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Activity density in the open field: a measure for differentiating the effect of psychostimulants

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Abstract

Traditional open-field activity measures do not provide a sharp behavioral differentiation across psychomotor stimulants such as *d*-amphetamine (AMPH) and cocaine (COC) in the mouse. We used Software for the Exploration of Exploration (SEE) to investigate and develop a novel behavioral endpoint to characterize the "structure" of AMPH- and COC-induced locomotor behavior in two inbred strains of mouse, C57BL/6 (B6) and DBA/2 (D2). We suggest a measure we term "activity density" as a means to differentiate the behavioral effects of COC and AMPH. Activity density is defined as the activity divided by the range over which it took place. It characterizes the restriction of behavioral repertoire that does not result merely from inactivity. In both the B6 and D2 mice, AMPH increased activity density in a dose-dependent fashion by restricting the range of activity compared with COC doses producing the same level of activity. While AMPH restricted the range in both genotypes, characterizing the geographical region in which the restriction took place further differentiated the genotypes. The newly developed activity density measure thus provides a more general measure than stereotypy of the path, and can differentiate the effects of AMPH and COC both within and across genotypes.

Keywords: Mouse; C57BL/6J; DBA/2J; Amphetamine; Cocaine; SEE; Locomotor behavior; Spatial behavior; Stereotypy; Behavioral phenotyping

1. Introduction

Open-field behavior and locomotor behavior are commonly used to assess the influence of genotype or drug on rat or mouse behavior. It is typically measured automatically using photobeam interruptions or video tracking. The variables recorded in these tests, however, typically include simple measures such as the distance covered by the mouse during a session or the ratio between staying in the periphery and center of the arena. These measures are usually cumulative and general, reflecting a common view that open-field behavior is largely stochastic in nature, and can be quantified mainly by some measure of "general activity" (but see Paulus and Geyer, 1991, 1993 for a different viewpoint). Such measures typically encounter difficulties in discriminating the effects of psychostimulant drugs, as all these drugs (by definition) increase locomotor activity.

In recent years, ethologically oriented studies in rats (Eilam and Golani, 1989; Eilam et al., 1989; Golani et al., 1993; Tchernichovski et al., 1998; Drai et al., 2000; Kafkafi et al., 2001) and more recently in mice (Drai et al., 2001; Benjamini et al., 2001; Kafkafi et al., 2003a,b; Lipkind et al., 2004) found that open-field behavior is structured and consists of typical behavior patterns. These patterns were found useful in psychopharmacological and psychobiological studies (Whishaw et al., 1994; Cools et al., 1997; Gingras and Cools, 1997; Szechtman et al., 1999; Whishaw et al., 2001; Wallace et al., 2002). Based on these structured patterns, Software for Exploring Exploration (SEE) was recently developed for the visualization and analysis of open-field data measured automatically by video tracking

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(Drai and Golani, 2001). SEE was shown to discriminate open-field behavior across inbred strains in a replicable way across laboratories (Kafkafi et al., 2003a; Lipkind et al., 2004.

The main advantage of SEE lies in its the ability to visualize, explore and quantify large amounts of locomotor data from many animals, using the interactive and powerful programming environment of Mathematica (Wolfram, 1999). This enables an open-ended approach in which new behavioral measures may be defined to better capture specific behavioral effects (Kafkafi et al., 2003a,b). In the present study we used this approach to explore the differences in the effects of *d*-amphetamine and cocaine on the open-field behavior of two common mouse inbred strains: C57BL/6 (B6) and DBA/2 (D2). The data presented here were initially developed as a part of a large database in a previous study (Kafkafi et al., 2003b). That study was focused on gathering measures for differentiating the behavior of B6 and D2 strains across laboratories, protocol conditions and different doses of cocaine and *d*-amphetamine. In the present study, we focus specifically on the development of new measures that specifically differentiate the effects of cocaine and d-Amphetamine across genotypes.

Cocaine (COC) and *d*-amphetamine (AMPH) have numerous neuropharmacological and behavior pharmacological properties in common. COC and AMPH are both considered indirect dopaminergic agonists in that they do not directly bind to dopamine receptors but rather increase the amount of endogenous dopamine available to stimulate dopamine receptors. The indirect dopamine agonist properties of AMPH and COC result in significant increases in ventral striatal dopamine (Di Chiara and Imperato, 1988) and nearly indistinguishable locomotor stimulant actions as measured by distance traveled (e.g., Xu et al., 2000; Kafkafi et al., 2003a). In addition, the discriminative stimulus properties of the two drugs are easily substituted for each other in measures such as drug discrimination (Li and McMillan, 2001) and either drug easily substitutes for the other in drug self-administration paradigms (Woolverton et al., 1980, 2001). Important distinctions between the two drugs can be made as well. While both compounds bind to the dopamine reuptake site, AMPH is transported into the cytoplasm of the nerve terminal where it increases dopamine efflux via transporter mediated exchange and increases the cytoplasmic levels of dopamine available for subsequent action-potential dependent release (Sitte et al., 1998; Khoshbouei et al., 2003). Additional effects on transporter cell surface expression also differ between AMPH and COC. Acute AMPH administration decreases cell surface DAT expression while acute COC increases it (Kahlig and Galli, 2003); these difference could have significant effects on extracellular dopamine kinetics. The neuropharmacological differences mentioned above likely result in slightly different electrophysiological (Sonders et al., 1997), neurochemical (Carboni et al., 1989; Pifl et al., 1995) and psychopharmacological (Jones and Holtzman, 1994; Jones et al., 1993; Vanderschuren et al., 2000) effects. The goal of the present study was to further develop a sensitive behavioral endpoint in the mouse that could differentiate the behavioral consequences of each drug's unique pharmacological properties.

In rats, AMPH is known to induce a repetition of the locomotor path ("stereotypy" or "preservation"), and several methods have been suggested to quantify this effect (Mueller et al., 1989; Paulus and Geyer, 1991). When exploring mouse data using SEE we found that even with the highest dose of AMPH, only some of the animals exhibited, during some part of the session, an exact repetition of the path. However, we have noticed a more general characteristic: while the AMPH-treated animals increased their activity, their spatial range was not increased by the same amount, and in high doses was even decreased. An exact repetition of the locomotor path was only the most extreme case of this phenomenon. The purpose of this report is to describe the quantification and analysis of an endpoint derived from the raw data to characterize this observation. We thus introduce a measure we term "activity density", which is simply the distance traveled divided by the range. We measure the range in two different dimensions: the radial dimension (from the walls of the circular arena into its center) and the angular dimension (along the perimeter of the arena).

2. Methods

2.1. Experimental methods

Subjects were 10–18 week old male B6 and D2 mice shipped from Jackson Laboratories and housed in the same room for at least 2 weeks before the experiment. They were kept in 12:12 light–dark cycle, housed 2–4 per cage under standard conditions of 22 °C room temperature and water and food *ad libitum*. Animals were tested once during the light phase of the photoperiodic cycle. Each animal was brought from its housing room, given an i.p. injection of either saline, cocaine (5, 10 or 20 mg/kg), or *d*-amphetamine (1, 2.5 or 5 mg/kg) and then introduced immediately into the arena. The subject was returned to the housing room immediately after the end of the 90-min session. Groups included 5–8 animals for each dose. Doses were assigned so that no two animals of the same cage received the same drug and dose. The experimental protocols followed the "Principles of Laboratory Animal Care" (NIH publication No. 86-23, 1996). The animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC).

The arena was a large, circular (250 cm diameter) area with a nonporous gray floor and a 50 cm high, gray painted

wall. The large size of the arena is an important requirement of our protocol, since in our experience it considerably increases the relative spatial resolution and the quality of the results (Kafkafi et al., 2003a). Several landmarks of various shapes and sizes were attached in different locations to the arena wall and to the walls of the room where the arena was located in order to enable easy navigation for the mouse. The arena was illuminated with two 40 W neon bulbs on the ceiling above the center of the arena.

Tracking was performed using a video camera installed on the ceiling, feeding directly into a PC computer running a Noldus EthoVision® video tracking system (Spink et al., 2001) in a tracking rate of 30 frames per second and spatial resolution was about 1.3 cm per video pixel. The system measures the location of the center of gravity of the animal's image in each video frame. The "subtraction" mode of the system was used, so the system was tracking spots either darker or brighter than a reference image of the empty arena. This setup is identical to that used in Kafkafi et al. (2003a,b). The data for each session thus included the coordinates of the path in 90min × 60s × 30frame/s= 162,000 data points. Coordinate files were exported from EthoVision® and analyzed using SEE. For the details of SEE analysis, see Drai and Golani (2001) and Kafkafi et al. (2003a).

2.2. Analysis and definition of measures

We define activity density as the distance traveled divided by the range over which this activity took place. As the path of the animal becomes more convoluted, interlaced or repetitive it can be more "dense", i.e., confine a longer mileage into a smaller range. In a hypothetical simplistic case proposed, the animal merely went in a straight line from point A to point B. In this case, both the distance traveled and the range are equal to the distance between A and B; the activity density (their ratio) in this case equals 1. If the animal went straight from A to B and back to A, the range remains the same but the distance traveled was doubled, so the activity density equals 2. If the animal repeated the ABA sequence five times taking a straight path from A to B then its activity density equals 10.

In the simplified example given above, the activity density was considered along a single dimension—a straight line. The spatial location of the animal, however, has two dimensions, which can be expressed either using the Cartesian representation (x, y), or the polar representation (r, θ), in which r (the radial dimension) is the distance in cm from the arena center and θ (the angular dimension) is the angular position in degrees around the perimeter of the arena (Fig. 1, left). In this study we used the polar representation since our experience with circular arenas indicates that the spatial behavior is typically organized relative to the arena wall. That is, the relevant variables for the animal are the distance from the wall (or its complement, the distance from the center r) and the direction from the center θ. The activity density was thus computed separately for the angular and radial dimensions. Technically, this was done by translating each data point of the path from its (x, y) Cartesian coordinates to the (r, θ) polar coordinates. Fig. 1 (right) demonstrates the time series of the angular component θ during a whole session in a single animal. A period of very high angular activity density can be clearly seen during minutes 10 to 20, when the animal was moving back and forth along a small section of the arena's perimeter, thus constraining long mileage into a small range. A period of low angular activity density is shown, for example, between minutes 0 and 10, when the mileage was also high, but spread over the whole perimeter of the arena. The radial component r

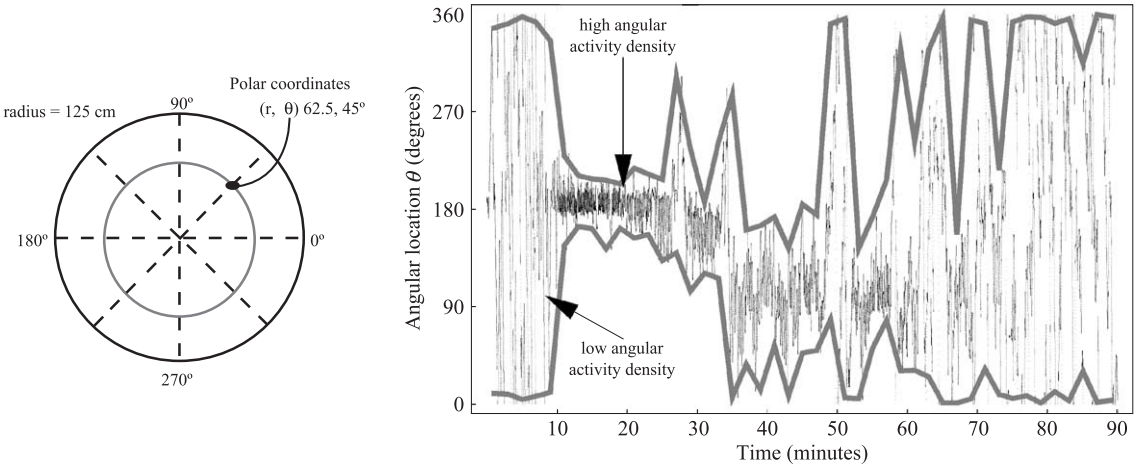

Fig. 1. Left: any location in a circular open-field arena can be represented by its polar coordinates (r, θ), including the radial component (r, distance from the center in cm) and angular component (θ, direction from the center in degrees). Right: angular location plot of a 90-min session of a D2 mouse injected with 5 mg/kg AMPH. Gray thick lines indicate the 98% angular range, computed in time bins of 2 min. This specific plot portrays a decrease of angular range, coupled with high activity (i.e., high "activity density") 15–60 min after injection. As shown in Results, this is typical for D2 mice with 5 mg/kg AMPH.

can be analyzed separately in the same way. The range in both r and θ was computed (see below), as well as the distance traveled, in time bins of 2 min. The bold lines in Fig. 1 (right) display the computed angular range.

The simplest way to compute the range in each dimension is the difference between the minimal and maximal values within this dimension during a given time frame. The problem with this way, however, is that it is very sensitive to outliers, since it depends only on the two extreme points. For example, if for most of an hour the animal went back and forth between points A and B that are 20 cm apart, but during the last 2 s of that hour it ran to point C that is 100 cm further, the range will be 120 cm. In order to prevent such outliers from critically affecting the results, the range in each dimension was computed as the distance between the 1st and 99th quantiles of the values (i.e., the largest 1% and smallest 1% of the results were disregarded).

As mentioned, the activity density was measured in time bins of 2 min. This time span was chosen since on the one hand it is long enough for animals to easily cover the range of the whole arena even when walking slowly, but on the other hand short enough so animals with high activity density will be able to cover only a small part of the arena.

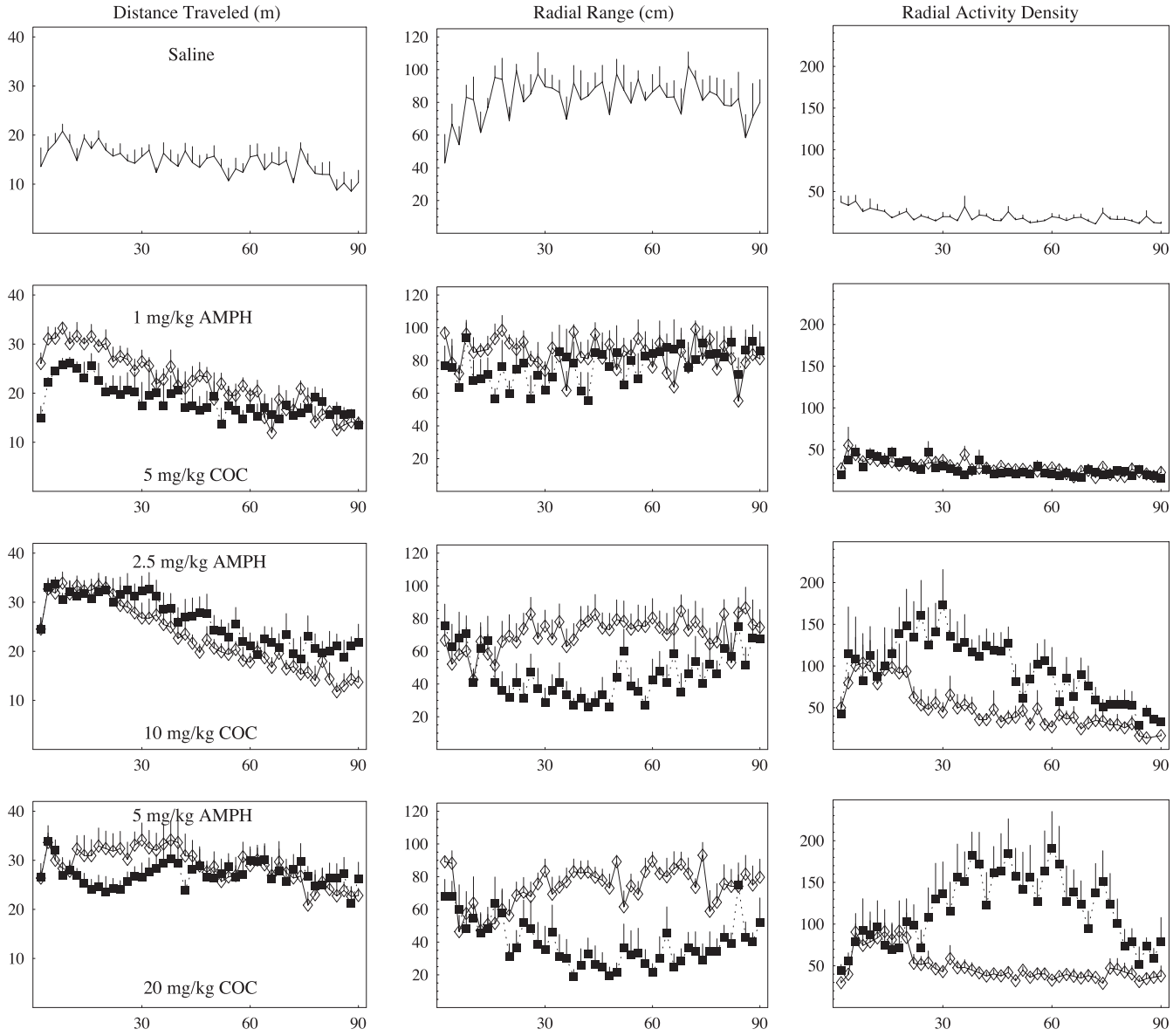

Fig. 2. The time development of radial behavior (i.e., going into the center) in the B6 mice under AMPH (closed squares), COC (open diamonds) and saline injections (lines, no symbols). The horizontal axis of all graphs is time in minutes from injection (start of the session), and all measures were taken in bins of 2 min. Symbols/lines represent group means, and vertical bars represent group standard errors (n=6–8 in each treatment group). The leftmost column graphs display the overall distance traveled. The middle column graphs display the radial range. The rightmost column graphs display the radial activity density. Dose is increased from top to bottom, with the doses for each row indicated in the leftmost graph. Doses of COC and AMPH that produced equivalent locomotor stimulant effects as measured by distance traveled are shown together.

In the angular dimension, the computation of range is slightly complicated technically by the fact that θ is cyclic, so the meaning of "smaller" and "larger" values is problematic. In order to overcome this, the distribution of θ was considered in each time bin, and the θ values were all shifted so that the least common value was redefined as zero. The range was then computed on these shifted results. Fig. 1 (right) shows an example of the angular range computed in this fashion.

The radial activity density in each 2 min time bin was computed as the distance traveled in this bin divided by the radial range (i.e., the distance between the farthest and nearest point to the center). Note that this is a pure number, i.e., distance divided by distance. The angular activity density was similarly computed from the distance traveled and the angular range, but in order to get a pure number the θ range in degrees was first converted into distance units by multiplying by the arena perimeter and dividing by 360. Note that this conversion is an approximation because it assumes that the animal moved along the wall, but this assumption is true most of the session, even in the animals that venture relatively more into the center.

A priori, our intent was to identify, within each genotype, doses of COC and AMPH that did not differ statistically as measured by the "traditional" distance traveled measure. To this end, a two-way repeated measures ANOVA (drug×time as repeated measure) was conducted on dose pairs that appeared to produce similar activity. COC/AMPH dose pairs that did not differ significantly from each other in distance traveled were

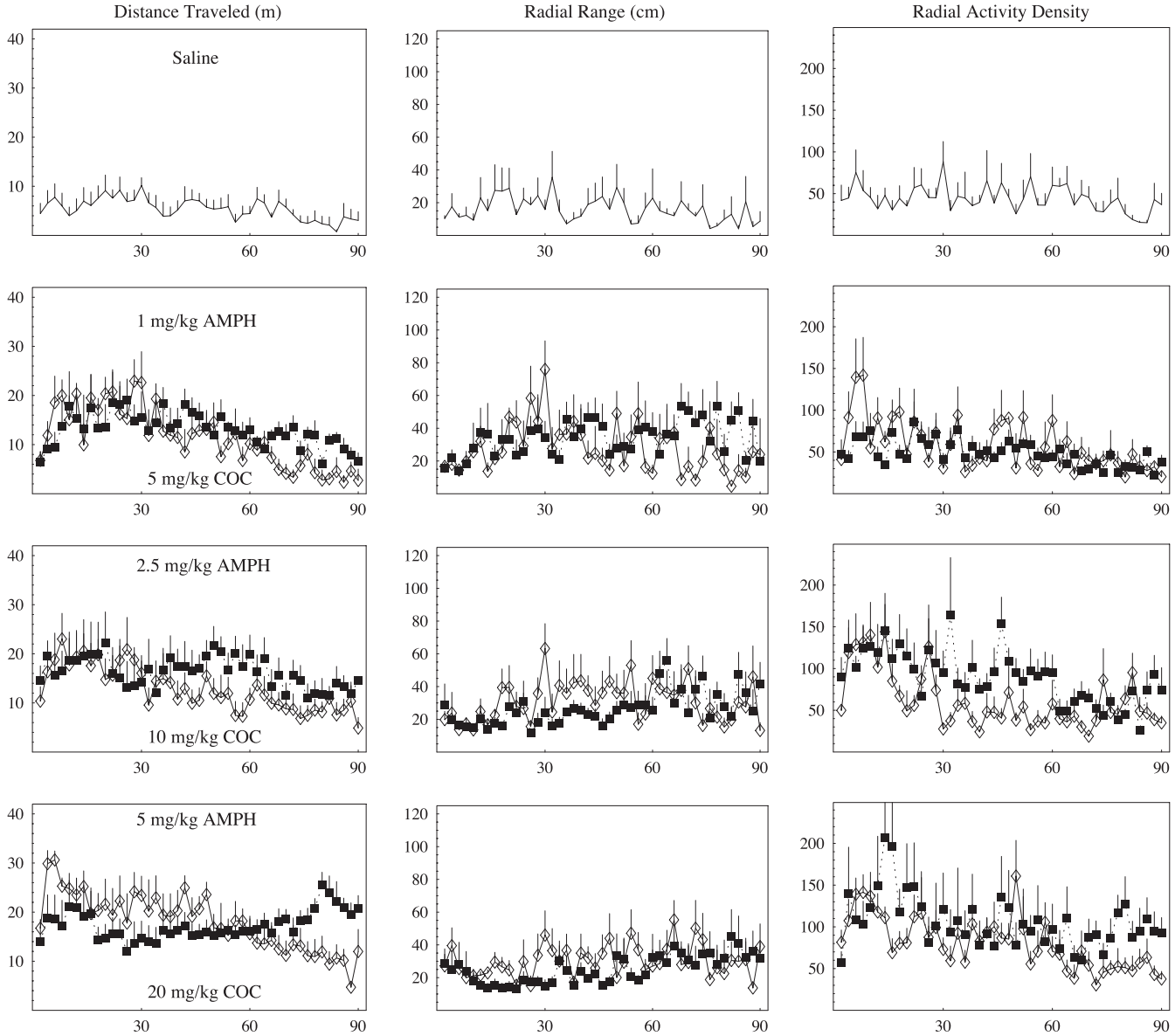

Fig. 3. The time development of radial behavior in the D2 mice under AMPH (closed squares), COC (open diamonds) and saline injections (lines, no symbols). All measures and doses are the same as in Fig. 2.

assigned to the same dose "level", thus producing three dose levels: low, medium and high. Analysis of the entire session yielded significant drug × time interactions. This would be expected given the pharmacokinetic profile of each drug. Subsequent analyses were conducted only on the first 44 min time window. This window provides an overlap with the peak effect and duration of stimulant action for both drugs. Within each measure and strain, the results were then analyzed with a three-way ANOVA of (drug × dose-level × time as repeated measure). Follow-up analysis for dose-effect functions within each drug were conducted with a two-way ANOVA (dose × time as repeated measure) using a Dunnet's post hoc test to determine doses that were significantly different than saline.

3. Results

The effects of COC and AMPH are compared in four figures, Figs. 2–5, corresponding to each of the two strains (B6 and D2) in each of the two dimensions (radial and angular). The first column in each figure shows the time course of the distance traveled in 2 min bins throughout the session. The second column shows the range, also computed in 2 min bins as demonstrated in Fig. 1 (right). The third

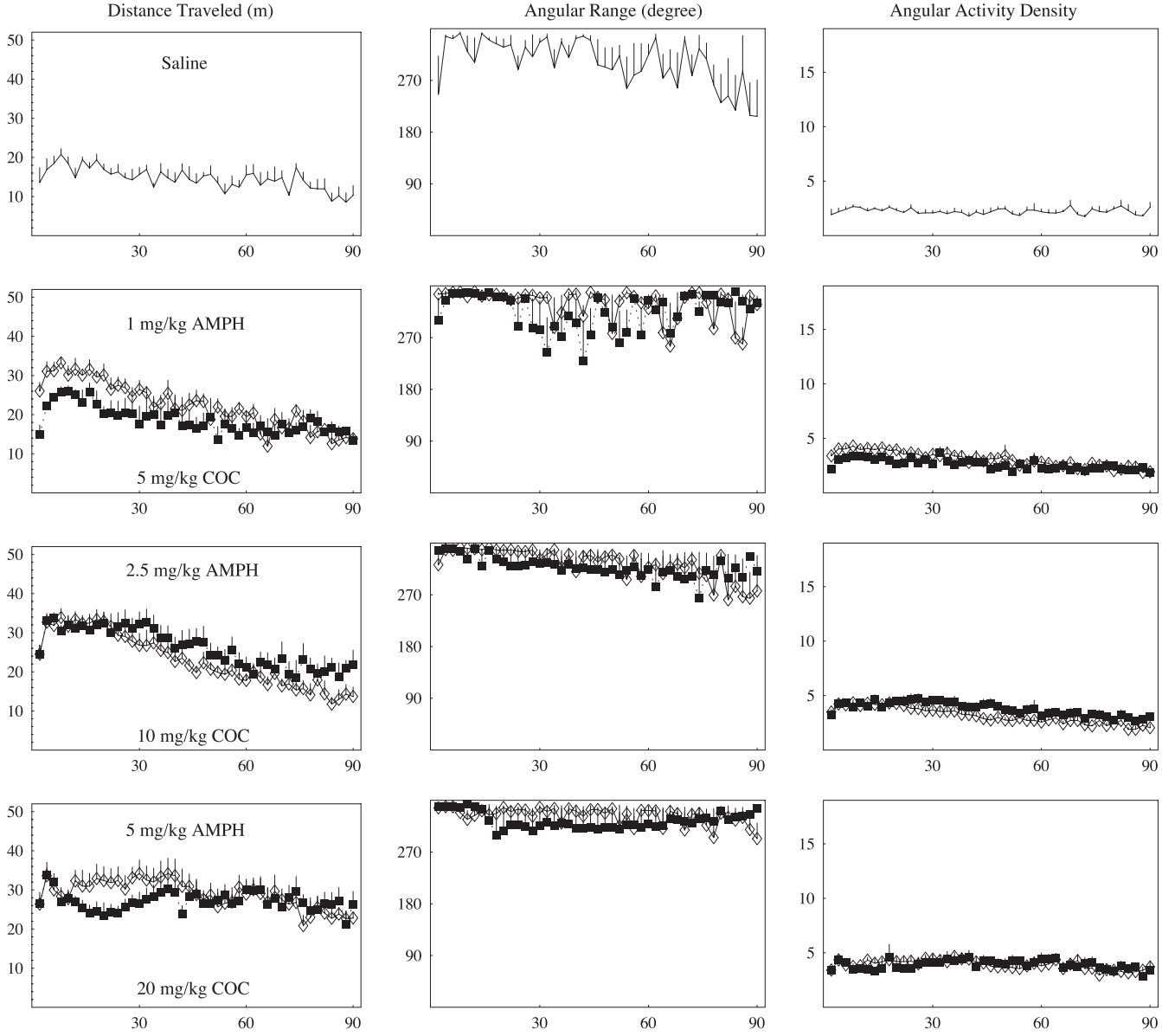

Fig. 4. The time development of angular behavior in the B6 mice under AMPH (closed squares), COC (open diamonds) and saline injections (lines, no symbols). The horizontal axis of all graphs is time in minutes from injection (start of the session), and all measures were taken in bins of 2 min. Symbols/lines represent group means, and vertical bars represent group standard errors. The leftmost column graphs display the overall distance traveled. The middle column graphs display the angular range, computed as demonstrated in Fig. 1. The rightmost column graphs display the angular activity density. Dose is increased from top to bottom, with the doses for each row indicated in the leftmost graph. Different COC and AMPH doses are coalesced together based on similar activity.

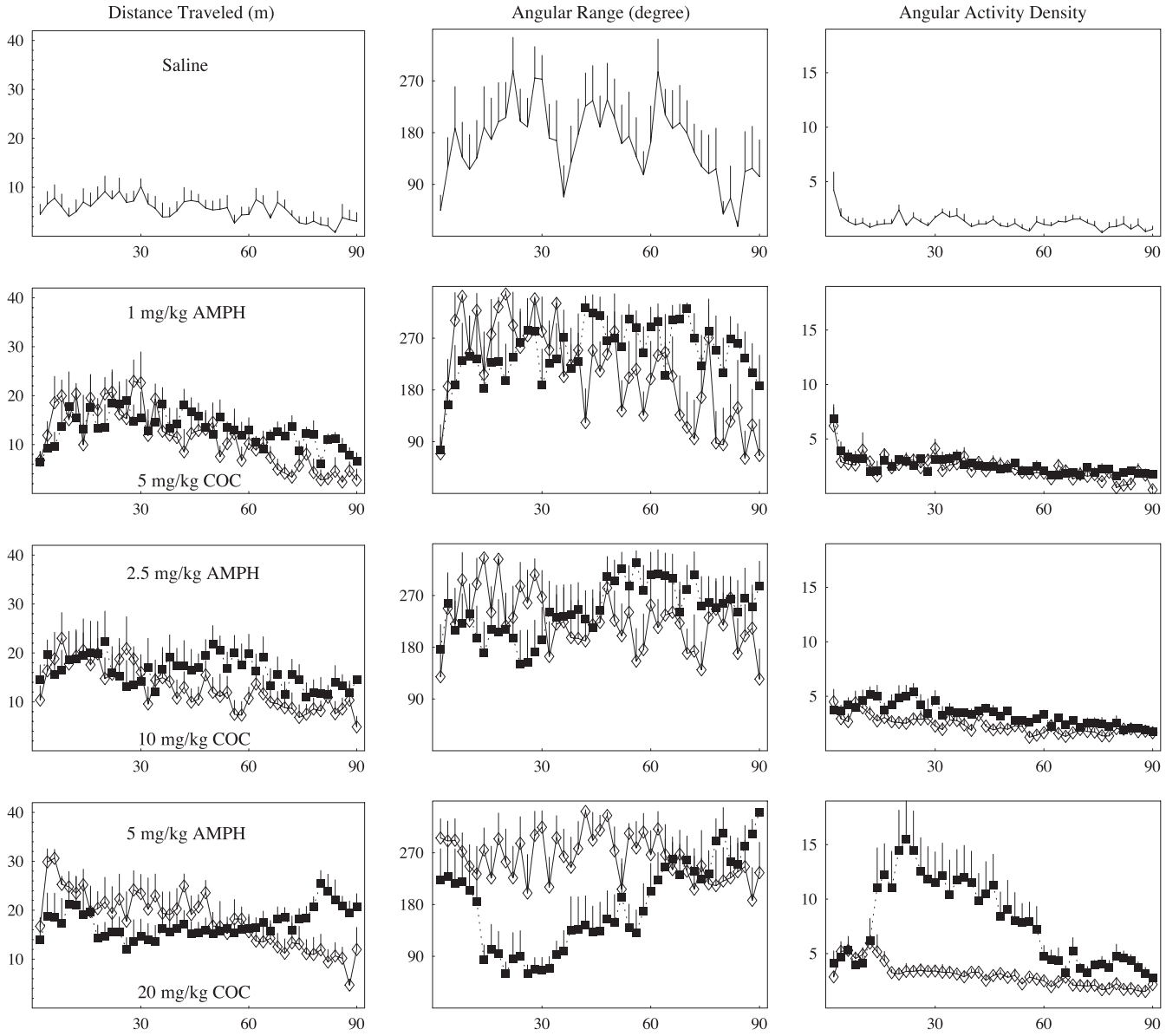

Fig. 5. The time development of angular behavior in the D2 mice under AMPH (closed squares), COC (open diamonds) and saline injections (lines, no symbols). All measures and doses are the same as in Fig. 4.

column shows the activity density, i.e., the ratio of the first column divided by the second column. Fig. 6 shows these results when summed over the first 44 min of the session.

As expected, both drugs increased the distance traveled in both genotypes in a dose-dependent manner [B6: AMPH ($F_{3,132}$=8.4, p<0.001); COC ($F_{3,132}$=8.6, p<0.001); D2: AMPH ($F_{3,132}$=6.1, p<0.01); COC ($F_{3,132}$=6.8, p<0.01)]. The dose-effect function in each genotype was similar in that there was no genotype×dose interaction for either drug (see Fig. 6, upper row). For results over the whole session, see Kafkafi et al. (2003b). The distance traveled in 2 min time bins is seen in the left column graphs of Fig. 2 (for B6 mice) and Fig. 3 (for D2 mice). Also as expected from the potency differences, higher COC doses were needed to get the same increase in distance traveled. Since the objective of this study is to find differences in the effects of the two drugs that cannot be revealed by distance traveled, we identified AMPH/COC dose pairs that produce similar (not statistically different) increases in the distance traveled endpoint. Specifically 1 mg/kg AMPH was compared with 5 mg/kg COC (low dose), 2.5 mg/kg AMPH with 10 mg/kg COC (medium dose) and 5 mg/kg AMPH with 20 mg/kg COC (high dose) [p>0.3 for all dose comparisons for each genotype]. When these dose pairs were analyzed in a two-way repeated measures ANOVA (drug × time as repeated), a significant interaction effect was observed at the low and high dose combinations in the B6 mice (p<0.05 in both cases) and at the high dose combination in the D2 mice (p<0.001). These results could be expected based upon the

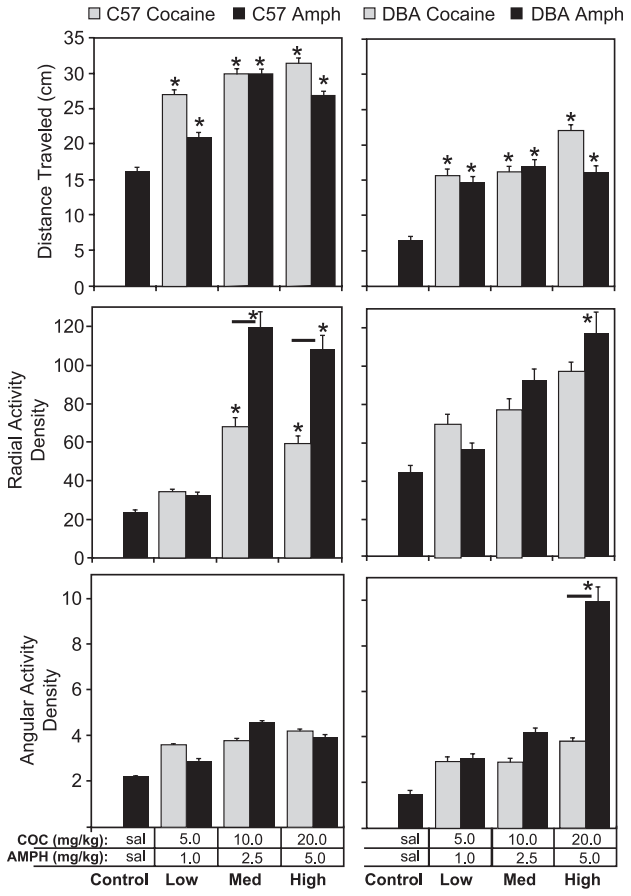

Fig. 6. Whole session distance traveled (upper row), radial activity density (middle row) and angular activity density (bottom row) in B6 mice (left column) and D2 (right column). * Denotes significant difference from saline. – Denotes significant difference between COC and AMPH.

pharmacokinetic profile of the two drugs and the extended length of the session. Consequently, the analysis period was limited to 44 min in order to provide an overlap with the peak stimulant action for both drugs. When the session window is limited to 44 min, there are no significant main effects of drug (AMPH vs. COC) nor any significant interaction effects (drug×time) for either genotype at any dose level (low, medium or high). Thus, the drug combinations meet the criteria both in terms of equivalent efficacy (no drug by dose interaction) and equivalent time profile (no time interaction).

When looking at in the radial range in B6 mice (Fig. 2, central column) a clear dose-related difference between AMPH and COC can be seen (F=12.8, p<0.001, drug×dose×time ANOVA). This difference arises because of a dose-related decrease in the radial range with AMPH relative to saline (F=6.7, p<0.01) using a two-way ANOVA (dose × time as repeated measure) with both the 2.5 and 5.0 mg/kg dose significantly lower than saline, expressing a tendency of the animals to wall hugging, while no such decrease is seen under COC (p=0.15).

Note, however, that the above decrease in range might result simply from inactivity (i.e., an animal that does not move has a zero range). This possibility is rejected by the activity density (Fig. 2, right column), which similarly shows a significant dose-related increase for both AMPH and COC (F=11.8, p<0.0001 and F=9.2, p<0.001, respectively), with no significant difference between drugs.

A similar difference between AMPH and COC in the radial range and radial activity density was not seen in the D2 mice (Figs. 3 and 6, middle and right row). This, however, should not be surprising, as the baseline radial range in the D2 mice (Fig. 3 top row, middle graph) was already narrower than that of the B6 even under the highest AMPH dose (Fig. 2 bottom row, middle graph). Indeed, B6 spend much more time in the center of a large arena than D2, and this is known to be one of the largest and more consistent behavioral differences between the two strains (Kafkafi et al., 2003a). The already low radial range of the D2 could not be considerably decreased by AMPH.

AMPH, on the other hand, did decrease the *angular* range of the D2 mice, so they tended to utilize only a part of the whole perimeter of the arena (an example of this phenomenon in a single mouse is seen in Fig. 1). This limitation of the range occurred despite of the increased activity, and thus led to a more dramatic increase in angular activity density with AMPH (Fig. 5, right column; Fig. 6, right column, bottom half) than with COC. There was a significant difference between AMPH and COC in angular activity density (F=11.7, p<0.05, drug × dose-level × time ANOVA). Post hoc contrast analysis shows that high dose level significantly distinguishes the two drugs. There was a significant dose-related increase following AMPH administration (F=11.7, p<0.05, dose×time ANOVA) and following COC administration (F=11.6, p<0.001, dose×time ANOVA).

In B6 mice, in contrast, the angular range was close to the upper limit of 360° with both drugs and all doses (Fig. 4), and the two drugs could not be differentiated according to their angular activity density (Fig. 6, bottom left). As seen above, however, they are differentiated in B6 by the *radial* activity density.

4. Discussion

In rats it is well documented that AMPH, relative to other psychomotor stimulants such as COC, generates more stereotypic behavior and repetition of locomotor path (Mueller et al., 1989; Paulus and Geyer, 1991). In mice this phenomenon is less established and apparently not so clear-cut, especially when different genotypes are considered. In this study we point out that repetition of path may be regarded as merely the severe form of a more general phenomenon: increasing the activity density, i.e., restricting the range of behavior while still being active. Note that the range alone is not enough to characterize the phenomenon, since decreasing it may be achieved simply by being

inactive. The activity density thus characterizes the restriction of spatial behavior repertoire that does not result merely from inactivity. When an animal has a very high activity density, repetition of the path is much more likely to occur. Using the more general measure of activity density may thus help differentiate subtler effects of AMPH and other psychomotor stimulants.

Activity density may be thought of as a simplified version of the spatial scaling exponent d, which was devised to quantify patterns of open-field behavior in rats (Paulus and Geyer, 1991, 1993; Paulus et al., 1993) and mice (Ralph et al., 2001; Powell et al., 2004). The activity density measures, in a single scale, a property very similar to that measured by d over several different scales. The scaling exponent method then considers how the logarithm of the result depends on the logarithm of the scale, and uses the slope of this dependency (d or the "fractal dimension") to characterize the behavior. There are, however, several differences between the two methods. First, in this study activity density is measured in fixed time bins (2 min each) rather than in scales of (spatial) length as in the spatial scaling method. In addition, this study was conducted in a circular arena of 250 cm diameter, in comparison with rectangular arenas of 41 cm (with mice) and 61 cm (with rats) that were used for the scaling exponent method. This increases the maximal possible range that the animal can achieve with the same mileage, potentially increasing the sensitivity of the method to drug-dependent differences. Finally, this study measured the activity density separately in the radial and angular dimensions, rather than pooling them together by using Euclidean distance in two dimensions. This choice enabled us to uncover the different behavior of the two strains in these dimensions.

Note also that activity density makes use of the range rather than the variability of the spatial location. It is possible to have very different spatial distributions (and therefore very different variabilities) over the same range. For example, a mouse that went once around the whole arena (thus already scoring the maximum possible angular range) might still sit in one place during the rest of the time, thus scoring low variability. Exploring both range and variability measures in our analysis suggested that it is the range that enables differentiation of drug and strain, and is thus more behaviorally relevant.

When characterizing the effect of different psychoactive drugs on the structure of behavior, we attempted to identify differences that are generalized across genotypes. However, there may exist a large drug-genotype interaction, so even if different psychoactive drugs can be discriminated according to unique behavioral patterns, this will have to be done anew for each additional genotype. Previous studies using inbred rat strains provide evidence to suggest that the psychomotor stimulant properties of these two drugs may be mediated, in part, by distinct set(s) of genes (George et al., 1991). Since these genes may segregate differentially across genotypes it may lead to unique behavioral patterns for each genotype. If possible, however, it would be desirable to single out differences between genotypes that are largely the same across drugs (Kafkafi et al., 2003b) and differences between drugs that are largely the same across genotypes. A main difficulty with the second objective is that the baseline behavior of these genotypes is generally very different. In our case, AMPH decreased entering into the center in B6 while COC did not, but this difference did not generalize to D2, probably because D2 mice enter very little into the center to begin with. This latter problem was overcome in this study by defining more general properties. In this case we defined the range of behavior into the center and along the perimeter of the arena in a similar way. This formulation suggests that AMPH's effect in B6 and D2 is similar: it limits the range of activity while increasing activity itself, while COC also increases activity but does not limit the range.

The capacity for activity density to discriminate the locomotor stimulant properties of a range of psychomotor stimulants and the specific pharmacological properties of the drug that differentiate the behavioral endpoints awaits further study. There are a number of reasons why COC might differ from AMPH. We have tried to eliminate kinetics as an obvious factor; what remains is ultimately reduced to the pharmacodynamic profiles that distinguish the two drugs such as dopamine releasing properties, cell surface DAT cycling and monoamine uptake affinity profiles (see Introduction). A potential consequence of the subtle differences in pharmacodynamic profile is differential activation of the mesolimbic dopamine system. With this in mind, acute AMPH administration has been shown to disproportionally activate the striasome component of the dorsal striatum while COC has been shown to activate both the matrix and striasome components (Graybiel et al., 1990; Canales and Graybiel, 2000). The striasome is preferentially linked to the limbic system while the matrix is preferentially linked to the sensorimotor system (Gerfen, 1992). The consequence of differential activation of these circuits may explain, in part, the different behavioral profiles. The genotype-dependent differences on radial vs. angular dimensions may further reflect subcomponents within these circuits or the effects of differential circuit activation on basal striatal activity associated with each genotype. In the behavioral context offered by Golani et al. (1999), the differential effects of COC and AMPH may reflect the balance of striasome- vs. matrix-induced restrictions on the animals behavioral repertoire (see also Graybiel, 1998). Clearly, more studies are needed to explore these hypotheses. Extended studies of across a range of compounds using structure activity relationships along with correlations with their indirect- and direct-agonist actions, dopamine releasing effects and nonspecific properties within the same genotype will provide a better understanding of the psychopharmacological properties of stimulants. Further studies across a range of compounds using pharmacological structure-activity relationships, var-

iations in indirect- and direct-agonist actions and monoamine uptake inhibition selectivity within the same genotype will provide a better understanding of the psychopharmacological properties of stimulants. Extended studies across a range of genotypes will further improve our understanding of the degree to which the behavioral effects of psychomotor stimulants are influenced by common or independent genes. The combination of the two approaches may lead to the identification of the genes and gene products that are responsible for unique behavioral effects.

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