Application of entropy measures derived from the ergodic theory of dynamical systems to rat locomotor behavior

(nonlinear dynamics/behavioral sequences/behavioral pattern monitor/amphetamine/3,4-methylenedioxymethamphetamine)

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ABSTRACT   Measures of complexity derived from ergodic theory of dynamical systems were developed and applied to an exemplary data set describing locomotor movements of rats in a bounded space. A symbolic dynamical system was obtained by partitioning the event space into equally probable partition elements, using a k-dimensional tree. The measures calculated from the symbolic sequences included the topological entropy (h_t)—i.e., the rate of increase of all *possible* sequences with increasing sequence length—and the metric entropy (h_m)—i.e., the rate of increase of all *likely* sequences with increasing sequence length. These measures were used to assess changes in rat locomotor behavior as recorded in the behavioral pattern monitor (BPM) that were induced by amphetamine (0.25, 0.50, 1.0, or 2.0 mg/kg) and 3,4-methylenedioxymethamphetamine (MDMA; 1.25, 2.5, 5.0, or 10.0 mg/kg). Amphetamine increased the mean activity, h_t, and h_m. MDMA resulted in a monotonic dose–response curve for activity but exhibited a biphasic dose response in h_t and h_m. In particular, some animals in the higher dose groups showed a h_t in the range of the saline controls, whereas other animals exhibited a significantly reduced h_t and a greater decrease in h_m, suggesting that two different behavioral reactions coexist within the same higher dose range of MDMA. An important implication of our method is that, in applied ergodic measure-theoretic approaches, the partition that determines the elements of the symbolic dynamical system should not be specified *a priori* on abstract mathematical grounds but should be chosen relative to its significance with respect to the data set in question. Here, the animal constructs its own spatiotemporal partition in behavioral phase space.

The assessment of spontaneous locomotor activity by rats in a bounded space has been used extensively to describe effects of psychoactive agents and to understand the functional significance of various neurotransmitter pathways that mediate their actions. It has been argued that any single descriptor of locomotor activity will be confounded with other aspects of behavior (1, 2), and several devices have been proposed that obtain multiple variables describing not only the amount of locomotion but also the path taken in the observation chamber (3–5). Rats exhibiting comparable amounts of locomotor activity in the behavioral pattern monitor (BPM) were found to follow different paths that changed in a dose-dependent fashion and were characteristic for the given substance (3).

Simple dynamical systems modeling biological processes can exhibit complicated behavior (6, 7). However, these nonlinear systems often generate low-dimensional strange attractors which are globally stable (8), can be characterized statistically, and have been used to classify the system's behavior (9, 10). Ergodic theory aims to describe the statis-

tical behavior of stochastic as well as deterministic systems and allows a comparison, using different measures and based on the isomorphism concept, of systems with respect to their evolution in phase space (11, 12). The Kolmogorov entropy of an experimental signal has been suggested (13) to quantify "how chaotic" or complex a signal is and is defined by

$$K_q = \lim_{\tau \to 0} \lim_{\varepsilon \to 0} \lim_{d \to \infty} \frac{1}{d\tau} \frac{1}{q-1} \log \sum_L p^q(l_1, \ldots l_d)$$

with q the order of the entropy, ε the subset size in L, d the number of elements 1 of a sequence in L, and p the probability of the sequence. Recently, these measures have been placed into the context of statistical physics involving ranges of scaling indices (14, 15). As in the case of trajectories of strange attractors, we assume that behavioral sequences reflect a global dynamical state of the brain and that locomotor and investigatory responses are deterministically generated. We regard the data as symbol strings and the underlying generator as a shift operator acting on these symbol sequences.

This study concentrates on two problems: first, to find an implementation that is relatively independent of the measuring instrument; second, to show the potential usefulness of ergodic measures and to indicate their interpretation in the context of behavioral pharmacology. Specifically, we examine the Lyon–Robbins hypothesis about the effects of stimulants, in particular amphetamine, on behavioral sequences (16). Amphetamine and 3,4-methylenedioxymethamphetamine (MDMA), which have complex effects on several neurotransmitter systems (17), were chosen to quantitatively assess the qualitatively different effects on behavior in the BPM (18, 19).

ANIMALS, PROCEDURES, AND APPARATUS

Male Sprague–Dawley-derived rats (300–350 g) housed on a reversed dark/light cycle and continuously provided with food and water were brought to the laboratory 1 hr prior to testing. In two separate experiments rats were injected s.c. 10 min before placement into the BPM chamber for a 120-min test session conducted during the dark phase of the 12/12-hr cycle. In the first experiment, 40 animals were divided into five groups of 8 rats each and injected s.c. with D-amphetamine at 0.0, 0.25, 0.50, 1.0, or 2.0 mg/kg. In the second experiment, 40 different rats were grouped similarly and injected s.c. with MDMA at 0.0, 1.25, 2.5, 5.0, or 10.0 mg/kg. Each rat was used only once for the test procedure and did not have any previous experience with the drug or the test environment. The sequential data from the BPM chamber, which consists of a 30.5 × 61 cm black Plexiglas holeboard with three floor and seven wall holes and equipped with a 4 × 8 array of infrared beams 2 cm above the metal floor, were sampled with 5-Hz resolution and stored on a computer. The status of the pho-

Abbreviations: BPM, behavioral pattern monitor; MDMA, 3,4-methylenedioxymethamphetamine.

tobeams was used to obtain the (x, y) position of the animal with 4-cm resolution, whether rearing or poking into a hole had occurred, and the time spent at the location in the BPM (3, 19). Thus, the data subsequently analyzed consist of sequences of $(x, y,$ rearing/poking/none, time spent) for 60 min in the BPM chamber. The results of this experiment were analyzed by using a one-way between-subject analysis of variance (20) to detect differences among the groups. The post-hoc Tukey studentized range method (20) was used to determine the significance of differences between groups receiving the various doses of the drugs.

MEASURES

The central idea, which is subsequently elaborated in detail, is to consider the recorded sequences—i.e., the behavioral events of the rat in the BPM—as representations of an evolution of a dynamical system. In this approach behavioral events are not evaluated with respect to their rate of occurrence, corresponding to a measure of activity of the rat, but with respect to the evolution of initially similar behavioral event sequences. The behavior of the rat is thought to be complex if one cannot predict subsequent event sequences from the initial event in the BPM. A further distinction is made by quantifying the number of different behavioral event sequences, representing a sample of the available behavioral repertoire, and estimating the probability for the different event sequences, corresponding to the most frequently observed subset of this repertoire. The definition of distinct behavioral events in the BPM, which could be made *a priori* by partitioning the ranges of the different experimental observations into an arbitrary number of divisions, is based here on a maximum entropy constraint. Thus, the individual rat "generates" its own partition, operationally defining distinct behavioral events. The biological significance of this approach is that it measures how the sequential organization of behavioral events is affected by different drugs and other manipulations in the central nervous system.

A dynamical system consisting of a space S, an algebra α, and a measure μ produces trajectories by repeated application of α on a subset of S—i.e., sequences of points in the measure space (S, α, μ). The position of the rat in the BPM chamber, whether rearing or poking occurred, and the time spent at this position constitute the elements of the measure space of our system. The rat behavior is recorded with a finite precision instrument that can be viewed as a set $L = \{l_1, \ldots l_m\}$ consisting of discrete subsets which defines a partition of the measure space. The resulting sequence of set elements $\{x^L_i, x^L_{i+1}, \ldots\}$ of the set L form the sequence space Σ_L, and the time evolution of these sequences can be described by a shift operator $\sigma: \Sigma_L \rightarrow \Sigma_L$ such that $\sigma(x^L_i) = x^L_{i+1}$ (ref. 21).

In a symbolic dynamical system (Σ, σ, μ), the shift operator maps sequences into an invariant subset of Σ—e.g., the characteristic pattern of locomotor and investigatory responses in the BPM induced by different psychoactive agents. Given the sequence $\{x^L_i, x^L_{i+1}, \ldots\}$ finite subsets (words) with length m—i.e., $\omega = \{x^L_i, x^L_{i+1}, \ldots, x^L_m\}$—are considered, corresponding to a collection of consecutive behavioral events, to characterize the complexity of the rat behavior. If a word ω^m_i can be found within the sequence $\{x^L_i, x^L_{i+1}, \ldots\}$ it is called admissible and the total number of admissible words [i.e., $N(\omega^m)$] with increasing word length, m, is closely related to the complexity of (Σ, σ, μ).

The topological entropy of the shift operator ω with respect to a particular partition L, describing the number of new sequences occurring with increasing sequence length, is defined by

$$h_t(L, \sigma) = \lim_{m \to \infty} \frac{\log N(\omega^m)}{m}$$

and the $h_t(\omega) = \sup_L h_t(L, \sigma)$, implying that the topological entropy of a system is obtained as the maximum number of words with increasing word length, considering all possible partitions of the measure space. The metric entropy is defined in terms of a measure ($\mu: \Sigma_L \rightarrow R$) on the sequence space that is invariant under σ [$\sigma(\mu) = \mu$]. Considering the probability of a word $P(\omega^m_i)$ and using Shannon's entropy function (22, 23) $H(\omega^m) = \Sigma_i P(\omega^m_i) \log[P(\omega^m_i)]$, the metric entropy is given in analogy to the definition of h_t by

$$h_m(L, \sigma) = \lim_{m \to \infty} \frac{H(\omega^m)}{m}$$

and $h_m(\sigma) = \sup_L h_m(L, \sigma)$. The metric entropy takes the frequencies of the occurring sequences into account and can therefore be interpreted as a measure of the probable subset of all possible words with increasing word length.

The partition elements that define a single behavioral event were chosen according to local densities of points in the measure space motivated by the generalized Frobenius–Perron equation (24), indicating that the densities of points in the measure space are dependent on the tangent space of the local manifold characterizing the dynamical behavior of the underlying system generating the orbit (8). Lacking a generic *generating* partition, a procedure was developed to find a *relative generator* consisting of the division of the measure space into equally probable elements. The sizes of the partition elements are inversely proportional to the density distribution of points, and by increasing the number of partition elements a rough estimate of the magnitude of the tangent space in that interval can be obtained. A behavioral event can therefore be the position of the rat in a circumscribed region in the BPM chamber, a poking or a rearing, a certain speed with which the rat is moving in the chamber, or a combination of these descriptors.

A k-dimensional (kd)-tree splitting procedure was used to obtain these elements (25). A partition size of 32 elements was selected for two reasons: first, it resulted in a balanced partition yielding up to 99% of the possible partition entropy [$\log(m)$, where m is the number of elements]; second, this partition size guaranteed a saturation of the Perron–Frobenius eigenvalue (λ_{PF})—i.e., λ_{PF} was not increased for partitions with larger numbers of elements. Transitions between k words, corresponding to $\sigma(\omega^m_i) = \omega^m_{i+1}$ were written as a $k \times k$ incidence matrix I, and the probabilities were used to define a $k \times k$ transition probability matrix P (21, 26). Using the Perron–Frobenius theorem, we computed the largest eigenvalue, λ_{PF}, of I as the growth rate after successively exponentiating the matrix and $\log(\lambda_{PF})$, and the topological entropy [$h_t(I)$] of the incidence matrix was used as an estimator for h_t of the shift operator. An estimator for $h_m(\sigma)$ was obtained by computing the conditional entropy $H(\omega^m | \omega^m)$ of P defined as

$$H(\omega^m | \omega^m) = \sum_{i,j} P(\omega^m_i)[P(\omega^m_i | \omega^m_j) \log(P(\omega^m_i | \omega^m_j))].$$

RESULTS

As described in more detail in refs. 18 and 19, both amphetamine and MDMA produce dose-dependent increases in locomotor activity. In Figs. 1 and 2, the locomotor paths exhibited by individual animals are shown for representatives of the saline control group and for two different doses of amphetamine and MDMA, respectively. The group results for all doses of amphetamine and MDMA are summarized in Tables 1 and 2, respectively. After various doses of amphetamine, the activity, measured as the total number of status changes in a 60-min period, showed significant group differences [$F(4, 41) = 18.07, P < 0.0001$] and was significantly
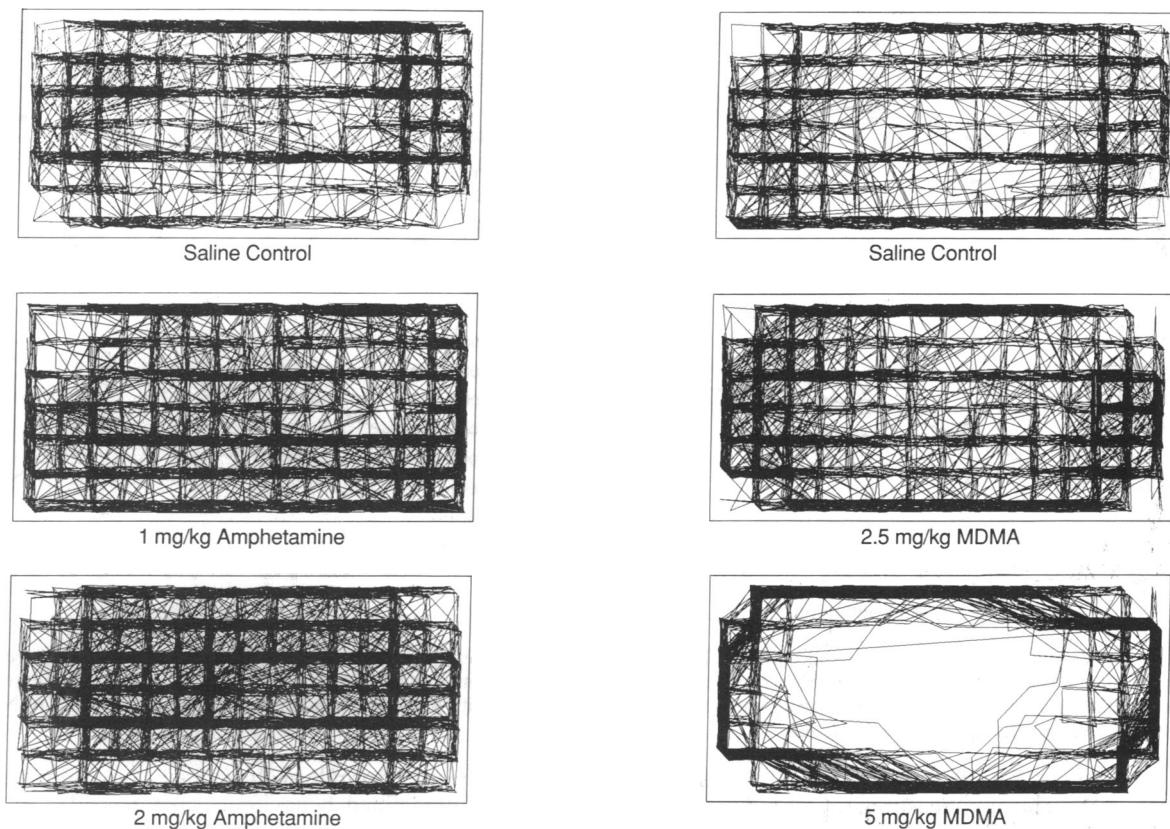
FIG. 1.   Spatial patterns of locomotion exhibited by saline control animal (*Top*) and animals treated with amphetamine at 1 mg/kg (*Middle*) and 2 mg/kg (*Bottom*). Each path consists of 60 min of activity in the BPM chamber. The possible positions within the 7 × 15 array defined by the infrared beams are plotted in such a way as to connect consecutive locations by lines and adding an additional noise term (25%) to facilitate the visual processing of frequently visited paths. As is typical, the saline-treated animal visited all parts of the BPM chamber and showed some frequently used paths along the long side as well as close to the short side of the chamber. In contrast, the amphetamine-treated animals displayed scattered paths with increased density (due to the hyperactivity) and the movements were distributed throughout all parts of the chamber. Nevertheless, some preferentially visited paths can be observed either close to the chamber wall (*Middle*) or in the center areas (*Bottom*). The activity and λ_{PF} for each of the animals shown are saline (4424, 16.27), 1 mg/kg (6363, 18.87), and 2 mg/kg (6675, 19.89).

increased compared with the saline control group. Similarly, amphetamine induced significant increases [$F(4, 41) = 12.46$, $P < 0.0001$] of the Perron–Frobenius eigenvalue (λ_{PF}) of the incidence matrix. Both the activity and entropy increased in a dose-dependent fashion. The topological entropy was significantly increased for 0.25, 0.5, 1.0, and 2.0 mg/kg compared to saline control (Table 1); furthermore, h_t for 2.0

Table 1.   Amphetamine dose response: Entropy measures for 60-min activity

Measure		Saline	0.25 mg/kg	0.50 mg/kg	1.0 mg/kg	2.0 mg/kg
Activity,	Mean	4290	5754*	6631*	6306*	6776*
counts	σ	730	662	783	613	866
λ_{PF}	Mean	16.4	18.0*	18.9*	19.3*	19.6*
	σ	1.39	1.11	0.79	1.43	0.89
h_t	Mean	2.80	2.89*	2.94*	2.96*	2.98*
	σ	0.08	0.06	0.04	0.07	0.04
h_m	Mean	2.30	2.37	2.42*	2.47*	2.46*
	σ	0.07	0.06	0.05	0.09	0.05

*Significantly different from saline control at $P < 0.05$ level.
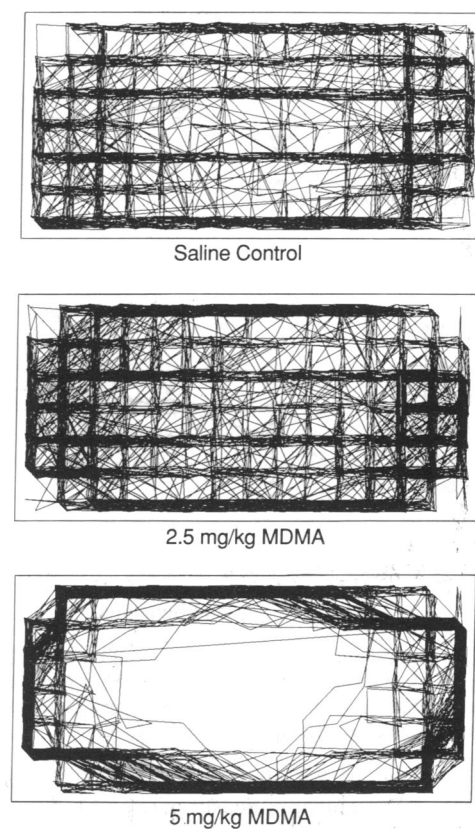

FIG. 2.   Spatial patterns of locomotion exhibited by saline control animal (*Top*) and animals treated with MDMA at 2.5 mg/kg (*Middle*) and 5.0 mg/kg (*Bottom*). The MDMA-treated animals showed an increasingly scattered path with lower doses (*Middle*) but displayed a primarily circling path along the sides of the chamber and strong avoidance of the center with higher doses (*Bottom*). The activity and λ_{PF} for each of the animals shown are saline (4221, 15.16), 2.5 mg/kg (5785, 17.55), and 5 mg/kg (5393, 13.78).

mg/kg was significantly higher than for 0.25 mg/kg and a plateau was reached in the 1.0–2.0 mg/kg dose range (Fig. 3 *Left*). The probable subset of sequences of behavioral events, h_m, increased dose-dependently after injection of amphetamine, as did the total number of different sequences, h_t. These results indicate that more transitions between partition elements occur under amphetamine; since these elements consist of (x, y, time, behavior) intervals, transitions between distinct elements in time—i.e., slowing and speeding up—and transitions between elements that are distinct in space—i.e., paths between different locations in the BPM chamber—contribute to this increase.

The activity during the 60-min session was increased significantly by MDMA [$F(4, 34) = 6.85$, $P < 0.0005$] and

Table 2.   MDMA dose response: Entropy measures for 60-min activity

Measure		Saline	1.25 mg/kg	2.50 mg/kg	5.0 mg/kg	10.0 mg/kg
Activity,	Mean	4457	5374	5991	6174*	6495*
counts	σ	855	807	1077	649	785
λ_{PF}	Mean	15.5	16.9†	17.6*†	16.1	14.5
	σ	1.28	1.07	0.60	1.80	1.65
h_t	Mean	2.74	2.83†	2.87*†	2.77	2.67
	σ	0.08	0.07	0.03	0.12	0.11
h_m	Mean	2.20	2.29†	2.34*†	2.21	2.16
	σ	0.08	0.07	0.04	0.16	0.09

*Significantly different from saline control at $P < 0.05$ level.
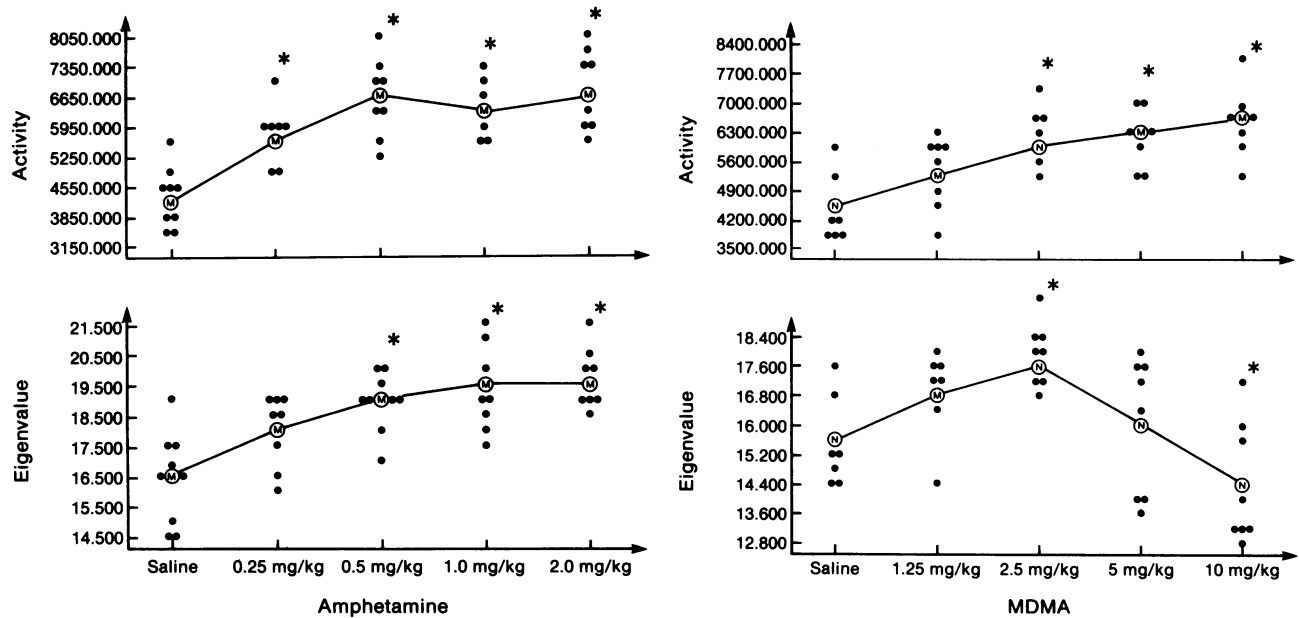†Significantly different from 10 mg/kg MDMA at $P < 0.05$ level.

FIG. 3. Dose–response plots of activity and entropy. The x-axes show five different groups of rats, a saline control and four treated with increasing doses of amphetamine (*Left*) or MDMA (*Right*). (*Upper*) Activity (in counts per 60 min). (*Lower*) Perron–Frobenius eigenvalue. The data for individual animals are shown as dots; group means are symbolized either with M if the mean corresponds to a data point or N if it does not; and * indicates significance on the 5% level.

reached a plateau at 5.0–10.0 mg/kg (Fig. 3 *Upper Right*). The results of the entropy measures reveal a more complicated picture: first, λ_{PF} with respect to the saline controls was increased significantly for the 2.5 mg/kg group; second, λ_{PF} of the 10 mg/kg group was decreased significantly from both the 1.25 mg/kg and the 2.5 mg/kg groups but not significantly different from that of saline control animals. This finding would point to a biphasic dose-dependent response of the entropy measures to MDMA (Fig. 3 *Lower Right*). A close examination of the data points from the 5 mg/kg and 10 mg/kg groups suggests, however, that some animals exhibited a high entropy response—i.e., the λ_{PF} was significantly higher than that of the saline control, whereas other animals in the same dose group showed a low entropy response with λ_{PF} being below the range of saline controls. These results were also seen in h_t and h_m (Table 2), which indicates that, within the same dose, some animals exhibited unpredictable sequences of behavior whereas others showed more predictable patterns. The ratio h_m/h_t was decreased markedly in the low entropy response animals, indicating that in addition to the decrease in number of possible paths there was a disproportionately greater decrease in the number of likely paths (data not shown). By inspection of the different rat paths and the kd-partitions resulting from these animals, these changes seem to correspond for the MDMA group to two geometrically distinct patterns of locomotion in the BPM chamber. The first pattern (Fig. 2 *Bottom*) is characterized by movement sequences that generate a circling path in the BPM chamber, whereas the second pattern consists of highly variable sequences leading to an almost space-filling path in the BPM chamber (Fig. 2 *Middle*).

DISCUSSION

The evaluation of rat locomotor behavior by using measures from ergodic theory of dynamical systems provides a macroscopic description of this complicated system. The major difference from the application of ergodic theory to physical systems is that, in this case, it is difficult to define the distinct behavioral events which constitute the microscopic variables describing the biological system. Some groups have sug-

gested the use of profile analyses based on extensive descriptions of predefined behavioral categories (27). In this approach the single behavioral event need not be defined *a priori* but may be determined as a partition element of a partition procedure that is sensitive to the changes in densities in the measure space. Comparing the result of the partition procedure to the intervals given by the fixed-resolution recording device shows that subsets of the measure space in which the rat is observed more frequently are resolved into more distinct behavioral events than in subsets measured infrequently. The kd-procedure factors out the resolution problem associated with the size of the elements influencing the calculation of the measures. In conclusion, the microscopic variable of the rat behavior depends on its macroscopic behavior—i.e. the patterns in the BPM observed during the test session—and consists of intervals in the measure space with characteristic probability densities.

It is assumed that locomotor behavior allows the observation of information processing in the central nervous system and that the process generating the sequences of behavioral events is a dynamical system. The state of the rat under the influence of psychoactive agents can be thought of as an "attractor" and its statistical characterization using h_m and h_t allows one to distinguish quantitatively between the different states. An effect of the temporal organization of behavioral sequences may contribute significantly to understanding the functions of certain brain areas as well as the effect of specific neurotransmitter systems. Healthy functioning may be described by "constrained randomness" (28), characterized by having many possible response options available (h_t) while choosing only a limited subset of these options (h_m).

The Lyon–Robbins hypothesis, involving behavioral frequencies as well as behavioral categories, can serve as an initial test to match its theoretical predictions with quantitative assessments. This hypothesis expresses that the stimulant action of amphetamine causes an increase in the initiation of behavioral sequences as well as a disruption in the completion of the sequences (16), eventually resulting in stereotypy (29). Translated into the situation of the rat in the BPM chamber, an increased initiation of behavioral responses corresponds to an increase of transitions between

different intervals in the measure space, resulting in an increase in λ_{PF} of the incidence matrix—i.e., a rat that starts specific sequences of behavioral events and shortly thereafter initiates a new sequence. The main effect of low doses of amphetamine in the BPM, therefore, is a decreased correlation of consecutive events. Hence, our findings appear to be consistent with the Lyon–Robbins hypothesis. Similar effects of amphetamine have been pointed out previously for rats in a complex decision task (30). Interestingly, comparable phenomena have been found in simple nonlinear systems as a result of increasing the nonlinearity (31).

For the low dose groups (1.25 and 2.5 mg/kg), the changes of h_t and h_m suggest a close resemblance of MDMA effects to amphetamine effects. Between the 5.0 and 10.0 mg/kg dose range, one interpretation is that there are two "attractors" within the same dose range, one with relatively high h_t and h_m, another with low h_t but still lower h_m. These two states seem to converge in the higher dose group to the latter state, indicating that, at high doses, MDMA results in a perturbation of the central nervous system that yields very constrained sequences of behavior. The coexistence of stable states within a dose range is consistent with evidence that MDMA has multiple effects both neurochemically (17) and behaviorally (18). Alternatively, a hysteretic change could have occurred in which one behavioral state becomes unstable, but based on the approach in the parameter space (i.e., the doses of MDMA) there exists a dose range in which both states can coexist. The description of a hysteretic jump of a behavioral state in the context of amphetamine effects on operant responding (32) suggests that hysteresis may occur under the influence of psychostimulants and that a similar process may account for the effects of the higher doses of MDMA. Such a transition may arise from an interaction between the nonlinear effects of habituation and drug action.

In conclusion, the characterization of a complicated system with measures from ergodic theory may lead to a more thorough description of biological systems and help to establish functional relationships between drug effects on different levels of observation.

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