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Low doses of *cis*-flupentixol attenuate motor performance

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Abstract. We evaluated the effects of *cis*-flupentixol on reinforced responding. The experimental subjects were rats and the reinforced response was a lever press. The procedure was a five-component multiple schedule that provided five different reinforcement rates. *Cis*-flupentixol produced dose-dependent decreases in reinforced responding. An equation, the matching law, was fitted to the results. One parameter of this equation represents the estimated response rate asymptote. *Cis*-flupentixol produced dose-dependent decreases in the asymptotes. A second parameter of the equation represents the rate of reinforcement that maintains a one-half asymptotic response rate. *Cis*-flupentixol did not appear to affect this measure. There is evidence that the response rate asymptote measures motor components of response rate and that the reinforcement parameter measures the efficacy of the reinforcement maintaining the response. According to these results, *cis*-flupentixol systematically affected the motor-component of reinforced responding – it slowed down lever pressing – without affecting the subject's sensitivity to the reinforcer maintaining the response. In contrast, other neuroleptics have decreased the subjects' sensitivity to reinforcement, according to the matching law measures.

Key words: *Cis*-flupentixol – Reinforced responding – Motor effects – Reinforcement efficacy – Dopamine receptors (D1 and D2) – Matching law equation – Variable-interval schedule – Water reinforcement – Lever press – Rat

Cis-flupentixol is the *cis*-isomer of the thioxanthene flupentixol. It was derived from the phenothiazines, and its behavioral effects are similar to those of the parent class of compounds. It is an effective anti-psychotic (e.g., Stauning et al. 1979), and in animal laboratory studies it inhibits reinforced responding (Hamilton et al. 1985) and antagonizes the effects of dopamine agonists (Herrera-Marschitz and Ungerstedt 1984; Nielsen and Jepsen 1985). However, a recent study suggests that the behavioral pathway for *cis*-flupentixol's effect on reinforced responding may be different from that of previously studied neuroleptics. In a study that used the matching law (Herrnstein 1970) definitions of motor performance and reinforcement efficacy, *cis*-flupentixol reduced motor performance without affecting reinforcement efficacy in two of three subjects (Hamilton et al. 1985). In contrast, in matching law studies of the neuroleptics pimozide, chlorpromazine, and sulpiride (Heyman 1983; Gallistel and Karras 1984; Hamilton et al. 1985; Heyman et al. 1986) there was a change in both reinforcement efficacy and motor performance, and the dose threshold for the reinforcement effect was lower. In this study, we tested the generality of the *cis*-flupentixol result reported by Hamilton, Stellar, and Hart.

Recently, a number of researchers have turned to the matching law to analyze the behavioral effects of psychotropics. The approach is based on the finding that in variable-interval reinforcement schedules, the relationship between response rate and reinforcement rate can be described by the equation for a rectangular hyperbola:

$$B=\frac{kR}{R+R_e}, \quad (1)$$

where B is response rate, R is reinforcement rate, and k and R_e are parameters whose values are obtained by fitting Eq. 1 to the data. In terms of logical or curve fitting definitions, k is the response rate asymptote and R_e is the rate of reinforcement that maintains a one-half asymptotic response rate (see Heyman et al. 1986 for a more detailed account). In terms of empirical relations, a recent literature review (Heyman and Monaghan 1987) showed that k but not R_e was changed in studies in which the response requirement was varied (McSweeney 1978; Bradshaw et al. 1983a; Hamilton et al. 1985; Heyman and Monaghan 1987); whereas R_e but not k was changed in experiments in which either the duration of the deprivation period or properties of the reward were varied (Guttman 1954; Conrad and Sidman 1956; Logan 1960; Kraeling 1961; Bradshaw et al. 1978; Hamilton et al. 1985; Heyman and Monaghan 1987). de Villiers and Herrnstein (1976) provided estimates of k and R_e for experiments conducted before 1962. For example, in an experiment on rats that used the same procedure as the study described in this report (Heyman and Monaghan 1987) increasing the weight of the response lever decreased k without affecting R_e; whereas increasing deprivation decreased R_e without affecting k. Our goal is to determine whether *cis*-flupentixol alters k, R_e, or both.

Materials and methods

Subjects. Eight, experimentally naive, male Wistar rats from Royal Hart (Kingston, New York) served as subjects. At

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the start of the study, the rats were about 3 months old and weighed between 250 and 350 g. The rats were housed two to a cage in a colony room that was illuminated 12 h a day (light on at 6:00 hours). In the home cage the rats had free access to food (Purina rat chow) but limited access to water. Water was the reinforcer and was available for 30 min following the session.

Apparatus. The experiments were conducted in eight standard, two-lever chambers (Coulbourn instruments, Modular Test Cage, Model E10–10: 28.5 cm, 20.5 cm, 24 cm). The right but not the left lever was functional. It was set into the front wall, 6.5 cm above the floor and operated by a force of about 0.30 N. To the left of the lever was a recessed opening that allowed access to a 0.025 ml dipper of water. The dipper sat in a trough of water and was raised into the recessed opening when the subject had fulfilled the reinforcement requirement. Stimulus lights were set into the front wall to the left and right of the dipper, and there was a clicker attached to the back of the front wall. The lights and clicker were used to signal different phases of the experimental session. The chambers were enclosed in sound attenuating, ventilated boxes. Experimental events were controlled and recorded by a PDP 8-a computer. The programs were written in SKED (Snapper et al. 1976).

Procedure. Experimental sessions consisted of a series of five variable-interval (VI) reinforcement schedules (a five-component multiple schedule). In each session, each schedule was available for 9 min. A 5-min time-out period separated consecutive schedules, and the schedule order was random, without repetition. Thus each subject was exposed to each of the five schedules in each session. The programmed inter-reinforcement intervals approximated an exponential distribution (Fleshler and Hoffman 1962), so that the conditional probability of a reinforcer was approximately constant as a function of time. The mean interval durations were 150 s, 75 s, 30 s, 10 s, and 5 s, which correspond to programmed rates of 24, 48, 120, 360, and 720 reinforcers per h. The reinforcer was 2.5 s access to the 0.025 ml dipper. For this period and the immediately following 1.5 s, the interval timer and stimuli were inoperative. The session began with a "warm-up" in which the subject earned five reinforcers according to a fixed ratio 5 or a fixed-time 10 s schedule, whichever came first. A 2-min time-out period separated the warm up from the first variable-interval schedule component.

Drugs. Cis-flupentixol was injected intraperitoneally 4 h before the experimental session. The injection volume was 1 ml/kg; the vehicle was saline; and at least 5 days separated injections. Doses tested were: 0.005, 0.01, 0.02, and 0.03 mg/kg. Pilot tests indicated that this was the widest range of doses that would produce interpretable behavioral effects: higher doses reduced responding to negligible levels and lower doses did not produce discernible changes. There were also 14 injections of the vehicle (saline). These occurred randomly throughout the course of the experiment. Injections began after response rates and parameter values appeared stable. This took about 30 sessions.

Data analysis. Equation 1 was fitted to the individual subject response and reinforcment rates for each condition of

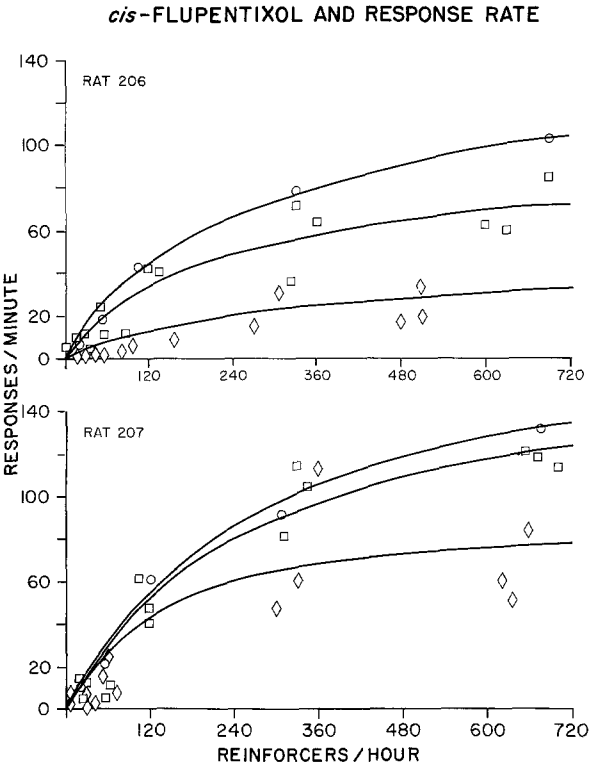

Fig. 1. The effects of *cis*-flupentixol on response rate in two representative subjects. The *circles* show the median response rates for the baseline sessions (day before drug injection, 14 sessions). the *open squares* and *diamonds* show the response rates in each component of each session that drug was administered (five components per session, three sessions at each dose). The curves were fit by the method of weighted least squares. o Baseline, □ 0.02 mg/kg, ◇ 0.03 mg/kg

the study. The comparisons were baseline (day before drug injection), vehicle injection, and drug injection. The sample sizes for the comparisons were 14 sessions for baseline and vehicle conditions and 3 sessions at each drug dose. For a given condition, response and reinforcement rates were not averaged but simply pooled. For example, parameter estimates were based on 15 data points in the drug conditions, because there were three sessions at each dose (each session supplied five response and reinforcement rates). Pooling has the advantage of increasing the number of data points and thus the reliability of the estimates. The parameters were obtained by a weighted least-squares technique (Wilkinson 1960), which is widely used in biochemical studies. The parameter estimates were then subjected to statistical analyses to determine the probability of the changes.

Results

Figure 1 shows the effect of *cis*-flupentixol on response rate at the 0.02 and 0.03 mg/kg doses for two representative subjects. Lower doses did not produce significant changes in behavior. The open squares and diamonds show the response rates for each component (5) of each session (3) that drug was given. There was a dose-dependent decrease in response rate. The magnitude of the decreases was independent of reinforcement rate, and at the 0.03 mg/kg dose, response rate decreases were approximately proportional

Table 1. Per cent change in response rates (median values)

Schedule	Dose			
	0.005 mg/kg	0.01 mg/kg	0.02 mg/kg	0.03 mg/kg
VI 150 s	+18	−35	−27	−70
	(−44, +36)[a]	(−59, +44)	(−79, +96)	(−93, −44)
VI 75 s	−8	−25	−46	−77
	(−31, +40)	(−61, +5)	(−70, +42)	(−89, −29)
VI 30 s	+9	−22	−43	−83
	(−7, +30)	(40, +29)	(−61, +6)	(−96, +26)
VI 10 s	0	−5	−19	−82
	(−45, +19)	(−13, +7)	(−69, +13)	(−94, −33)
VI 5 s	−10	−6	−32	−67
	(−38, −8)	(−22, +3)	(−43, −15)	(−89, −38)

[a] Between subject range

to the baseline response rates. For example, at the 0.03 mg/kg dose, the median decreases in response rate for Rat 207 were: −84%, −90%, −97%, −83%, and −90% (in order of increasing reinforcement rate), and for the group, the median decreases in response rate at the 0.03 mg/kg dose were −70%, −79%, −83%, −82%, and −67% (see Table 1 for results for other doses).

Table 2 summarizes the results for the response and reinforcement rates for the eight subjects. The rates were similar in baseline, vehicle, and the lowest drug dose (0.005 mg/kg). However, the range of response rates for a given rate of reinforcement was typically quite large, which is to say, there were large individual differences in quantitative aspects of the relationship between responding and reinforcement. For example, in the two richest schedules (VI 10 s and VI 5 s) Rat 204 pressed the lever at rates of more than 300/min, whereas Rat 208 did not respond more than 100/min.

Figures 2 and 3 show the effect of *cis*-flupentixol on the parameters of the matching law equation. The parameter k (Fig. 2) is the response rate asymptote and the parameter R_e (Fig. 3) is the rate of reinforcement that maintained a one-half asymptotic response rate. *Cis*-flupentixol typically decreased the response rate asymptote. At the 0.02 and 0.03 doses, each of the eight subjects showed a decrement, and at the 0.005 and 0.01 doses all but one subject showed lower values of k. In contrast, changes in the reinforcement parameter were inconsistent. At the 0.005 and 0.01 mg/kg doses most of the subjects showed some decrease in the reinforcement rate necessary for a half-asymptotic response rate, but at the two higher doses (0.02 and

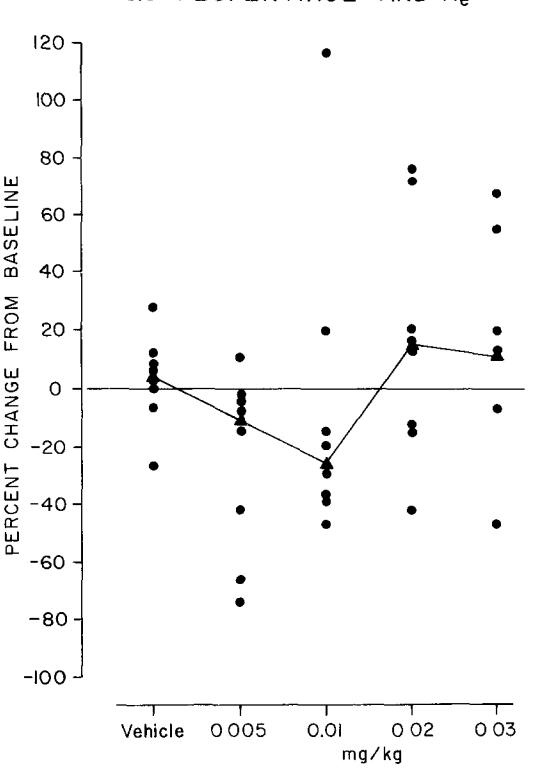

Fig. 2. The effect of *cis*-flupentixol on the response rate asymptote (k of the equation $B = kR/(R - R_e)$, see text for details). The *points* show the per cent change in k relative to the baseline condition. The data for each subject in each condition are displayed. The line connects the *medians*. See Table 3 for significance levels, according to analysis of variance. ▲ median

Table 2. The effect of *cis*-flupentixol on response and reinforcement rates

	VI 150 s		VI 75 s		VI 30 s		VI 10 s		VI 5 s	
	rf/h	res/m	rf/h	res/m	rf/h	res/m	rf/h	res/m	rf/h	res/m
Baseline	21	10[a]	49	23	109	73	343	109	679	131
	(20–25)	(4–14)[b]	(47–51)	(10–28)	(94–118)	(44–137)	(311–365)	(78–303)	(645–706)	(79–337)
Vehicle	20	8	50	16	108	69	340	119	646	121
	(12–24)	(5–18)	(34–49)	(8–25)	(106–110)	(39–127)	(321–360)	(65–261)	(653–717)	(83–335)
0.005 mg/kg	21	9	46	19	114	78	355	127	687	118
	(7–35)	(5–19)	(35–65)	(4–26)	(97–122)	(42–155)	(309–377)	(71–292)	(605–729)	(83–301)
0.01 mg/kg	17	5	46	14	114	61	340	107	698	128
	(7–28)	(4–13)	(28–50)	(5–24)	(97–131)	(27–178)	(334–370)	(68–115)	(64–727)	(68–316)
0.02 mg/kg	18	6	50	14	113	47	323	86	670	102
	(7–35)	(3–12)	(28–65)	(5–17)	(105–131)	(20–145)	(297–373)	(29–264)	(376–710)	59–288)
0.03 mg/kg	11	2	45	4	93	11	256	18	505	42
	(7–42)	(1–6)	(35–57)	(1–16)	(35–122)	(6–102)	(197–336)	(8–93)	(228–686)	(13–208)

[a] Median for eight subjects
[b] Range for eight subjects

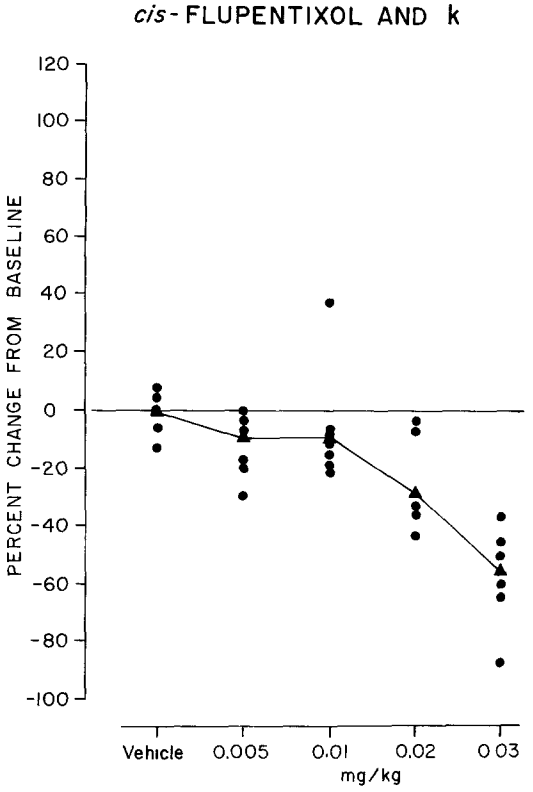

Fig. 3. The effect of *cis*-flupentixol on the rate of reinforcement that maintained a one-half asymptotic response rate (R_e of the equation $B=kR/(R+R_e)$, see text for details. The *points* show the per cent change relative to baseline. The data for each subject in each condition are displayed. The line connects the *medians*. See Table 3 for significance levels, according to analysis of variance. ▲ median

Table 3. ANOVA of effects of *cis*-flupentixol on parameters of matching law equation

Parameter of variation	Source	Mean square	*df*	*F*	Probability
k	*cis*-flupentixol	17080	4	10.91	<0.0001
	BL vs 0.005	2280	1	1.46	<0.2385
	BL vs 0.01	4418	1	0.28	<0.6002
	BL vs 0.02	11556	1	7.38	<0.0116
	BL vs 0.03	55399	1	35.37	<0.0001
	error	1566	26		
R_e	*cis*-flupentixol	6400	4	0.80	<0.5381
	error	8032	26		

0.03 mg/kg), increases and decreases in the reinforcement parameter were about evenly divided.

A repeated measures design 4 (drug dose) × 8 (subject) ANOVA was performed on k and R_e (Winer 1971, chapter 4). The approach can also be described as a 2-way mixed model ANOVA, with animal as random effect and one observation per cell. There was a significant relationship between drug dose and changes in k ($P<0.05$, see Table 3 for summary). Post-hoc comparison, pair-wise F tests, which used estimates of variance from the ANOVA (Winer 1971, pp 257–258) were used to determine the probability of the changes in k relative to baseline. At the 0.02 and 0.03 doses, the values of k were significantly lower than in baseline ($P<0.01$, see Table 3). In contrast there was no detectable relationship between R_e and drug dose ($P<0.80$, see Table 3).

Table 4. The effect of *cis*-flupentixol on the parameters of the matching law equation

	k resp/min	R_e rf/hr	% VAC[a] (pooled data)	% VAC (averaged data)
Baseline	166[b] (110–415)[c]	212 (100–282)	86 (79–90)	96 (93–99)
Vehicle	163 (109–513)	196 (113–305)	82 (81–87)	98 (95–99)
0.005 mg/kg	171 (78–467)	142 (50–262)	83 (54–94)	94 (81–96)
0.01 mg/kg	152 (109–476)	156 (92–552)	81 (58–94)	96 (71–99)
0.02 mg/kg	141 (78–376)	221 (116–347)	75 (56–91	96 (81–99)
0.03 mg/kg	92 (21–284)	223 (120–266)	74 (64–85)	91 (83–94)

[a] Per cent variance accounted for (r^2)
[b] Median of eight subjects
[c] Range of eight subjects

It is possible that the ANOVA did not reveal a significant relationship between *cis*-flupentixol and R_e because of individual differences. For example, Fig. 3 shows both large increases and decreases in R_e, suggesting that *cis*-flupentixol may have increased this parameter in some subjects but decreased it in others. However, there was no evidence of individual differences in the direction in which the matching law parameters changed. In six of eight subjects *cis*-flupentixol invariably decreased k (four doses), and in the other two subjects, there were decreases at three of four doses. Similarly, subjects did not differ in terms of R_e changes. Six of eight subjects showed both increases and decreases, and the other two showed either small decreases (−7 to −11%) or small increases (11–20%).

Table 4 provides a summary of the fit of the matching law equation to the data. Included are median parameter values and the median goodness of fit scores (amount of variance accounted for or r^2). The r^2 values listed in the third column were obtained by fitting Equation 1 to the pooled data and those in the fourth column were obtained by fitting the equation to the averaged data. For example, in the fits to the pooled vehicle sessions there were typically 68 degrees of freedom since there were 14 sessions in which just vehicle was administered [(14 × 5) − 2], whereas when this same data set was averaged (as a function of reinforcement rate schedule) there were 3 degrees of freedom. Differences between the two methods of analyzing the data could be due to systematic or non-systematic factors. To evaluate this, we applied an F-test to the residuals [(error average-fit)/(d.f.)/(error pool-fit)/(d.f.)]. In 44 of 48 tests (subject × condition), the differences in the residuals were not significant. Thus, the better fits for the averaged data simply reflect the consequences of removing random, session-to-session variation in response rates. Similarly, the k and R_e value for the two ways of organizing the data were indistinguishable.

Summary and discussion

The basic finding in this study was the *cis*-flupentixol systematically decreased the estimated response rate asymptotes without affecting the rate of reinforcement necessary for a one-half asymptotic response rate (R_e). This pattern of parameter changes was also produced by altering the response requirement (e.g., adding a weight to the lever: Bradshaw et al. 1983a; Hamilton et al. 1985; Heyman and Monaghan 1987). Thus, we concluded that *cis*-flupentixol altered the topography of responding – that is, slowed responding – without affecting the efficacy of the reinforcer maintaining responding. In two ways this results builds on the findings of Hamilton et al. (1985). First, the previous study used three subjects, and the present one used eight; second, in the previous study, brain stimulation was the reinforcer, and in the present study water was the reinforcer. Thus the way in which *cis*-flupentixol changed behavior was independent of whether or not the reinforcer was consumed.

That *cis*-flupentixol reduced k without affecting R_e appears to be similar to the results reported by Morly, Szabadi, and Bradshaw (1984). They studied the effects of pimozide on responding maintained by two variable-interval schedules, each presented by itself for a period of several weeks, with the richest reinforcement rate first. Although with just two data points (one for each reinforcement rate), it is not possible to estimate two parameters, Morley et al. concluded that pimozide affected k without altering R_e. In contrast, in every study in which the experimenters ran a series of reinforcement rates (five to ten) and estimated k and R_e analytically or graphically, pimozide increased R_e (Heyman 1983; Gallistel and Karras 1984; Hamilton et al. 1985; Heyman et al. 1986). As pointed out elsewhere, Morley et al.'s discrepant finding may have been due to their failure to control for order (Heyman et al. 1986).

Along with pimozide, chlorpromazine and sulpiride (also neuroleptics) produced dose-dependent increases in R_e. Consequently, we checked if *cis*-flupentixol's failure to alter R_e was an artifact of the data analysis. Instead of pooling sessions, we fitted Equation 1 to the data from each session and entered the resulting parameter estimates into an ANOVA (for example, there were 14 baseline estimates of k and R_e), and we also estimated the parameters from the averaged response rates. These two approaches led to the same conclusions as did the ANOVA based on pooled session results (Table 3). Of course, more fundamental problems may exist; however, the same experimental methods have shown systematic changes in R_e as a function of deprivation (Heyman and Monaghan 1987) and drugs (e.g. Heyman et al. 1986).

Neuroleptics differ in terms of their affinity for binding to different dopamine receptor sub-classes. Gallistel and Davis (1983) investigated whether dopamine receptor subclasses differed in their capacity to attenuate reinforcement efficacy. They found a positive correlation between reinforcement effects and binding to D2 dopamine receptor sites and a slight negative correlation between reinforcement effects and binding to D1 dopamine receptor sites. In line with these data, *cis*-flupentixol has a higher affinity for D1 dopamine receptors than do any of the neuroleptics that affected R_e (Titeler 1983). However, *cis*-flupentixol also has a high affinity for binding to D2 receptor sites (Murrin 1983). Thus, if there is any relationship between dopamine receptor classes and the parameters of the matching law, it is a complex one.

The matching law has been applied to the analysis of the behavioral effects of pento-barbitol (Ruddle et al. 1984), amphetamine (Bradshaw et al. 1981; Heyman 1983), and the neuroleptics mentioned above. *Cis*-flupentixol is the only drug that affected k without also altering R_e. It seems to us that this finding is worth pursuing, for if it holds up, it offers a means for more precisely assessing the pharmacology of the motor and reinforcement components of operant behavior.

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