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Quantifying the molecular structure of behavior: separate effects of caffeine, cocaine, and adenosine agonists on interresponse times and lever-press durations

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One difficulty in analyzing the molecular structure of behavior lies in reducing the data to a manageable size so that they can be described concisely but without a loss of important information. An approach to quantifying and comparing distributions of interresponse times (IRTs) and lever-press durations is described and then used to examine the acute effects of caffeine (an adenosine antagonist), cocaine, and three adenosine agonists in rats chronically consuming either tap water or water containing 1.0 mg/ml caffeine. The adenosine agonists used were R(-)N^6-(2-phenylisopropyl)adenosine [R-PIA (preferential A_1 receptor agonist)], 5′-(N-cyclopropyl)-carboxamidoadenosine [CPCA (preferential A_2 agonist)], and 5′-N-ethylcarboxamidoadenosine [NECA (about equal agonist activity at A_1 and A_2 receptors)]. The rats' behavior was maintained under a Multiple Fixed-Interval (FI) 120 s, Duration > 5 s schedule of reinforcement. Under the FI schedule, the first lever-press after 120 s resulted in pellet delivery. Under the Duration > 5 s schedule, all lever-press durations greater than 5 s were reinforced. Molecular analyses of distributions of true IRTs (exclusive of lever-press durations) and lever-press durations were conducted by regressing percentiles of the distribution obtained from drug conditions against percentiles obtained from control conditions, a technique called empirical percentile–percentile analysis (or quantile–quantile analysis). The pattern of effects on response durations differed from that seen in IRTs. After acute administration of adenosine agonists, distributions of lever-press durations under the FI schedule and subcriterion durations under the Duration > 5 s schedule were shifted rightward by a constant proportion, indicative of a generalized slowing of responding by these drugs. The effects of adenosine agonists on IRTs could be described by a power–function relationship whereby long IRTs were increased more than shorter ones. A rate-increasing dose of caffeine (10 mg/kg) did nothing to the molecular structure of lever-press durations or of IRTs, indicating that rate increases seen after this dose were due to an earlier onset of responding in the fixed-interval and were unaccompanied by disruptions in the physical execution of the response. The molecular structure of interresponse time distributions seen at the rate-decreasing dose of caffeine (60 mg/kg) resembled that of a rate-decreasing dose of cocaine, but not of the adenosine agonists. Both caffeine and cocaine produced a curvilinear relationship between drug and control percentiles such that very short IRTs were unaffected, but long ones were lengthened five- to 10-fold. This same dose of caffeine lengthened lever-press durations in a manner that resembled adenosine agonists but not cocaine. Percentile–percentile analyses reveal details about drug effects on the temporal structure of behavior and its physical execution that are not visible in molar analyses.

Keywords: **Adenosine agonists – Caffeine – Cocaine – Chronic caffeine – Interresponse time analysis – Lever-press duration – Motor effects – Percentile–percentile analysis – Rat**

INTRODUCTION

Many drugs and toxicants influence the molecular structure of behavior, and these effects have been revealed as alterations in the distribution of interresponse times (IRTs) (Weiss, 1970; Rice, 1988; Iversen, 1991). One of the difficulties in analyzing the molecular structure of behavior lies in reducing data to manageable units so that they can be described concisely, but without a loss of information. A second problem lies in the manner by which data sets deriving from different conditions are compared. Statistical procedures such as the Kolmogorov–Smirnov test can determine whether distributions are different but say little about the nature of the differences. The peak-deviation analysis (Richards *et al.*, 1993), in which the IRT distribution obtained from an

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experiment is subtracted from a theoretical distribution, provides information about how a distribution differs from a theoretically derived one, but requires that one be able to specify in advance the shape of the theoretical distribution.

The present paper applies a procedure described by Cleveland (1985) to describe and compare distributions using nonparametric techniques, and therefore can be applied where there is no theoretical justification for assuming that the distribution assumes a particular form. The technique is identical in spirit to the approach taken by many statistical packages to compare a distribution of data against the normal distribution to determine whether data are normally distributed. The difference is that the standard, or control, distribution is not a theoretical one, but is empirically derived from the control conditions. The technique permits the visual comparison of distributions of large numbers of data. More important, by regressing the loci of points taken from a drug condition against those from a control session, a quantitative description of the effect of a drug on the entire distribution can be advanced.

In the present case, baseline distributions of IRTs and lever-press durations are established under a schedule of reinforcement. This distribution is described with five loci that anchor important points: the 5th, 25th, 50th, 75th, and 95th percentiles. Then the same five loci are determined after an intervention such as a drug injection. The loci from the drug conditions are regressed against those from the control condition. If the slope is 1.0 and the intercept is 0.0, then it can be concluded that there is no difference between the intervention and the control condition. Changes in the slope and intercept lead to different conclusions about a drug's effect.

IRT distributions, used to describe molecular structure in behavior, typically include both response durations and true IRTs since they describe the time between, say, the depression of a lever and the next time that the lever is depressed. However, molecular details about response rate and durations can provide different information about drug effects (Walker *et al.* 1981; Fowler, 1987; Newland, 1994, 1995), even when only session averages or medians are examined. In the present report, lever-press durations and true IRTs were analyzed separately to isolate potential motor effects of drugs from disruptions in the temporal structure of responding.

This approach was used to characterize compounds whose behavioral actions are thought to be related to activity at adenosine receptors. The compounds R(-)-N^6-(2-phenylisopropyl)adenosine (R-PIA), 5′-N-ethylcarboxamidoadenosine (NECA) and 5′-(N-cyclopropyl)-carboxamidoadenosine (CPCA), function as adenosine A_1, mixed A_1/A_2, and A_2 agonists, respectively (Katims *et al.*, 1983; Jarvis and Williams, 1990; Reddington and Lee, 1991; Collis and Hourani, 1993), and reduce locomotor activity and response rates under several schedules of reinforcement (Carney *et al.*, 1985; Spealman and Coffin, 1986; Jarvis and Williams, 1990; Glowa and Spealman, 1984; Newland and Brown, 1996). These effects bear some similarity to sedative–hypnotics (Coffin and Spealman, 1985; Commissaris *et al.*, 1990; Dar, 1990). Caffeine resembles psychomotor stimulants in its actions on response rate (Glowa, 1986) and can function as a competitive antagonist at the adenosine receptor, an interaction manifested in behavior (Snyder *et al.*, 1981; Spenser and Lal, 1983; Glowa and Spealman, 1984; Logan and Carney, 1984; Glowa *et al.*, 1985; Goldberg *et al.*, 1985; Mumford and Holtzman, 1990; Spealman, 1988; Nikodijevic *et al.*, 1991; Williams, 1991).

Newland and Brown (1996) reported that compounds that act on the adenosine receptor system have separable effects on measures of response rate and of lever-press durations when behavior is maintained under a Multiple Fixed-Interval (FI) 120 s. Duration > 5 s schedule of reinforcement. Caffeine and all adenosine agonists increased lever-press durations under the FI schedule but their effects on the Duration > 5 s schedule were equivocal. One important difference between the two schedule components was the baseline lever-press durations, which were much longer under the Duration > 5 s schedule than under the FI schedule. The possibility that the absence of an increase in durations was due to the already elevated baseline level is examined in the present report.

The adenosine agonists reduced overall response rates at doses that also increased lever-press durations under the FI schedule, suggestive of a general sedation. Caffeine had a more complex spectrum of actions. It elevated overall response rates at low doses, an effect showing insurmountable tolerance, and decreased rates at higher doses. Rate-reducing doses of caffeine also elevated lever-press durations, as did the rate-decreasing doses of adenosine agonists.

The Multiple FI 120 s, Duration > 5 s schedules permit the investigation of lever-press durations in which no explicit reinforcement contingency was applied to the lever-press duration (the FI schedule). The presence of a schedule in which long durations are explicitly reinforced permits a comparison of lever-press durations as an indirect effect of an FI schedule of reinforcement with those resulting from a schedule in which long durations are directly incorporated into the contingencies of reinforcement.

Several elements of the drugs' effects are examined at the molecular level in the present paper. The pattern of effects on lever-press durations and IRTs was examined to determine if the different drugs studied here can be characterized according to these patterns. If so, then motor effects of the drugs, such as might be revealed in lever-press durations, might differ from effects on the patterns of response rates as revealed by the IRTs. In addition, it was determined whether rate increases were accompanied by an increase of short IRTs, as would occur if the drug produced bursts of responding.

METHOD

Subjects

Fourteen male Long-Evans derived rats purchased from Harlan Sprague Dawley were used. The subjects were weighed 5 days/week and fed Purina Rat Chow on a diet designed to maintain their body weights at 300 g, a weight compatible with good health and at which food remains an effective reinforcer. They were individually housed and kept on a 12h : 12h light–dark cycle (lights on at 06.00 h).

Apparatus

Conventional operant chambers (LVE), 30 × 25 × 30 cm surrounded by sound-attenuated cubicles were used. An exhaust fan and white noise in the cubicle masked extraneous noise. The front wall of the chamber contained two levers, a light above each lever, and a pellet dispenser midway between the two levers. Each lever required about 20 g to operate. A PDP 11/23 computer (Digital Equipment Corp.) running SKED software (State Systems) was used to control behavioral sessions and collect data.

Procedure

Behavior was maintained under a Multiple FI 120 s Duration > 5 s schedule of reinforcement in 30 min sessions conducted 5 days a week. The FI component operated on the left lever and the Duration > 5 s component operated on the right lever. The schedules were presented in strict succession and a light was illuminated over the active lever. Under the FI 120 s schedule, the first response to occur after 120 s had elapsed resulted in the delivery of a single food pellet. Under the Duration > 5 s schedule, each lever-press duration greater than 5 s was reinforced by the delivery of a food pellet. During the Duration > 5 s component, a tone sounded and a response timer began the moment the rat pressed the lever. When the response duration reached 5 s the tone turned off and the reinforcement cycle began. The reinforcement cycle included a 0.15 s tone of a higher frequency and the delivery of a food pellet.

Schedule components alternated approximately every 2 min. The FI component ended after the reinforcement cycle or if 2 min passed and 15 s had elapsed without a response. The Duration > 5 s schedule ended after 2 min if the rat was not holding the lever when the component timed out. Otherwise, the Duration > 5 s schedule ended after the rat released the lever and, if the response met the criterion, a pellet was delivered. The Duration > 5 s component did not terminate until the rat released the lever. Details about the shaping of behavior can be found in Newland and Brown (1996).

Caffeine exposure

Three groups were formed by assigning rats such that average group values for response rate during each component and the number of initiations/reinforcer during the Duration > 5 s schedule were approximately equal before caffeine exposure began. One group had 0.5 mg/ml caffeine (anhydrous, purchased from Sigma Chemical Co., St Louis, MO) in their drinking water, a second group had 1.0 mg/ml, and the third group had tap water with no caffeine added. Only the tap-water and 1.0 mg/ml groups are described here.

Drugs

Acute doses of the following drugs were administered i.p.: R-PIA (the *l* isomer and sometimes abbreviated l PIA), an adenosine A_1 receptor agonist; CPCA, an adenosine A_2 receptor agonist; NECA, which has approximately equal potency at A_1 and A_2 receptors, caffeine, and cocaine hydrochloride. A small amount of lactic acid was added to the solution to dissolve R-PIA, NECA, and CPCA. All drugs were dissolved at a concentration such that 1 ml/kg could be administered. Drugs were administered i.p. 10 min before the session began. Acute dose–effect curves were collected in the following order: caffeine, R-PIA, cocaine, CPCA, and NECA. Drugs were administered on Tuesdays and Fridays and sessions conducted on Thursday served as noninjected controls.

For rats with caffeine in their drinking water, acute drug injections and vehicle injections were made after 23 h of caffeine abstinence, achieved by replacing the water bottle containing caffeine with one containing tap water. On occasion R-PIA (80 μg/kg, a dose that reduced most end-points by 50%) or CPCA (10 μg/kg, a dose that nearly eliminated responding) was administered under conditions of no abstinence, achieved by leaving caffeinated water in the rats' home cages.

Full dose–effect relationships describing the effects of the drugs examined here can be seen in the accompanying paper (Newland and Brown, 1996). Monophasic dose–effect curves were obtained with adenosine agonists and cocaine (cocaine dose–effect curves are not presented), so a dose that reduced response rate by approximately 50% was selected for examination, for each of those drugs. Caffeine, administered acutely, produced a biphasic dose–effect relationship on overall response rates in the rats consuming tap water and decreased response rates in the rats consuming caffeinated water. Therefore, a dose that elevated response rates in nontolerant rats and a dose that decreased response rates in all rats were selected for examination.

Dependent measures

Response rates and average lever-press durations were determined for each component and the results are presented in the accompanying paper (Newland and Brown, 1996). The duration of each lever press and each IRT was recorded with 0.01 s resolution for each component and these data are described here. The IRT was determined exclusive of the lever-press duration, so these two measures provide independent descriptors of the molecular structure of behavior. The distribution of these data was summarized by storing the 5th, 25th, 50th, 75th, and 95th percentiles. To obtain the percentiles, each IRT and each lever-press duration was recorded with 0.01 s resolution and stored. A Fortran program was written to read these data, sort them (using a tree-sort algorithm available in many Fortran texts), and extract and store the relevant percentiles. Group averages of percentiles were determined after each dose of each drug and the percentile–percentile analysis was conducted on these averages. Individual percentile–percentile analyses were also conducted for individual rats under selected conditions and the results were compared with those taken from the group averages. The conclusions from these two different ways of conducting the analysis did not differ appreciably.

Fig. 1 illustrates the empirical percentile–percentile analysis. A 'control' distribution is illustrated by the filled circles in the top two rows. The top row shows how the distribution of a molecular descriptor, such as IRT, is usually displayed. A Chi-square distribution was used to generate this example because it provides a skew similar to that observed in the data presented below. Most of the events lay between 0.15 and 0.6 s. Three different effects of an intervention, called the 'drug' distributions, are illustrated by open circles and open triangles. The left column, illustrating a proportional increase in values, will be described first.

A proportional increase in the distribution is illustrated in the left column: a 20% increase is seen across the range of the distribution. The middle panel shows a cumulative form of the distribution seen in the top panel. The horizontal axis is scaled logarithmically (base 10), a tactic that makes the full range of the distribution visible and prevents excessive weighting by large values. Horizontal lines are placed in the distribution at the critical points: the 5th, 25th, 50th, 75th, and 95th percentiles.

In the left column the proportional shift in the distribution appears as a parallel rightward shift on the cumulative distribution (middle panel, left column) using a logarithmically scaled horizontal axis. The bottom panel of the left column illustrates the empirical percentile–percentile analyses. To see how this figure was constructed, consider the cumulative distributions in the middle panel of the left column. The 5th percentile under control conditions falls at a value of 0.12 s. The 5th percentile after the intervention falls at a value of 0.14 s. Therefore, the bottom-left-most point on the empirical percentile–percentile graph has the coordinates (0.12 s, 0.14 s), representing the control 5th percentile and drug 5th percentile, respectively. The other points are determined similarly. Both axes are scaled logarithmically but the original units, seconds, are used as labels. The effect of drug administration on the entire distribution can be described by regressing the drug percentiles against control percentiles. In this example, the regression yields the result $\log(Y) = 1.0*(\log(X)) + \log(1.2)$ or, if the antilog is taken, $Y = 1.2*X$, which is readily interpretable as a 20% increase across all values.

The right column of Fig. 1 shows two power-function relationships. Open circles represent a drug distribution produced by raising the control value to the power 1.2, i.e. $\text{drug} = \text{control}^{1.2}$. Triangles represent the same power function multiplied by a constant different from 1.0; in this example $\text{drug} = 2*\text{control}^{1.2}$. Both effects might be described as rate-dependent because large values are affected differently than small values.

The effects illustrated in the right column are more complex, but still amenable to analysis. A simple power-function shift (open circles) results in a larger change for small numbers than for large numbers. While this can be seen in the distribution in the top panel, it is easier to visualize in the cumulative distribution. Multiplying the power-function by a factor of 2 has two effects which can be understood by referring to the triangles in the cumulative distribution in the middle right panel and the percentile–percentile plot in the bottom panel of the right column. First, the multiplicative factor positions the curve describing the cumulative distribution on the horizontal axis of the cumulative distribution and, in this sense, it is a scaling factor reflecting the units chosen for the original measurement. The measurement units affect the location of the intercept on the percentile–percentile plot but not, of course, the drug effect. The intercept appears at a value of (0,0) after a logarithmic transform, corresponding to a value of (1 s, 1 s) in the original data ($10^0 = 1$ so the log of $1 = 0$). The origin (1,1) would be

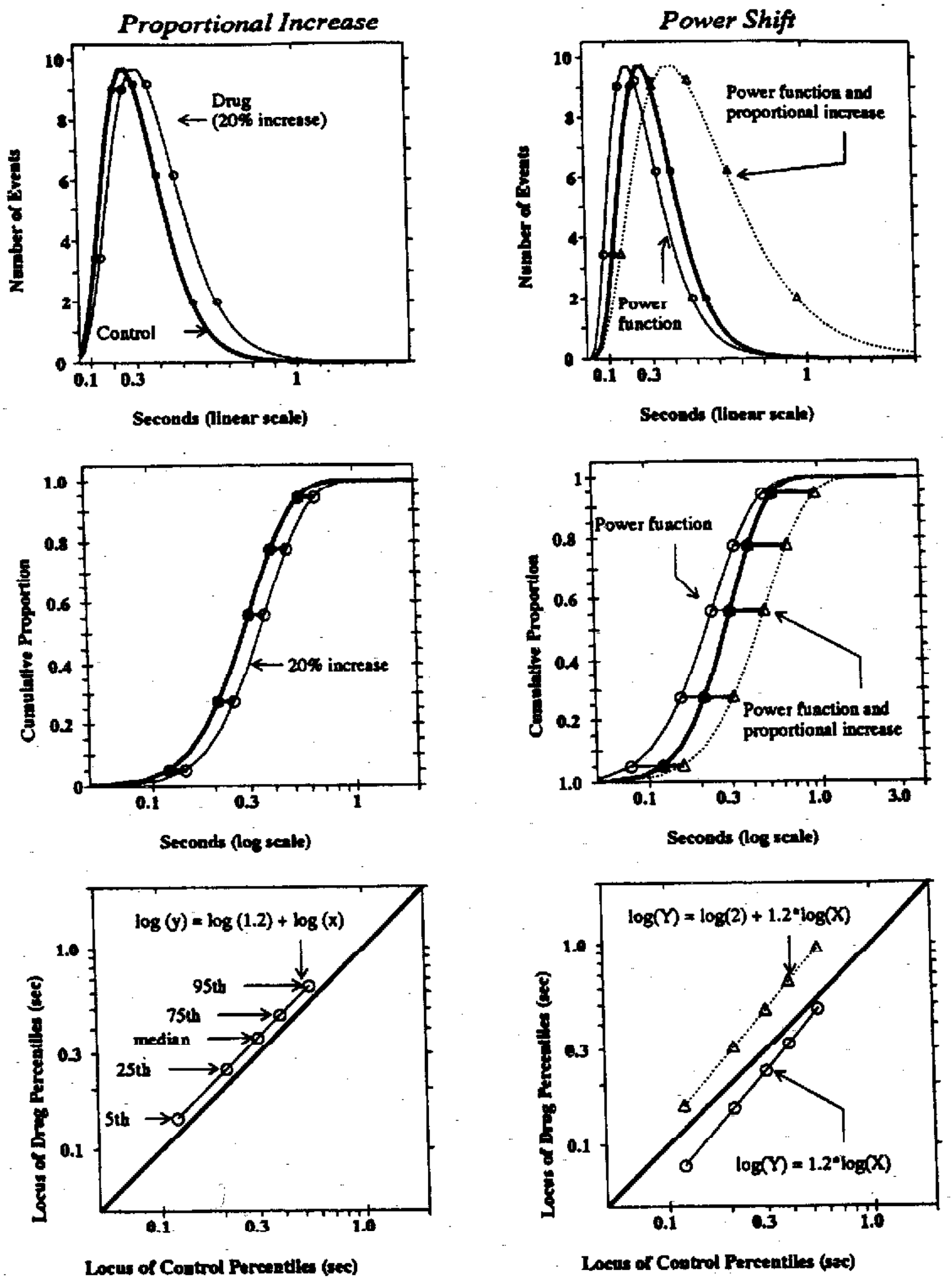
The Percentile-Percentile Plot

FIG. 1. The conversion of a distribution of interresponse times into a percentile–percentile graph. The left column illustrates a proportional shift, in which the drug distribution (open circles, thin line) represents a 20% increase over the control distribution (filled circles, thick line), across the entire distribution. The right column illustrates two types of power-functions. In one, the drug distribution (open circles, thin line) is generated by raising control values (closed circles, thick line) to the power 1.2. In a second (triangles, dotted line), the same power-function is used, but also multiplied by 2. The top panels show conventional distributions. The middle panels show cumulative distribution, with horizontal lines indicating the 5th, 25th, 50th, 75th, and 95th percentiles. The bottom panels show the percentile–percentile plots, in which percentiles from the control distribution are plotted horizontally and the percentiles from the drug distribution are plotted vertically. The thick, diagonal line shows the major diagonal (or the line of no effect). Different drug effects can be en in the slope and intercept of the other lines. Note logarithmically scaled axes. See text for additional details and interpretation.

different if times were measured in milliseconds instead of seconds.

The multiplicative factor also shows whether the net effect is towards an increase, decrease, or a mixture (e.g. decrease small values and increase large values) since this factor determines the position of the cumulative distribution (middle panel) describing drug effects, relative to the cumulative distribution describing control conditions. If the drug curve is positioned far to the left then all values are decreased by the drug but large ones are decreased more than small ones. If the curve is positioned far to the right (i.e. the Y intercept is relatively small) then all values are increased but large ones are increased less than small ones. If the factor is such that the curve from drug conditions crosses the control curve in the range of values studied, then small values may be decreased while large values are increased. The graphical expression of the distribution following drug administration would not be influenced by a change of scale, since it is expressed relative to the distribution under control conditions (except that the magnitude of the intercept would be different).

The bottom right panel shows a percentile–percentile analysis for the two situations in the right column. The regression analysis results in the equation $\log(Y) = 1.2*\log(X) + \log(1)$ or $Y = X^{1.2}$ (open circles, right column) for the power-function relationship. A slope greater than 1.0 indicates greater variability, or a wider range of values, after the intervention, and an effect that is unevenly distributed across the distribution (e.g. large numbers affected more than small numbers). A slope less than 1.0 would indicate that the intervention compressed the variability in the distribution, but again with the effect being unevenly distributed across the distribution, and that short values are increased and long values decreased, a classic rate dependency (or constancy) phenomenon. An interpretation of a slope term different from 1.0 is that the intervention affected large values differently than small values, or that the magnitude of the effect depended upon the baseline value.

Interpretation of the line illustrating the power-function relationship and a multiplicative factor (open triangles) draws from statistical and visual examination of the results. The equation obtained from the percentile–percentile analysis is $\log(Y) = \log(2.0) + 1.2*\log(X)$ or, on linearly scaled axes, $Y = 2*X^{1.2}$. The regression analysis supports a conclusion that the intervention produced an effect, that the effect was not the same across all points on the curve, and that variability increased as part of the effect. The presence of both a slope and intercept term in log coordinates, or bias (scaling) and power term in linear coordinates, means that there was neither a simple proportional nor a simple power-function shift in the distribution. The intercept slides the percentile–percentile line vertically above or below the major diagonal, which can be thought of as a line of no effect. Visual inspection reveals, in this example, that short values were slightly affected and that long values were increased a lot. Such visual interpretation is essential for a full description.

Some effects obtained in the present experiments could best be described by a quadratic relationship. These will be interpreted graphically and are not illustrated here.

In summary, a drug's effect can be read by comparing the vertical location of a point against its horizontal location on an empirical percentile–percentile display. The vertical axis represents the drug distribution and the horizontal axis represents the control distribution. The axes are scaled logarithmically so proportional increases appear as equal displacements. The distributions described in the left column show a 20% increase. The distributions in the right column show power-function or baseline-dependent changes.

RESULTS

Fig. 2 summarizes the effects of three adenosine agonists on the distributions of lever-press durations and IRT. Filled circles and unfilled triangles represent groups consuming 0 and 1.0 mg/ml caffeine, respectively. They show the result of regressing the percentiles representing acute drug administration against those representing control sessions. All data were log-transformed before conducting the regression, so the scaling performed for statistical treatment matches that used for graphical presentation. The dotted line represents the major diagonal, or the no-effect line: a line with a slope of 1.0 and an intercept of 0 passing through the point (0,0). The numbers on the axes represent the raw, not the logarithmically transformed data, and because the logarithm of $1 = 0$, the 'origin' corresponds to the point (1 s, 1 s). The slopes and intercepts of the lines appear in Table I, which also contains the standard error in the measure of these coefficients.

Under control conditions, the 0.05 and 0.95 percentiles of response durations during the FI component spanned a 20–40 fold range from 0.05 s to 1 or 2 s, around a median of about 0.2 s, as can be seen by the location of the points on the horizontal axis. All the three adenosine agonists produced a constant proportional increase in the distribution of lever-press durations under the FI schedule: the data points form a line that is parallel to the major diagonal. As shown in Table I, the magnitude of this elevation ranged from about 41 to 110%. The smallest intercept is 0.15; its antilog is $10^{0.15} = 1.41$, and this represents a 41% increase. The

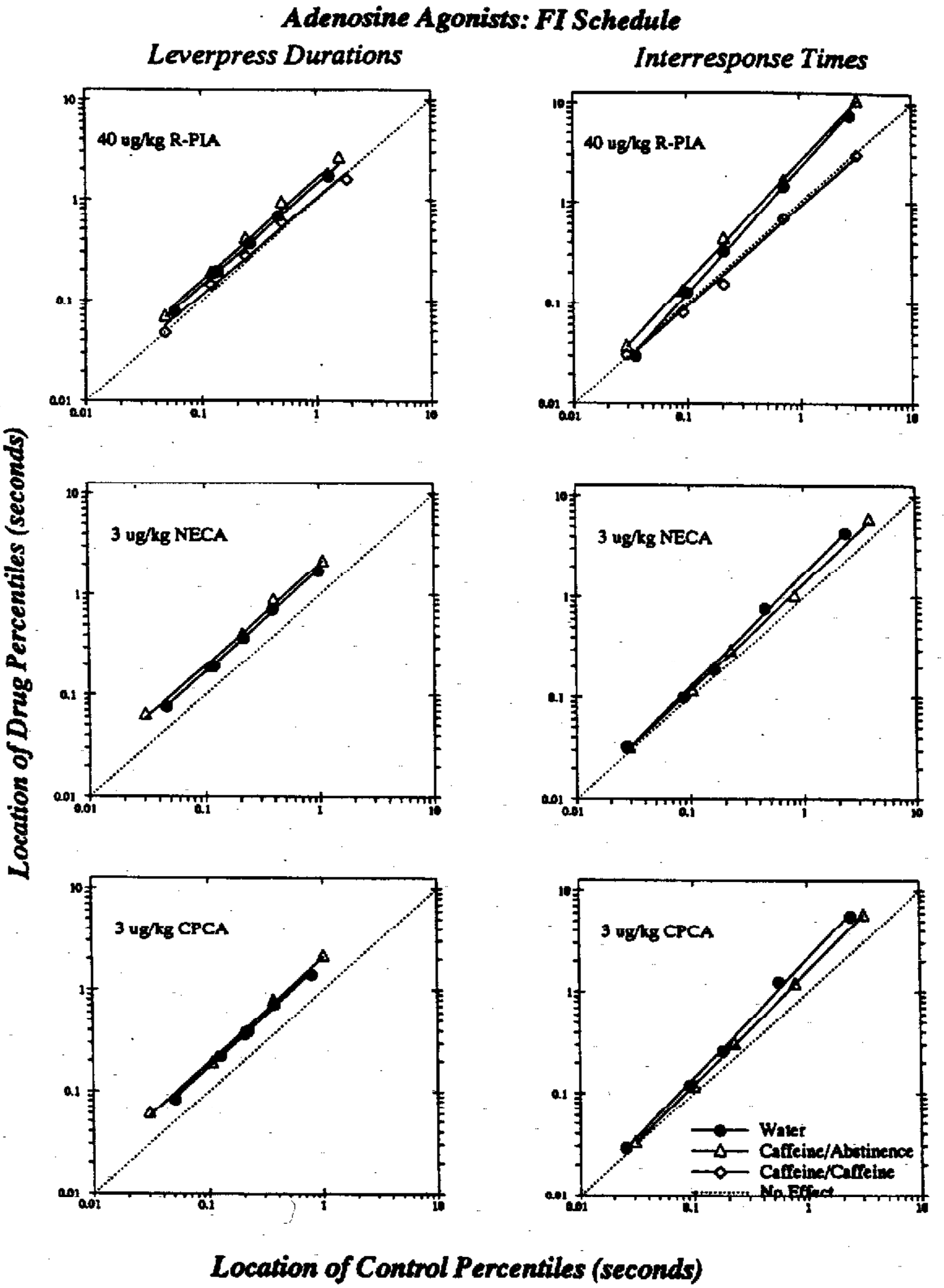

FIG. 2. Empirical percentile–percentile plots summarizing the effects of different adenosine agonists on the distribution of lever-press durations (left) and interresponse times, exclusive of duration (right), under the fixed-interval schedule. Two groups are illustrated: tap water (filled circles) and 1.0 mg/ml caffeine (triangles). The dotted line illustrates a no-effect curve: slope = 1.0 and intercept = 1 (log intercept = 0). Regression coefficients describing the lines are contained in Table I. The parallel displacement in the curves representing durations represents a constant proportional increase in durations. The curves with slopes greater than 1.0 for the IRTs curves show that IRTs were increased by a greater proportion than short IRTs. CPCA, 5′-(N-cyclopropyl)-carboxamidoadenosine; NECA, 5′-N-ylcarboxamidoadenosine; R-PIA, R(-)N^6-(2-phenylisopropyl)adenosine.

TABLE I. Slopes and intercepts resulting from empirical percentile–percentile analyses of fixed-interval lever-press durations and interresponse times

	Lever-press duration[1]				Interresponse time[1]					
	Water		Caffeine 1 mg/ml		Water exposure			Caffeine 1 mg/ml		
Drug (and dose)	Slope	Intercept	Slope	Intercept	Quadratic	Slope	Intercept	Quadratic	Slope	Intercept
R-PIA	1.01	0.15[4]	1.01	0.21[4]		1.26[3]	0.34[4]		1.20[3]	0.41[4]
(40 μg/kg)	(0.02)	(0.02)	(0.05)	(0.04)		(0.02)	(0.02)		(0.02)	(0.02)
NECA	1.02	0.26[4]	1.01	0.31[4]		1.13[3]	0.23[4]		1.07[3]	0.13[4]
(3 μg/kg)	(0.02)	(0.02)	(0.04)	(0.04)		(0.04)	(0.04)		(0.02)	(0.02)
CPCA	1.02	0.27[4]	1.02	0.32[4]		1.18[3]	0.33[4]		1.12[3]	0.21[4]
(3 μg/kg)	(0.03)	(0.02)	(0.03)	(0.03)		(0.03)	(0.03)		(0.01)	(0.01)
Caffeine	0.99	−0.01	1.02	0.02		0.99	0.02		1.01	−0.07
(10 mg/kg)	(0.02)	(0.01)	(0.02)	(0.01)		(0.03)	(0.02)		(0.03)	(0.03)
Caffeine	1.09	0.36[4]	0.96	0.16[4]	−0.45	1.10	0.78[4]	−0.50[2]	0.85	0.60[4]
(60 mg/kg)	(0.05)	(0.04)	(0.03)	(0.02)	(0.20)	(0.20)	(0.10)	(0.13)	(0.13)	(0.07)
Cocaine	0.84[3]	−0.18[4]	0.78[3]	−0.01[4]	0.45[2]	0.78	0.97[4]	−0.46[2]	0.73[3]	0.72[4]
(30 mg/kg)	(0.09)	(0.07)	(0.03)	(0.02)	(0.08)	(0.12)	(0.14)	(0.13)	(0.10)	(0.05)

[1] Value in parenthesis is the standard error of the estimate.
[2] Quadratic term different from 0 with $p < 0.05$.
[3] Slope different from 1 with $p < 0.05$.
[4] Intercept different from 0 with $p < 0.05$.

largest is 0.32 and its antilog is $10^{0.32} = 2.1$, a 110% increase, or more than doubling. The same range of durations seen in control conditions was present under drug conditions, but each element of the distribution was proportionally longer after the drug. The water-exposed and caffeine-exposed rats were indistinguishable from one another on this measure both in their baseline values and in the effects of the three adenosine agonists.

Drug effects on the IRT distributions differed from those seen on the distribution of lever-press durations. Under control conditions the 0.05 and 0.95 percentiles of IRT during the FI component were about 0.03 s and 2–4 s, respectively. The greater than 1.0 slopes describing the regression of drug percentiles upon control percentiles show that there was greater variability in IRT under drug conditions and that long IRT were more greatly affected than short ones. For R-PIA, the short IRT were barely affected but longer IRT, those greater than about 1 s, increased two- to threefold under drug conditions. NECA and CPCA produced a similar pattern but the increase in long IRTs was of a smaller magnitude after these drugs.

A regression was also conducted on data from sessions in which R-PIA or CPCA was administered while caffeine was still in the drinking water. The effect is exemplified (diamonds in Fig. 2) with a dose of R-PIA that severely disrupted behavior when administered after caffeine abstinence, but whose disruption was abolished by leaving caffeine in the drinking water. When 80 μg/kg R-PIA was administered after the caffeinated water remained in the home cages, the lever-press duration and IRT distributions matched those of control conditions. The equations describing the percentile–percentile graphs for lever-press durations and IRT were (after log transforms) $Y = 0.96{*}X + 0.01$, and $Y = 0.99{*}X - 0.04$, respectively. Neither slope was distinguishable from 1.0 and neither intercept was distinguishable from 0. After an acute dose of 10 μg/kg CPCA, administered while caffeine was still on the home cage, the mean lever-press duration and response rates matched those from the 3 μg/kg conditions (Newland and Brown, 1996), as did the molecular distributions (data not shown). In short, alterations in the molecular structure of lever-press durations and IRT produced by these adenosine agonists were eliminated or reduced by leaving caffeine in the drinking water.

Fig. 3 shows distributions of lever-press durations taken from the Duration > 5 s schedule for individual rats, after administration of the adenosine agonists. IRT distributions on this schedule were not examined, since each criterion response was reinforced. Thus the value of the reinforced IRT was greatly influenced by the time required to eat the food pellet, leaving only unreinforced IRT uncontaminated by this artifact.

When only the mean durations were described (Newland and Brown, 1996), the data were highly variable and no drug effects were detected. Viewed at the molecular level, consistent and clear effects appear. The distributions of subcriterion lever-press durations were shifted toward longer durations by a constant proportion, whose magnitudes were virtually identical to that seen in the FI schedule. To emphasize the similarity between the

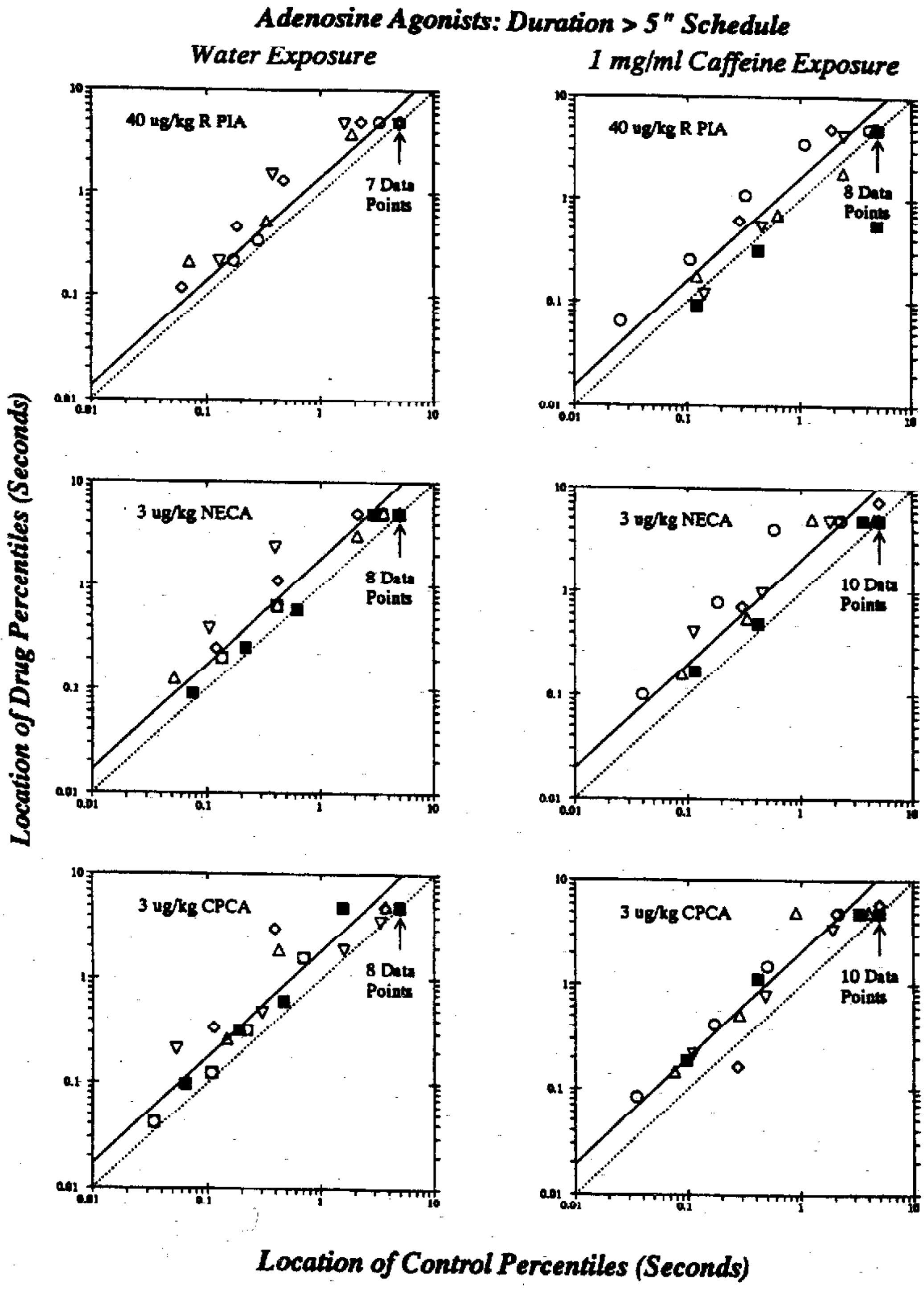

FIG. 3. Empirical percentile–percentile plots summarizing the effects of different stimulants on the distribution of response durations under the Duration > 5 s schedule for water-exposed and caffeine-exposed rats. Symbols represent individual rats. The solid lines represent the best-fit regression taken from the fixed-interval schedule illustrated in Fig. 2. Otherwise the details are as in Fig. 2. Note that most points are shifted in the direction of longer durations (above the dashed, no-effect line), for all but the criterion duration, and hat the regression from the fixed-interval schedule summarizes the effects well. CPCA, 5'-(N-cyclopropyl)-carboxamidoadenosine; ECA, 5'-N-ethylcarboxamidoadenosine; R-PIA, R(-)N^6-(2-phenylisopropyl)adenosine.

FI and the Duration > 5 s schedules on this measure, the regression line describing the group average from the FI schedule, whose coefficients are shown in Table I, were superimposed on these data, and it falls close to the center of the subcriterion points from individual subjects.

The longer end of the distribution of lever-press durations was increased, such that a greater percentage of durations met the 5 s criterion for reinforcer delivery under drug conditions. This can be seen as a horizontal scatter whose y-intercept is 5 s. Criterion durations were unaffected, so that the control over response termination exerted by the onset of the reinforcement cycle was unimpaired by these drugs. Two exceptions to this conclusion are seen by a diamond after NECA and CPCA in the caffeine-exposed group representing durations longer than 5 s.

Fig. 4 shows the effects of two different doses of acute caffeine and a single dose of cocaine on IRT and lever-press durations. Acute doses of 10 and 60 mg/kg increased and decreased, respectively, overall response rate for all animals (Newland and Brown, 1996). The dose of cocaine illustrated in Fig. 4 decreased overall response rates and increased lever-press durations under the FI schedule.

The rate increases produced by 10 mg/kg caffeine were not accompanied by changes in either the molecular structure of behavior, as revealed by the IRT distributions, or by changes in lever-press durations. In each case, the slope and intercepts of the regression of drug against control percentiles were indistinguishable from 1.0 and 0, respectively. This was true for both tap-water and caffeine-exposed rats.

The 60 mg/kg dose of caffeine shifted all lever-press durations toward longer durations, by a constant fraction of 0.16 and 0.31 log units for the tap-water and caffeine-exposed rats, respectively, corresponding to increases of 45 to 100% for the two groups. The rate decreases were accompanied by severe disruption in the molecular structure of behavior, as revealed by the IRT distributions. Visually, it appears that all but the very shortest IRT showed a substantial increase, and that this occurred for both caffeine and cocaine. Visual inspection suggests a bowing in the percentile–percentile plots for both the 60 mg/kg dose of caffeine and the 30 mg/kg dose of cocaine. Short IRTs are not affected, or perhaps even further shortened, but longer IRT were increased. The successful fitting of a quadratic equation to these data confirmed their curvilinear appearance. The quadratic component contributed only slightly to the fit for the data from the tap-water condition, but was significantly different from zero for the high-dose condition and for the cocaine conditions (Fig. 4 and Table I). It is possible that a greater number of percentiles would have resulted in less variability and more statistically significant coefficients.

An insert in Fig. 4, generated from the equation in Table I, illustrates how this quadratic relationship would appear in a conventional IRT analysis. Short IRT were barely changed, but the modal IRT increased by nearly an order of magnitude and the very long IRT seen in the right tail of the distribution were increased even more.

Close inspection of Table I indicates that the three adenosine agonists had similar effects on all measured features of the molecular structure of behavior, but that caffeine's effects were more complex. A pattern is visible in Fig. 5, which summarizes Table I by plotting one regression parameter against another for the different conditions. The three adenosine agonists (circles) tended to cluster together on all measures. Caffeine (60 mg/kg, shown as triangles; the 10 mg/kg dose of caffeine is not included in Fig. 5 because there was no effect) lengthened lever-press durations at the higher dose, and in that resembled the three adenosine agonists. This is seen in the left column of Fig. 5, where triangles, like circles, are located at positive intercepts and slopes are between 0.95 and 1.10 (i.e. no effect). Cocaine is seen at a slope less than 0.85 and negative intercept. The rate-reducing doses of caffeine and cocaine were similar to one another, however, in their effect on IRT distributions (right column). The intercepts were larger than 0.5, and the quadratic component was nonzero for all conditions involving caffeine and cocaine. The slope was less than 1.0 for all 'stimulant' (caffeine and cocaine) conditions, except for the case where caffeine was administered to nontolerant rats (i.e. those consuming tap water).

DISCUSSION

Molecular analyses of drug effects on IRT are performed to characterize precisely alterations in response topography or the pattern of responding (Weiss, 1970; Rice, 1988; Iversen, 1991). The analysis conducted in the present study separated these two components of the traditionally defined IRT time into two components: a lever-press duration and a true IRT. This separation permitted the isolation of drug effects on the physical dimensions of response topography, as revealed in the distribution of lever-press durations, from response patterns, as described in the IRT distribution. The drugs' effects on the molecular characteristics of responding, as indicated by the distribution of IRT, were quite different from their effects on the molecular characteristics of lever-press durations, an independence that supports arguments that lever-press durations and response rate or IRT provide separate information about drug effects (Walker *et al.*, 1981; Fowler, 1987; Newland, 1994, 1995).

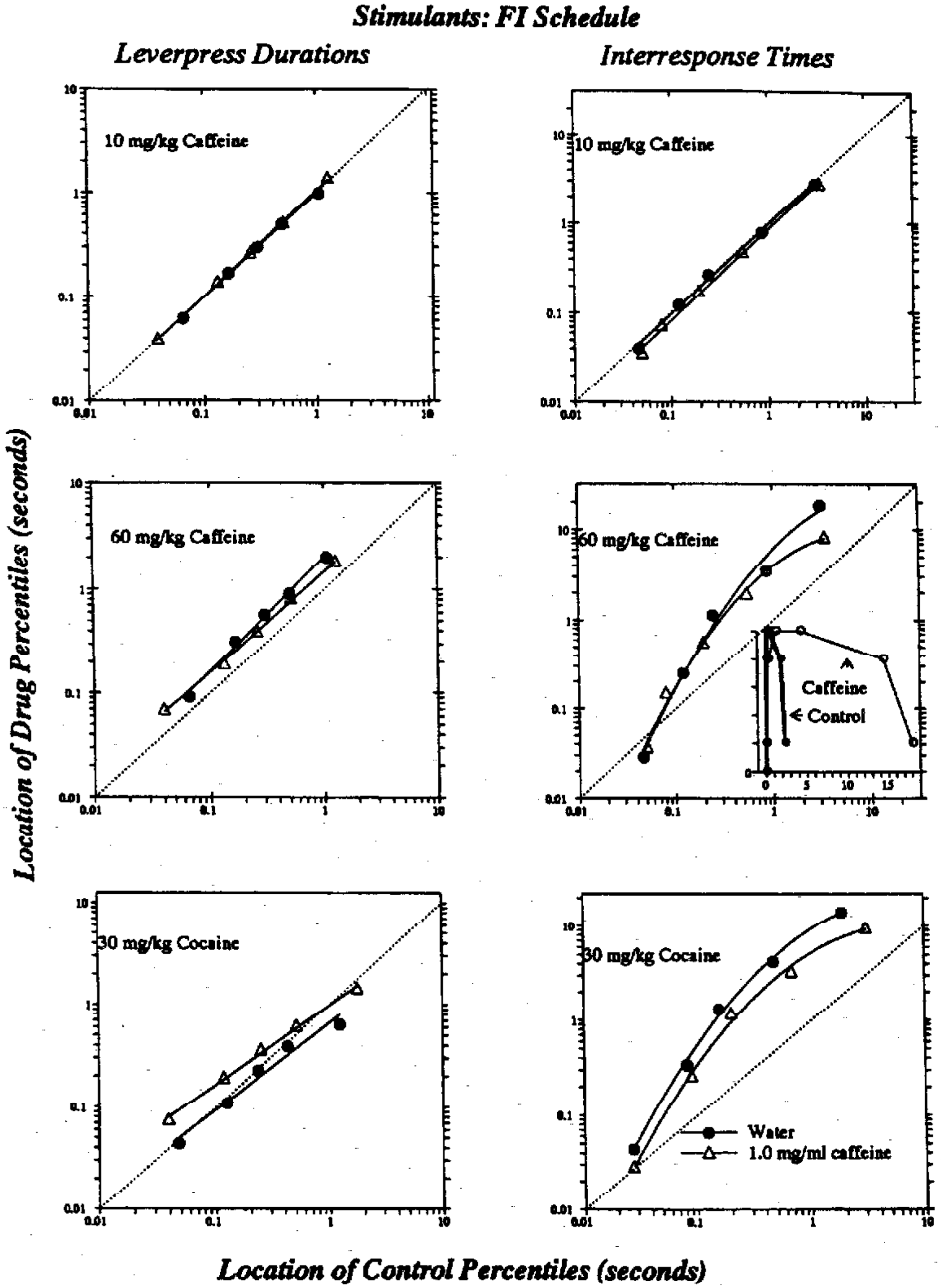

FIG. 4. Empirical percentile–percentile plots summarizing the effects of a rate-increasing dose of caffeine (top panels) and rate-decreasing doses of caffeine or cocaine (middle and bottom panels). Details as in Fig. 2. The insert in the middle panel of the right column illustrates the two interresponse time distributions as they would be shown conventionally (the horizontal axis is scaled in conds). The thick line and filled circles describe the control distributions shown as in Fig. 1. The open circles and single line illustrate adratic functions shown in the bottom two panels of the right column of this figure.

Empirical percentile–percentile analyses were used to separate drug effects on lever-press durations from those on IRT as well as to classify drug effects according to these behavioral effects. This approach has several advantages over classical ways of describing distributions of data. Comparisons can be made statistically, using parameters derived from conventional regression techniques. The full range of the distribution can be described adequately using five loci, meaning fewer numbers must be stored and managed. More loci should be used if required to describe the distribution fully. The baseline, or control distribution is empirically derived so the approach is applicable even when there is no theoretical reason to presume a certain shape to a distribution. While visual comparisons have served very well in describing the molecular structure of behavior, the sheer number of numbers used, when comparing distributions visually, typically requires one to report representative distributions from an isolated set of conditions and subjects, or to rely on a single measure of central tendency, such as a median. Empirical percentile–percentile analysis is a data-reduction strategy that permits statistical analyses to be accomplished on numbers that describe the entire distribution of points, rather than representative numbers such as a mean or a median.

Adenosine agonists

The IRT distributions at doses that reduced response rates by about 50% were examined and the effects of all three adenosine agonists were found to be similar to one another but different from those of caffeine. The slope of the regression lines comparing distributions of IRT from drug sessions with control sessions ranged from 1.07 to 1.26, with most of the points clustering around 1.2. That these slopes were greater than 1.0 on log–log coordinates indicates a power-function relationship: long IRT were affected proportionately more than short ones. In fact, Fig. 2 shows that the shortest IRT of 0.03 s were barely affected by the drugs while long IRT were increased approximately twofold. The power-function relationship suggests a gradual lengthening of IRT as the baseline IRT became progressive longer.

The picture provided by analyses of drug effects on distributions of lever-press durations was quite different from that seen with the IRT. Under control conditions, lever-press durations during the FI schedule spanned about 1.5 orders of magnitude, ranging from approximately 0.03 s to 1 s. All three drugs shifted the response duration distribution by a constant proportion on the log–log coordinates, indicative of a constant proportional change in the distribution. The slopes of all the linear regressions were indistinguishable from 1.0 but the intercepts were all positive, with magnitudes ranging from 0.15 and 0.21 for R-PIA and 0.26 to 0.32 for NECA and CPCA. Since the analyses were conducted on the logarithms, this indicates a 41 to 110% increase in the entire distribution. Such a proportional shift results in a larger absolute increase in the magnitude of long durations, represented by the right end of the distribution.

The distribution of lever-press durations expand the description of performance over that provided by the mean duration (described in Newland and Brown, 1996). Added clarity was especially notable in the Duration > 5 s schedule. As with lever-press durations under the FI schedule, lever-press durations under the Duration > 5 s schedule spanned about 1.5–2 orders of magnitude under control conditions. A large percentage of lever-press durations, from 25 to 50% under control conditions, met the criterion of 5 s under control conditions, while few, if any, responses were that long under the FI schedule. The generality of the pattern seen in the increase in lever-press durations from the FI schedule, after drug exposure, was assessed by applying the linear regression derived from the FI schedule directly to the durations from the Duration > 5 s schedule. Two classes of durations, criterion and subcriterion, could be identified according to drug effects on behavior under this schedule. All three drugs shifted subcriterion durations, those shorter than the 5 s reinforcement criterion, by approximately the same proportion as was seen under the FI schedule. The best-fit line describing durations under the FI schedule provided an excellent description of subcriterion lever-press durations under the Duration > 5 s schedule.

The magnitude of the increase in lever-press duration depended jointly upon the baseline duration and the consequences applied to a duration. When lever-press duration was not directly reinforced in the FI schedule, and therefore only indirect reinforcement contingencies applied to it (Zeiler, 1977; Newland, 1995), lever-press durations were increased by a constant proportion by the adenosine agonists. A similar conclusion applies to the class of subcriterion durations in the Duration > 5 s schedule. However, the onset of a discriminable reinforcement cycle at the end of 5 s occasioned the release of the lever on the Duration > 5 s schedule component and this was not affected by the drugs.

In summary, adenosine agonists prolonged all lever-press durations under the FI schedule. No effect was seen on long durations established by a reinforcement contingency, as in the Duration > 5 s schedule. IRT were also lengthened, but long ones were lengthened more than short ones.

Caffeine and cocaine

Caffeine produced a biphasic dose–effect curve, with moderate doses increasing response rates and higher

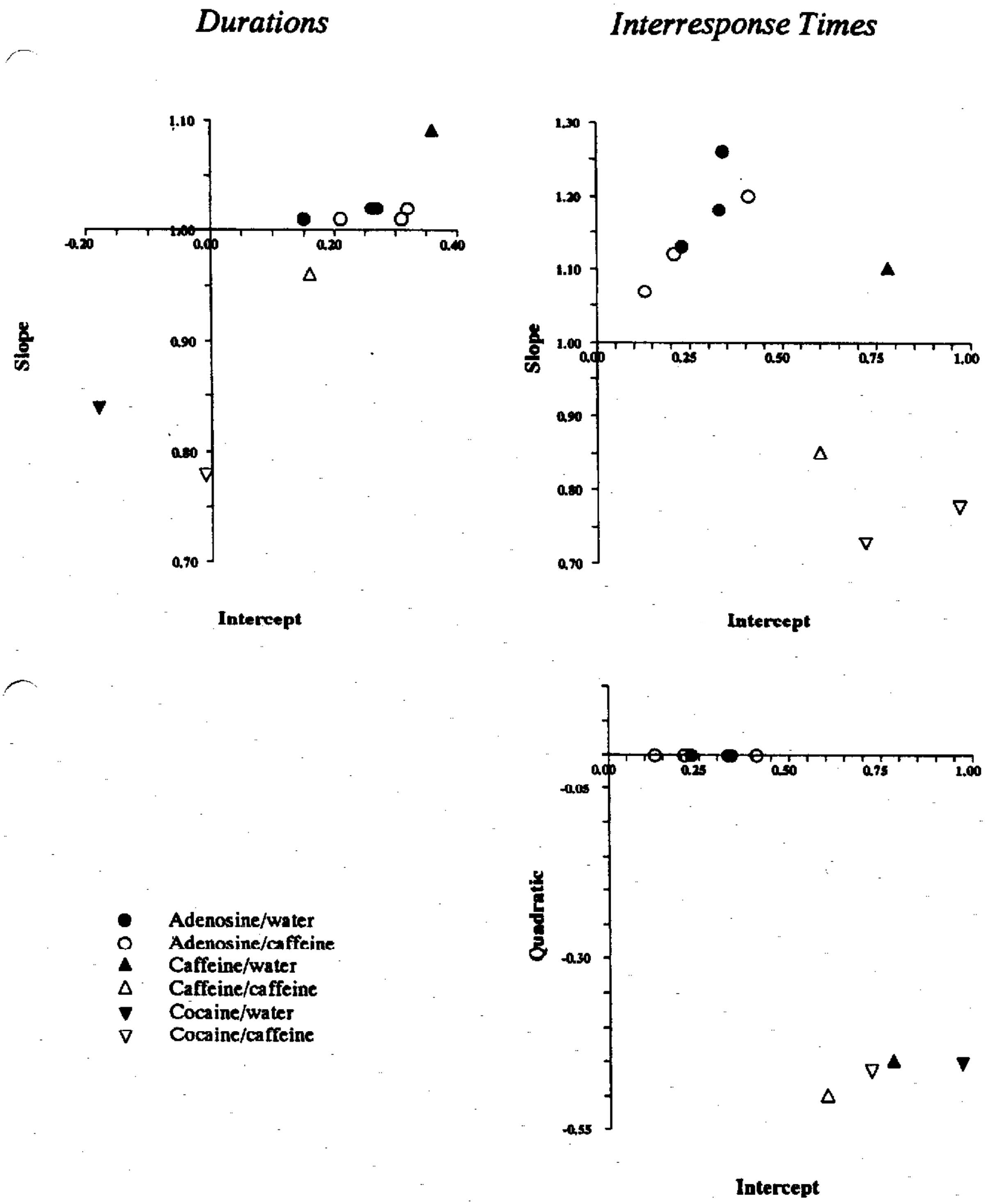

FIG. 5. Summary of the percentile–percentile analyses for different conditions. The horizontal axes are the intercept from the regression analyses of percentile–percentile plots. The vertical axes are either the slope or quadratic component for the interresponse time analysis, or the slope for the lever-press duration analyses. Because a slope of 1.0 represents no-effect, the origin of the slope axes is located at 1.0. Filled symbols represent the tap-water groups. Unfilled symbols represent rats with 1.0 mg/ml caffeine in the drinking water. Circles represent the different adenosine agonists. Triangles represent acute caffeine (60 mg/kg) administration and inverted ngles acute cocaine administration. The three adenosine agonists form a cluster on all measures. Caffeine resembles the adenosine onists on lever-press durations. Caffeine resembles cocaine in its effect on the interresponse time distribution.

doses decreasing it (Newland and Brown, 1996). Cocaine only reduced response rates, replicating other studies with rats (Harris *et al.*, 1978; Logan *et al.*, 1989). Molecular analyses of caffeine's actions were conducted at two doses of caffeine: one that increased overall response rates in rats consuming tap water and a second that decreased rates in all groups. The lower dose, 10 mg/kg, elevated response rates in nontolerant rats but not in rats chronically consuming caffeine, an effect interpreted as insurmountable tolerance to this effect of caffeine (Newland and Brown, 1996). This dose did not change the distribution of IRT or lever-press durations of either group of rats in the present experiment. The latter effect indicates that the rate-increasing dose had no effect on the physical execution of the response, or at least this measure of it. The former indicates that the rate increasing dose had no effect on the pattern of IRT and that rate increases occurred in the absence of the shortening of IRT.

There are two ways in which rate increases can occur: IRT can shorten or responding can begin earlier in the fixed interval. The absence of a shorter IRT distribution in the present experiment directly implies an earlier onset of responding. This extends other observations using squirrel monkeys (Katz and Goldberg, 1987; Spealman, 1988) and rats (Logan *et al.*, 1989), that rate increases induced by caffeine in nontolerant animals correspond to elevated rates of responding early in the fixed interval. Logan *et al.* (1989) used a rate-dependency analysis to conclude that caffeine elevated the absolute rate of responding consistently throughout the interval, but that relative rate was unaffected, and therefore that the rate increase possibly reflected elevations in local rates of responding. The rate dependency analysis, by averaging response rates over 30 s intervals, provides different information about the pattern of responding from that seen in the IRT analyses, which emphasizes the fine structure of behavior as resolved at intervals of less than a few seconds. The IRT analyses in the present report revealed no increase in local rates of responding and suggest that rate increases must coincide with either an earlier onset of responding or, possibly, a decrease in pauses of longer than a few seconds.

The higher dose of caffeine, 60 mg/kg, resembled the adenosine agonists in its action on lever-press durations, by producing a proportional shift across the entire distribution. The proportionality is indicated in the elevation of the intercept, coupled with no effect on the slope of the empirical percentile–percentile graphs. It represents a broadly based, nonspecific slowing in the physical execution of the response, as illustrated in Fig. 1.

The higher dose differed from the adenosine agonists in that it lengthened all but the shortest IRT. In this respect, the higher dose resembled the rate-reducing dose of cocaine. The percentile–percentile plots taken from sessions after administering adenosine agonists looked like straight lines, while those taken from caffeine were bowed. Caffeine increased all but the very shortest IRT and may even have decreased slightly the extremely short IRT of about 0.05–0.06 s. Short IRT represent bursts of responses, so response bursts were either unaffected or occurred at a higher rate. The bowing, or quadratic component, indicates that the relationship between the distributions of IRT under control and drug conditions can be described as an abrupt increase in their length. This analysis indicates that the structure of these bursts was unaffected by caffeine and cocaine, but that many pauses of 1 s or more were introduced by these drugs. This stands in contrast to the relationship seen with the adenosine agonists, where the increase was more gradual and did not become pronounced until control IRT were greater than about 1 s.

In summary, molecular analyses revealed that the effect of caffeine on lever-press durations resembled that of adenosine agonists, in that the entire distribution of durations was shifted by a constant proportion. Caffeine's effect on IRT indicated that response bursts were unaffected, even as lever-press duration was lengthened, but long pauses were introduced. In this respect, caffeine resembled cocaine and not the adenosine agonists.

Interaction between caffeine and R-PIA

The disruption of the molecular structure of behavior produced by the R-PIA was abolished by leaving caffeine in the drinking water. The presence of caffeine in the drinking water eliminated R-PIA's increase of lever-press duration, even though acute administration of caffeine never shortened lever-press durations when administered alone. This interaction between caffeine, an adenosine antagonist, and R-PIA, an adenosine agonist, is consistent with adenosine involvement in the molecular structure of IRT and lever-press durations.

Low doses of caffeine had no effect on the IRT distributions, and higher doses had qualitatively different effects from those of the adenosine agonists. It seems unlikely that the two drugs interacted arithmetically to eliminate the adenosine agonists' increases of the IRT or lever-press durations. Again, it is more likely that this effect, too, represents a pharmacological interaction.

Molecular analysis and drug classification

Molecular analyses reveal important details about the interactions among drug actions, the physical execution of the response, and the pattern of responding. Rate-reducing effects of adenosine agonists were distinguishable from those of psychomotor stimulants at the molecular level, even when these distinctions were not detectable in descriptions of overall rate. The IRT distributions divided these drugs into two classes: caffeine resembled cocaine and the adenosine agonists resembled one another. Moreover, tolerance to caffeine's effects could be seen as being related to the onset of responding in the FI schedule, and not to the fine structure of responding once it begins. Caffeine, however, resembled the adenosine agonists rather than cocaine in its action on lever-press durations.

Because motor and rate-altering effects of the drugs were isolated, comparisons with other classes of behaviorally active drugs might be possible. Sedative-hypnotics elevate response durations at doses equal to or lower than those that have rate-altering behavioral effects, while neuroleptics tend to increase measures of response durations at higher doses than those that affect response rate (Fowler *et al.*, 1977; Fowler, 1987; Tang *et al.*, 1988). In the present study the adenosine agonists reduced rate and increased lever-press durations at about the same dose, and in that regard adenosine agonists bear some resemblance to sedative hypnotics. This is consistent with other evidence of an interaction between these classes of compounds on motor function (Dar, 1990; Garrett and Holtzman, 1995), operant behavior (Coffin and Spealman, 1985), and actions at the GABA-chloride ionophore (Phyllis and O'Regan, 1988). More important, and less speculatively, these different patterns of effects on the molecular structure of behavior may point to different pharmacological mechanisms underlying effects on duration, rate-increases, and rate reductions.

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