13 Amphetamine-induced Stereotypy in Rats: Its Morphogenesis in Locale Space from Normal Exploration

DAVID EILAM AND ILAN GOLANI
Department of Zoology, Tel-Aviv University, Ramat-Aviv, Israel

INTRODUCTION

Although stereotyped behaviour, both in captivity (Cronin and Wiepkema, 1984; Cronin, 1985; Hediger, 1964; Stevenson, 1983), and with psychoactive drugs (Cooper and Dourish, 1990; Lyon and Robbins, 1975; Schiorring, 1971), clearly evolves in time out of normal behaviour, few attempts have been made to characterize the morphology of the transition from one to the other. Drug-induced stereotypy, for example, is commonly divided into locomotor stereotypies, characterized by repetitive pacing on the same routes (Eilam *et al.*, 1989; Geyer, 1982; Muller *et al.*, 1989; Randrup and Munkvad, 1970; Schiorring, 1979; Szechtman *et al.*, 1993), and in-place stereotypies characterized by the absence of locomotion and by repetitive head movements and intense sniffing, licking or biting of a highly restricted area (Arnt *et al.*, 1987, 1988; Brodi and Meller, 1989; Costall and Naylor, 1975; Fray *et al.*, 1980; Kelly, 1977). There are several studies which characterize the morphogenesis of in-place stereotypy from normal behaviour via locomotor stereotypy (Adani *et al.*, 1991; Eilam, 1987; Eilam *et al.*, 1991; Golani, 1992; Szechtman *et al.*, 1985). In these studies, the transition has been described in terms of the relations and changes of relation between the parts of the body (motor behaviour). In the present study, we describe the morphology of the transition in relation to places in the environment, i.e. in relation to *locale space*.

Studies of locomotor stereotypies in locale space typically represent the paths traced by the rat by drawing them on paper within a rectangle representing the testing environment, thereby conveying the confinement of the rat to a restricted part of the rectangle (Eilam *et al.*, 1989, 1991; Flicker and Geyer, 1982; Geyer *et al.*, 1986a, 1986b). Various methods discriminate between locomotor stereotypies under different drugs (Eilam *et al.*, 1991, 1992; Geyer,

Ethology and Psychopharmacology. Edited by S.J. Cooper and C.A. Hendrie

1982), assess qualitative aspects of locomotor stereotypy (Muller *et al.*, 1989), establish when a repetition of a route is indeed a replication of the previous one (Paulus and Geyer, 1991) and describe the regular appearance of parameters of stereotypy (Szechtman *et al.*, 1993). These methods provide measures for quantifying locomotor stereotypy. They do not address, however, the question of how locomotor stereotypy arises from normal behaviour, and more specifically, what is the natural source of repetitive locomotion along the same paths.

In the present chapter we describe how incessant repetition of the same path is gradually derived from normal exploratory locomotion in rats. The database for this study was obtained from studies of 31 tamed wild rats (*Rattus norvegicus*) exploring an open field (1.6 × 1.6 m glass platform without walls) for a 1 h period. Each of the animals was videotaped with and without (+)-amphetamine (s.c. in the nape at concentrations of 0.5, 1, 2.5 and 5 mg/kg; $n = 8$ in three groups, $n = 7$ in one group). The animals, the observation platform, the experimental procedure and the methods of data acquisition are described in Eilam and Golani (1989, 1990).

When placed in a novel environment, a normal rat alternates between progressing and stopping; it locomotes forward, stops, performs lateral and/or vertical scanning movements while staying in place, locomotes again, stops in a new place, etc. Its behaviour thus consists of intervals of 'stops' or 'visits' to places, the movements performed during these intervals, and the paths of locomotion between the places of stopping. Our testing environment was divided into 25 squares (Figure 2), and whenever a rat stopped, the location, timing and duration of stopping was recorded (for a detailed exposition of criteria and method see Golani *et al.*, 1993). Since rats tend to locomote in a relatively straight path between two stopping places, the sequence of stopping places provides a reasonable approximation of the rat's path.

When a rat explores a novel environment there are one or two places where it stays for a significantly longer cumulative time than in all the other places, and where it typically stops for the highest number of times. In this place, the values of these measures are of *a higher order of magnitude* compared to the respective values scored in all the other places. In it, the rat also shows a high and often the highest incidence of grooming—significantly higher in proportion compared to that expected by the proportion of time spent there. Finally, this place is also marked by the highest incidence of rearing, and by crouching and pivoting around the forelegs—two behaviours which are exclusive for this place. This place, which can be readily identified by any observer using the above criteria, has been termed a home base (Eilam and Golani, 1989).

From the home base the rat performs excursions into the environment. Excursions consist of round trips which start and end at the same home base, and, in the case of rats which establish two home bases, also trips which start at one base and end in the other. It has been shown that: (i) the way out from base is relatively slow and interrupted with stops in several places, whereas the way back to base is relatively rapid, including fewer stops (Eilam and Golani,

1989); (ii) there is an intrinsic upper bound on the number of times a rat stops during an excursion (Golani *et al.*, 1993); and (iii) the session's upper bound on the number of stops per excursion does not increase with the size of the explored area (Golani *et al.*, 1993).

What happens to this organization with psychoactive drugs? With (+)-amphetamine, for example, home-base behaviour is preserved (Eilam and Golani, 1990). This leads to the question of what happens to excursions when locomotor stereotypies develop after treatment with the drug. In this chapter we describe how amphetamine-induced stereotyped locomotion is derived from normal exploration through processes of reduction in the number of stops per excursion and sequencing of stopping places into a few relatively rigid routes, each constituting an excursion from (and back to) base.

Figure 1 represents the paths traced by a rat in the course of the first hour after treatment with 5 mg/kg amphetamine. In this rat's session the home base

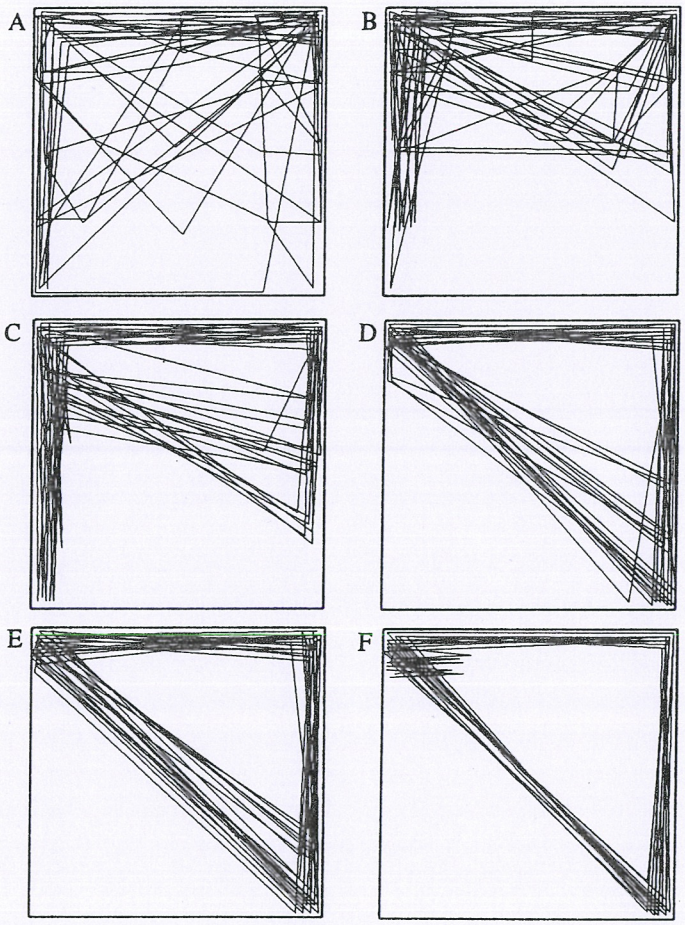


Figure 1 The paths of locomotion traced by a rat in the course of the first hour after injection of 5 mg/kg amphetamine. Blocks A–F represent the first 20 excursions performed during each of successive non-overlapping 10 min intervals. As shown, the paths became gradually more stereotyped, culminating in a repetition of one and the same path in E. Towards the end of the hour locomotion became confined to the left far corner (block F).

was located in the upper right corner. To avoid cluttering, only the first 20 excursions of six successive intervals of 10 min each are represented. The same paths, together with all the other paths performed by that rat in that session, are represented in Figure 2 in terms of symbols designating the rat's stopping places. These are written from left to right and from top to bottom in the order of their occurrence. Each line describes an excursion performed from 1, the rat's home base. In this type of representation, one can readily discern three processes: (i) the maximal number of stops per excursion is reduced in the transition from block A to block E from nine to two (excluding the home base itself); (ii) the order of stopping places becomes increasingly fixed; and (iii) the number of different routes is reduced (while each two successive excursion paths in block A are different, all excursions paths in block E follow a single route).

In the following we will show how the three processes illustrated in Figure 2 together with two additional processes—a dramatic increase in the incidence of excursions, and a change in the number of home bases—account for the establishment of amphetamine-induced stereotypy.

The case represented in Figure 2 is an example of the behaviour of all the rats treated with amphetamine: the sequence of stops is partitioned into excursions (defined below), each of which starts with a stop at the home base. As the behaviour becomes more stereotyped, the distinction between a stop at a home base and a stop elsewhere becomes increasingly difficult or even impossible to draw on the basis of the criteria established by us (Eilam and Golani, 1989, 1990). Nevertheless, as we will show, even the most stereotyped excursion following amphetamine includes a visit to what had been, at the beginning of the session, a home base location.

Figure 2 A symbolic representation of the paths of locomotion performed in the same session already presented in Figure 1. A numeral designates each of the 25 places on the platform. A map of the places on the platform is provided in block G; places in the central area are designated by large bold characters. The numerals in blocks A–F represent the places in which the rat stopped in the order of their occurrence, from left to right and from top to bottom, within each block. The blocks represent successive periods of behaviour. All stopping places in the session are presented. Each row in blocks A–F represents one excursion, starting at the home base, which is located in this rat session in the right far corner of the platform, and is designated by 1. Blocks A and B represent the first few minutes after injection, when the only apparent regularity was the frequent return to the home base, 1, and the limited number of stops per excursion. In the first excursion the rat leaves the home base, 1, and locomotes along the far edge of the platform, stopping at 0′, then at 0, then leaves the edge, stops at **0**, proceeds to the near left corner of the platform, 5, stops there, then proceeds to 5′, and returns to the home base, 1, from where it starts a new excursion to 0′, 2, 2′ . . . etc. Note that as the number of stops per excursion decreases from A to E, the variety of stopping locations decreases, stopping in the central area of the platform is eliminated, and the sequence of stopping places becomes fully predictable. Finally, the rat stays in the far left corner, engaging in side-to-side head movements.

A

10'0055'
10'22'3667
11'22'330'
106'54'43'
10'076'
11'0
11'21
1077'
10'07'765
10'07'76'65'65'1'
10'76'5'55'0
177'
1066'65'5
176'6577
1226'70
11'1C7
1466'77'
122'67
11'1165'56'7
12'76'7
11'16'
10'07
11'77'0667 7'0
10
11'276'70C57
12
11'1C77'
116'6570C6'5'

B

11'77'
11'76'7
112C77'
11'26'
100767
11'276'67
127
11'2765'7'
17
11'2767
11765'7
11'2276757'
1167
1265'
176'
16'5'7
176'5'7
126'7
1265'
11'5
15'
11'25'
11'5'
125'51
1C5'7
126'7

C

1756'C5'7
15'
125
15'
126'70
16'
15'
126'65'57
1267
16'5'
1265'
11'5'
11'67
12'6'
122'7
11'6'57'
16'77'
12'765'5
16'5'7'
16'57
167
12'7
137
126'57

D

12' 6' 7
1 3 7
1 6' 7
1 3 7
1 36' 7
1 3 7
1 7
1 3 7
1 3 7
1 7
12' 7
12' 7
12' 7
1 3 7
1 3 7
12' 7
1 3 7
1 3 7
1 3 7
1 36' 7

E

1 37
12' 7
12' 7
12' 7
12' 7
12' 7
137
12' 7
137
137
137
137
137
137
137
137
137
137
137
137
137
137
137
137
137
137
137
137
137
137

F

1 377'
1 37
1 37
1 377'
1 37
11' 37
1 377'
1 2'377'
11' 377'
11' 377'
11' 377'
11' 377'
77'
77'
77'

G

7	7'	0	0'	1
6'	7	0	1	1'
6	6	C	2	2
5'	5	4	3	2'
5	4'	4	3'	3

EXCURSION, PATH AND ROUTE

A home base is defined in the present study in terms of the statistical properties of the behaviours performed in it. An *excursion* is defined as a trip taking place between two successive stops at a home base. A particular excursion is characterized by the path taken by the rat, and by the places along this path where the rat stopped. A *path* is thus defined as the line traced by a rat during its progression in the environment in the course of a single specific excursion from home base and back to it. A *route* is defined as a *class* of paths taking more or less the same course in the environment.

Following treatment with amphetamine, the behaviour of an individual rat varies in terms of the number of stops per excursion, the degree of maximal observed stereotypy of routes, the number of different routes and the number of bases visited by the rat. After illustrating amphetamine's effects on each of these aspects of stereotyped behaviour separately, we will examine some of these effects in relation to dose and the time-course of drug action.

ASPECTS OF STEREOTYPY IN LOCALE SPACE AFFECTED BY AMPHETAMINE

Rats perform fewer stops per excursion after amphetamine

As shown in more detail elsewhere (Golani and Eilam, 1994), with amphetamine (0.5–5 mg/kg), there was a large increase in the overall number of stops (Figure 3A), and in the number of excursions made in the course of the hour (Figure 3B). The ratio between these two means yields the mean number of stops per excursion (Figure 3C). The mean of normal rats, i.e. 6.5 stops, was reduced to a mean of three to four stops per excursion. This degree of reduction did not vary across dose. The reduction in the mean number of stops per excursion was mainly due to an increase in the percentage of excursions with few stops, so that with the drug 90% of the excursions included up to six stops. We have shown that the reduction in the mean number of stops per excursion was not a mere by-product of amphetamine's effects on several other parameters of the excursion. Thus, while amphetamine's effects on excursion length and interstop distance was variable in individual animals, it reduced the mean number of stops per excursion in almost all rats (Golani and Eilam, 1994). We could not establish a causal relationship between the increased speed observed in amphetamine-treated rats and the decrease in the number of stops (Golani and Eilam, 1994).

The degree of stereotypy of routes and of stopping locations after amphetamine

With amphetamine treatment, routes may be classified into three types.

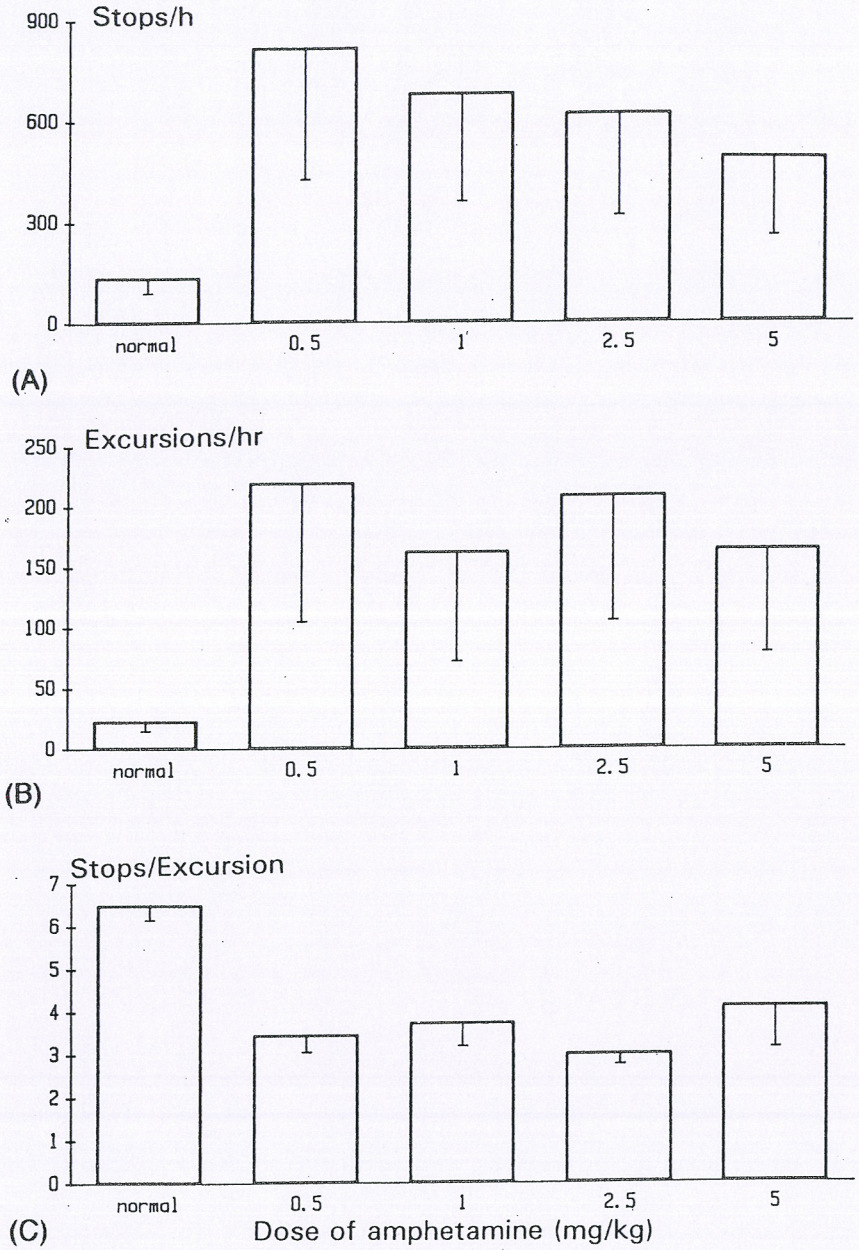


Figure 3 Means (− s.e.m.) of the overall number of stops (A), the number of excursions (B), and the number of stops per excursion (C), during an hour of exploration in normal and amphetamine-treated rats. While the difference between normal and drugged behaviour is apparent, there is no such difference among the drug groups.

A rigid route (no variability across paths and across sequences of stopping locations in different excursions)

During successive excursions the rat follows the same route in the same direction, stopping in the same places (Figure 2, block E). Figure 4 presents an example of the whole morphogenetic process, which consists of a gradual transition to a fully predictable route and a subsequent reduction in predictability.

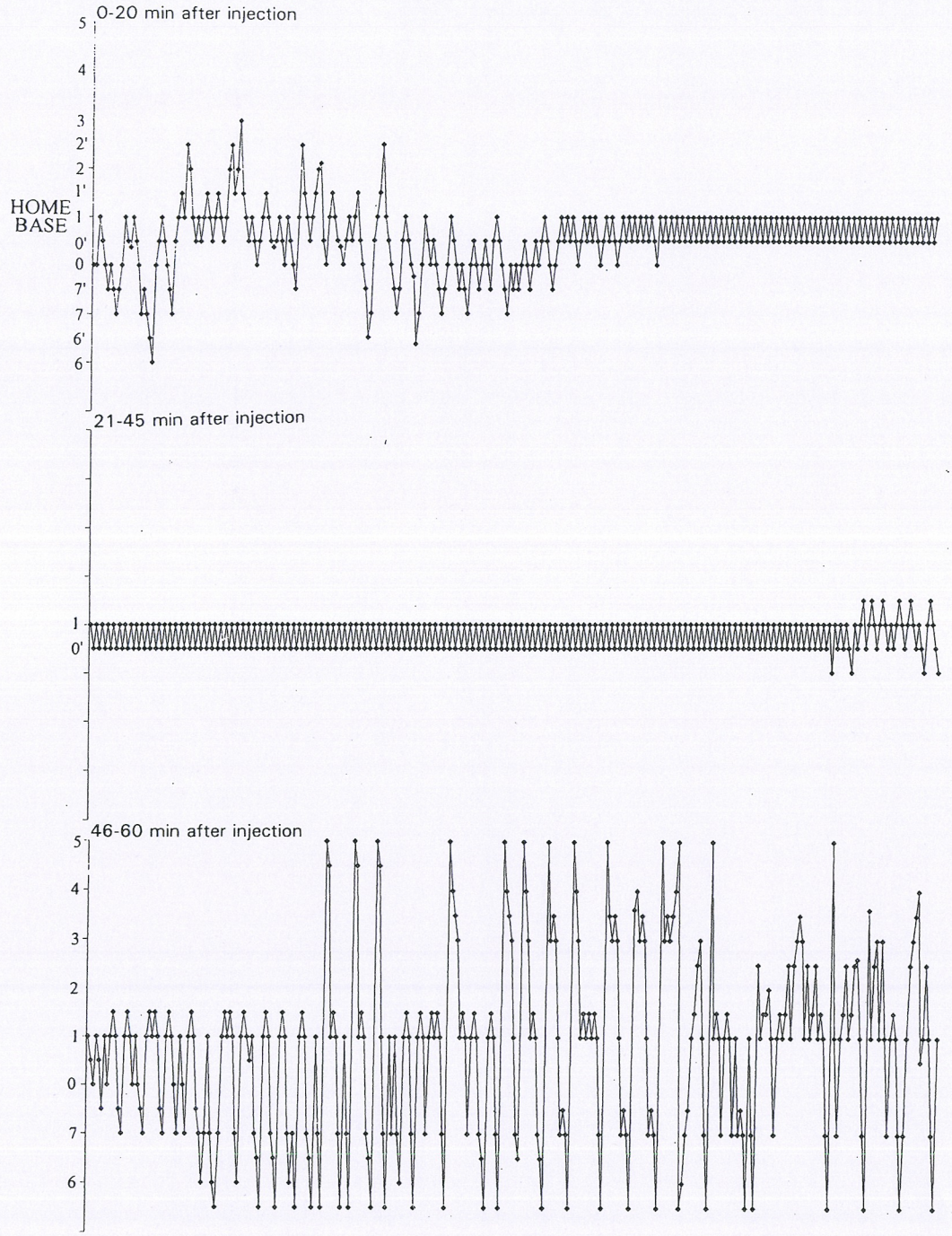


Figure 4 The morphogenesis of a rigid route in relation to a single home base is represented as a temporal series of stopping places. The *y*-axis represents the places on the platform (1 designates the home base; the places located in a clockwise direction in relation to it are arranged on the *y*-axis, on top of it, in their proper spatial order. The places located in a counterclockwise direction are similarly arranged below and away from the home base). The *x*-axis represents successive stops; data points designate places of stopping. The graph represents all the 912 successive stopping places (partitioned into three successive sections of 304 stops each), performed by a rat after 2.5 mg/kg amphetamine. As shown, after some 150 stops, the route became constrained to a performance of the sequence 1,0′ (see Figure 2G) which was repeated about 200 times. Then, both clockwise and counterclockwise excursions reappeared, growing in length to encompass the whole perimeter of the platform, with a relatively small number of stops per excursion.

A fixed route (no variability across paths, variable stopping places across excursions)

This is the same as above, but the rat stops irregularly in different places along the fixed route. Such a route is illustrated in Figure 5, where the rat locomoted for 57 (out of 60) min along one and the same edge of the platform, stopping irregularly at different places along this edge.

A flexible route (variability across paths and stopping places)

Such a route is illustrated in Figure 6 which represents a sequence of successive excursions of a rat treated with 2.5 mg/kg. In all excursions the rat departed from the home base, which was located in the right-hand corner, 1, to the centre of the platform, stopped anywhere in the central area, then progressed to the left hand corner, 7 or nearby, and returned along the far (top) edge to the right-hand corner, performing one or two stops somewhere along the edge.

Rats have one to four routes after amphetamine

A decrease in the number of stops per excursion does not imply a stereotyped route. Given the 25 predefined places on the platform, the rats could execute a

A	B	C	D
7 6 5'	6 5'	7 6 5'	6'
7 6 5	7 6	6'	6 5' 5
6' 5' 5	7	7 6'	5'
7 6 5'	6	6 6'	6 6' 5' 5
6	7 6 5'	7 6 5'	5' 5
7 6 5'	7 6	7 6 6'	5'
7 6 5' 5	7 6 5'	6	6'
6'	7 6	7 6	6 5' 5 4'
7 6 5' 5	7 6 5'	7 6 5'	5'
7 6'	7 6 5' 5	6'	6'
6 5'	5'	7 6 5'	5' 5
7 6 5' 5	7 6 5' 5	6'	6'
7 6 5' 5	5'	6 5' 5	7 5'
7 6 5' 5	7 6 5' 5	6'	6'
5'	6 5' 5	7 6 5'	6 5' 5
7 6 5'	7 6 5' 5	6' 5'	7 6 6'
7 6 5' 5	7 6 5' 5	6'	7 6 6'
7 6'	7 6 6'	6 5' 5	7 6 5' 5

Figure 5 A fixed route is illustrated by a sequence of 72 successive excursions performed by a rat, 20 min after injection of 2.5 mg/kg amphetamine. Sequence should be read from left to right and from top to bottom, in each of the columns A–D. This rat had two home bases, in 7 and in 5′ (see Figure 2G). Locomotion was confined to one edge of the platform, where stopping places varied from one excursion to the next.

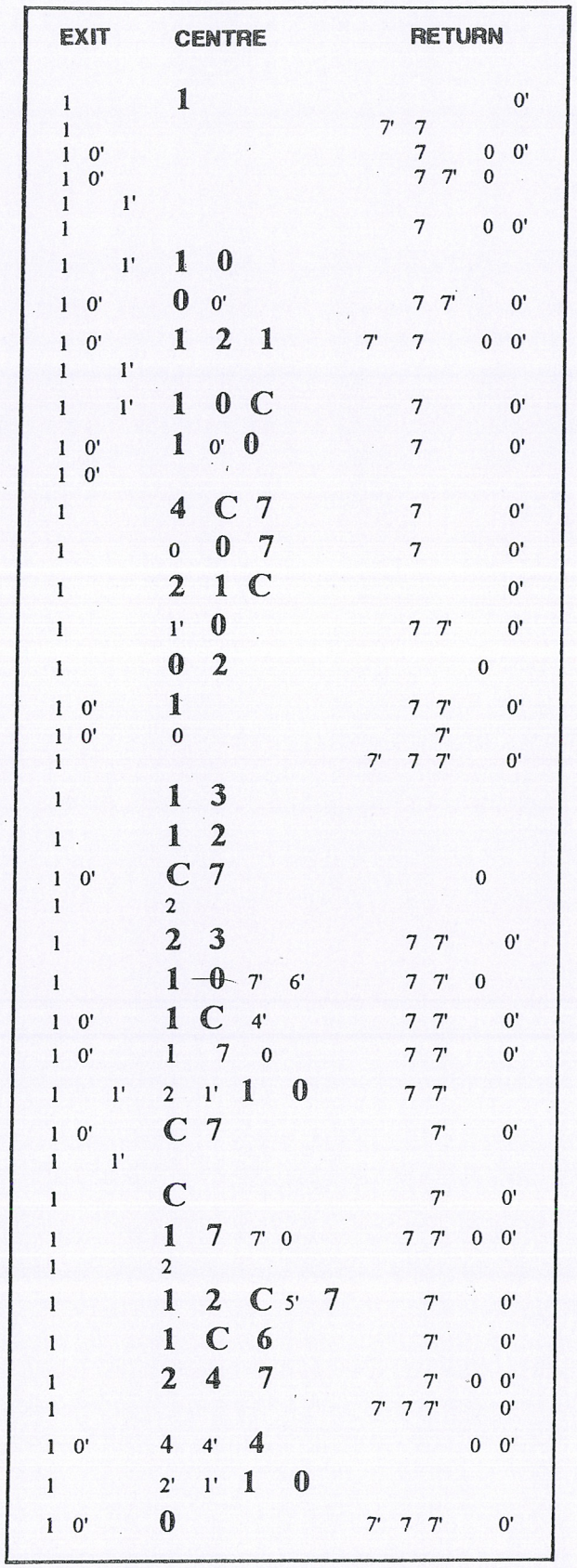


Figure 6 A flexible route is illustrated by a sequence of 42 successive excursions performed by a rat 20 min after injection of 2.5 mg/kg amphetamine. In these excursions the exit and the return portions of the route were fixed, whereas the centre part was variable in path, in the repertoire of stopping places of each path, and in the sequencing of stopping places.

wide variety of sequences of stopping places even within a range of three to four stops per excursion. Nevertheless, in the particular environment used by us, each of the drugged rats performed between one and four routes.

A single route

Rats with a single route had a rigid (Figures 2 and 4), a fixed (Figure 5) or a flexible route (Figure 6).

Two routes

Rats with more than one route had only fixed or flexible routes. The behaviour of a rat with two (fixed) routes is presented in Figure 7. The rat performed two fixed routes from its home base in 1 (at the far right corner): one along the far edge, and another along the right edge. Each of the routes consisted of a fixed path and a flexible sequence of stops. The order of performance of these routes appears to be unpredictable: once the rat was at base, it was impossible to predict which of the two routes it would follow next.

Three or four routes

When a rat had three or four routes, the routes were always flexible. As with the performance of two routes, so here the order of routes could not be predicted (Figure 8, block III). Note that if the routes are presented in the order of their performance (Figure 8, block I), it is difficult to discern a regularity in the identity of places of stopping and in their sequencing. Such regularity is highlighted once the paths are sorted into routes (Figure 8, block II).

No discernible routes

The paths of locomotion of an individual intact rat are illustrated in Figure 9. There is not enough similarity between the excursions to allow classification into routes. Each stopping place is an elementary building block of behaviour in locale space, and the combinations between these building blocks are unpredictable.

Rats may have one or two bases with amphetamine

Locomotion with reference to one base across the session

All the excursions of the rats described so far were organized in reference to a single home base. In the course of the first exposure to a novel environment, both normal (Eilam and Golani, 1989) and amphetamine-treated rats (Eilam and Golani, 1990) may, however, have more than a single base, but rarely more than two bases.

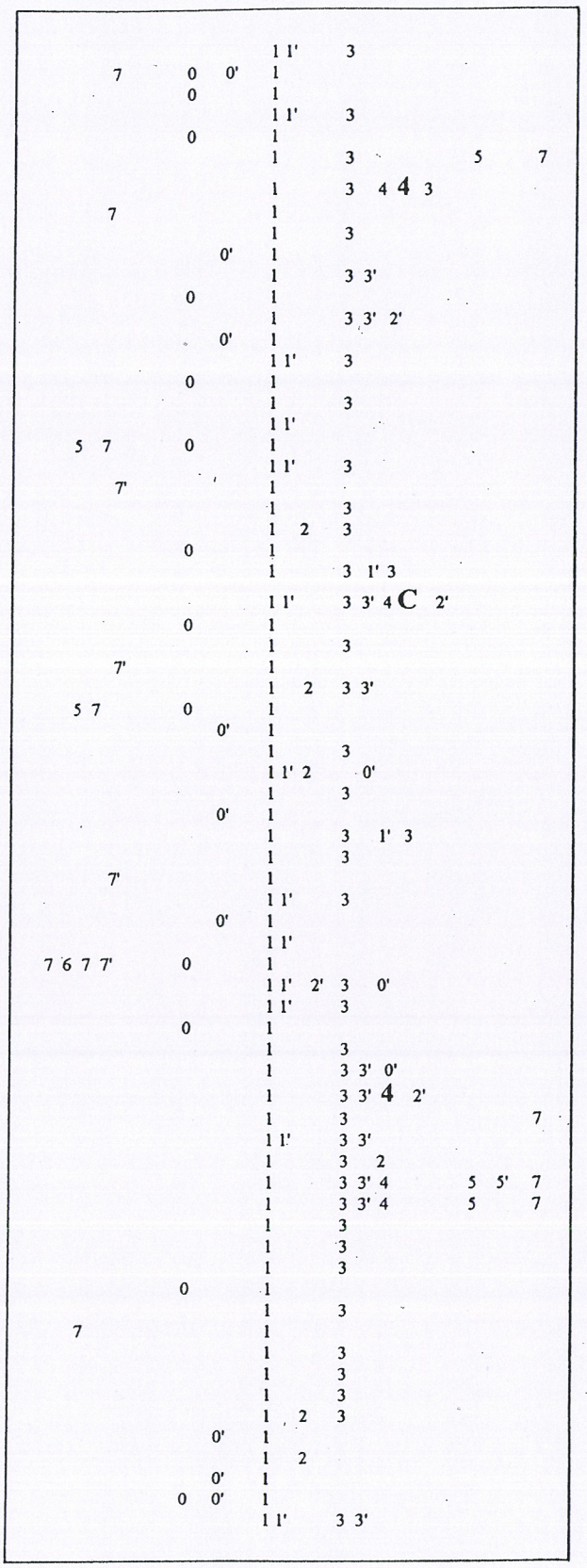


Figure 7 Two fixed routes are illustrated by 69 successive excursions performed by a rat 20 min after injection of 5 mg/kg amphetamine. The numeral representing the home base, 1, is aligned in the central column, and the stopping places along the two routes are shown in proper order on both of its sides. The route which was performed on the

Locomotion in reference to two bases across the session

When there are two home bases, they are visited in two different temporal modes. (i) Each of the two bases was used as a single base for a specific interval of time. In this way, each excursion included a stop at only one of the bases, but the cumulative record of excursions across the session included excursions organized around either of the two bases. (ii) Both bases were visited during the same excursion, so that excursions, including stops at both bases, were performed repeatedly for extended periods.

When two bases were visited at separate times (first mode), a rat typically performed a series of relatively short excursions in reference to one corner, and then switched to another corner and performed short excursions in reference to it. The rat thus had two bases (in two corners), but at a given time interval it was moving in reference to only one of them (Figure 10).

In two bases per excursion (second mode), a relatively long path connected the two bases (which were often located at two far ends of the platform). In Figure 11, the rat locomoted around the platform's perimeter in a counterclockwise direction with a certain flexibility in the sequence of stopping places, yet it rarely skipped a stop in 5 and in 7, which were used as its home bases.

TIME-COURSE OF DRUG ACTION

Number of stops per excursion and excursion rate

Figure 12 presents the frequency distribution of excursion types (in terms of the number of stops included in them), in the course of an hour. Graphs are presented for each of four rats, first without (left), and then with (right) amphetamine. Excursions are classified on the x-axis, in terms of the number of stops included in them; frequency per 5 min bins is plotted on the vertical, z-axis. Time, in 5 min bins, is presented on the y-axis, from top to bottom across the hour.

With amphetamine, the early portion of the hour was similar to that observed in normal rats during peak activity. Then, excursions with a large number of stops were eliminated, and excursions with a small number of stops were performed at exceedingly high rates throughout the hour (note change of frequency scale in three of the right-hand graphs). The reduction in the number of stops per excursion with amphetamine was accompanied by an increase in the rate of excursions.

---

table's edge clockwise is shown on the right of the home base numeral, and the counterclockwise one, on its left; the rat visited the places shown in the figure, from top to bottom, in the following order: 1,1′,3,1,0′,0,7,1,0,1,1′,3 . . . etc. As shown, the rat switched, in what appears to be an irregular order, between the two fixed routes, but each route had a 'fixed' structure.

I

A 4 3
D 4 4 0 1 3
B 4 4
D 4 5 6 0 1 2' 3
B 4 4' 5
A 4 2' 3
A- 4 2' 2
D 4 4' 5 5' 7 1 2' 3
A 4 3
A 4 3
D 4 4 6 7 1 3
C 4 3 2' 1 3
D 4 4 5' 7 1 3
A 4 3 3
A 4 3
A 4 3
B 4 5 5'
C 4 3 1 3
A 4 4 2' 3
A 4 3
D 4 3 4 5' 7 1 3
A 4 3
A 4 3
A 4 3
A 4 3
B 4 4
A 4 3
B 4 5
A 4 3 2'
B 4 5'
A 4 3
B 4 4 5'
C 4 1 3
C 4 3 1 3
A 4 3 2'
A 4 3
A 4 3
B 4 5 5'
A 4 3
B 4 5'
A 4 3

II

A

4 3
4 2' 3
4 2' 2
4 3
4 3
4 3 3
4 3
4 3
4 4 2' 3
4 3
4 3
4 3
4 3
4 3
4 3
4 3
4 3 2'
4 3
4 3 2'
4 3
4 3
4 3
4 3
4 3
4 3
4 3
4 2' 3
4 3
4 2'
4 3
4 3
4 4 2 3
4 3
4 4 2 3

A (Cont.)

4 3
4 3
4 3
4 3
4 3
4 3
4 3
4 2'
4 3
4 3
4 3
4 3
4 3 2'
4 2' 3
4 3 2'
4 3
4 3
4 3
4 3
4 2' 3
4 3
4 3
4 3
4 3
4 3
4 3
4 3
4 3
4 2' 3
4 2' 3
4 3
4 3
4 3
4 3

B

4 4
4 4' 5
4 5 5'
4 4
4 5
4 5'
4 4 5'
4 5 5'
4 5'
4 4
4 5' 5 5'
4 4
4 5
4 5' 5
4 6
4 5
4 5' 5
4 5 5'
4 4
4 5
4 6
4 5' 5
4 5
4 5 6
4 4
4 5
4 5
4 5
4 5
4 4
4 5 5'
4 4' 5'
4 5' 5
4 5' 5
4 5'

C

4 3 2' 1 3
4 3 1 3
4 1 3
4 3 1 3
4 3 1 3
4 1 3
4 2' 1 3
4 1 3
4 1 3
4 3 3 1 3

D

4 4 0 1 3
4 5 6 0 1 2' 3
4 4' 5 5' 7 1 2' 3
4 4 6 7 1 3
4 4 5' 7 1 3
4 3 4 5' 7 1 3
4 5 6 7 1 3
4 5 7' 1 3
4 5' 6 7 1 3
4 5 7 1 3
4 0 1 3
4 4 7 1 3
4 7 1 2' 3
4 6 7 1 3

III

A D B D B A A D A A D C D A A A B C A A D A A A A B
A B A B A B C C A A A B A B A A A C B A A A B A D A
A B B A D A A D A B A B A B D B A B D B B B A A
B C A A A B A A A B A C A A A C A D C B A B A B A B
B A A A A A A A A C A A A A B A D B B A A A B C B A
C B A B A A 3 B A B D

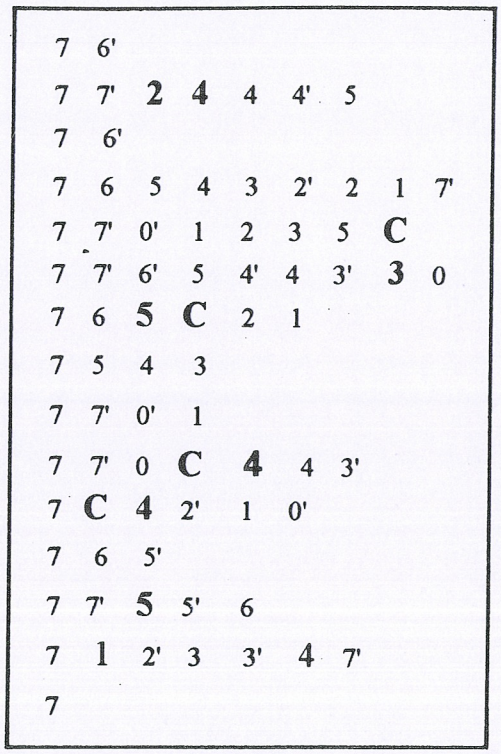


Figure 9 The temporal sequence of stopping places, partitioned into excursions, performed by an intact rat in the course of 1 h after being introduced to the platform. The rat was placed in the centre of the platform, and performed three stops (not shown) before arriving at the home base, 7, for the first time. It then performed 14 excursions and settled for the rest of the hour in the home base.

Mean number of stops across the session

We have already shown that when examined cumulatively for the whole hour, there was no effect of dose on the number of stops per excursion (Figure 3). Figure 13(A) presents the means (+ s.e.m.) of the number of stops per excursion in 20 min bins, across the hour. As shown, all four doses reduced these measurements, without a dose-dependent effect.

Figure 8 A repertoire of four routes is illustrated in the sequence of excursions performed by a rat after injection of 0.5 mg/kg amphetamine. In each block, numerals represent the order of stopping, from left to right and from top to bottom (the mapping of the platform is presented in Figure 2G). Block I represents the first 41 excursions in the session, in the original order of their performance; the column on the left classifies the excursions into routes. Block II presents sorted lists of each of the four routes. The routes are presented within each list in the order of their performance, so that stereotypy versus variability in stopping locations can be examined visually across the session. The home base 4 is located in the middle of the near edge of the platform; A and B are, respectively, routes to the nearest left and nearest right corner (and back to base): C is a route to the far right corner (and back); and D is a clockwise route around the platform's perimeter. Block III represents the sequence of routes performed by the rat throughout the session.

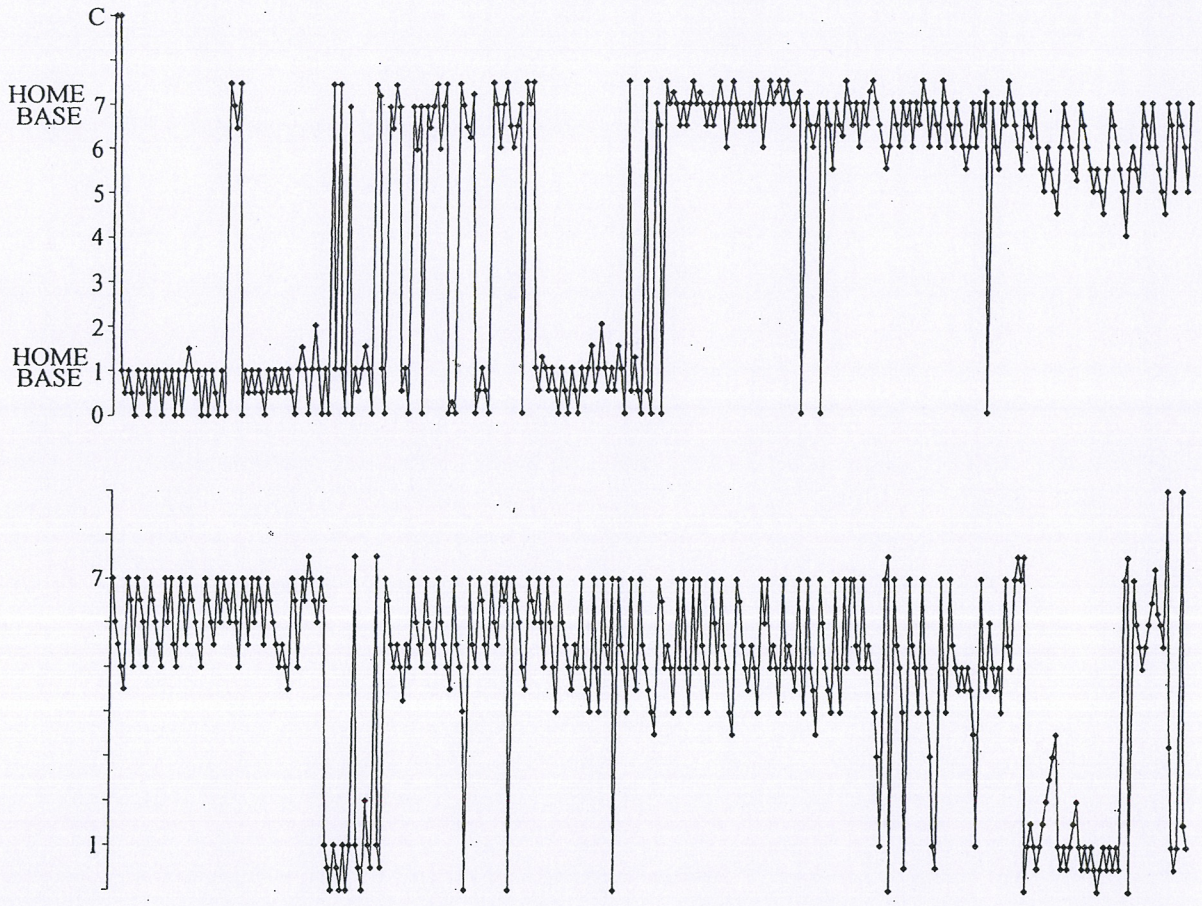


Figure 10 Locomotion with reference to two bases, separated in time. The *y*-axis represents the places on the platform's perimeter (for a map see Figure 2G). The *x*-axis represents the temporal order of stops. Each data point thus represents a stopping place. In this rat session, the home bases were located in 1 and in 7. This rat, treated with 5 mg/kg amphetamine, performed 756 stops during the hour. It started to perform excursions in reference to base 1 (beginning of top section), then, after several occasional visits to 7 and its vicinity, switched to perform excursions in reference to 7, now visiting the first home base, 1, occasionally (second half of the upper section, and most of the lower section).

Number of routes

Figure 13(C) presents the mean number of routes followed by a rat, in 20 min bins, across the session. The bin size is too large to show the initial reduction in the number of different routes, illustrated in Figure 2. This process of restriction in the number of routes was observed only in the rats which were active from the start of the session and was often completed within the first few minutes after injection. Rats that were inactive in the first few minutes started with few routes with the onset of locomotion. Figure 13(C) does show, however, that there is a distinction between low (0.5–1 mg/kg) and high (2.5–5 mg/kg) doses in the mean number of routes.

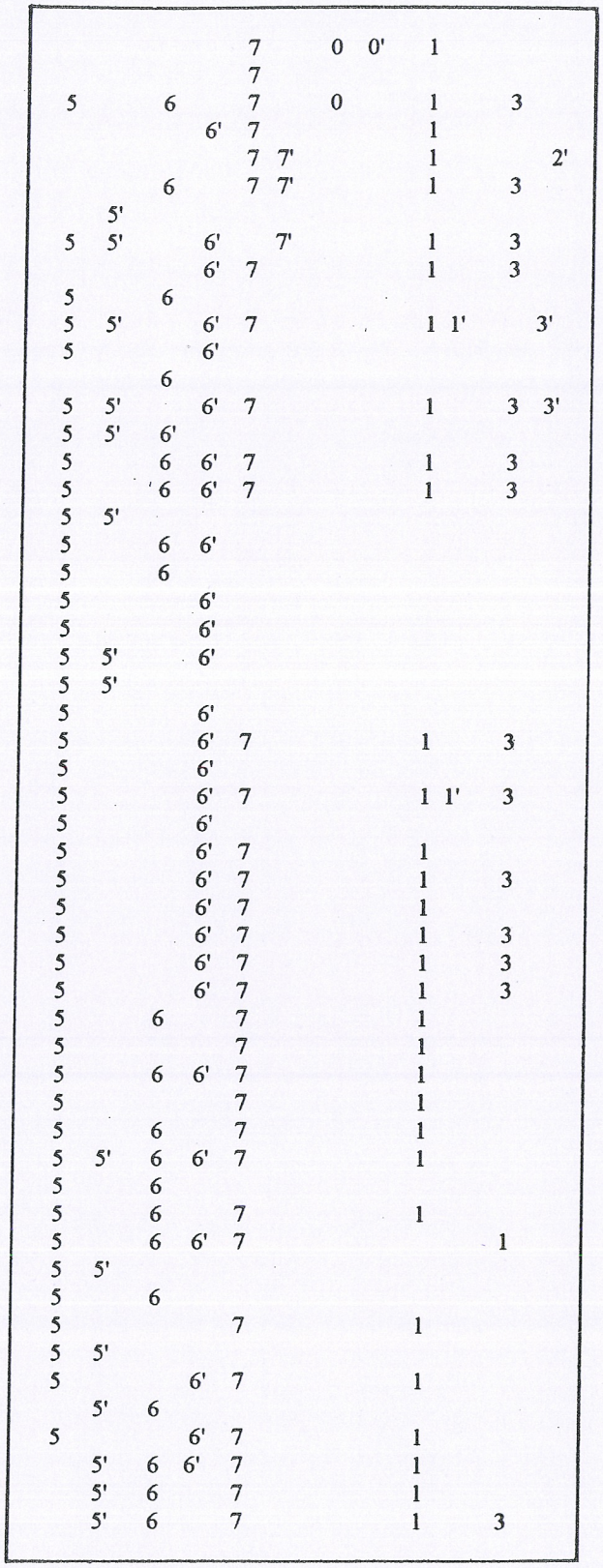
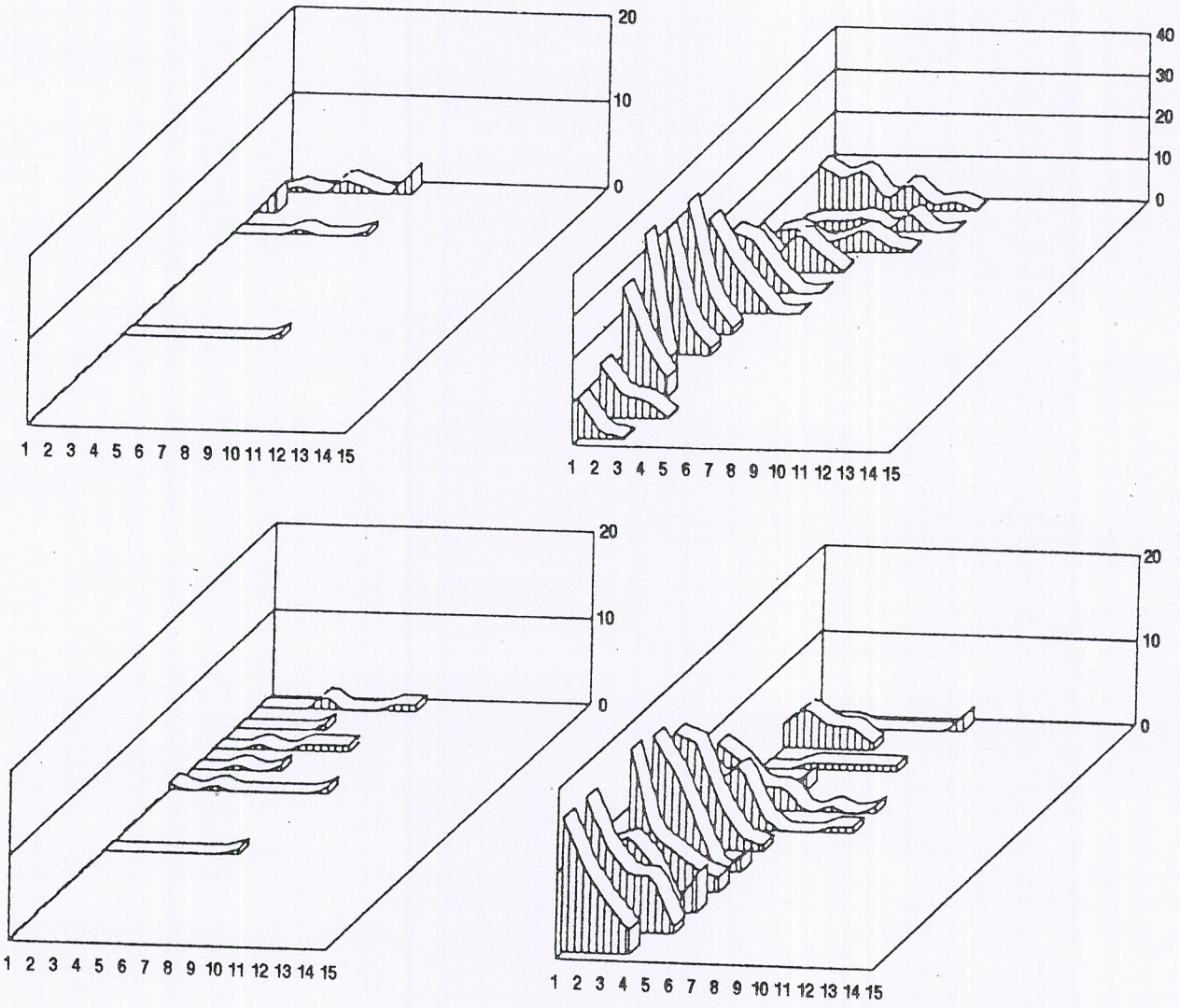


Figure 11 A single route traverses two home bases during successive excursions of a rat, 20 min after injection of 5 mg/kg amphetamine. Except for two short periods during which the rat moved in reference to only one of the bases, it traversed both bases in the same excursion, for most of the time.

NORMAL

AMPHETAMINE



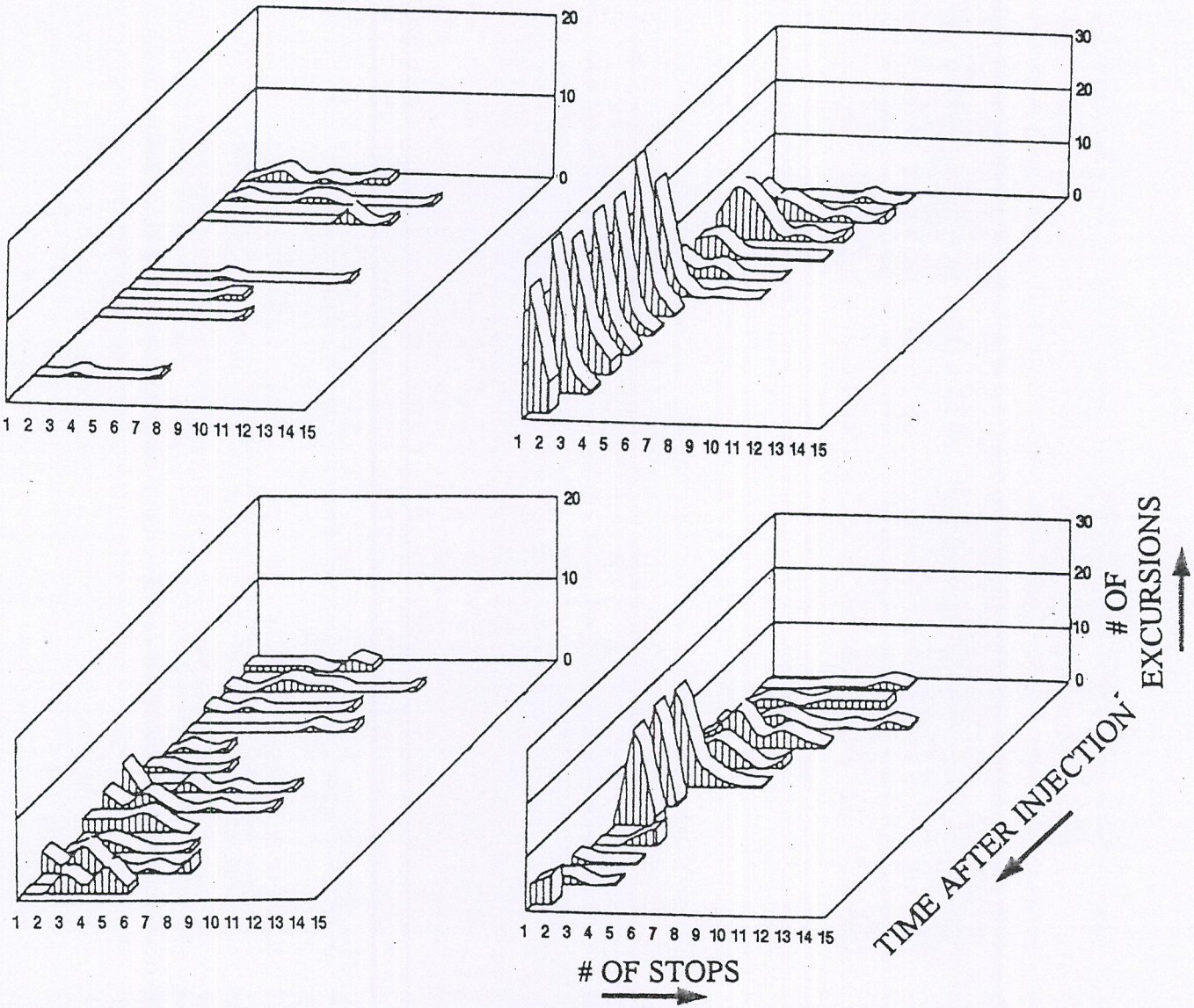


Figure 12 The effect of amphetamine on the frequency distribution of excursions with different numbers of stops, across the session; four individual examples (0.5 mg/kg, top row; 1 mg/kg, second row; 2.5 mg/kg, third row; 5 mg/kg, bottom row). Data are presented in 5 min bins. Each row represents the same rat as normal (left) and with amphetamine (right). *x*-axis: number of stops per excursion; *y*-axis: time *z*-axis: frequency of excursions.

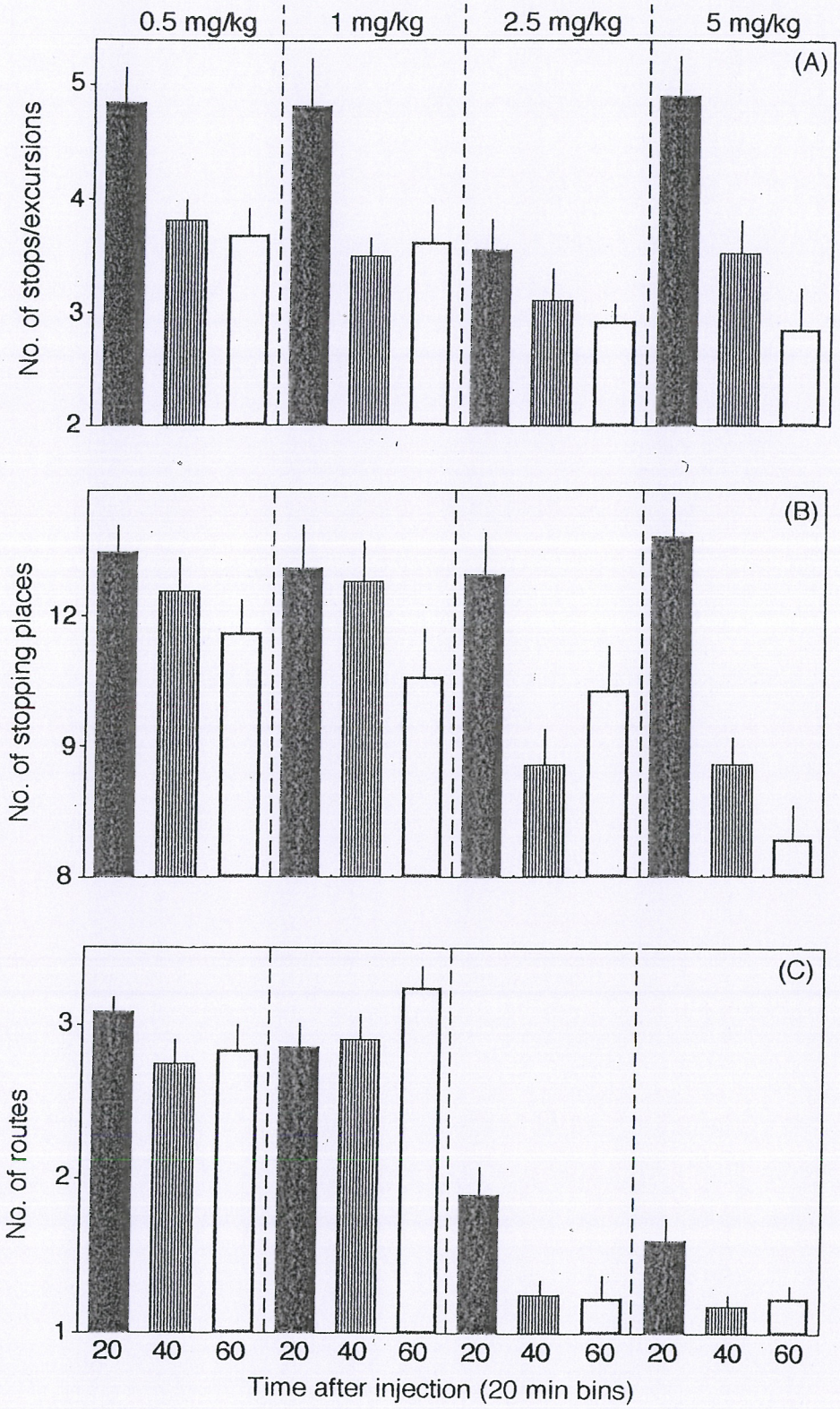


Figure 13 Changes in the mean (+ s.e.m.) number of stops per excursion (A), the mean (+ s.e.m.) number of different stopping places (B), and the mean (+ s.e.m.) number of different routes (C), in three successive 20 min time bins, over the course of drug action. For each measure, the four dose groups are represented, separated by vertical dashed lines. To facilitate comparison both across the session and across parallel time intervals with different doses, measures for the first 20 min after injection are depicted by solid bars, for the next interval of 21–40 min are depicted by hatched bars,

Table 1 Dose of amphetamine, number of bases, and the degree of stereotypy of routes. Numerals in the dose columns indicate the number of rats which exhibited the specified type of route

Type of route	Number of bases	Dose of amphetamine (mg/kg)			
		0.5	1	2.5	5
Flexible route	1	8	6	1	–
	2	–	1	–	–
Fixed route	1	–	–	–	1
	2	–	–	5	1
Rigid route	1	–	–	1	1
	2	–	–	1	4

EFFECTS OF DOSE ON THE DEGREE OF STEREOTYPY OF EXCURSIONS AND NUMBER OF BASES

Table 1 relates the amphetamine dose to the degree of stereotypy of routes at the time when the rat's behaviour is most restricted, and to the number of the rat's bases. The table suggests a dose-dependent tendency to reduce the flexibility of routes from flexible (the low doses), through fixed, to rigid (the higher doses), and increases the number of bases from one to two (with increasing dose, the ratio of two-base rats is 0/8, 1/7, 6/8 and 5/7).

EPILOGUE: 'PACKAGES' OF PLACES OF STOPPING

In summary, the rat's behaviour was organized with reference to home base over the whole range of amphetamine doses which we examined. Therefore, it is an appropriate reference place for the measurement of the drug's action (Eilam and Golani, 1990). Stopping at this reference place divides the flow of both normal and amphetamine-induced behaviour into natural morphogenetic units called *excursions* (Golani *et al.*, 1993). In the present report, we provide a first-approximation description of the morphogenesis of excursions with amphetamine in locale space. The process appears to be characterized by the shaping of routes, by a dose-dependent reduction in the number of routes, by an increase in the rigidity of routes, by a decrease in the mean number of stops per excursion compared to the normal, and by an increase in the number of bases.

Examination of the individual records reveals that during most of the session, except for the first few minutes, the drug also reduced the maximum

and for the 41–60 min interval are depicted by empty bars. (A) In all groups there was a decrease in the mean number of stops per excursion. (B) The number of different places in which the rat stopped decreased in the course of drug action. A marked decrease was observed with 2.5 and 5 mg/kg after 20 min. (C) A low mean number of roughly three routes characterizes the two lower doses. The mean was further decreased to less than two routes with the two higher doses.

number of stops per excursion (e.g. Figures 2, 3 and 12). To evaluate this process quantitatively, however, it would be necessary to establish the type(s) of the distribution of the number of stops per excursion dose dependently, using similar statistical tools to those used in the examination of normal stopping behaviour (Golani *et al.*, 1993).

Examination of the individual records also reveals that with the higher doses there is a gradual reduction in the number of different visited places across excursions and an increase in the rigidity of their sequencing (i.e. during successive excursions the rat tends to stop in the same places, and in the same order; Figures 2, 3, 7 and 8). Figure 13(B) presents the number of different stopping places in 20 min bins across the session. As it shows, there was a marked decrease in this measure with the two high doses. To examine this phenomenon further quantitatively, it would be necessary to establish a formal method for the classification of routes. In the absence of a formal definition, we presently define routes intuitively, in much the same way that classical ethologists define 'behaviour patterns' (Barlow, 1977).

We may now re-examine the transition from normal behaviour to drug-induced stereotypies. Normal exploratory behaviour is constrained by the existence of a home base whose attraction increases after each stop performed by the rat. This is expressed by the existence of an upper bound on the number of stops per excursion. Within this bound, however, the rat appears to have relatively direct access to all the places in the environment: the location of the next place of stopping cannot be predicted on the basis of knowledge of the previous place(s) of stopping.

A low dose reduces the mean number of stops per excursion and also the maximum number of stops per excursion. It also partitions the list of all places in the environment into three to four 'packages' (Hultsch and Todt, 1989). Each package includes several specific places in which the rat has a relatively high probability of stopping. These are the flexible routes described above.

With a high dose the number of packages is reduced, the list of visited places is shorter and the sequencing of these places becomes increasingly more fixed. As with normal behaviour, the flow still consists of repeated performance of excursions, but the variety of routes, and the variability of stopping places within them, is gradually reduced. In its most extreme form, behaviour becomes consolidated into one or two packages, each consisting of the same few places in which the rat stops in a fixed order. Direct free access to places in the environment is lost; the packages are executed *en bloc*; once started, the rat proceeds in a fixed order through the full sequence of places included in this package (see Figure 2). The package, and not the individual place, now becomes both the elementary building block and the highest recognizable unit of organization of topographically specific behaviour in locale space.

This consolidation of exploratory behaviour into packages of stopping places is reminiscent of similar processes of chunking taking place during learning in humans (Miller, 1957), and in the formation of packages of songs in night-

ingales, during song acquisition in ontogeny (Hultsch and Todt, 1989). Chunking has been considered a strategy for coping with an increasing load on information-processing capacity, in the context of the establishment of habits, and in the consolidation of memory (DeGroot, 1965; Moats and Schumacher, 1980; Murdock, 1961; Simon, 1974). The establishment of spatiotemporal packages under amphetamine could also be explained in terms of a hypothetical mechanism for coping with a drug-induced reduction in information-processing capacity. At the present stage of knowledge, however, it might be more fruitful to continue with the study of morphogenesis of behaviour in locale space at the level of observables.

ACKNOWLEDGEMENTS

We thank the staff of the Meir Segals Garden for Zoological Research for their help in keeping and filming the animals. This research was supported by the Israel Institute for Psychobiology, Charles E. Smith Foundation, Grant 6-92 to D.E., and by the Israel Science Foundation, administered by the Israel Academy of Sciences and Humanities to I.G.

REFERENCES

Adani, N., Kiryati, N. and Golani, I. (1991) The description of rat drug-induced behaviour: kinematics versus response categories. *Neurosci. Biobehav. Rev.*, **15**, 455–460.

Arnt, J., Hytell, J. and Perregaad, J. (1987) Dopamine D_1 receptor agonists combined with the selective D_2 agonist quinpirole facilitate the expression of oral stereotyped behaviour in rats. *Eur. J. Pharmacol.*, **133**, 137–145.

Arnt, J., Bogeso, K.P., Hytell, J. and Meier, E. (1988) Relative dopamine D_1 and D_2 receptor affinity and efficacy determine whether dopamine agonists induce hyperactivity or oral stereotypy in rats. *Pharmacol. Toxicol.*, **62**, 121–130.

Barlow, G.W. (1977) Modal action patterns. In: *How Animals Communicate* (ed. T.A. Sebeok). Indiana University Press.

Brodi, F. and Meller, E. (1989) Enhanced behavioural stereotypies elicited by injection of D_1 and D_2 dopamine agonists in intact rats. *Brain Res.*, **504**, 276–283.

Cooper, S.J. and Dourish, C.T. (1990) *The Neurobiology of Stereotyped Behaviour*. Oxford Science Publications, Oxford.

Costall, B. and Naylor, R.J. (1975) Actions of dopaminergic agonists on motor function, *Adv. Neurol.*, **9**, 285–297.

Cronin, G.M. (1985) *The Development and Significance of Abnormal Stereotyped Behaviour in Tethered Sows*. PhD thesis, Agricultural University of Wageningen, The Netherlands.

Cronin, G.M. and Wiepkema, P.R. (1984) The development and significance of abnormal stereotyped behaviours in tethered sows. *Ann. Rech. Vet.*, **15**, 263–270.

De Groot, A.D. (1965) *Thought and Choice in Chess*. Mouton, The Hauge.

Eilam, D. (1987) *Exploratory Behaviour in Norway Rats (Rattus norvegicus): Normal Behaviour and the Behaviour under the Psychoactive Drug Amphetamine*. Doctoral dissertation, Tel-Aviv University, Ramat-Aviv, Israel.

Eilam, D. and Golani, I. (1989) Home base behaviour of tame wild rats (*Rattus norvegicus*) in a novel laboratory environment. *Behav. Brain Res.*, **34**, 199–211.

Eilam, D. and Golani, I. (1990) Home base behaviour of tame wild rats (*Rattus norvegicus*) injected with amphetamine. *Behav. Brain Res.*, **36**, 161–170.

Eilam, D., Golani, I. and Szechtman, H. (1989) D-2 agonist quinpirole induces perseveration of routes and hyperactivity but no perseveration of movements. *Brain Res.*, **460**, 255–267.

Eilam, D., Clements, K.V.A. and Szechtman, H. (1991) Differential effects of D1 and D2 dopamine agonists on stereotyped locomotion. *Behav. Brain Res.*, **45**, 117–124.

Eilam, D., Talangayan, H., Canaran, G. and Szechtman, H. (1992) Dopaminergic control of locomotion, mouthing, snout contact, and grooming, opposing roles of D1 and D2 receptors. *Psychopharmacology*, **106**, 447–454.

Flicker, C. and Geyer, M.A. (1982) Behaviour during hippocampal microinfusions: I. Norepinephrine and diversive exploration. *Brain Res. Rev.*, **44**, 79–103.

Fray, P.J., Sahakian, B.J., Robbins, T.W. *et al.* (1980) An observational method for quantifying the behavioural effects of dopamine agonists. Contrasting effects of *d*-amphetamine and apomorphine. *Psychopharmacology*, **69**, 253–259.

Geyer, M.A. (1982) Variational and probabilistic aspects of exploratory behaviour in space: four stimulant styles. *Psychopharmacol. Bull.*, **18**, 48–51.

Geyer, M.A., Russo, P.V. and Masten, V.L. (1986a) Multivariate assessment of locomotor behaviour: pharmacological and behavioural analyses. *Pharmacol. Biochem. Behav.*, **25**, 277–288.

Geyer, M.A., Russo, P.V., Segal, D.S. and Kuczenski, R. (1986b) Effects of apomorphine and amphetamine on patterns of locomotor and investigatory behaviour in rats. *Pharmacol. Biochem. Behav.*, **28**, 393–399.

Golani, I. (1992) A mobility gradient in the organization of vertebrate movement: the perception of movement through symbolic language. *Behav. Brain Sci.*, **15**, 249–308.

Golani, I. and Eilam, D. (1994) Amphetamine constrains stopping behaviour in rats (*Rattus norvegicus*) during exploration. *Behav. Pharmacol.* (submitted).

Golani, I., Benjamini, Y. and Eilam, D. (1993) Stopping behaviour: constraints on exploration in rats (*Rattus norvegicus*). *Behav. Brain Res.*, **3**, 21–33.

Hediger, H. (1964) *Wild Animals in Captivity*, Dover Publications, New York.

Hultsch, H. and Todt, D. (1989) Memorization and reproduction of songs in nightingales (*Luscinia megarhynchus*): evidence for package formation. *J. Comp. Physiol. A*, **165**, 197–203.

Kelly, P.H. (1977) Drug-induced motor behaviour. in: *Handbook of Psychopharmacology*, Vol. 8 (eds L.L. Iversen, S.D. Iversen and S.H. Snyder). Plenum Press, New York, pp. 295–331.

Lyon, M. and Robbins, T.W. (1975) The action of central nervous system stimulant drugs: a general theory concerning amphetamine effects. In: *Current Developments in Psychopharmacology*, Vol. 2 (eds W. Essman and L. Valzelli). Spectrum, New York, pp. 89–163.

Miller, G.A. (1956) The magic number seven plus or minus two: some limits on our capacity for processing information. *Psychol. Rev.*, **63**, 81–97.

Moats, D.R. and Schumacher, G.M. (1980) *An Introduction to Cognitive Psychology*. Wadsworth, Belmont, CA.

Muller, K., Hollingsworth, E.M. and Cross, D.R. (1989) Another look at amphetamine-induced stereotyped locomotor activity in rats using a new statistic to measure locomotor stereotypy. *Psychopharmacology*, **97**, 74–79.

Murdock, B.B., Jr (1961) The retention of individual items. *J. Exp. Psychol.*, **62**, 618–675.

Paulus, M.P. and Geyer, M.A. (1991) Temporal and spatial scaling hypothesis for the behavioural effects of psychostimulants. *Psychopharmacology*, **104**, 6–10.

Randrup, A. and Munkvad, I. (1970) Biochemical, anatomical and psychological investigations of stereotyped behaviour induced by amphetamines. In: *Amphetamines and Related Compounds*. (eds E. Costa and S. Garattini). Raven Press, New York, pp. 695–713.

Schiorring, E. (1971) Amphetamine induced selective stimulation on certain behaviour items with concurrent inhibition of others in an open field test with rats. *Behaviour*, **39**, 1–17.

Schiorring, E. (1979) An open field study of stereotyped locomotor activity in amphetamine-treated rats. *Psychopharmacology*, **66**, 281–287.

Simon, H.A. (1974) How big is a chunk? *Science*, **183**, 482–488.

Stevenson, M.F. (1983) The captive environment: its effects on exploratory and related behavioural responses in wild animals. In: *Exploration* (eds J. Archer and L. Birke). Van Nostrand Reinhold, UK, pp. 176–197.

Szechtman, H., Ornstein, K., Teitelbaum, P. and Golani, I. (1985) The morphogenesis of stereotyped behaviour induced by the dopamine receptor agonist apomorphine in the laboratory rat. *Neuroscience*, **14**, 783–798.

Szechtman, H., Talangbayan, H., Canaran, G. *et al.* (1994) Dynamics of behavioural sensitization induced by the dopamine agonist quinpirole and a proposed central energy control mechanism. *Psychopharmacology* (in press).