Psychopharmacology (1991) 104:6–16
0033315891000714

Psychopharmac

A temporal and spatial scaling hypothesis for the behavioral effects of psychostimulants

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Received January 2, 1990 / Final version October 20, 1990

Abstract. A variety of psychoactive substances (amphetamine, nicotine, scopolamine, apomorphine, lisuride, and MDMA) were tested to examine whether a proposed scaling hypothesis is appropriate for the description of the amount and the structure of rat locomotor paths recorded in the Behavioral Pattern Monitor (BPM). The analytical approach was based on the assumption that the scaling behavior of a few collective variables may characterize sufficiently changes in the animal's behavior induced by different drugs. The temporal scaling exponent α, describing the ratio of fast to slow responses in the BPM, sensitively reflected the different stimulant properties of the substances. The spatial scaling exponent *d*, which relates the average pathlength to the resolution used to measure consecutive responses, was found to discriminate substances that had been separated previously via qualitative descriptions. Several behavioral response categories emerged from comparisons of the locations of different drugs on a two-dimensional *d*–α plane. Scopolamine, MDMA, lisuride, and high doses of apomorphine increased α while decreasing *d*, whereas amphetamine, nicotine, and caffeine produced an increased α with no change or an increase in *d*. Stereotypies could be identified on the opposite ends of the spatial scaling exponent scale and were interpreted as reflecting two kinds of perseveration. These results suggest that scaling approaches can be used to assess quantitatively the state of the animal based on its locomotor behavior and that the exponents can serve as collective variables providing a macroscopic description based on the microscopic elements of behavior.

Key words: Psychostimulants – Amphetamine – Dopamine – Locomotor activity – Behavioral pattern monitor – Spatial scaling exponent – Temporal scaling exponent

The assessment of locomotor behavior using measures of activity allows one to characterize the unconditioned behavioral effects of acute drug treatments and to d mine whether substances have stimulant prope (Robbins 1977; Robbins and Sahakian 1983; Geyer e 1986; Harvey 1987). Locomotor behavior, howe consists of a variety of responses presumably purp fully organized in sequences to allow a successful ada tion of the animal to the test environment. Therefore. assessment of patterns of motor activity has prom several investigators to develop measures capturing information (Lat 1965; Schiorring 1971; Ljungberg Ungerstedt 1976). This effort to extract more infor tion from experiments using the unconditioned loco tion paradigm has intensified during the last dec (Nickolson 1981; Adams and Geyer 1982; Flicker Geyer 1982; Stoff et al. 1983; Geyer et al. 1986; Sanl et al. 1987; Kernan et al 1988). In some cases, exp measures of investigatory behavior, such as rearii holepokes or object contacts, have been added to m sures of locomotion in order to determine the contri tion of stimulus-directed behavior to the frequently served qualitative differences in the effects of vari stimulant drugs (Ljungberg and Ungerstedt 1977; Ge et al. 1986). Similarly, attempts have been made to qu tify differences in drug-induced changes in the patte of the locomotion per se, using measures such as coefficient of variation, the spatial correlation functi and the dynamical description based on ergodic the (Geyer et al. 1986; Kernan et al. 1988; Paulus et al. 19 Some groups have followed a different approach by beling different sequences of motions as behavioral c egories and describing sequences of categories and changes within these sequences (Teitelbaum 1982; B ridge et al. 1987). Others (Stahle 1987) have compu latent variables underlying the linear relationship l tween linear factors to detect and describe subtle dr effects. Most of these approaches are based on assun tions about the discrete nature of behavioral respor categories (Norton 1968), operational measures hypothetical constructs such as conflict, novelty, or u certainty (Berlyne 1960), analyses of the range of sponse categories as influenced by specific drug treatmer (Lyon and Robbins 1975), and/or multivariate char

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terizations of locomotor and investigatory behavior (Geyer et al. 1986; Sanberg et al. 1987; Stahle 1987).

Even though major insights into the unconditioned behavioral effects of acute treatments with psychoactive substances have been gained using these approaches, several shortcomings are inherent in the assumptions and techniques used to date. First, the amount of locomotor activity is described typically by counting the number of interruptions of photobeams in a photocell cage (for review: Robbins 1977; Geyer 1990). A limitation of this approach is that the distance between photobeams serves as an intervening variable, which can lead to qualitatively and quantitatively different results for the same treatment. For example, a drug which increases ambulation may increase activity counts even if the photobeams are separated widely, while the effects of a substance that specifically increases small movements can be measured sensitively only with closely spaced photobeams. With the advent of video-tracking systems and other more sophisticated measuring devices, the distance traveled, velocity, and the distribution of movements within the test environment can now be used to describe locomotor activity more precisely (Nickolson 1981; Sanberg et al. 1987). For example, the Behavioral Pattern Monitor (BPM) chamber was designed to assess the animal's locomotor, exploratory, and investigatory responses in detail. The paths of the animals can be reconstructed graphically and their geometrical and dynamical properties can be analyzed. Initial evaluations of the effects of various stimulant drugs (Geyer 1982; Geyer et al. 1986) revealed substance-induced differences in the *structure* of the paths despite similar levels of locomotor hyperactivity. This work led to the proposition of three different path patterns: (A) the partially structured path characteristic of untreated or saline control animals; (B) a non-repetitive, less smooth path; and (C) a smoother path with more repetitive movement patterns.

Second, the description of the relationship between neurochemical and anatomical manipulations and behavioral effects has become increasingly complicated, partially due to the assessment of an increasing number of predefined behavioral variables. Typically, however, treatment effects are described only in terms of significant differences in particular variables without addressing the overall change in the pattern of activity. For example, substances influencing monoaminergic neurotransmission have been differentiated based on significant differences in holepoking (Ljungberg and Ungerstedt 1976). On the other hand, acute treatments with substances like amphetamine and nicotine, which act via different neurochemical mechanisms (Fung and Lau 1988) and produce mixed results in locomotor paradigms, have not been differentiated reliably using behavioral testing paradigms (Jerome and Sanberg 1987). Thus, increasing the number of variables recorded may not lead to a satisfactory solution establishing a simplified relationship between behavioral characteristics and psychoactive substance effects.

Third, a complex interplay between D1 and D2 dopamine receptors is proposed to produce differential behavioral effects as reflected in measurements of locomotor activity, stereotypy rating scales (Braun et al. 1986; Arnt et al. 1988), and more specific behaviors such as yawning (Scheel-Krueger 1986) and climbing (Davis et al. 1990). Nevertheless, the quantification of differences in the structure of locomotor activity induced by the activation of dopamine receptor subtypes has not been investigated, even though the involvement of the receptors in varied versus stereotyped locomotion (Braun et al. 1986) has been suggested and descriptive differences have been reported (Eilam et al. 1989).

The goal this investigation was to define and establish the utility of a specific type of measure, scaling measures, that are based neither on multivariate profiles nor predefined behavioral categories but on sets of sensitively chosen variables describing micro-events of unconditioned motor activity. While we and others have used sequential information previously (Berridge et al. 1987; Paulus et al. 1990), this paper examines the utility of scaling measures capturing structural information. By measuring the animal's movements with different levels of resolution, scaling measures examine the relationship between the movements and changes in experimental parameters such as the sampling rate and the distance between photobeams. Typically, such parameters are held constant, here they are varied systematically. The evaluation is based on two scaling assumptions and involves the computation of spatial *(d)* and temporal (α) scaling exponents. Both measures are used to make comparisons between drugs by locating the different substances in a (d–α) plane constructed from these exponents. The general hypothesis tested was that spatial and temporal scaling exponents can capture emergent behavioral states induced by psychostimulant drugs adequately, sensitively, and dose-dependently. Specifically, d and α were calculated from rats treated with amphetamine, apomorphine, scopolamine, lisuride, nicotine, caffeine, and 3,4 methylenedioxy-4-methylamphetamine (MDMA). Several response categories could be identified based on the location and the dose response curve in the d–α plane, pointing towards macroscopic behavioral "styles" that quantitatively distinguish stimulant substances with similar amounts of activity.

Material and methods

Animals. Male Sprague-Dawley rats weighing 250–300 g (Simonsen Laboratories, Gilroy, CA, or Harlan, Indianapolis, IN) were used. All animals were housed in pairs on a reversed 12/12 light–dark cycle. The groups were allowed at least 7 days for acclimation to the animal facilities before behavioral testing. Each animal was used only once for testing in the BPM. The experiments have been described in more detail elsewhere (Adams and Geyer 1985; Geyer et al. 1986, 1987; Gold et al. 1988).

Drugs. The following drugs were tested: *d*-amphetamine sulfate (Sigma) 0.25, 0.5, 1.0, 2.0, 4.0, and 8.0 mg/kg; MDMA HCl (NIDA) 1.25, 2.5, 5.0, and 10.0 mg/kg; apomorphine HCl (Sigma) 0.1, 0.5, 1.0 and 2.0 mg/kg; nicotine (Sigma) 0.0625, 0.125, 0.25, and 0.5 mg/kg; caffeine (Sigma) 2.5, 5.0, 10.0, 15.0, and 20.0 mg/kg; scopolamine HBr (Sigma) 0.125, 0.25, 0.5, and 2.0 mg/kg; lisuride H-maleate (Schering, Berlin) 5, 15, 30, and 60 µg/kg. The drugs were injected subcutaneously 10 min prior to testing. Doses are expressed as the salt except for amphetamine, for which free base

doses are given. A separate vehicle control group was tested with each dose-response study.

Apparatus. The data acquisition system has been described in detail elsewhere (Flicker and Geyer 1982; Geyer et al. 1986). Briefly, each BPM chamber consists of a 30.5 × 61 cm black Plexiglas holeboard with a total height of 38 cm. The chambers are equipped with three floor holes which are located in the front, middle, and rear part of the floor, six wall holes, three along either side of the long walls respectively, and an additional hole in the back wall of the chamber. An infrared photobeam in each 2.5 cm hole allows the recording of holepokes and rearing against the walls of the holeboard is detected by touchplates located 15 cm above the floor. In the holeboard arena a 4 × 8 array of infrared photobeams placed 2 cm above the floor is used to obtain the animal's position with a resolution of 3.8 cm. Each of the eight chambers is enclosed in a ventilated wooden box. A microcomputer samples the status of the photobeams with a sampling frequency of 10 Hz and compares it to a reference state of the chamber. If any change has occurred from this state, then the new state becomes the reference state and the previous state is stored in memory together with the time it served as the reference state. All data are stored permanently in disk files and can be used for subsequent data analysis.

Experimental procedure. For an experimental session, animals were brought to the laboratory 1 hour prior to testing. Each animal was placed in the left front corner of the BPM chamber and a button was pushed signaling the beginning of the test session for that animal. The sessions lasted for 1 or 2 h (only 1 h of data was used for the analyses below) and were conducted in dark chambers and during the animals' dark cycle. Dose groups were always balanced for chambers and time of day.

Data processing. The binary data files obtained by the data acquisition system were transferred to an IBM PC-compatible computer through a serial interface and converted into ASCII data fi The observables consisted of the (x,y) position of the rat in the BP as well as the time (t) the rat remained at that position. Th variables *(x,y,t)* defined a *micro-event* and sequences of mic events were used subsequently for the analysis. The total durati of all micro-events equaled the observation period, 1 h, and t number of observed micro-events was used as a convenient indi tor of the amount of locomotor activity (range: 3000–8000 cou per hour). The graphic displays of the animals, paths were obtain from the sequence of micro-events and 40% white noise was add to the graphical representation of the data in order to avoid squ patterns reflecting an artifact resulting from the lower resolut limit of the data collection system.

Measures. The two scaling exponents used to describe the data evolved from the following considerations. First, the duration micro-event quantifies a degree of local activity, i.e. how much animal is "active" or "inactive" at this particular event. Surpris ly, based on the distribution of the durations of micro-events clear distinction was found between "active" and "inactive". Ra er, continuous distributions were found that revealed an interest relationship between the duration of a micro-event and its f quency of occurrence. Simply stated, the longer the duration of micro-event, the less likely it was found, quantitatively expressed

$$N(t,\Delta t) \approx t^{-\alpha}$$

where $N(t,\Delta t)$ denotes the number of observed micro-events. any particular duration, the exponent, α, yields an approximat of the number of micro-events of that event duration. It also scribes how many counts are to be expected when the samp frequency is changed. Hence, α provides a sensitive indicator of t ratio of fast responses to slow responses, i.e. the ratio of "acti to "inactive". By definition, a psychostimulant should result in m "active" micro-events and therefore increase the ratio of fast to sl responses, or α. Conversely, a sedative drug should decrease

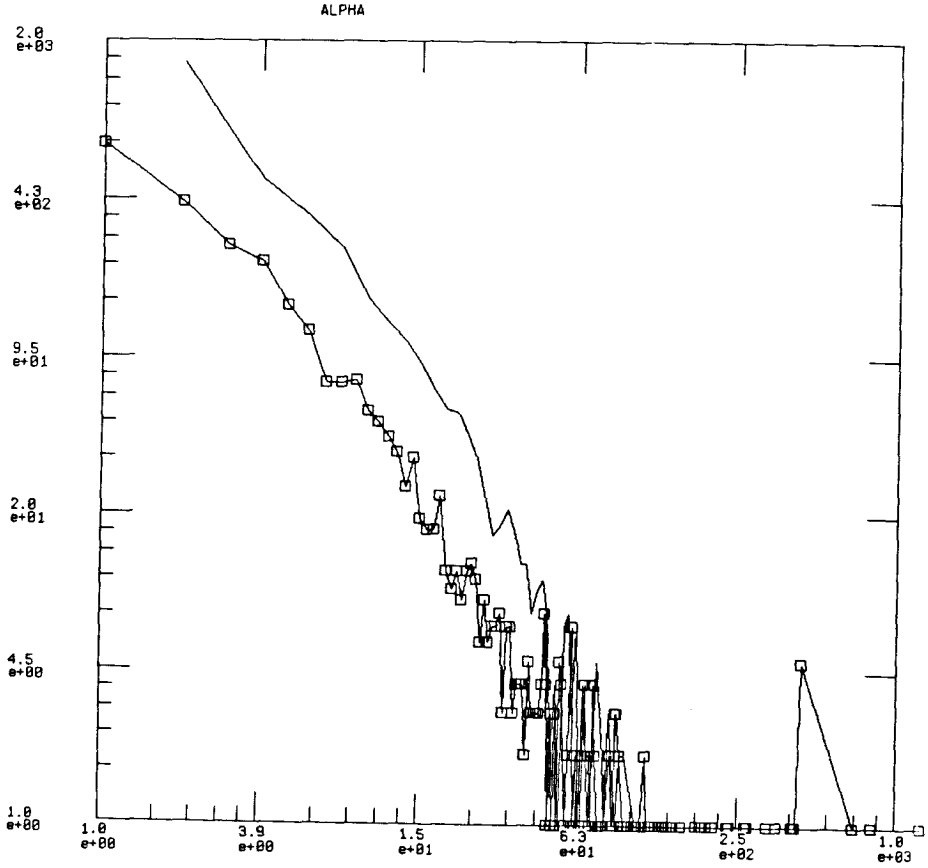

Fig. 1. This figure displays two typical distributions of micro-events in a double-logarithmic coordinate system. Th linear portion is described by its slope corresponding to −α. A more "active" animal under the influence of amphetamine (2.0 mg/kg) *(line)* exhibits relatively more fast responses leading to steeper slope when compared to a saline control animal *(line and boxes)*

...o of fast to slow responses as well as α. An example for two ...erent animals is given in Fig. 1. Given a constant observation ...od, a change in the number of micro-events for any given rat ...l also result in a corresponding change of the number of micro-...nts of other durations thereby affecting their ratio and thus α ...sitively. In short, an animal that makes more fast responses will ...e fewer slow responses during a 60 min observation period. ...e α provides a comprehensive description of the temporal struc-... of micro-events it was called the *temporal scaling exponent.*

Second, a rat moving in the BPM is tracing a sequence of ...ro-events describing the path that the animal is taking in the ... For example, segments of this path may lead straight from one ... of the box to another, e.g. to bring the animal into contact with ...erent stimuli (Berlyne 1960), or remain locally confined in a ...ific area of the chamber, e.g. to establish a "home corner" ...ver et al 1986). The structure of these movement patterns may ... conceptualized as consisting of local, small-scale movements ...h as grooming, head movements, or rearing, and large distance-...ering movements such as running and "exploring" different ...ts of the BPM chamber. Without arbitrarily and a priori defining ... distinction between large and small movements, the following ...metrical description of the path structure incorporates a con-...uous range of movements. A descriptor is obtained that averages ... range from the smallest detectable movements at one extreme ...ong straight movements at the other. To quantify these structur-... different paths, the length of the path is measured using dif-...ent measuring resolutions, k. Specifically, given N micro-events, ... distance between the 1st and the (k+1)th micro-event $d(x_1, y_1)$ based on their (x,y) coordinates followed by the distance ...ween (k+1)th and the (2*k+1)th event etc. yields $\left[\frac{(N-1)}{k}\right]$ ...asurements, which are added together to obtain the total path ...gth $L(k)$ with resolution k,

$$L_k(k) = \frac{\sum_i d(x_{m+i\times k}, x_{m+(i-1)\times k})}{k}$$

Using a large k corresponds to a "rough" look at the animal's path, whereas smaller k's are analogous to "zooming in" to describe the fine structure of the path. In Fig. 2, two examples of idealized path segments are given, demonstrating that the measured path-lengths in units of k change differently for the different segments when the resolution is changed. Thus, measures of "distance travelled" are not absolute, rather they depend necessarily upon the length of the ruler (e.g., distance between photobeams) used to define distance. In the case of a straight line (A), the length of the line is linearly related to the resolution, whereas the length of a more curved or bent line (B) changes more non-linearly with the resolution k. The general relation between path-length and resolution can be expressed by

$$L(k) \approx k^{-d}$$

Thus, for the first case, the resolution is directly proportional to the length and $d=1$, the second case yields $d=c$ with $c>1$, i.e. the measured length is shorter when a coarser resolution is employed. This increase in d indicates that an increased "amount of structure" is observed when the resolution is increased. A rat that frequently moves in a straight line will have a lower d compared to an animal that is moving predominantly in a small part of the box. Since d captures structural information about the geometry of the rat's movement pattern, it was called the *spatial scaling exponent.*

This exponent, d, is related closely to the fractal dimension concept (Mandelbrot 1977) where scaling is assumed within a large or even infinite scaling range, whereas here the scaling range is limited below by the measuring instrument (3.8 cm) and above by the boundaries of the BPM chamber (61 cm). With any given resolution k, there are k estimates of the path-length possible, i.e. starting points for the estimate range from the first to the (k+1)th etc., from the second to the (k+2)th etc., up to the kth to the (2*k)th micro-event. Therefore, an average length of the path, which increases the accuracy of the estimated path is computed by (Higushi 1988)

$$\langle L_k \rangle = \frac{\sum_i L_i(k)}{k}$$

The scaling exponent d is estimated by plotting $\log(\langle L_k \rangle)$ vs $\log(k)$ and fitting the slope with a least-square straight line approximation.

Data analysis. The data were compared on two different levels: intra-drug group comparisons and inter-drug comparisons. In the first case, analyses of variance (ANOVA, Dixon 1988) were performed on the data and differences were evaluated using Tukey post-hoc tests. The distribution differences were assessed by Levene's test for equal variances. For inter-drug comparisons, the data were z-transformed $x_d = \frac{\langle x_s \rangle - \langle x_d \rangle}{\sigma_s}$, to provide a coordinate system with the control group mean as origin and the control group standard deviations as units. This coordinate system was used to compare the changes induced by the different drugs. All significances are given for the 5% level unless indicated otherwise.

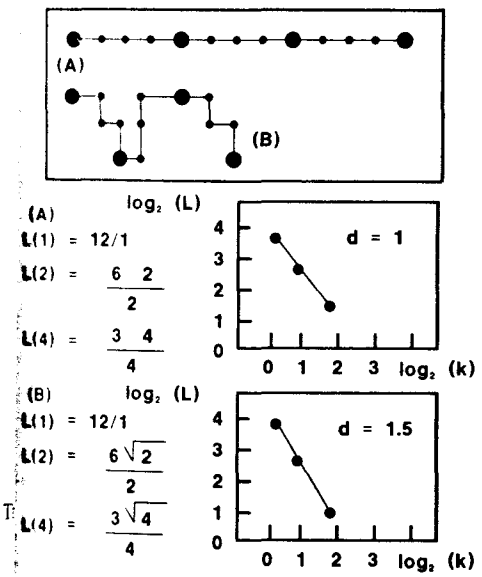

Fig. 2. This figure shows two schematic segments of consecutive micro-events in the BPM. For comparison, every fourth micro-event is emphasized by a larger dot. An exemplary computation of the spatial scaling exponent d is performed based on measurements of the length of the segments (L) with different resolutions (1, 2, and 4), see text

Results

Intradrug comparison

The result for the different psychoactive substances are summarized in Table 1. The spatial scaling exponent, d, the temporal scaling exponent, α, and the number of observed micro-events in 1 h, *counts*, are displayed as group means with standard deviations. Asterisks indicate significant differences and the superscript numbers indicate groups from which each treatment group differed according to Tukey's post-hoc analysis.

with $P<0.05$ and the superscript numbers indicate groups from

analysis. The detailed description is given in the text

d-Amphetamine (I)

Dose	0.0		0.25		0.5		1.0		2.0	
d	1.493	0.043	1.513	0.014	1.512	0.023	1.511	0.053	1.507	0.055
α	1.149*2,3,4,5	0.158	1.521*1,4,5	0.176	1.761*1	0.235	1.824*1,2	0.166	1.946*1,2	0.141
Counts	4524*2,3,4,5	722	6476*1	920	6946*1	719	6772*1	703	7213*1	761

d-Amphetamine (II)

Dose	0.0		2.0		4.0		8.0	
d	1.38*4	0.02	1.42	0.08	1.508	0.169	1.601*1	0.131
α	1.22*2	0.17	1.84*1	0.30	1.12	0.096	1.086	0.40
Counts	3969*2	465	6195*1	890	4073	296	4383	1464

Apomorphine

Dose	0.0		0.1		0.5		1.0		2.0	
d	1.513*2,4,5	0.038	1.603*1,3,4,5	0.036	1.523*2,4,5	0.057	1.437*1,2,3	0.050	1.411*1,2,3	0.067
α	1.096*2,4,5	0.174	0.864*1,3,4,5	0.107	1.167*2,4,5	0.119	1.398*1,2,3	0.130	1.511*1,2,3	0.230
Counts	5518*2	1274	3412*1,3,4,5	816	5144*2	1140	6187*2	976	6071*2	1117

Caffeine

Dose	0.0		2.5		5.0		10.0		15.0		20.0	
d	1.497	0.018	1.481	0.033	1.502	0.036	1.509	0.038	1.518	0.056	1.512	0.02
α	1.124*2,3,4,5,6	0.152	1.380*1	0.154	1.374*1	0.151	1.525*1	0.225	1.551*1	0.121	1.591*1	0.08
Counts	4281*4,5,6	757	3444*4,5,6	944	5255*2	823	5541*1,2	1000	5782*1,2	404	5400*1,2	344

Nicotine

Dose	0.0		0.0625		0.125		0.25		0.5		0.25	
d	1.493	0.023	1.487*5	0.053	1.487*5	0.044	1.509	0.053	1.553*2,3	0.040	1.504	0.03
α	1.022	0.062	1.099	0.162	1.056	0.206	1.102	0.178	1.136	0.154	1.230	0.17
Counts	4686	588	4929	1211	4552	1246	4632	912	4993	1230	5976	895

Lisuride

Dose	0.0		0.005		0.015		0.030.0		0.060	
d	1.462*4,5	0.053	1.482*4,5	0.039	1.437*4,5	0.063	1.366*1,2,3	0.047	1.302*1,2,3	0.020
α	1.174*2,3,4,5	0.136	0.824*1,5	0.165	0.836*1,5	0.077	0.979*1,5	0.117	1.386*1,2,3,4	0.132
Counts	5443*2,3,4	1073	2675*1,5	922	2343*1,5	391	2919*1,5	455	5254*2,3,4	1686

MDMA

Dose	0.0		1.25		2.5		5.0		10.0	
d	1.366*4,5	0.045	1.324	0.034	1.330	0.048	1.291*1	0.056	1.277*1	0.031
α	1.469*4,5	0.488	1.507*4,5	0.152	1.585*4,5	0.307	2.058*1,2,3	0.218	2.123*1,2,3	0.131
Counts	4861*3,4,5	1453	5601	880	6322*1	893	6670*1	709	6829*1	593

Scopolamine

Dose	0.0		0.125		0.5		2.0	
d	1.510*3,4	0.039	1.439	0.070	1.374*1	0.063	1.388*1	0.065
α	1.057*2,3,4	0.107	1.512*1,3	0.234	1.719*1,2	0.140	1.600*1	0.142
Counts	5201*2,3,4	783	7187*1	1050	7796*1	362	7774*1	361

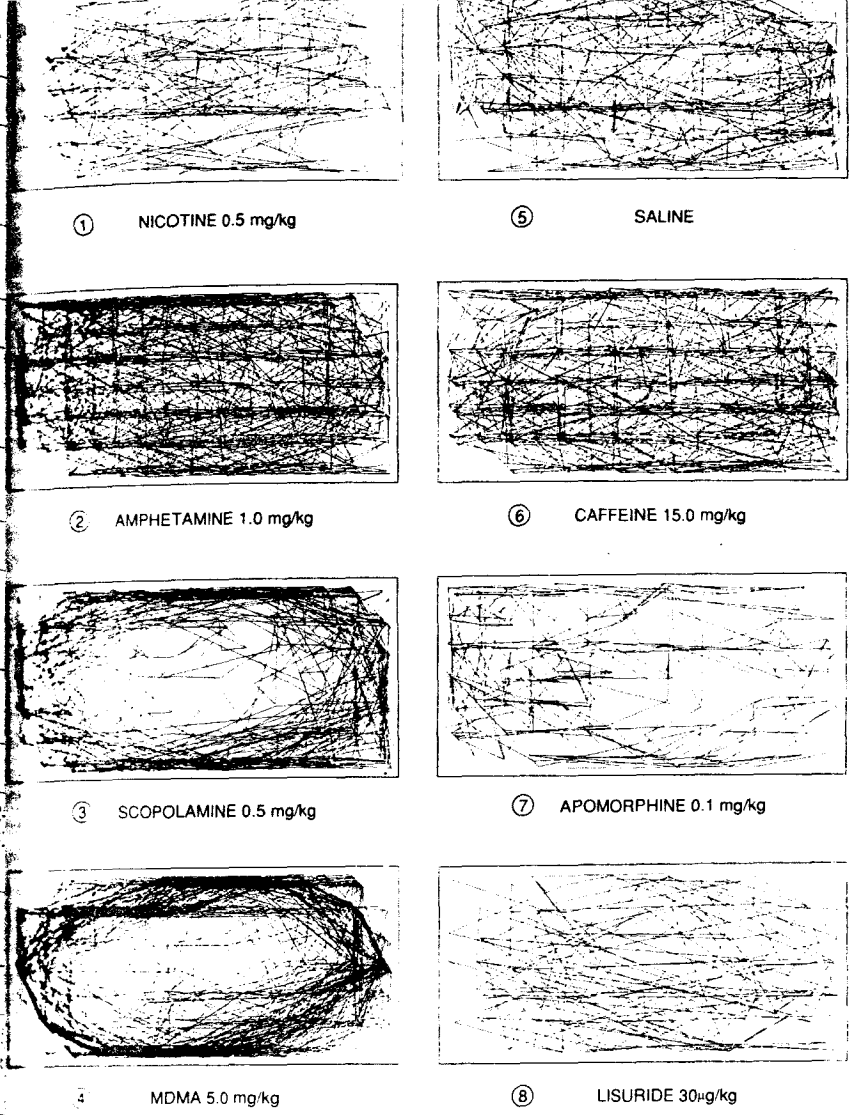

Fig. 3. This composite shows typical examples of the rat locomotor paths for 60 min exposure to the BPM. The animals were selected to be close to the respective group means. In addition, 40% noise was added to facilitate the visual image of frequently visited paths

Amphetamine (0.25–2.0 mg/kg) led to the well-known stimulation of locomotor activity indicated by significant main effects for both the counts of micro-events [$F(4,37) = 18.83$] and the temporal scaling exponent α [$F(4,37) = 26.99$]. With both measures, all amphetamine doses differed significantly from the saline control group. In addition, significant group differences were found for α between 0.25 mg/kg and 1.0 or 2.0 mg/kg, suggesting a dose-dependent progression of fast micro-events and a compensatory reduction of long duration micro-events. These differences were not detected with the *counts* measure. In a separate experiment, high doses of amphetamine (4.0 or 8.0 mg/kg) showed no significant differences of counted micro-events compared to saline controls. Animals under the influence of amphetamine (0.5–2.0 mg/kg) explored all areas of the BPM chamber (Fig. 3), without exhibiting a strong tendency to remain in a particular part of the box or a path structure that differed from saline controls. This impression was supported quantitatively by a lack of significant treatment effect for these doses on the spatial scaling exponent, d, [$F(4,37) = 0.61$]. In higher doses (4.0 and 8.0 mg/kg), however, some rats exhibited repetitive local movements with occasional excursions through the chamber leading to significant increases in d, the 8.0 mg/kg dose of amphetamine being significantly different from controls (Table 1).

Animals treated with 0.1 mg/kg apomorphine, a dose that acts presumably on presynaptic dopamine receptors (Carlsson 1975), showed the expected reduced levels of activity, as indicated by significant decreases in activity counts relative to saline controls [main effect: $F(4,42) = 8.89$]. The shift towards long duration micro-events for the low dose group also led to significant group differences in α: $F(4,42) = 29.97$. With higher doses of apomorphine (1.0 or 2.0 mg/kg), a stimulating effect became apparent in the duration of the micro-events with a shift towards fast responses and significant increases in α. By contrast, the total count of micro-events was not significantly different from saline animals at these doses

of apomorphine. The reconstructions of the locomotor paths of apomorphine-treated rats (Fig. 3) revealed that the animals with relatively more long duration micro-events remained preferentially in parts of the box, typically one of the short sides or near a corner, and made few excursions throughout the chamber. With higher doses (1.0 or 2.0 mg/kg), however, the paths were predominantly oriented along the walls of the chamber. This biphasic effect on the structure of the motor activity was reflected in significant group differences for the spatial scaling exponent [d: $F(4,42) = 6.10$]. While the lowest dose (0.1 mg/kg) increased the spatial scaling exponent, the highest dose (2.0 mg/kg) reduced d to a level that was significantly below controls. Thus, the biphasic effect of apomorphine on the distribution of durations of micro-events was associated with a change in the geometrical structure of the locomotor paths.

Caffeine stimulated motor activity in the BPM, as reflected by a significant effect on both the micro-event counts as well as the temporal scaling exponent [*counts*: $F(5,51) = 13.47$; α: $F(5,51) = 11.88$]. Low doses of caffeine (2.5 mg/kg) had an interesting effect on the number of counts versus the distribution of micro-event durations. A slight reduction of the counts was associated with an increased α, suggesting that even though the number of events was reduced, indicating less activity, more fast than slow micro-events occurred. The increased number of fast events relative to slow events was found to be significantly different starting at the 2.5 mg/kg dose, whereas the counts of micro-events differed significantly from saline animals at doses of 10, 15 or 20 mg/kg. The structure of the locomotor paths did not show significant differences compared to controls [d: $F(5,51) = 1.29$]. The standard deviations of the caffeine-treated animals for the d measure indicated that there was increased variability within these groups which was not evident in the group means [Levene's test for variances: $F(5,51) = 2.72$].

Nicotine treatment did not result in significant changes of motor activity in the BPM chamber as indicated by the counts of micro-events and α [*counts*: $F(5,43) = 1.72$; α: $F(5,43) = 1.31$]. The ANOVA revealed a significant main effect for d [$F(5,43) = 3.13$]. However, no nicotine treatment group was significantly different from saline controls. Instead, lower doses of nicotine (0.0625 and 0.125 mg/kg) resulted in locomotor paths that were relatively straight and had more long distance-covering movements compared to higher doses of nicotine (0.25 and 0.5 mg/kg) which increased local activity. Therefore, the former groups showed a lower d compared to the latter groups. In contrast to the behavioral effects of the other stimulant drugs, this effect of nicotine was not readily apparent by observation of the animals or the graphic displays of their movement patterns. While nicotine did not change the amount of motor activity, as indicated most sensitively by α, it seemed to alter the geometrical structure of the paths taken in the BPM chamber.

Lisuride treatment resulted in group differences reflected in the counts of micro-events [$F(4,38) = 18.54$], the distribution of micro-event durations indicated by the temporal scaling exponent [α: $F(4,38) = 28.36$], and the geometrical structure of the locomotor paths [d: $F(4,38) = 21.93$]. Animals injected with low doses of lisuride (0.005 mg/kg) showed decreased levels of motor activity and relatively more long duration micro-events compared to saline controls or high doses of lisuride (0.06 mg/kg). The paths of these animals were found to be similar to those of saline-treated rats, supported by unchanged d, but significant path differences existed between the effects of low and high doses of lisuride. A complex transition was observed in the dose range between 0.015 and 0.06 mg/kg. First, animals treated with 0.03 mg/kg displayed a decreased ratio of fast to slow responses, significantly different path structures dominated by long distance-covering movements along the walls and a decreased d. Second, rats treated with 0.06 mg had significantly more short versus long response durations, i.e. increased α, when compared to lower doses of lisuride or saline controls, and a significantly reduced spatial scaling exponent, d, when compared to saline animals. The biphasic dose response in the temporal domain indicated by the increased α following 0.06 mg/kg lisuride was not evident from the micro-event counts which were significantly different from lower doses of lisuride but not compared to saline animals. Therefore, a biphasic dose response in the activity-related measure was observed as with apomorphine.

MDMA, which is known to increase locomotor activity (Gold et al. 1988), produced significant group differences in both the counts of micro-events and the temporal scaling exponent [*counts*: $F(4,34) = 5.5$; α: $F(4,34) = 9.50$]. In addition to differences between saline and the 5.0 or 10.0 mg/kg dose groups, which were obtained with both measures, the counts and α, differences in the micro-event durations were also found between the low doses of MDMA (1.25, 2.5 mg/kg) and the high doses. It has been reported that higher doses of MDMA led to an avoidance of the center (Gold et al. 1988) and locomotor paths predominantly along the wall, which has been described as rotation within the chamber. In accord with these descriptions, the spatial scaling exponents revealed a significant difference between the groups [$F(4,34) = 4.60$]. High doses of MDMA led to a significant reduction of d compared to saline control animals.

The acute administration of scopolamine produced substantial increase in motor activity indicated by significant effects on both the counts of micro-events and the temporal scaling exponent [*counts*: $F(3,35) = 28.3$; α: $F(3,35) = 31.57$]. Scopolamine has been reported previously to decrease center entries, produce a "more structured path", and to induce a pattern of locomotor hyperactivity superficially similar to MDMA (Geyer et al. 1986). The spatial scaling exponent, d, supported these observations quantitatively [d: $F(3,35) = 6.7$]. Scopolamine (0.5 or 2.0 mg/kg) significantly reduced d compared to saline animals. To summarize, animals treated with scopolamine showed a dose-dependent increase of fast responses versus slow responses, traveled longer distances in the BPM, and exhibited straighter paths with less local movements and more long distance-covering movements.

Fig. 4 ... exponential ... x-axis ... is given ... control ... deviation ... direction

Interdrug comparison (z-transform)

To compare how different psychostimulant substances change the distribution of the duration of micro-events and the structure of locomotor paths, the individual dose response curves were projected onto a two-dimensional plane – the d–α plane – with α, the temporal scaling exponent on the x-axis, and d, the spatial scaling exponent on the y-axis (Fig. 4). The changes induced by the different substances were computed in units of standard deviations from the respective saline control. Substances that stimulated activity, increasing the number of short-duration events versus long-duration events, and therefore increasing a, but without affecting the geometric path structure were found along the x-axis in the positive direction. Amphetamine, and low doses of MDMA comprised this group. Substances that increased and changed the path structure towards long straight movements are displayed in the lower right quadrant of the plane. Scopolamine, high doses of MDMA, and to a lesser extent high doses of apomorphine and lisuride were grouped together in this quadrant. Biphasic dose response curves were obtained for apomorphine and lisuride along the "activity dimension", i.e. lower doses of both substances favored long micro-event durations, whereas higher doses increased the short-duration micro-events. However, the two substances differed to some extent in the changes they induced in the path structure. Whereas apomorphine increased the contribution of local movements together with an increased ratio of long versus short event durations, locomotor paths observed with lisuride showed increasingly straight paths even with relatively more slow responses. For higher doses of apomorphine (2.0 mg/kg) and lisuride (0.06 mg/kg) both drugs are located close together in the d–α plane supporting a similar effect of these substances on unconditioned locomotion. Nicotine showed a unique dose response pattern that confirmed that the path structure can change without a significant effect on the response durations. It appears that the motor activity under the influence of nicotine is shifted to more local movements contributing to an increase in the spatial scaling exponent. To summarize, distinct structural information and sensitive assessment of the activity levels could be obtained from both d and α which might serve as collective measures to describe qualitative and quantitative changes of motor behavior on a macroscopic level.

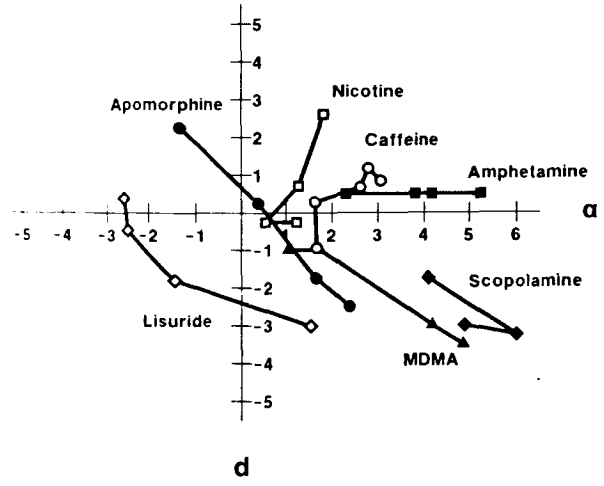

Fig. 4. This figure shows the results of the z-transformed scaling exponents. The temporal scaling exponent α is displayed on the x-axis versus the spatial scaling exponent d on the y-axis. The origin is given by the average value for d and α for the corresponding saline control group and deviations are measured in units of standard deviation. Successive doses are connected by lines to indicate the direction of the dose response. For detailed description see text

Discussion

The description of the acute behavioral effects of psychoactive substances on unconditioned motor activity using d and α provides a dose-dependent, sensitive, and discriminative "fingerprint" for each of the substances tested without the use of pre-defined behavioral categories or the assumption of linearity in the relationship between dependent and independent variables. The term "psychostimulant" is motivated primarily by the fact that these substances increase measures of the amount of unconditioned motor activity (Harvey 1987). Discriminations between drugs within this category require descriptors of their effects on the structure of the activity. Discrete predefined variables and their quantification using durations, occurrence frequency or categorical ratings of these variables carry the implicit assumption that the particular categorizations of responses represent sensitive and appropriate dissections of the observed variables. The scaling approach exploits the possibility that the characteristic behavioral effects of a drug may be extracted by studying the relationship between the recorded variable of interest (location of the animal in the chamber) and the experimental parameters (observational resolution). For example, the often used concepts of "forward locomotion" (Ljungberg and Ungerstedt 1976, 1977; Nickolson 1981) or "ambulation" (Geyer et al. 1986) imply that a change in the coordinates above a certain threshold (measured length) constitutes a new variable (e.g. "cross-overs"). The use of such a variable assumes that discrete behavioral events take place when an animal is moving from one part of the box to another rather than moving within a circumscribed area or sitting still. Instead of setting a threshold, the scaling approach uses the full potential of automated recording devices, defining a functional relationship between the measured length and the consecutive locations in the chamber in order to extract a continuum of motor responses from straight paths to local movements. Thus, the spatial scaling exponent d expresses quantitatively how straightforwardly the animal is moving in the box.

Similar reasoning applies to the use of scaling measures in the temporal domain. The main difference between the usage of counts as an indicator of how active an animal is and the temporal scaling exponent α is a "global" versus "local" viewpoint. Counts cumulated over a specific time period express an overall level of activity, whereas using the duration of each micro-event specifies a local "degree of acting" or a microscopic

of these micro-event durations is described simply by a function that can be characterized by a scaling exponent allows an enormous contraction of information into one number. Comparing the differences between the treatment groups using the *F*-values as well as post-hoc significances supports the hypothesis that α is more sensitive than activity counts. It is clear that α is subject to the animal's habituation and other processes that depend on the duration of exposure to the experimental enclosure. Future studies will further incorporate the temporal dependency of the microscopic description of activity by parameterizing α by time and computing additional coefficients such as its rate of change.

The adequacy of the description provided by the combination of the temporal and spatial scaling exponents requires that the results should reflect differences in activity or path structures that have been described previously by traditional measures of locomotor activity or by direct observation of the rat paths. Apomorphine had been distinguished from amphetamine on the basis of holepoking counts (Ljungberg and Ungerstedt 1976; Geyer 1982), path structures (Geyer et al. 1987), and complex measures of exploration (Kelley et al. 1986; Ljungberg and Enquist 1987), even though both substances act primarily through the dopamine system. The biphasic effect of apomorphine on activity has been attributed to the presynaptic actions of low doses and the postsynaptic actions of high doses (Carlsson 1975), though this hypothesis has been questioned recently (Scheel-Krueger 1986; Stahle and Ungerstedt 1989). In any case, low doses of apomorphine decrease exploration, whereas higher doses increase locomotor activity and produce paths which typically stay along the walls of the test chamber (Geyer 1982). Consistent with these observations, the biphasic response of apomorphine in the *d*–α plane reflects changes in both activity and the path structure. After the low dose (0.1 mg/kg), the animals were less active and engaged mainly in local movements, so α was decreased and *d* was increased. By contrast, higher doses (1.0 and 2.0 mg/kg) increased activity and therefore α, while producing long straight movements and a decrease in *d*.

In addition to identifying differences in activity and path structures, behavioral patterns described previously as similar should produce similar changes in *d* and α. The path structures characteristic of animals injected with apomorphine or scopolamine have been described previously as highly structured and graphically similar (Geyer et al. 1986). Similarly, the effects of higher doses of MDMA (5.0 and 10.0 mg/kg) have been compared to scopolamine and apomorphine insofar as they are characterized by thigmotactic behavior (Gold et al. 1988). It was therefore expected that these substances should be located closely together in the *d*–α plane. Figure 4 clearly confirms this expectation and emphasizes that the spatial scaling exponent *d* was able to quantitatively substantiate previous descriptive characterizations.

For the description of unconditioned motor activity using scaling exponents to be useful, detection of changes

observed. The z-transforms of the present data demonstrate that neither the spatial scaling exponent *d* nor the temporal scaling exponent α show "ceiling" or "floor" effects. The standard deviations and the statistical comparisons of the variances indicate that the distributions of saline and drugged animals are typically similar. Caffeine, however, seems to increase the variability among the animals for these measures. This result may be relating to reports of strong individual differences in the reinforcing properties of caffeine in human subjects (Griffiths and Woodson 1988; Stern et al. 1989). The sensitivity of the α exponent might suggest that it will always indicate differences no matter what the underlying effect may be. The results of the nicotine experiment show that "negative" results can be obtained, i.e. nicotine did not produce significant changes in α.

It is clear from these results that α and *d* are not redundant measures of drug effects and that the combination of the two provides more information than does either measure alone. Using the *d*–α plane reveals at least four distinct categories of drug effects in the BPM paradigm, based on the similarity of their dose response curves. The first group has increased α and unchanged *d* and consists of amphetamine and low doses of caffeine. The second group exhibits increased α and decreased *d* and is represented by scopolamine, MDMA, apomorphine (high doses), and lisuride (high doses). The third group is characterized by an increase in *d* with small changes in α; nicotine and low doses of apomorphine exemplify this group. Lastly, lisuride and apomorphine may be grouped together, since both drugs show a biphasic dose response even though they can be distinguished based on their differential effects on *d*. The substances whose effects are thought to be mediated by different pharmacological actions were placed in similar locations on the *d*–α plane suggests, however, that the description cannot be linked simply to one biochemical substrate. These substances may be differentiated via a natural extension of this method considering subsets of micro-event sequences and their local scaling exponents rather than an overall "average" scaling exponent, which is currently under investigation (Paulus et al. 1991).

The differential effects of low doses of apomorphine and lisuride on *d* suggest a complex interaction between D1 and D2 receptors on local versus global movement. The D2 receptor has been implicated in the mediation of stereotypic behavior, whereas D1 stimulation has been associated with varied forms of hyperactivity (Braun et al. 1986). Receptor binding studies (Seeman and Ulpian 1986) indicate that lisuride has a D2:D1 affinity ratio (p 8:1, apomorphine 2:1, and amphetamine, as a dopamine releasing agent, a 1:15 ratio. The fact that continuous climbing behavior was induced most readily by a combined activation of D1 and D2 receptors (Davis et al. 1990) and the observation that low doses of apomorphine reduced exploration and elicited yawning in the presence of elevated synaptic dopamine (Stahle and Ungerstedt 1989), suggest that both receptors may act postsynaptically in a complicated synergetic fashion (White 1987). With the assumption that both the ratio

tivation and the amount of activation of D1 and D2 ceptors are important determinants for the effects on e structure of unconditioned motor behavior, the fol- wing scenarios can be constructed. The contribution of creased local movements to the path structure may be sociated with a significant relative D2 activation in the presence of a "D1 tone". Because a high affinity post- naptic D2 receptor site has been hypothesized, increas- g the dose of a D2 agonist should result in a relatively stronger increase of D2 versus D1 activation and lead to an increasingly fixed locomotor pattern, thus explaining the reduction of d with high doses of lisuride and apo- morphine. A predominant activation of postsynaptic D2 receptors in the absence of a "D1-tone", e.g. with sub- stances having high affinity for the D2 receptor such as lisuride, should lead to more fixed activity pattern (Braun et al. 1986; Arnt et al. 1988) even at low doses of the substance. Therefore, lisuride may reduce d even at low doses because of a lack of "D1-tone". Consequently, one should expect to find extremely repetitive path structures and a decrease in the spatial scaling exponent with a D2 agonist. Eilam et al. (1989) reported that 2 mg/kg quin- pirole resulted in repeated travel along a few paths in a limited portion of the environment, which seems to cor- respond to a decrease in the spatial scaling exponent. Furthermore, in the presence of a strong "D1-tone" together with increasing activation of D2 receptors, as exemplified by amphetamine treatment, one would ex- pect to find a tendency toward local behavior favoring an increase in d. This speculative model is being tested explicitly using combinations of D1 and D2 agonists.

The fact that high doses of amphetamine (4.0 or 8.0 mg·kg) led to an increase in d with α being within the control range supports the view of a combined D2 stimu- lation "D1-tone" hypothesis. In this context, the in- creased d values for amphetamine, which is known to produce local stereotypies (Randrup and Munkvad 1967), increase sniffing and holepoking (Ljungberg and Ungerstedt 1976), disrupt behavioral sequences (Ljung- berg and Enquist 1987), and increase rearings in the pre- and post-stereotypy phases (Schiorring 1971), signifies the consequences of these stereotypies on the geometrical characteristics of the path structure. Amphetamine presumably influences the competition between different responses for expression, leading to an "increased num- ber of responses in a decreased number of response cat- egories (p 85)" (Lyon and Robbins 1975). Descriptively, the effects of amphetamine are characterized by "de- creased variation, continuous repetition of behavioral patterns or items and behaviour which appears aimless (p 1)" (Randrup and Munkvad 1967; Schiorring 1971). Geometrically, a repetition of similar micro-events can lead to two kinds of perseverative behavior. First, con- secutive rhythmic head and/or body movements result in paths that are confined to a small subset of the test environment and increase the contribution of local ver- sus long distance-covering movements, thereby increas- ing d. Therefore, the spatial scaling exponent will indicate this perseverative behavior with a strong increase in d, which may be termed *local perseveration*, e.g. the in- creased d for high doses of amphetamine. Second, con- secutive movements in the same direction produce a straight path which is only constrained by the shape of the test environment; consequently d will be reduced. Thigmotaxcis or "wall hugging" (Geyer 1982) represents a typical example and may be called *locomotor perseveration*. Kelley et al. (1986) described the locomotor behav- ior exhibited by apomorphine-treated animals as highly automated and speculated that the behavior does not appear to be influenced by sensory feedback. Since the spatial scaling exponent is closely associated with the fractal dimension (Mandelbrot 1977) that describes the number of degrees of freedom of a physical system, a reduction in d corresponds well with the notion of per- severation in combination with a reduction of external sensory input. With both high d and low d behavior, the animal's behavioral repertoire is deprived of some of its normal aspects.

To summarize this approach, a scaling exponent de- scription of the effect of psychoactive substances on unconditioned motor activity results in a quantitative assessment of differences between substances on a behav- ioral level that is sensitive, dose-dependent, and can be validated by observations of the path structures. This description may then be used to compare these numerical results with quantitative measures on other levels of description such as receptor binding, microdialysis, elec- tro-voltammetry, and electrophysiology. It appears that there exist distinct macroscopic behavioral response cat- egories which are characterized by a certain d–α plane region.

Acknowledgements. This work was supported by grants from the National Institute on Drug Abuse (DA06325, DA02925). M.A. Geyer was supported by a Research Scientist Development Award from the National Institute of Mental Health (MH 00188). We thank Lynne Adams, Ryan Babineaux, Lisa Gold, Diana Martinez, Virginia Masten, and Richard Sharp for their assistance in the conduct of these studies.

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