

BRIEF COMMUNICATION

# Differential Movement Patterns But Not Amount of Activity in Unconditioned Motor Behavior of Fischer, Lewis, and Sprague–Dawley Rats

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PAULUS, M. P., M. A. GEYER AND E. STERNBERG. *Differential movement patterns but not amount of activity in unconditioned motor behavior of Fischer, Lewis, and Sprague–Dawley rats.* *PHYSIOL BEHAV* **65**(3) 601–606, 1998.—Histocompatible Fischer 344 and Lewis rats have been shown to differ on a wide variety of behavioral, chemical, and molecular measures. This investigation aimed to clarify strain differences in unconditioned motor behavior with respect to the amount and patterns of movements. Twenty female Fischer 344, Lewis, and Sprague–Dawley were tested in the Behavioral Pattern Monitor for 30 min. The locomotor activity and movement patterns, quantified by counts of photobeam breaks and the spatial scaling exponent,  $d$ , were assessed. The level of locomotor activity did not differ significantly between Fischer, Lewis, and Sprague–Dawley rats. In contrast, movement patterns differed significantly between the strains. Specifically, Sprague–Dawley rats exhibited significantly more straight movements than both Fischer and Lewis rats. Moreover, Lewis rats showed significantly more straight movements compared to Fischer rats during the first 10 min in the enclosures. Differences in movement patterns across strains may provide an important behavioral variable to further explore the genetic and developmental aspects of behavior. © 1998 Elsevier Science Inc.

Locomotor activity    Patterns    Strains

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HISTOCOMPATIBLE Fischer 344 and Lewis rats differ in a wide range of biochemical (1–3,7,13), electrophysiological (18), immunological (28), and behavioral measures (6,11). Moreover, these animals have been used to discern the influence of genetic background on immune response, hypothalamo–pituitary–adrenal (HPA) axis regulation (20), the susceptibility to a neonatal lesion (16), and the susceptibility to drug dependence (5,15,19). Results of recent studies indicate that these functions are not independent, but are, in fact, tightly intertwined components sharing molecular, biochemical, and electrophysiological commonalities. Hence, these ani-

mals reflect a complex phenotype resulting from distinct genetic differences.

Unconditioned motor behavior in a novel environment involves many different behavioral responses including movements, grooming, and rearing, local exploration, and investigatory responses. The analysis of animal behavior is typically based on predefined behavioral categories that are thought to reflect heuristically derived distinct behaviors (29). Most commonly, multiple indices are used to describe changes in patterns of behavior (10,26). We have recently proposed an alternative approach that can be used to quantify patterns of

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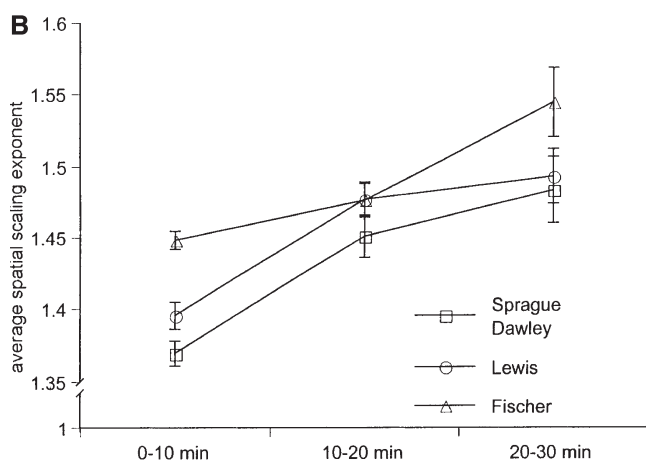
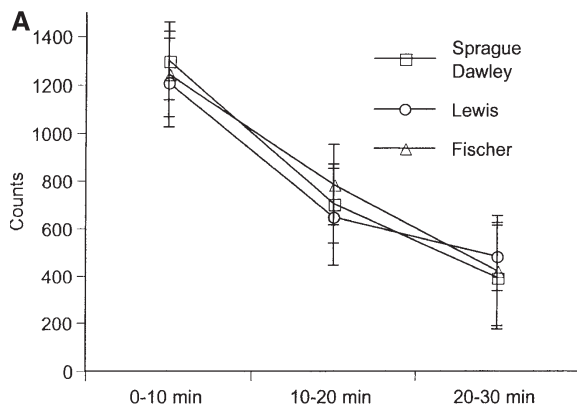


FIG. 1. (A) Mean and standard errors of the locomotor activity measure counts for three 10-min time blocks for Sprague-Dawley, Lewis, and F344 rats. (B) Mean and standard errors of the locomotor pattern measure  $d$  for three 10-min time blocks for Sprague-Dawley, Lewis, and F344 rats.

behavior based on the notion of behavioral organization (22,24,25). This approach is based on the phenomenon of scaling, which has been widely observed in complex physical systems (17,27).

Both indirect serotonergic agonists, for example, MDMA or MBDB (23), and direct 5-HT<sub>1B</sub> agonists, RU24969 (24), sensitively increase the contribution of straight or directed movement sequences based on this scaling approach. This investigation was motivated by the hypothesis that strains of rats, which have been shown to differ in functional status of their serotonin (5-HT) systems, exhibit different patterns of unconditioned motor behavior. Specifically, some groups have found that in comparison to Fischer and Sprague-Dawley rats, Lewis rats contain lower concentrations of cortical

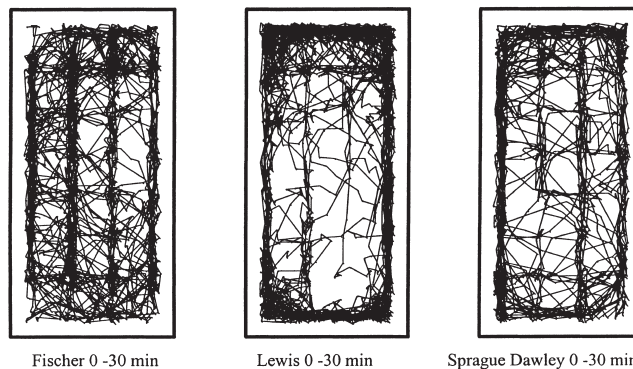


FIG. 2. Exemplary movement patterns for 30 min of a representative animal from the Fischer, Sprague-Dawley, and Lewis group.

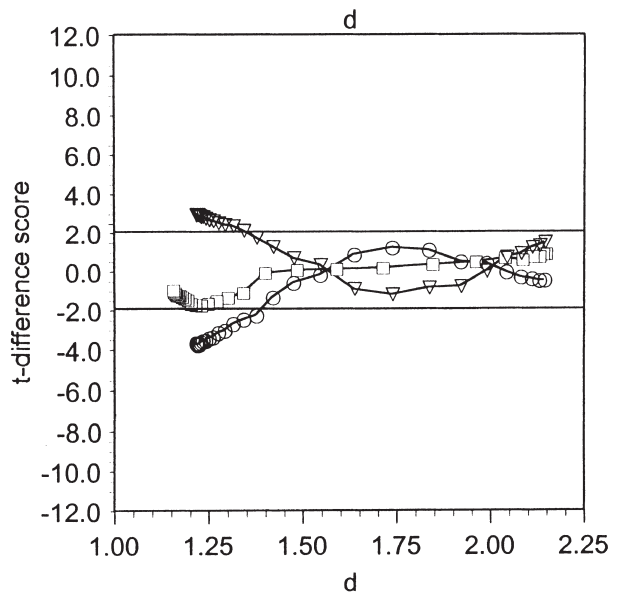
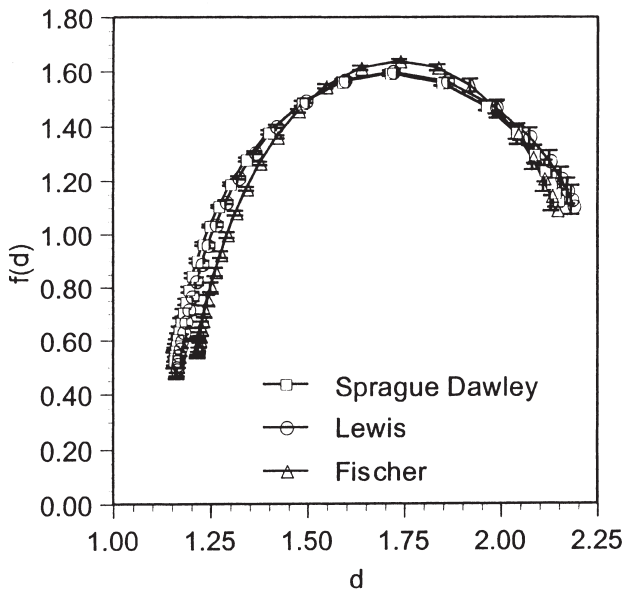
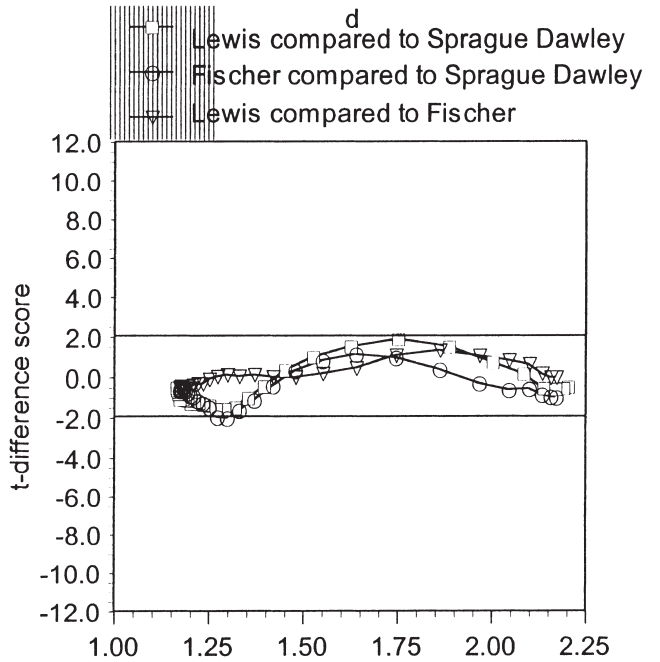
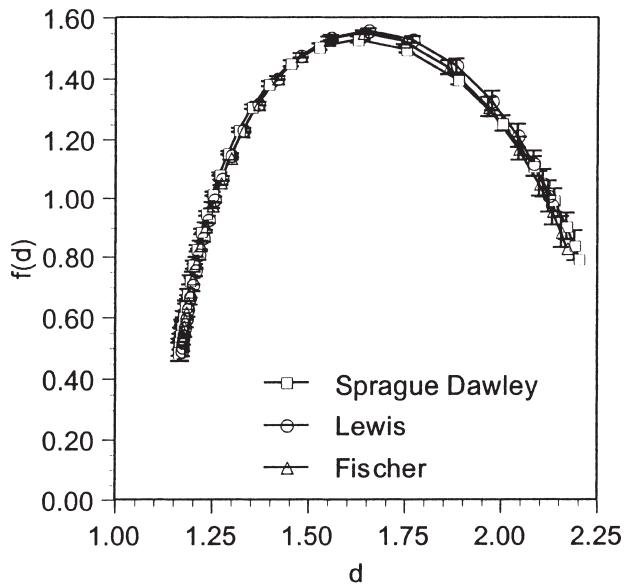
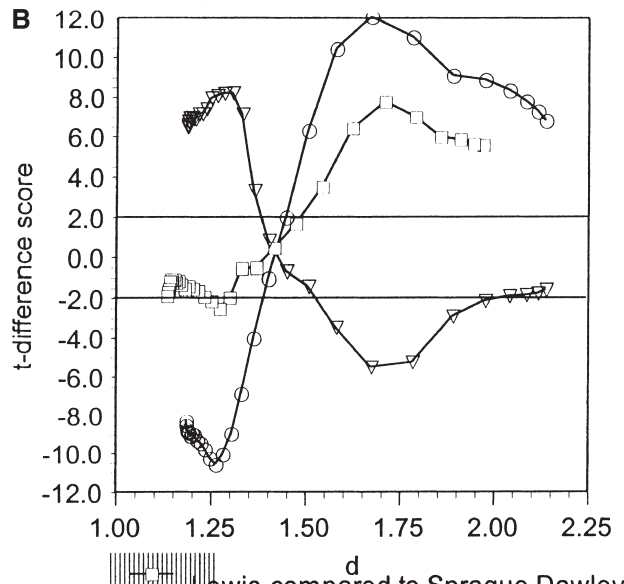
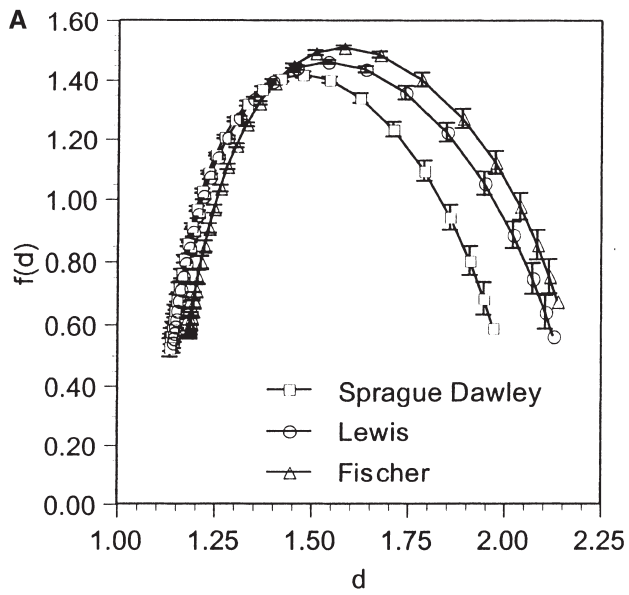
and hippocampal 5-HT<sub>1A</sub> receptors (4). In addition, Lewis rats were shown to express significantly fewer hippocampal and frontal cortical 5-HT<sub>1A</sub> agonist binding sites and less 5-HT<sub>1A</sub> mRNA compared to Fischer rats (2). It has been argued that these changes reflect a general decrease of serotonergic function in Lewis rats. If these changes reflect a downregulation of receptors secondary to an overactive serotonergic system, one would expect an increase in straight movements in Lewis compared to Fischer rats. Alternatively, if the observed molecular changes in Lewis rats result from a decrease in serotonergic modulation, a decrease in straight movements is expected.

#### METHODS

For the experiment, 20 female rats of three different strains (Fischer 344, Lewis, and Sprague-Dawley) weighing 90–130 g were kept on a reverse 12-h dark-light cycle and allowed to acclimate to the animal facilities for at least 7 days before behavioral testing. As part of the comprehensive experimental testing, each animal was also exposed to the startle paradigm [data have been reported (11)]. For the assessment of motor activity, the animals were brought to the laboratory 1 h prior to testing. Each animal was tested during its first exposure to the Behavioral Pattern Monitor (BPM).

For a detailed description of the data acquisition system (9). Briefly, eight BPM chambers, each enclosed within a ventilated wooden box, were used. Each chamber consists of a 30.5 × 61.0 × 38.0 cm Plexiglas holeboard equipped with three floor holes in the front, middle, and rear part of the floor, six wall holes, three along either side of the long walls, and a hole in the back of each chamber. Due to the small size of the animals, exploratory holepoking behavior was disabled by plugging tightly the holes described above with a rubber plug. The location of the rats in the BPM chambers was obtained from a grid of 4 × 8 photobeams 2 cm above the floor in each chamber. Subsequently, the raw data files were transformed into ASCII data files comprised of the (x,y) location of the rat in the BPM chamber with a resolution of 3.8 cm,

FIG. 3. (A) The average fluctuation spectrum and its standard error is shown for the first (upper), second (middle), and third (lower panel) 10-min time block for three strains. (B) The  $t$ -score difference function is shown for the first (upper), second (middle), and third (lower panel) 10-min time block for three strains. Statistically significant differences are indicated by the straight lines at  $t = \pm 2.0$ .



yielding  $7 \times 15$  different possible positions and the duration of each event ( $t$ ).

The behavioral assessment for the different strains of animals is based on the sequences of microevents. Simple descriptors of the motor activity were obtained from the sequences of microevents. The counts measure consists of the total number of  $(x,y,t)$  microevents within a given time interval and quantifies the amount of activity. The temporal scaling exponent,  $\alpha$ , was calculated from a least-squares fit of the logarithm of the number of microevents with a duration between  $t$  and  $t \pm t$  versus the microevent duration,  $t$  [for details see (21)]. The spatial scaling exponent,  $d$ , was calculated as described in (22). This measure quantifies the degree to which an animal generates a sequence of movements that are characterized by a straight line ( $d = 1$ ) or within a circumscribed area ( $d = 2$ ). Finally, the fluctuation spectrum of local spatial scaling exponents,  $f(d)$ , was computed as described in (24) for each animal to determine the contribution of movements with different geometric characteristics. Group differences of the  $f(d)$  function were quantified by a  $t$ -score difference function as described in (24).

Based on the hypotheses advanced above, a one-way (strain) analysis of variance (ANOVA) for repeated measures (time in enclosure) was computed from the scores of the different groups. All effects are described in the results section with their associated significance level and degrees of freedom. The calculations were performed using the BMDP 2v software (8).

## RESULTS

### *Levels of Locomotor Activity: Counts and $\alpha$*

There was a significant main effect for the counts measure for the repeated measure design,  $F(1, 54) = 1694.27$ ,  $p < 0.0001$ . All three rat strains exhibited significant attenuation of the amount of activity as indicated by the decline of counts over the 30-min exposure to the BPM,  $F(2, 108) = 503.60$ ,  $p < 0.0001$ , shown in Fig. 1A. There was no significant strain effect indicating that Fischer, Lewis, and Sprague–Dawley rats showed comparable levels of activity,  $F(2, 54) = 0.30$ , NS. However, there was a significant interaction between strain and time in enclosure,  $F(4, 108) = 3.81$ ,  $p < 0.006$ , indicating that these animal strains habituate differently to the novel environment.

Similar to the counts measure, there were no significant differences in the temporal scaling exponent,  $\alpha$ , across strains,  $F(2, 54) = 0.04$ , NS. There was a significant change of over time,  $F(2, 108) = 308.36$ ,  $p < 0.0001$ , but no significant interaction between strain and time in the chamber,  $F(4, 108) = 1.88$ , NS, indicating that changed significantly but not differentially with habituation to the novel environment.

### *Overall Behavioral Organization: Spatial Scaling Exponent $d$*

Figure 2 shows movement patterns for 30 min in the BPM of three rats representative for the different strains. Rat movements are found predominantly along the perimeter of the chamber and particularly near the corners. The Fischer rat exhibits a moderate amount of movements covering the center of the enclosure. In contrast, both Lewis and Sprague–Dawley rats exhibit movements that are predominantly along the walls of the chamber.

There was a significant main effect for the average spatial scaling exponent,  $d$ ,  $F(2, 54) = 7.39$ ,  $p = 0.002$ . Moreover, there was a significant effect of time,  $F(2, 108) = 38.15$ ,  $p <$

$0.0001$ , but no interaction between time and strain,  $F(4, 108) = 1.34$ , NS. Thus, the average spatial scaling exponent differed across strains with Fischer rats exhibiting more circumscribed movements (30-min average  $d = 1.47 \pm 0.007$ ) than Lewis (30 min average  $d = 1.44 \pm 0.008$ ), and Sprague–Dawley rats (30 min average  $d = 1.41 \pm 0.01$ ). In addition, for all three strains the  $d$  measure increased over time, indicating more circumscribed movements with increased habituation to the novel environment. Comparing the  $d$  measure across strains for different periods of time revealed that the effect size was most pronounced during the first 10 min in the chambers and decreased with increased habituation (see Fig. 1B).

### *Detailed Assessment of Behavioral Organization: Fluctuation Spectrum of Local Spatial Scaling Exponents, $f(d)$*

The detailed analysis of the movement patterns further confirmed the assessments obtained from the average spatial scaling exponent,  $d$ . Specifically, Fig. 3A shows the fluctuation spectrum of local spatial scaling exponents,  $f(d)$ , and the  $t$ -score difference function  $ft(d)$  is shown in Fig. 3B. These functions indicate that the movement patterns of these rat strains differ both in straight or directed movements and in local or circumscribed movements. These differences are most significant during the first 10-min time block. Lewis rats exhibit significantly more straight movements (local  $d < 1.4$ ) and significantly less circumscribed movements ( $d > 1.6$ ) than Fischer rats. Moreover, Lewis rats show significantly more circumscribed movements compared to Sprague–Dawley animals. Fischer rats exhibit significantly less straight or directed movements and significantly more circumscribed movements when compared to Sprague–Dawley rats. There are no significant differences between the strains during the second 10-min time block. During the third 10-min time block, Lewis rats exhibit significantly more straight movements compared to Fischer rats but do not differ significantly from Sprague–Dawley animals. In contrast, Fischer rats engage in significantly less straight movements than Sprague–Dawley rats.

## DISCUSSION

This investigation yielded four main results. First, there is no significant difference in the level of motor activity across the three strains. Second, Fischer rats exhibit movement patterns that are significantly more circumscribed than those of both Lewis and Sprague–Dawley rats. Third, the detailed analysis of the movement patterns revealed that the overall changes in movement patterns reflect a simple shift toward more circumscribed movements rather than a more complex reorganization of movement patterns. Fourth, the behavioral differences were most pronounced during the first 10 min in the chamber and attenuated with increased habituation.

The increase in straight movements in Lewis relative to Fischer rats is similar to changes in movement patterns observed with both direct and indirect serotonin agonists (23,24). These pattern changes support the hypothesis that behavioral differences between Lewis rats in comparison to Fischer animals may be related to an altered function of the serotonergic system. Changes in movement patterns similar to those seen with direct and indirect 5-HT agonists in Lewis rats may relate to findings that these animals have an altered functional status of the 5-HT<sub>1A</sub> receptor (3), exhibited lower hippocampal 5-HT<sub>1A</sub> receptor binding and lower activity of tryptophan hydroxylase in comparison to Fischer rats (6).

Alternatively, the observed behavioral differences may be attributable to CRF mediated behavioral effects. CRF is well

known to generate complex behavioral profile characterized by hyperlocomotion in habituated animals and hypolocomotion and neophobia in an open field environment (14). These strains not only differ in their responsiveness at the level of the HPA axis, but also with respect to their behavioral response to CRF. Specifically, while both Fischer and Lewis rats respond robustly with an increase in corticosterone to CRF administration, Lewis rats show only moderate or nonsignificant changes in locomotor activity, grooming, and rearing following CRF infusion. In contrast, Fischer rats respond to CRF with a profound decrease in locomotor activity and rearing. The dissociation of the behavioral response from the neuroendocrine response to CRF in these strains has been taken to suggest that under enhanced "stressful" conditions both strains respond with a similar behavioral repertoire.

The increase in straight movements observed in Lewis relative to Fischer rats points toward long straight movement patterns and reduced number of circumscribed movements. These findings agree with previous behavioral descriptions that Lewis rats were found to cross less frequently the inner squares of a novel environment, and groomed less in the open field (6,12). The profound changes in movement patterns can also explain the equivocal findings related to levels of locomotor activity. Although some investigators have reported significant decreased locomotor activity in Lewis relative to Fischer rats (6), others have found no difference (15). The increase in

straight movements in Lewis rats relative to Fischer rats can result in differential effects on measures of locomotor activity, depending on the measuring device.

In summary, Fischer, Lewis, and Sprague-Dawley rats differ significantly with respect to their movement patterns in response to a novel environment particularly during the first 10-min interval. These pattern differences may be related to differences in serotonergic function in these strains. If these behavioral changes were due to 5-HT-mediated mechanisms, the present findings would support the hypothesis that Lewis rats are more susceptible to the acute 5-HT influence on the organization of motor behavior. This relative lack of extended exploration may be related to an increase in baseline anxiety-related behaviors, which has been reported for these strains (6). The significant attenuation of the differences between these strains as habituation develops supports the notion of a phasic adjustment that involves the regulation of the neurobiological system rather than baseline states or levels of neurotransmitters.

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#### REFERENCES

- Beitner-Johnson, D.; Guitart, X.; Nestler, E. J.: Dopaminergic brain reward regions of Lewis and Fischer rats display different levels of tyrosine hydroxylase and other morphine- and cocaine-regulated phosphoproteins. *Brain Res.* 561:147-150; 1991.
- Burnet, P. W.; Mefford, I. N.; Smith, C. C.; Gold, P. W.; Sternberg, E. M.: Hippocampal 8-[<sup>3</sup>H]hydroxy-2-(di-n-propylamino) tetralin binding site densities, serotonin receptor (5-HT<sub>1A</sub>) messenger ribonucleic acid abundance, and serotonin levels parallel the activity of the hypothalamo-pituitary-adrenal axis in rat. *J. Neurochem.* 59:1062-1070; 1992.
- Burnet, P. W.; Mefford, I. N.; Smith, C. C.; Gold, P. W.; Sternberg, E. M.: Hippocampal 5-HT<sub>1A</sub> receptor binding site densities, 5-HT<sub>1A</sub> receptor messenger ribonucleic acid abundance and serotonin levels parallel the activity of the hypothalamo-pituitary-adrenal axis in rats. *Behav. Brain Res.* 73:365-368; 1996.
- Burnet, P. W.; Michelson, D.; Smith, M. A.; Gold, P. W.; Sternberg, E. M.: The effect of chronic imipramine administration on the densities of 5-HT<sub>1A</sub> and 5-HT<sub>2</sub> receptors and the abundances of 5-HT receptor and transporter mRNA in the cortex, hippocampus and dorsal raphe of three strains of rat. *Brain Res.* 638:311-324; 1994.
- Camp, D. M.; Browman, K. E.; Robinson, T. E.: The effects of methamphetamine and cocaine on motor behavior and extracellular dopamine in the ventral striatum of Lewis versus Fischer 344 rats. *Brain Res.* 668:180-193; 1994.
- Chaouloff, F.; Kulikov, A.; Sarrieau, A.; Castanon, N.; Mormede, P.: Male Fischer 344 and Lewis rats display differences in locomotor reactivity, but not in anxiety-related behaviours: Relationship with the hippocampal serotonergic system. *Brain Res.* 693:169-178; 1995.
- Dhabhar, F. S.; McEwen, B. S.; Spencer, R. L.: Stress response, adrenal steroid receptor levels and corticosteroid-binding globulin levels—A comparison between Sprague-Dawley, Fischer 344 and Lewis rats. *Brain Res.* 616:89-98; 1993.
- Dixon, W. J.: BMDP statistical software manual: To accompany the 1988 software release. Berkeley: University of California Press; 1988.
- Geyer, M. A.; Russo, P. V.; Masten, V. L.: Multivariate assessment of locomotor behavior: Pharmacological and behavioral analyses. *Pharmacol. Biochem. Behav.* 25:277-288; 1986.
- Geyer, M. A.; Russo, P. V.; Segal, D. S.; Kuczenski, R.: Effects of apomorphine and amphetamine on patterns of locomotor and investigatory behavior in rats. *Pharmacol. Biochem. Behav.* 28:393-399; 1987.
- Glowa, J. R.; Geyer, M. A.; Gold, P. W.; Sternberg, E. M.: Differential startle amplitude and corticosterone response in rats. *Neuroendocrinology* 56:719-723; 1992.
- Glowa, J. R.; Sternberg, E. M.; Gold, P. W.: Differential behavioral response in LEW/N and F344/N rats: Effects of corticotropin releasing hormone. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 16:549-560; 1992.
- Guitart, X.; Kogan, J. H.; Berhow, M.; Terwilliger, R. Z.; Aghajanian, G. K.; Nestler, E. J.: Lewis and Fischer rat strains display differences in biochemical, electrophysiological and behavioral parameters: Studies in the nucleus accumbens and locus coeruleus of drug naive and morphine-treated animals. *Brain Res.* 611:7-17; 1993.
- Koob, G. F.; Heinrichs, S. C.; Pich, E. M.; Menzaghi, F.; Baldwin, H.; Miczek, K.; Britton, K. T.: The role of corticotropin-releasing factor in behavioural responses to stress. *Ciba Found. Symp.* 172:277-289; 1993.
- Kosten, T. A.; Miserendino, M. J.; Chi, S.; Nestler, E. J.: Fischer and Lewis rat strains show differential cocaine effects in conditioned place preference and behavioral sensitization but not in locomotor activity or conditioned taste aversion. *J. Pharmacol. Exp. Ther.* 269:137-144; 1994.
- Lipska, B. K.; Weinberger, D. R.: Genetic variation in vulnerability to the behavioral effects of neonatal hippocampal damage in rats. *Proc. Natl. Acad. Sci. USA* 92:8906-8910; 1995.
- Mandelbrot, B. B.: *The fractal geometry of nature*. San Francisco: W. H. Freeman, 1982.
- Mayo-Michelson, L.; Young, G. A.: EEG, EEG power spectral, and behavioral differences in response to acute ethylketocyclazocine administration in two inbred rat strains. *Brain Res. Bull.* 31:345-351; 1993.
- Nylander, I.; Vlaskovska, M.; Terenius, L.: Brain dynorphin and

- enkephalin systems in Fischer and Lewis rats: Effects of morphine tolerance and withdrawal. *Brain Res.* 683:25–35; 1995.
20. Ortiz, J.; DeCaprio, J. L.; Kosten, T. A.; Nestler, E. J.: Strain-selective effects of corticosterone on locomotor sensitization to cocaine and on levels of tyrosine hydroxylase and glucocorticoid receptor in the ventral tegmental area. *Neuroscience* 67:383–397; 1995.
  21. Paulus, M. P.; Geyer, M. A.: A scaling approach to find order parameters quantifying the effects of dopaminergic agents on unconditioned motor activity in rats. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 15:903–919; 1991.
  22. Paulus, M. P.; Geyer, M. A.: A temporal and spatial scaling hypothesis for the behavioral effects of psychostimulants. *Psychopharmacology (Berlin)* 104:6–16; 1991.
  23. Paulus, M. P.; Geyer, M. A.: The effects of MDMA and other methylenedioxy-substituted phenylalkylamines on the structure of rat locomotor activity. *Neuropsychopharmacology* 7:15–31; 1992.
  24. Paulus, M. P.; Geyer, M. A.: Quantitative assessment of the microstructure of rat behavior: I,  $f(d)$ , the extension of the scaling hypothesis. *Psychopharmacology (Berlin)* 113:177–186; 1993.
  25. Paulus, M. P.; Geyer, M.A.: Three independent factors characterize spontaneous rat motor activity. *Behav. Brain Res.* 53:11–20; 1993.
  26. Sanberg, P. R.; Hagenmeyer, S. H.; Henault, M. A.: Automated measurement of multivariate locomotor behavior in rodents. *Neurobehav. Toxicol. Teratol.* 7:87–94; 1985.
  27. Stanley, H. E.; Buldyrev, S. V.; Goldberger, A. L.; Hausdorff, J. M.; Havlin, S.; Mietus, J.; Peng, C.-K.; Sciortino, F.; Simons, M.: Fractal landscapes in biological systems: Long-range correlations in DNA and interbeat heart intervals. *Physica A* 191:1–12; 1992.
  28. Sternberg, E. M.; Licinio, J.: Overview of neuroimmune stress interactions. Implications for susceptibility to inflammatory disease. *Ann. NY Acad. Sci.* 771:364–371; 1995.
  29. Szechtman, H.; Ornstein, K.; Teitelbaum, P.; Golani, I.: The morphogenesis of stereotyped behavior induced by the dopamine receptor agonist apomorphine in the laboratory rat. *Neuroscience* 14:783–798; 1985.