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Reproducibility of Time Structure in Motor Activity of Rats Under Nocturnal Conditions

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HOPPER, D. L., W. J. KERNAN AND M. P. BOWES. *Reproducibility of time structure in motor activity of rats under nocturnal conditions.* PHARMACOL BIOCHEM BEHAV **42**(2) 245–250, 1992.—Computer pattern recognition systems for the study of spontaneous rat behavior have introduced a new analytical technique, the *K* functions, that expands the definition of experimentally induced changes in behavior. Such studies normally evaluate three measures, a measure of the number of initiations of specific behavioral acts, a measure of the total time of each act, and a measure of behavioral time structure, the *K* functions. Such measures have been shown to be very stable and reproducible among control rats observed under normal light conditions. This study examines the stability of results from these three measures as applied to nine different groups of control Sprague-Dawley male rats observed under red light during their normal nocturnal hours. All three measures provided stable and reproducible results, but the measure of time structure, the *K* function analysis, provided the greatest consistency, producing values that vary by only a few percent.

Spontaneous behavior Time structure *K* function Measure stability Sprague-Dawley rats

RECENTLY, a computer pattern recognition system for the study of rat behavior has been introduced (11), along with new techniques for the analysis of the time structure of spontaneous behavior (12–14). To study the time structure of activity, this technique utilizes the *K* functions, a subject of recent statistical development dealing with spatial point processes (3,17,18). The estimates of the standard deviations of the *K* functions are obtained using a technique known as the bootstrap (2,5,6,7,8). The combination of all these new techniques and their application to behavioral studies naturally raises questions as to the validity of the estimates of uncertainty and about the stability and reproducibility of the results. For observations under normal light conditions, a study of 14 sets of control data, drawn from different experiments (all done at Forsyth Research Institute, Boston, MA) but all using Sprague-Dawley male rats of approximately 6 weeks of age (10), has shown that these measures are very stable and very reproducible. A second-generation version of the hardware for this system (9) is in use in our laboratory and can be used to observe the behavior of rats under either normal lighting conditions or under red light. The present study examines whether similar stability is present in data sets taken under red light (nocturnal) conditions.

At present, nine sets of data corresponding to control male Sprague-Dawley rats experiencing their first use in the observational environment are available for comparison. These nine sets of data contain between 10 and 20 control animals. For each set, the computer pattern recognition system was used to record and classify individual behaviors. The number of occurrences, total time, and time structure of behavior were determined using the same analytical procedures each time. Seven of the nine sets of controls consisted of rats of approximately 6 weeks of age when their behavior was observed, similar to the age of animals used in the normal light study (10). The last two sets of animals used were approximately 16 weeks of age. One might expect changes in the activity due to this age difference; however, to the extent that the results are consistent between all groups this consistency must be despite the differences. Although treatment of rats was not the same across all groups, all treatments were control procedures selected for minimal impact on behavioral function.

METHOD

Animals

Sprague-Dawley male rats were obtained from Laboratory Animal Resources, Iowa State University. They were housed in individual animal cages in the Laboratory Animal Re-

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sources facility and given food and water ad lib. A 12-h light (0300–1500) to 12-h dark cycle was maintained for animals for a period of at least 2 weeks prior to observation of their behavior. All behavioral tests were conducted in the same facility, which was outside the normal animal quarters.

The nine control groups received one of two treatments. Seven groups (data sets 1–7) were not exposed to any manipulation other than placement in the novel environment for the behavioral test. Two groups (data sets 8 and 9) had a single oral dose of 15% ethanol:distilled water at a volume of 1.0 ml/300 g bw administered by gavage approximately 52 h prior to the observational period. This dose is such that each rat received 0.4 g/kg ethanol. To the extent that the measures examined in this study are stable and reproducible, it can only be despite these control differences and the differences in ages mentioned earlier.

Data for one behavioral act at one exposure level from the treated group in data set 4 (see Table 8) are presented only to show that, in addition to producing stable control data under red light, the pattern recognition technique is capable of detecting chemically induced behavioral changes. The treated group from data set 4 consisted of 20 male Sprague-Dawley albino rats exposed to 10.0 mg/kg idazoxan IP, a potent α_2-adrenergic antagonist (4) 20 min prior to observation. Rats were housed in a temperature-controlled environment (22–24°C) and maintained on a reversed 12 L:12 D cycle with lights off at 0800 h. Food (Simonsen 1525 rat/mice diet) and water were available ad lib except during testing. Behavioral testing began when rats were 80–90 days of age. The complete data from this study have been previously reported (1).

Behavioral Tests

Behavior was tested between 1900–2300 h. The test for all control groups consisted of placing a pair of rats simultaneously into a divided Plexiglas observation chamber (11). The experimental and control rats were separated by a clear partition with small holes, which allowed rats to see and smell one another while they explored the novel environment. Two videocameras taking a frame per second were used to monitor their spontaneous behavior for a 15-min period. The video signals were transferred to an IBM PC/AT for data acquisition and then to an Apollo DN4000 for pattern analysis, behavioral classification, and data analysis. The overall system of cameras, computers, and software has been described elsewhere (9,11) and hereafter will be referred to as the RAPID system.

The behaviors identified by the RAPID system consisted of five possible major body positions—"stand," "sit," "rear," "walk," and "lying down"—each of which is combined with one of eight possible modifiers—"blank" (no recognized activity), "groom," "head turn," "turn," "look," "smell," "sniff," and "washing face." Operational definitions of these acts have been previously described (9,15).

In a previous study (16) using a different method, other investigators found that the time structure of the body positions and modifiers for certain acts had similar time structures. Three such sets of acts were identified and arbitrarily labeled "grooming," "exploratory," and "attention." We also examined the results using this list of "acts" instead of the usual stand, sit, etc. We will refer to this list as "combined acts." For these combined acts, when a cooccurring body position and modifier belong to different components of this structure a full and mutually exclusive list would include "attention-explore," "attention-groom," and "explore-groom." The list for combined acts, therefore, contains six possibilities. For more details on the relationship between the individual acts such as sit and the combined acts, consult either Table 1 in Mullenix and Kernan (14) or Table 2 in Hopper, et al. (9).

Data Analysis

In all nine experiments from which control data were extracted, three measures of spontaneous behavior were analyzed. The first was the count of initiations of any act. The second was a measure of the total time that each act was performed. The third was a measure of the time distribution of the initiations of individual acts and of sequences of joint acts. The first two measures are similar to those incorporated in a variety of activity studies, but the third is unique to data generated from either time-lapse photographic analysis (13,14) or the RAPID system (9,10,12). Although the third of these measures is the focus of this study, results using the first two measures are presented for purposes of comparison.

Calculation of act initiations. The number of frames where a specific act was initiated was totaled for the 15-min observation period for each rat. In a standard experiment, the mean number of initiations for each act would be determined for the control and experimental groups and the *t*-test would be used to assess the statistical difference with significance being accepted at the $p < 0.05$ level. In the present study, comparisons are made only between the averages of the various control groups.

Calculation of the total time for each act. The number of frames that a behavior continued, including the initiating frame, was totaled for the 15-min observation period. The mean total time for each act in control and experimental rats would be determined in a standard experiment, and significant differences between control and experimental groups would be determined using the *t*-test. Again, in the present study comparisons are made only between the various control groups.

Calculation of time distribution and time sequence. The time distribution of the initiations of individual acts was calculated using an equation described elsewhere (13):

$$K_\alpha(t) = \frac{\tau_\alpha}{(N_\alpha)^2}\left[\sum_{i \neq j}\sum W_{ij}^{-1} I_t(U_{ij}^\alpha)\right]. \quad (1)$$

In this equation, N_α is the number of initiations of act α, τ_α is the total observational time corrected for the extension of act α, W_{ij} is an edge correction term, and $I_t(U_{ij}^\alpha)$ is 1 (or 0) depending upon whether the pair (ij) of initiations of act α occurred (did not occur) within a time separation t. The function $K_\alpha(t)$, evaluated at eight time points (2, 5, 10, 20, 30, 45, 100, and 200 s), is referred to as the time distribution of act α.

Observation time is corrected to minimize the effects of changes in the number of initiations and the average duration of act α. The corrected observational time for this act is (13):

$$\tau_\alpha = (T - t_\alpha) + N_\alpha. \quad (2)$$

The total observational time was T, the number of initiations was N_α, and the total time observed for act α was t_α. Throughout this article, "time" is treated as a mathematically discrete variable and N_α is present in eq. (2) so that the time of initiation was included in the count for the corrected time.

The W_{ij} factor in eq. (2) is an edge correction term that is important only for acts initiated near either the beginning or end of the 15-min observation period. The effect of this term

is at most a few percent. For a complete discussion of this term and all terms in eq. (2) (as well as those in eqs. (3) and (5) below), see Kernan et al. (13).

To assess sequences of acts and their multivariate relationships, the following equation of Kernan et al. (13) for the K function for the joint acts was applied:

$$K_{\alpha\beta}(t) = (N_\alpha N_\beta)^{-1}\tau_{\alpha\beta}\left[\sum_{i=1}^{N_\alpha}\sum_{j=1}^{N_\beta} W_{ij}^{-1} I_t(U_{ij}^{\alpha\beta})\right]. \quad (3)$$

Each term has a meaning similar to that discussed for eq. (1). In this use, $\tau_{\alpha\beta}$ was corrected for the extension of each of the two different acts for the sequence analysis, and it became:

$$\tau_{\alpha\beta} = (T - t_\alpha - t_\beta) + N_\alpha + N_\beta. \quad (4)$$

In eq. (4), the meaning of each term is the same as in the discussion accompanying eq. (2).

In eq. (3), $U_{ij}^{\alpha\beta}$ is the separation between the ith event of act α and the jth event of act β. The $I_t(U_{ij}^{\alpha\beta})$ term is changed to fit the behavioral sequence situation. To retain information on possible causal relationships among the acts, the formulation is intentionally and specifically asymmetrical in the time relationship. $I_t(U_{ij}^{\alpha\beta})$ equaled 1 if event j of act β occurred within a time interval t later in time than event i of act α, and $I_t(U_{ij}^{\alpha\beta})$ equaled 0 if event j occurred earlier than event i or if the time separation exceeded t. That is, the sum over j was only for events of act β later than event i of act α.

A restriction is placed upon the calculation of the K functions. To limit these calculations to those cases where there is sufficient information to justify their consideration, the K functions are calculated only if the act(s) involved have an average number of initiations equal to or greater than 10 for each of the control and exposed groups considered separately.

Estimates in the uncertainty in K(t). The function $K(t)$ was computed in any data set from the observation of p pairs of animals, with p ranging from 10–20 depending upon the data set. Each pair was composed of one control and one experimental animal. In a standard experiment, the set of data from p pairs of control and exposed animals was used to calculate a K function for the control group, a K function for the experimental group, and $\Delta K(t)$ (the difference between $K(t)$ for the control and exposed groups) for a given value of t. The replication involving p such pairs allowed the use of the bootstrap technique to estimate the standard deviation. This technique (2,5,6,7,8) uses Monte Carlo methods to generate an estimate of the variance of a statistic based only on the data. A random number generator was used to construct 1,000 simulations of this calculation, each time generating a list of p pairs randomly selected from the original set of animal pairs. Obviously, one or more pairs may have been dropped in any one of these simulations, whereas others were included more than once. Standard statistical formulae were then used on the 1,000 simulations to obtain an estimate of the standard deviations of $K(t)$ for the control and exposed groups separately and of $\Delta K(t)$.

TABLE 1

AVERAGE INITIATIONS AND AVERAGE TOTAL TIME FOR STAND

	Initiations		Total Time (seconds)		
Data Set	Average	SD	Average	SD	n
1	118.2	18.7	578.2	64.7	20
2	115.8	24.9	590.0	57.8	20
3	130.6	11.3	552.1	43.8	10
4	119.4	26.9	568.5	60.5	11
5	117.4	14.1	538.3	70.4	12
6	117.8	17.1	536.8	58.5	12
7	121.7	19.6	543.1	56.3	12
8	111.8	20.5	499.9	91.1	15
9	96.4	21.9	471.6	92.3	17
Average	116.6	19.4	542.1	66.2	
SD	8.6		35.3		

TABLE 2

AVERAGE INITIATIONS AND AVERAGE TOTAL TIME FOR REAR

	Initiations		Total Time (seconds)	
Data Set	Average	SD	Average	SD
1	33.0	10.2	105.9	37.3
2	33.6	13.2	103.5	42.5
3	29.9	4.9	95.9	29.7
4	27.5	12.1	79.5	40.8
5	27.3	10.1	87.3	40.7
6	26.5	7.6	91.9	36.1
7	29.7	11.7	81.6	29.7
8	19.8	9.1	61.7	33.7
9	19.3	9.1	71.2	44.5
Average	27.4	9.8	86.5	37.2
SD	4.8		13.8	

RESULTS

The stability of the three measures of spontaneous activity can be demonstrated by results from a few representative acts. The results for all comparable behavioral acts, that is, for all individual acts (sit, stand, rear, smell, etc.) considered together, or for all combined acts (attention, explore, etc.) considered together, were quite similar. For the act stand, the average number of initiations and average total time per animal, plus the respective standard deviations, are shown in Table 1 for all nine control data sets. The number of rats per set is given in Table 1 as well. Tables 2 and 3 present the identical information for the acts rear and smell, respectively. These acts were chosen for presentation since they are the same ones presented previously (10), thus facilitating easy comparison.

The K function was defined and normalized in a manner that minimized the influence of the number of initiations of an act and the total time spent by animals in performing that act. Consequently, the third measure of spontaneous behavior revealed information about the time relationships of initiations of acts without having the results depend strongly upon the first two measures. However, demonstration of the stability of this new information is not as simple as in the first two measures given in Tables 1–3. It is more complex in that the K function is evaluated at eight discrete time points and not as a continuous function. Moreover, evaluation of a K function at

TABLE 3
AVERAGE INITIATIONS AND AVERAGE TOTAL TIME FOR SMELL

	Initiations		Total Time (seconds)	
Data Set	Average	SD	Average	SD
1	90.2	21.7	245.0	109.9
2	93.8	20.5	263.0	107.2
3	96.5	25.0	254.1	114.9
4	79.3	25.2	206.5	93.1
5	76.0	19.4	191.3	78.6
6	77.8	22.5	201.0	92.9
7	86.1	21.4	235.0	91.7
8	85.5	17.2	210.0	44.6
9	74.6	15.2	220.2	66.2
Average	84.4	20.9	225.1	88.8
SD	7.5		23.8	

TABLE 4
K FUNCTIONS AT THE 20-s TIME POINT FOR STAND, REAR, AND SMELL

	Stand		Rear		Smell	
Data Set	*K*	SD	*K*	SD	*K*	SD
1	22.84	0.297	33.87	2.676	56.42	1.817
2	22.72	0.426	30.08	1.585	53.03	1.669
3	22.93	0.244	25.51	1.849	53.77	2.392
4	22.80	0.596	32.42	4.329	55.80	3.155
5	23.35	0.571	32.65	2.384	51.02	2.856
6	23.31	0.527	27.93	1.725	52.37	2.024
7	22.84	0.618	28.32	2.231	53.65	2.775
8	24.15	0.638	34.87	4.760	53.22	2.391
9	25.97	0.810	36.45	3.566	53.72	1.555
Average	23.43	0.525	31.34	2.789	53.67	2.293
SD	0.99	(0.167)	3.40	(1.096)	1.54	(0.532)

a 20-s time point, for example, includes all data evaluated at shorter times such as the 10-s time point. The *K* function, therefore, is an integrated function and, as such, it is a monotonically increasing (or at least nondecreasing) function.

The stability and reproducibility of the *K* function is illustrated in Fig. 1, which presents the entire range of *K* functions for the first six time points (2, 5, 10, 20, 30, and 45 s) for the act stand from the nine control data sets. Although this measure is not evaluated as a continuous function, the graph is drawn, for convenience only, as if the measure was continuous.

For a more detailed discussion of the relationship between the value of the *K* function and its meaning for the behavior being studied, the relationship between initiations, total time, and the *K* function values, and the validity of the estimates of the standard deviations for the *K* functions, see Kernan and Mullenix (10).

The *K* function values of the 20-s time point for the acts stand, rear, and smell, as well as the estimated standard deviations for each measurement, are listed in Table 4 for all nine control data sets. The average of these nine values, along with the associated standard deviation, are also listed. The obvious stability is not an artifact of having chosen the 20-s time point for purposes of illustration. On the contrary, this finding is reiterated by the data in Table 5, which show the *K* function values at all eight time points for the nine control data sets for the behavior stand. Likewise, the data from the nine control data sets for all eight time points are given in Table 6 for the sequence stand-walk and in Table 7 for the combined act attention. Again, these tables are for the same acts for which data was previously presented in Kernan and Mullenix (10) to facilitate comparison.

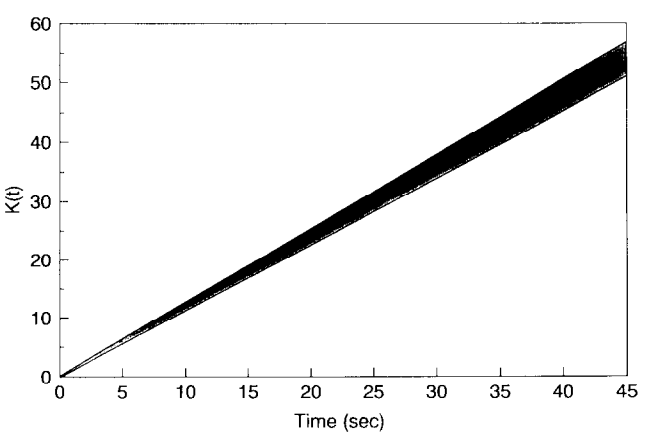

FIG. 1. Range of values of the *K* function, evaluated for the act stand, for all nine data sets.

DISCUSSION

Earlier work (10) showed that the results of 14 control data sets, taken under normal white light conditions, were very stable and reproducible. These authors emphasized that of all three measures the time distributions and time sequences, evaluated using the *K* functions, were the most reproducible and stable. This report corroborates these earlier findings and extends them to include data taken under red light conditions during the animal's normal dark cycle.

Careful examination of Tables 1–7 suggests that the entries for data sets 8 and 9, the sets where animals are somewhat older than those of other data sets, are often somewhat out of line with the other data. Elimination of these data sets would reduce the number of sets in an already limited amount of data, but such elimination would typically reduce the quoted standard deviations. For example, in Table 6 under the time point <30 s the average and standard deviation are listed as 32.9 and 1.5, respectively. A calculation based upon only the first seven data sets would result in values of 32.2 and 0.3, respectively, yielding an estimated error of only 1%. Considering the nature of behavioral data, any attempted claim of stability at a percentage as low as 1% would seem to require more than seven data sets to be fully warranted.

For a useful technique in the study of behavioral disruption caused by exposure to chemical agents or other manipulations of experimental animals, stability and reproducibility alone are not enough; one must also demonstrate that changes in behavioral measures can be observed. The control group used in this report, labeled data set 4, was part of an experiment in which the experimental group was exposed to 10 mg/kg ida-

TABLE 5

K FUNCTIONS AT EIGHT TIME POINTS FOR STAND

	Time Points (seconds)							
Data Set	≤2	≤5	≤10	≤20	≤30	≤45	≤100	≤200
1	1.93	5.40	11.32	22.84	34.06	50.70	109.9	210.3
2	1.87	5.37	11.26	22.72	34.07	50.86	111.1	212.5
3	1.93	5.32	11.35	22.93	34.12	50.69	110.0	212.3
4	1.95	5.42	11.43	22.80	34.27	50.93	110.3	215.4
5	2.03	5.58	11.56	23.35	34.64	51.39	112.0	217.6
6	2.03	5.49	11.53	23.31	34.69	51.56	111.9	212.1
7	1.95	5.40	11.28	22.84	34.38	51.25	110.2	214.9
8	2.17	5.86	12.16	24.15	35.68	52.51	116.1	224.8
9	2.31	6.30	12.86	25.97	38.43	56.28	120.6	225.5
Average	2.02	5.57	11.64	23.43	34.93	51.80	112.5	216.2
SD	0.13	0.30	0.50	0.99	1.33	1.67	3.40	5.20

TABLE 6

K FUNCTIONS AT EIGHT POINTS FOR THE SEQUENCE STAND-WALK

	Time Point (seconds)							
Data Set	≤2	≤5	≤10	≤20	≤30	≤45	≤100	≤200
1	3.2	7.3	12.3	22.5	32.0	45.5	90.0	148.2
2	3.1	7.2	12.3	22.3	31.9	45.8	90.6	150.0
3	3.0	7.1	12.1	22.2	31.9	45.7	90.5	153.5
4	3.2	7.2	12.3	22.7	32.7	47.2	93.7	159.2
5	3.4	7.4	12.5	22.9	32.7	46.7	92.6	156.7
6	3.3	7.4	12.4	22.5	32.1	46.3	91.8	154.6
7	3.2	7.1	12.3	22.6	32.6	47.3	93.1	159.3
8	3.5	7.7	13.1	23.4	33.0	46.5	94.2	163.3
9	4.1	8.7	14.6	26.1	36.9	51.8	101.7	170.1
Average	3.3	7.5	12.7	23.0	32.9	47.0	93.1	157.2
SD	0.3	0.5	0.7	1.1	1.5	1.8	3.3	6.4

TABLE 7

K FUNCTIONS AT EIGHT TIME POINTS FOR COMBINED ACT ATTENTION

	Time Points (seconds)							
Data Set	≤2	≤5	≤10	≤20	≤30	≤45	≤100	≤200
1	1.69	5.18	10.97	22.28	33.38	49.85	109.4	213.7
2	1.67	5.15	10.96	22.36	33.62	50.24	110.3	215.6
3	1.64	5.14	11.02	22.20	33.38	49.86	109.3	214.4
4	1.70	5.34	11.39	22.75	33.96	50.50	108.7	214.4
5	1.86	5.42	11.30	22.83	34.12	50.41	111.1	218.0
6	1.71	5.30	11.11	22.48	33.72	50.38	110.4	214.7
7	1.73	5.28	11.21	22.68	33.94	50.77	109.7	216.7
8	1.95	5.84	12.07	23.86	35.30	52.01	113.4	222.6
9	2.06	6.12	12.66	25.09	37.19	54.73	116.2	222.7
Average	1.78	5.42	11.41	22.95	34.29	50.97	110.9	217.0
SD	0.14	0.32	0.55	0.89	1.16	1.46	2.30	3.30

TABLE 8

K FUNCTIONS AT EIGHT TIME POINTS FOR THE ACT STAND FROM CONTROLS AND IDAZOXAN-TREATED (10.0 mg/kg) RATS

	Time Points (seconds)							
	≤2	≤5	≤10	≤20	≤30	≤45	≤100	≤200
Control	1.95	5.42	11.43	22.80	34.27	50.93	110.3	215.4
Exposed	2.89	7.51	14.86	28.23	41.03	60.15	128.3	241.5
Difference	−0.94	−2.09	−3.43	−5.43	−6.76	−9.22	−18.0	−26.1
SD of difference	0.372	0.726	1.266	1.897	2.522	3.691	8.713	19.37
Difference/SD	−2.53	−2.88	−2.71	−2.86	−2.68	−2.50	−2.06	−1.35

zoxan by IP injection 20 min prior to the observational session. The data for both the control and exposed groups for the act stand are presented in Table 8. First, the *K* functions for both control and exposed groups for all eight time points are listed. Second, the difference at each time point (control value minus the exposed value) is given along with the bootstrap estimate of the standard deviation in this difference. Finally, the ratio between the difference and the estimated standard deviation in this difference is shown so the significance of the difference can be appreciated. For a standard experiment, a significant change in the time structure of behavior is concluded when that ratio exceeds a magnitude of 2.0 at three or more adjacent time points all with the same positive or negative sign. These criteria were established in an ad hoc manner in prior tests (10,12,13). The true measure of this significance can be seen by comparison of the values for the exposed group listed in Table 8 with the values for the entire set of nine control groups listed in Table 5 for that same act stand. It can be seen that the exposed values in Table 8 exceed, at each of the eight time points, the values of all nine control groups. This type of stability underlines the confidence that can be placed in the results of the study of time distributions and time sequences utilizing the *K* functions.

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