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Rats and mice share common ethologically relevant parameters of exploratory behavior

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Abstract

Detailed studies of rat exploratory behavior reveal that it consists of typical behavior patterns having a distinct structure. Recently we have developed interactive software that uses as input the automatically digitized time-series of the animal's location for the visualization, analysis, capturing and quantification of these patterns. We use this software here for the study of BALB/cJtau mouse behavior. The results suggest that a considerable number of rat patterns are also present in the mouse. These ethologically-relevant patterns have a significant potential as a phenotyping tool. © 2001 Published by Elsevier Science B.V.

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1. Introduction

In behavior genetics there is, on the one hand, a need for robust measures of mouse behavior that will show resistance to the experimental conditions of particular laboratories [4], and on the other hand a need for high throughput phenotyping [14]. In our own work on rats we use two methodological tools that could help fulfill these needs. We look for innate patterns, which, by definition, should show resistance to environmental manipulations, and we search for these patterns by using algorithms that allow automatic analysis of large quantities of data [7]. These tools could also be used in the phenotyping of mouse behavior.

Anyone can see that when a rat or a mouse are placed in a novel environment they alternate between progression and stopping. Each time the animal stops it performs scanning movements—sniffing, establishing snout contact with the substrate, and/or looking around. The type, rate, and number of scans presumably determine the amount and type of information gathered by the animal. Forward progression carries the animal from one location to the next, while stopping and scanning involve investigation of particular locations [2]. These two patterns constitute locomotor behavior, a *par excellence* innate pattern [13]. Only recently has it been shown that the inverse relationship between stepping and scanning is mediated by the hypothalamus [15]. Clearly, these patterns serve separate and distinct functions, and it is only reasonable to expect that measuring and quantifying their sizes, durations and rates, separately, would help differentiate between species, strains, and preparations.

Because, in rodents, stopping largely implies scanning and scanning implies cessation of progression and stopping, measuring stopping entails an indirect measuring of scanning, which in turn implies measuring of information acquisition and attention-involving processes. The type of a scan determines the duration and the spatial spread of a stopping episode: a forward scan involving only the head and neck is shorter in duration than that of a scan recruiting the whole body. While performing these scans the animal's center of gravity

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changes its location; the spatial spread of this change, i.e. the length of the path traced by the animal on the ground while performing the scan, is small for head scans and large for whole body scans involving stepping. The number of scans performed during a stopping episode also determines the duration and the spatial spread of a stopping episode. All these ethologically meaningful patterns influence the duration and spatial spread of stopping episodes. Capturing and quantifying their spatiotemporal features should, therefore, prove a fruitful phenotyping tool.

Capturing stops is, however, not a straightforward task. This is because: (i) stopping is not to be equated with arrest, i.e. it does not necessarily consist of zero speed; and because (ii) the cutoff speed values distinguishing between progression and 'stopping' differ from species to species and from strain to strain. To distinguish between stopping and progression we have to estimate speeds, i.e. the first derivative of the (noisy) location data. This further increases the level of the noise so that smoothing the data becomes even more essential. On the other hand, because of their ethological significance, we do not want to lose stops (which are sometimes as short as 0.2 s) in the process of smoothing the data. We accomplish this with a smoothing algorithm, Robust LOWESS [3]. Having at hand the speed values, we can finally classify episodes of motion into progression episodes and stopping episodes. The term stopping is, however, misleading for segments of behavior that often show a considerable 'smear' in space. Therefore, we also term this mode of motion 'lingering', 'staying in place behavior', or '1st gear mode' (so as to distinguish it from the 2nd and sometimes 3rd gear modes that involve extensive progression [6]).

Having established the distinction between stopping and progression in the rat, we have noted that the rat tends to stop repeatedly in the same or near-by locations. In this way it establishes operational places in the environment. One (or two) of these places, which stand out from all the other places in terms of the number of stops performed in them and in terms of the cumulative time spent in them has been termed a home base [9]. From the home base the rat performs round trips (excursions) into the environment. The number of stops per excursion is bounded and not increasable by increasing the size of the environment [10]. Excursions gradually grow in amplitude; their outbound portion is slow and intermittent, and their inbound portion is fast and continuous. With extended exposure, the velocity profile of excursions changes in a predictable manner [17,18].

The growing interest among behavior geneticists in the phenotyping of mouse behavior begs the question of whether similar patterns can also be isolated in the mouse. Do mice also establish a home base upon being introduced into a novel environment? Do they also perform excursions from this home base? And if so, are these excursions composed of an alternation between progression and stopping episodes? Is the velocity profile in mice similar to that characterizing hooded rat behavior? A description of mouse behavior in terms of these and other ethologically-relevant parameters should promote the mapping of the mouse genome/behavior interface by first characterizing the repertoires of inbred strains, and then the repertoire of congenic lines, knockouts, transgenic lines, and populations obtained by selective breeding.

A step in this direction is taken in the present study by using the descriptive model obtained in the rat as a search image in the examination of the behavior of one gender belonging to a single strain of mice: that of male BALB/cJtau mice.

Recently we have developed interactive software for analyzing exploratory behavior. This software, named SEE (Software for Exploring Exploration; see http://www.tau.ac.il/~ilan99) generates visualizations and quantifies the patterns of rat exploratory behavior using as input the automatically digitized time-series of the animal's location [7]. In the present paper we use SEE for the analysis of mouse exploratory behavior. In this way we also examine this software's potential as a phenotyping tool of mouse behavior.

The behavioral parameters established in the rat reveal a natural structure that is relatively independent of the animal's level of activity. They reflect processes involving motivation, navigation, spatial memory and learning. They can be measured automatically and efficiently, using setups and hardware that are already in use in many laboratories. The establishment of corresponding parameters in the mouse should promote an algorithmic approach to the study of behavioral expression and encourage inter-disciplinary research between the fields of behavioral neurogenetics, ethology, and cognitive psychology.

2. Materials and methods

2.1. Animals

Experimental animals were eight BALB/cJtau mouse males from the Tel-Aviv University medical school stocks, 62 days old, weighing 22–26 g at the time of the experiment. All animals were experimentally naive, housed in groups of four and given unlimited access to food and water. Lights were turned off at 19:00 h and on at 07:00 h. Videotaping of mice was performed between 19:00 and 0:00 h, in a 3.30 m diameter circular arena devoid of proximal objects, with a 10 cm plastic cylinder marking home base location, a concrete floor and 40 cm high walls. The cylinder was placed in the

arena in order to standardize home base location, only after it has been ascertained in a pilot study that Balb mice establish a home base in an arena devoid of such cylinder. Animals were individually transported by hand from the home colony room located 10 m away from the arena, placed in the arena near the cylinder, and videotaped for a 25 min period. Arena floor was cleaned with a water hose and swept with a mop between sessions. Tracking was performed by our own developed automatic tracking system with a time resolution of ~ 0.1 s and a spatial resolution of less than 1 cm. A detailed protocol of the data acquisition method, and of SEE is presented in [8].

2.2. The segmentation of the animal's trajectory into progression and stopping episodes

After smoothing (with Robust LOWESS [3] with a time window of 0.4 s, and a polynom degree 3 in order not to loose short stops), and estimating speeds, segmentation is accomplished by the following steps: (i) we establish the noise level of the system; (ii) we define 'sub-noise' periods as periods of 'arrest'; (iii) we use arrest periods to segment the velocity time series into 'motion segments' ('inter-arrest' intervals); (iv) we establish the speed maxima of each of the motion segments; (v) for each rat-session we plot the density of the log speed maxima of all its motion segments and establish the need for a Gaussian mixture model to analyze the distribution of these maxima. Such a model is commonly used in electrophoresis, for example, for recognizing distinct components within a mixture. In electrophoresis, when plotting concentration of proteins against distance from origin, one gets a single curve showing peaks corresponding to the medians of each Gaussian (each distinct component); (vi) we estimate the parameters of each component and the proportion within the component by fitting a Gaussian mixture model to the data (see Fig. 3 bottom). For the good correspondence between the mixture model and the density plot we use the Expectation-Maximization (EM) algorithm [5]. This algorithm estimates the maximum likelihood parameters (proportions, means, and standard deviations) of a mixture with a given number of Gaussians. Having the estimated parameters for the Gaussians at hand, we can finally derive the threshold that distinguishes between them by monitoring the minima of the deeps between the peaks. Most important, we can establish the threshold that distinguishes between the leftmost Gaussian, representing the mode with the lowest maximal velocities, and the Gaussians on its right, which represent progression segments. It is the leftmost component which was previously termed 'stopping', which is now also termed 'lingering', 'staying in place behavior', or '1st gear mode'. Bouts in which the animal alternates between full arrest and lingering episodes are joined into a single episode of lingering behavior [6].

3. Results

Fig. 1 presents the cumulative path traced by four individual mice in a 25 min session during successive 5 min intervals. As illustrated, all animals tend to proceed mostly along the walls, but also across the center. In all, the paths converge to one location (09:00 h—where the cylinder is located in the mouse's arena). The mean cumulative mileage per session covered by the BALB/cJtau population is 103.2 m (75.26, 131.1 m).

As illustrated, in all four animals there is a gradual occupancy of the environment, starting from the cylinder's location and proceeding along the periphery and only then into the center. Examination of this process for the whole mouse population (Fig. 2) reveals that the gradual increase in activity characterizes the whole BALB/cJtau population.

To summarize this phenomenon by a single measurement we subtract the activity in the second half of the session from that of the first half. We obtain in this strain mostly a positive value of the mean (meaning that activity in the second half is higher than in the first half), of 5.84 m (-1.18, 12.88 m). During the first 5 min the mice perform a small proportion of the total mileage, with a mean of only 6.55 m (2.14, 20.11 m).

The graphs presented in Fig. 2 are based on an arbitrary slicing procedure of the path (per 5 min). To obtain a more faithful representation based on intrinsic constraints, we first partition the rat's path into distinct segments of motion. We will first briefly summarize the results of the segmentation process, then describe one of its products, the lingering episodes, and only then return to path growth.

As already outlined in Section 1, the segmentation of the animal's trajectory into modes of motion [6] is the corner stone of our analysis. This is what allows us to articulate the time series of coordinates of the animal's location into lingering episodes, principal places (places which are preferred by the animal) [16], home base(s), progression episodes, speeds attained within movement segments, and connectivity between places, i.e. the routes and the traveling speed among places.

Fig. 3 presents the empirical distribution of the log-transformed peak velocities of motion segments (top) and their decomposition into distinct Gaussian populations (bottom) during the session of a male BALB/cJtau mouse (see Section 2; for detailed explanation see [6]). In Fig. 3 bottom, the distinction between the leftmost Gaussian and the rest of the population is provided by the threshold value, here at about 3 SD distance to the right of the mean of the leftmost Gaussian, i.e. at 9.9 cm/s (see Fig. 3). Similar decompositions

were obtained for all BALB/cJtau mice. The velocity thresholds between lingering and progression for all the Balb mice amounted to a mean of 8.45 cm/s. The distinction between lingering and the faster progression segments thus holds for the Balb mice.

Once classified and tagged, various aspects of both lingering and progression episodes can be visualized and measured. The spatial spread of lingering episodes, i.e. how far does this mouse progress during single lingering episodes, amounts to -0.74 cm (0.44, 1.04 cm). This means that progression without leaving 1st gear corresponds, at least in this mouse strain, to the ethological ad hoc notion of stopping behavior. In other words, these mice (in contrast to C57BL/6Jtau, see below) hardly progress during lingering (in hooded rats the spatial spread of lingering amounts to a median of 10 cm).

Lingering topography and dwell time can be visualized by drawing bubbles whose coordinates indicate the starting location of a lingering episode, and whose diameter represents absolute dwell time (Fig. 4). As illustrated, home base location is indicated by the highest concentration of bubbles (visits) and by the highest cumulative time (size) of staying in place episodes. The mean maximal speed of lingering episodes is 3.35 cm/s (2.61, 4.3 cm/s).

These mice spend in this mode a mean of 55% (45, 65%) of their time, out of which only a mean of 5.5% (1, 23%) is spent away (10 cm) from walls.

As for progression episodes, their spatial spread amounts to a mean of 14.84 cm (9.6, 20.08 cm). This mean does not convey the special mode of progression of this strain of mice, which includes normal stops and many very short stops, of durations of 0.2 s or so. These short stops which constitute a distinct population were not considered in the current calculation. They segment the path into even shorter progression segments with a mean of 11.88 cm (8.82, 14.94 cm) [8].

A special measure termed global diversity has been devised to quantify the spatial dispersion of stops and the degree to which dwell time is evenly distributed in the environment [16]. Roughly, when stops (bubbles) differ maximally in size and located at the same neighborhood, global diversity is low, whereas when stops are equal in size and spread evenly over the whole arena, global diversity is high. The formula for the measure of diversity is:

$$\sum_{i=1}^{n} \sum_{j=1}^{n} p_i p_j d_{ij},$$

where p_i is the proportion of time spent at stopping place i and d_{ij} is the distance between the location of the i and jth episodes.

The dynamics of the diversity of lingering in this strain is illustrated in Fig. 4: during the first 5 min interval the mouse stays only in the vicinity of the home base. Maximal diversity, suggesting maximal freedom of movement [16] is accomplished in this mouse-session only in the 5th interval.

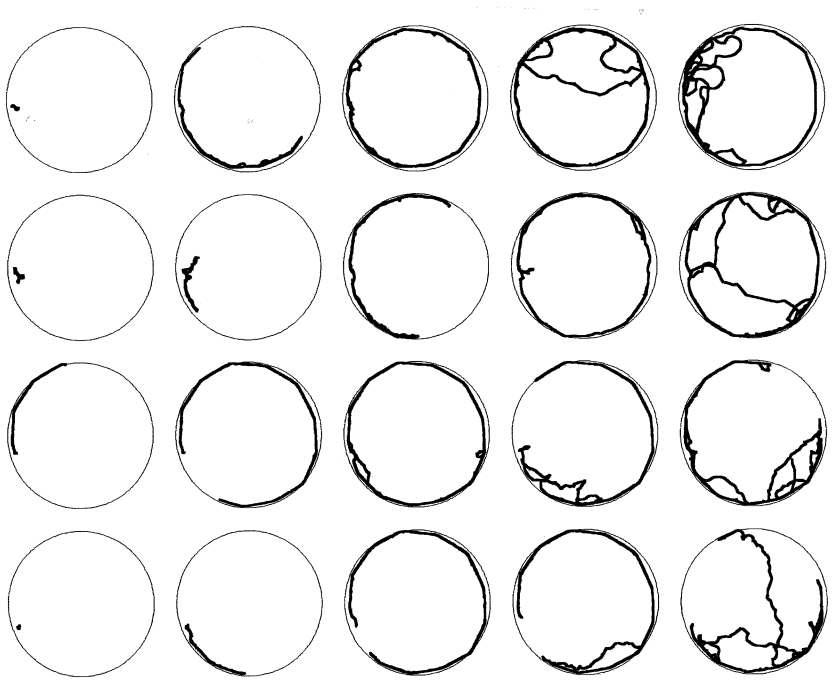

Fig. 1. The paths traced by each of four BALB/cJtau in the arena. Each horizontal set of circles represents the behavior of a single mouse. The lines within a circle represent the path traced during a 5 min interval. Circles, from left to right, represent successive 5 min intervals. To improve visibility, arena walls are slightly removed from the path traces.

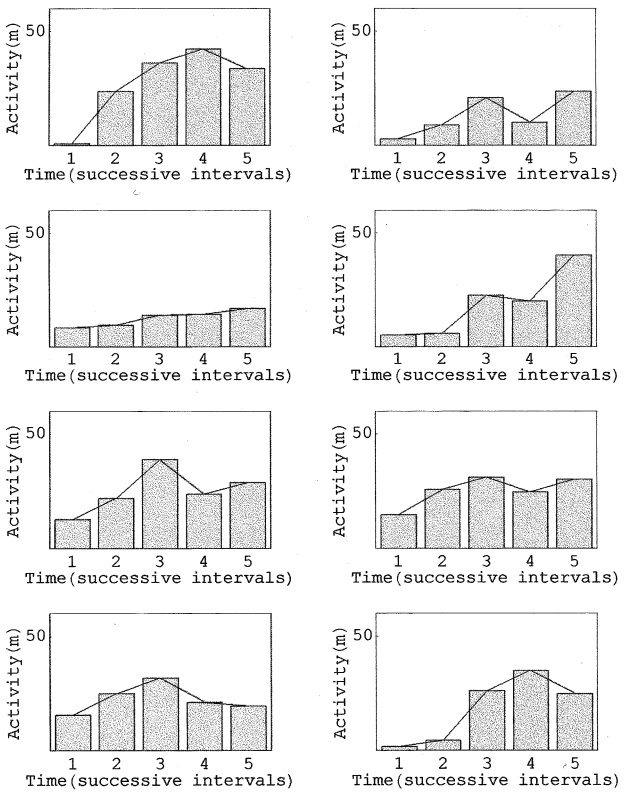

Fig. 2. Activity in meters ('mileage') per 5 min intervals across the session in all eight mice.

The numerical diversity values graphs corresponding to the bubble graphs displayed in Fig. 4 reveal that the increase in diversity reaches a peak quite late in the session in the whole experimental population (Fig. 5).

The increase in diversity concurs with an increase in activity (compare with Fig. 2); this is not a self evident result; some strains or preparations may show an increase in activity with a concurrent decrease or no change in diversity—as when an animal develops a stereotyped path in a restricted part of the arena.

Subtraction of late-half-of-session diversity from early-half diversity provides another behavioral endpoint characterizing the population: in this strain the mean difference in diversity between the two halves of the session is always positive, meaning that diversity is higher in the second half of the session: 53.2 (29.33, 77.07).

Having established in BALB/cJtau mice the presence of lingering behavior, of progression segments, and of the gradual increase in activity and diversity across the session, we can now examine the presence of excursions. We use the place (neighborhood) with the highest cumulative dwell time and number of visits as our origin of axes. In Fig. 6 we trace a graphics array of the first 12 excursions performed from that place (the 12th excursion was performed after the 25 min time boundary of the session). The excursions are traced in their order of performance, from left to right, and from top to bottom.

As in the rats [18], excursion length grows in this representative mouse-session incrementally across the session; the mouse moves first along the walls and only then away from them. Movement away from walls typically appears first in the inbound portion of the excursion (Fig. 6, excursion 11, top loop), then in the outbound portion (excursion 11, bottom loop); incursions tend to appear relatively late (excursions 11, 12). Finally, as in the hooded rat, at a certain point in time (excursions 10–12) there is a burst of activity involving the performance of full circles with incursions. The

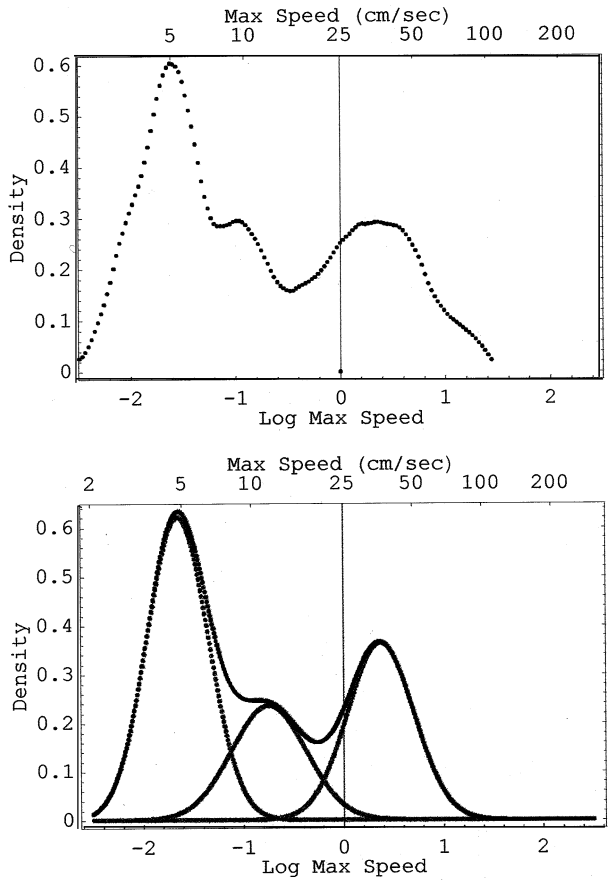

Fig. 3. Top: An estimate of the density function for maximal values during episodes of motion belonging to a selected Balb mouse-session. Bottom: The maximum likelihood Gaussian mixture model of the data whose empirical density estimation is shown on the top. The x- and the y-axis are as in Fig. 3 top, the encompassed curves show the individual Gaussian components. The encompassing solid line shows the computed sum of the Gaussians, as estimated by the EM algorithm. Co-ordinates on the lower x-axis represent the log-transformed values of the maximal speed values of motion segments (the log-transformation is used here in order to constrict the right part of the x-axis, thus 'pushing' the data to the left, and increasing thereby the deeps between components). Coordinates on the upper x-axis represent the 'real' values after transforming the x-values back from the log-transformation that has been used in the procedure.

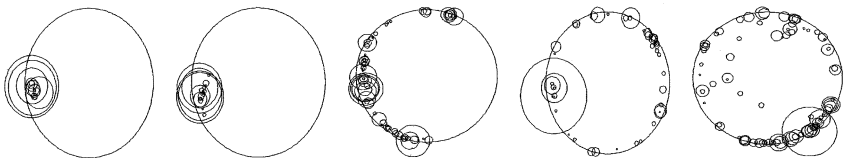

Fig. 4. A dynamic representation, per 5 min intervals, of lingering episodes with their dwell time, across a 25 min session. Bubble location represents lingering location in arena and bubble diameter represents absolute dwell time in this lingering episode. Note the higher density of lingering episodes with longer dwell time near the home base (at 09:00 h), and the gradual increase in diversity across the session.

endpoints that relate to excursion structure in BALB/cJtau mice are, so far: (i) mean number of excursions (normalized by dividing it by activity): 0.356 excursions/m (0.099, 0.61); and (ii) mean number of stops per excursion (upper quartile) of 10.12 stops/excursion (3.28, 16.96).

4. Discussion

When placed in a novel empty arena in the vicinity of an object placed along the wall (see Section 2), BALB/cJtau mice first freeze for several minutes. Then, they proceed to alternate between progression episodes characterized by higher (than 8.45 cm/s) speeds, thus moving from location to location, and lingering episodes characterized by lower (than 8.45 cm/s) speeds. The distinction between the two modes is an intrinsic one, and is not based on an arbitrary cutoff point superimposed from the outside. Peak velocities during progression amount to up to 32 cm/s. In this mouse strain the alternation between progression and stopping occurs at a high rate of about 2/m, resulting in relatively short progression segments. These segments become even shorter if very short stops, of 0.2 s duration or so, typical of this strain, and constituting a distinct population, are considered as well. After the initial freezing that follows the introduction into the arena, the mice show a pattern of incremental growth of excursions performed from their point of origin, first along the arena wall and only then into the center. The vast majority of stops are performed along the walls. Maximal diversity in stopping places and dwell time is accomplished only in the second half of the session. It presumably reflects high freedom of movement in the arena [16].

A quantitative comparison of mouse exploratory behavior to that of rats, the species that has been studied in a similar setting in our laboratory, is not possible at this time because of the different size of the arena in which the rats were tested (6.5 m diameter vs. 3.2 m in the mouse). Furthermore, current tracking technology does not allow us to track mice in the large arena, whereas testing the rats in a small arena might not reveal the incremental growth in excursion length observed in the large one. We are thus lead to compare the two species qualitatively: as with the Balb mice, the Long Evans hooded rats also show a distinction between lingering and progression segments. In the rats, however, the cutoff point between the two modes is at about 16 cm/s, twice as much as in the mice. In the large arena the rats reach peak speeds of up to 336 cm/s [6]! The rats, like the Balb mice, show a gradual growth of excursion length when placed in the arena. This growth has been suggested to reflect the rat's increasing familiarity with the environment. It has been furthermore shown that the growth proceeds at a similar rate across individuals both within sessions and across multiple daily sessions, implying some learning or habituation process [18]. In addition, the rats perform the

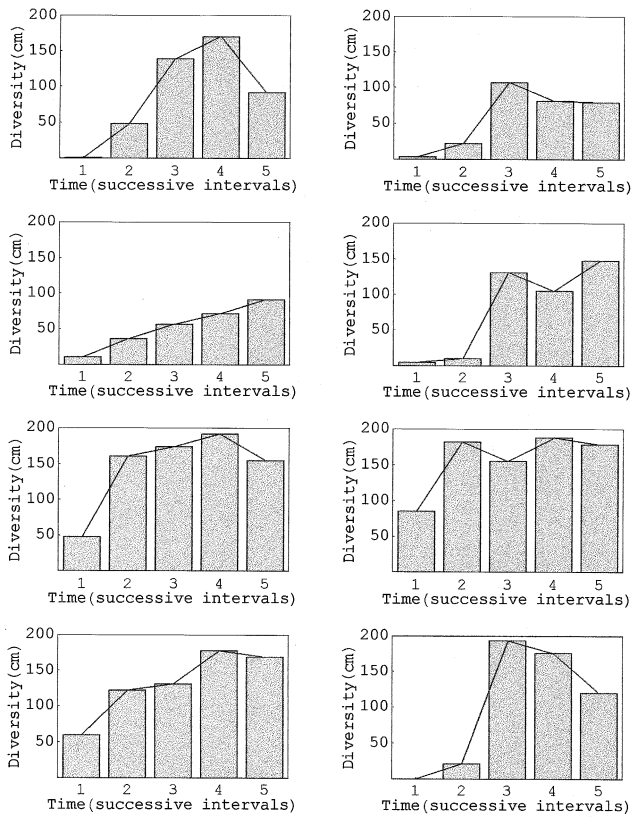

Fig. 5. Diversity per 5 min intervals across the session in the eight mice.

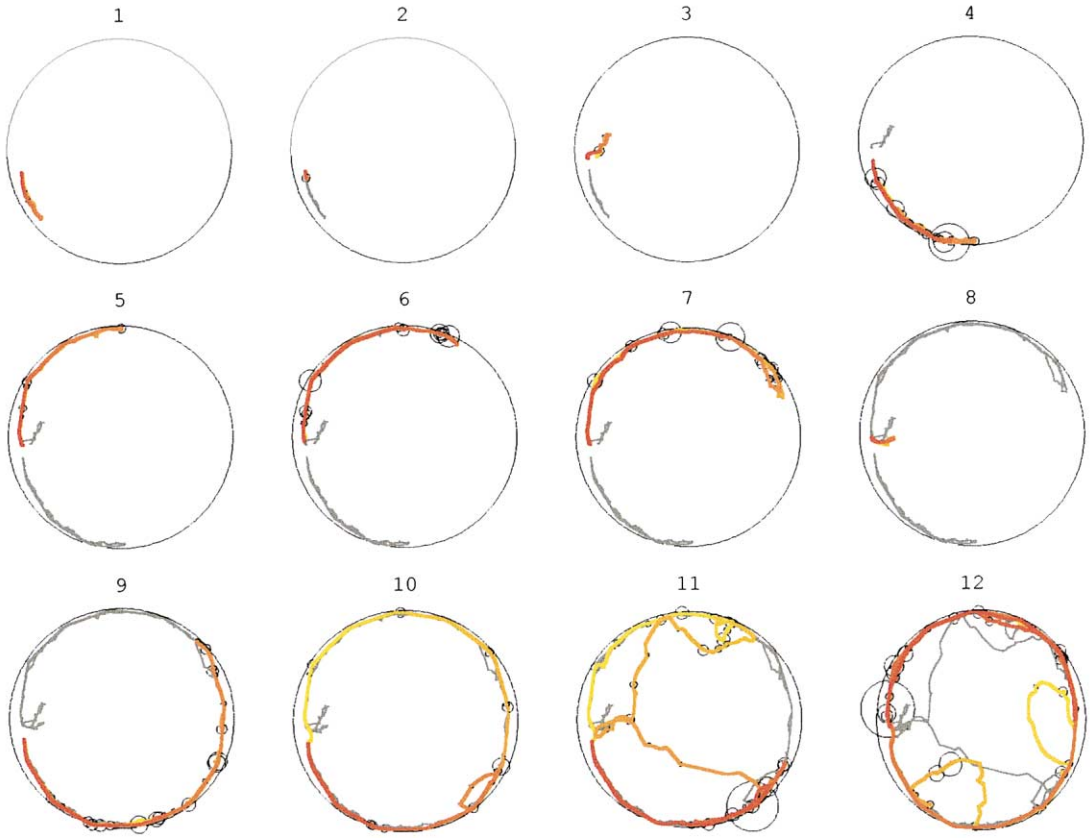

Fig. 6. A representation of the first 12 excursions (round trips from home base) performed in our representative BALB/cJtau mouse session. The excursions are temporally ordered from left to right and from top to bottom. Each excursion is displayed in color (from yellow = start, to red = end) against a light gray background of the cumulative path traced earlier, up to the beginning of the current excursion. Bubbles whose diameter represents dwell time stand for lingering episodes.

outbound portion of the excursion slowly and intermittently and the inbound portion fast and with fewer or no stops, sometimes from far away. Because the mice stop much more frequently, one does not observe in them long non-stop inbound trips. Also, the upper bound on the number of stops phenomenon that was demonstrated in the rats was not found in the mice. Before examining the number of stops per excursion in mice it would be necessary to classify stops according to their duration and spatial spread. It appears that in the Balb mice in particular, there are at least two types of stops, and that they differ distinctly from each other both in terms of their duration and the scanning movements included in them.

In the hooded rat the home base has been established on several grounds (fast non-stop inbound trips, increasing probability of returning home after each stop, incremental growth of excursions) whereas in the Balb mouse it has been established until now only on the basis of incremental growth.

It may thus be concluded that some of the parameters found to be relevant and measurable in rat exploratory behavior are also relevant and measurable in at least one strain of mice. It is our expectation that most of these parameters will also be relevant in other strains and preparations, and that the values taken by these parameters will vary significantly from strain to strain. A concurrent study performed by us on C57BL/6Jtau mice indeed reveals that most of the above listed parameters are also relevant in that strain. Interestingly, in C57BL/6Jtau, the dynamics of activity and diversity across the session are opposite to that observed in the hooded rats and in the BALB/cJtau mice: when introduced into the arena they start with full circle excursions and only then proceed with smaller, part-circle ones. They reach maximal diversity, i.e. maximal freedom of movement, in the first half of the session rather than in the second half. They have significantly longer durations of lingering episodes, they trace significantly longer paths during lingering, and they attain significantly higher speeds during lingering. A comparison between the two mouse strains yields eight significantly different behavioral endpoints out of the 17 that were compared [1]. While the two strains do not differ in the traditional endpoints of overall activity and proportion of activity in the center, the common denominator of seven (out of the eight) endpoints in which the C57BL/6Jtau score significantly higher is a

higher freedom of movement. The higher scores in lingering reflect the fact that the C57BL/6Jtau have a larger repertoire of scanning movements, both in terms of type and in terms of number per lingering episode. The higher scores in the dynamics of activity and in the dynamics of diversity (implying that in this strain the animals were active and free already during the first half of the session) also reflect a higher freedom of movement (for a discussion of the concept of freedom of movement or mobility see [11]).

The fact that several common kinematic parameters emerged out of the analysis of rats and mice suggests that these parameters may be part of the 'skeletal anatomy' of rodent locomotor behavior. Since these parameters capture features related to basic functions of information processing and allocation of attention, they might prove more resistant to environmental influences than the more vulnerable activity measure commonly used to characterize open field behavior [4]. Other traditional measures such as the frequency of grooming, of rearing, and of wall hugging, are probably as useful for phenotyping as the measures we use in the present study. However, the state of the art in computerized tracking does not allow yet their full use in high throughput studies of mice (for promising advances in tracking these patterns in rats see [12]). Furthermore, in a substantial proportion of the scans only the head or the forequarters are recruited. Even if the full-blown forms of these patterns, involving recruitment of the whole body could be recorded, the smaller scans, which characterize BALB/cJtau would not have been accessible to present day tracking technology. These smaller scans, which indicate a lower freedom of movement [11] are indirectly represented in the significantly shorter durations and spatial spread values of lingering episodes of the BALB/cJtau vs. C57BL/6Jtau mice.

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