-induced psychosis, there is first an apparent expansion of the scope of attention and then its severe reduction to the point where the patients explore portions of their own body in increasing detail. A shrinkage of the space to which monkeys attend after being treated with amphetamine has been reported.²⁷ Our results (Fig. 8) demonstrate a similar shrinkage of explored space in apomorphine-treated rats. During the early action of the drug, some rats rear excessively and at the same time appear to look at distant objects and to react to distant moving stimuli. As the snout is lowered to the ground, tactile and/or olfactory examination become dominant, the

Table 2. Comparison of the change along some kinematic variables during the course of recovery from lateral hypothalamic akinesia, ontogeny of exploratory behavior in infant rats and in the course of action of apomorphine

In lateral hypothalamic recovery (after Golani <i>et al.</i> , 1979) ¹⁵	In ontogeny (after Golani <i>et al.</i> , 1981; ¹⁶ Eilam, 1982 ⁷)	Under apomorphine
From arrest, progressive incorporation of lateral, then forward, then vertical movements, first along, then away from surfaces	From arrest, progressive incorporation of lateral then forward, then vertical movements	From rearing*, to forward walking, to progressive incorporation of lateral movement, then relative arrest of hindquarters
Lateral, forward and vertical movements emerge successively, reaching an exaggerated peak one after the other and then subsiding to normal in the same sequence	Lateral, forward and vertical movements emerge successively, reaching an exaggerated peak one after the other and then subsiding to normal in the same sequence	Forward and lateral emerge successively reaching a peak one after the other and then subsiding in the same sequence
From plantigrade, low gait, to digitigrade, high gait and back to normal	From low to normal gait	From high digitigrade to low plantigrade gait
From continuous snout contact to phasic, regular release of contact	From irregular release of snout contact, through continuous contact, to regular, phasic release of contact	From regular phasic release to continuous snout contact throughout
From backward stepping of ipsilateral hindleg (in relation to the direction of turning), to forward stepping of contralateral	From backward stepping of ipsilateral, to forward stepping of contralateral hindleg	From forward stepping of contralateral, to backward stepping of ipsilateral hindleg
From immobility through increased, then exaggerated then back to normal transport in the environment	From immobility to increased transport in the environment	From extensive transport to relative immobility
Repetition of earlier movements of the sequence before and after the incorporation of new movements	Repetition of earlier movements of the sequence before and after the incorporation of new movements	Repetition of earlier movements of sequence before and after the incorporation of new movements

*Excessive rearing away from surfaces is observed briefly in some animals.

space explored shrinks in area and eventually the animal may bite or lick at its own body parts. It is noteworthy that both the shrinkage of the space attended and the sequence in which the components of movement emerge is not only opposite to that seen in recovery but also to that seen in ontogeny (Table 2). In this sense, the behavior seen under apomorphine might be interpreted neurologically as a form of regression.^{12,18,36}

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