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Use of a Fixed Consecutive Number Schedule of Reinforcement to Investigate the Effects of Pimozide on Behavior Controlled by Internal and External Stimuli

CAROLYN SZOSTAK AND TOM N. TOMBAUGH

Department of Psychology, Unit for Behavioral Medicine and Pharmacology
Carleton University, Ottawa, Ontario, Canada K1S 5B6

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SZOSTAK, C. AND T. N. TOMBAUGH. *Use of a fixed consecutive number schedule of reinforcement to investigate the effects of pimozide on behavior controlled by internal and external stimuli.* PHARMAC. BIOCHEM. BEHAV. 15(4) 609–617, 1981.—The effects of the neuroleptic pimozide, a specific dopamine receptor blocker, on behavior maintained under different degrees of stimulus control was examined by using a fixed consecutive number (FCN) schedule of reinforcement with pigeons. This schedule requires that at least eight consecutive responses be made on one key (work key) before a response on a second key (reinforcement key) will be reinforced. For half the birds no change in external stimuli accompanied the eighth response (FCN-8) while for the other half the color of the work key changed from white to red after the eighth peck (FCN-SD). Both schedules resulted in equal rates of baseline responding. Four doses of pimozide (vehicle, 0.1, 0.3, 0.5 mg/kg) were administered in a Latin Square sequence after baseline responding was stable. Similar pimozide-induced decreases in responding were observed in both conditions. However, pimozide selectively altered response patterns under the FCN-8 condition. The failure of the FCN-SD procedure to display a similar effect demonstrated that the use of salient exteroceptive stimuli can modulate behavioral deficits induced by pimozide. This conclusion has important implications for theories hypothesizing that dopamine subserves reward processes.

Pimozide Stimulus control Fixed consecutive number Dopamine

PHARMACOLOGICAL blockade of dopamine (DA) receptors by neuroleptic drugs (e.g., pimozide, spiroperidol, haloperidol) produces a variety of behavioral alterations including catalepsy, akinesia, suppression of learned behaviors and subtle changes in eating patterns [1, 5, 7, 22, 25]. Research designed to determine the precise role which DA plays in mediating these effects has primarily concentrated on the motoric consequences of neuroleptics and the degree to which they alter rewarding attributes of stimuli. Few experiments have examined the interaction between neuroleptics and stimulus control. However, the limited evidence that does exist suggests that stimulus control variables may play a central role in modulating neuroleptic-induced changes. For example, pimozide did not impair the ability of rats to learn the significance of aversive environmental cues [3] nor did it influence accuracy of responding in either successive or simultaneous discrimination tasks even though it produced large decrements in response rates [21,23]. Similarly, it has been found that pimozide did not alter the significance of a discriminative stimulus previously acquired in a drug-free state where electrical self-stimulation served as the reinforcing stimulus [8]. Together these data support the general hypothesis that behaviors controlled by internal stumuli are more sensitive to modification by drugs than behaviors controlled by external, environmental stimuli [6,20]. However, in two studies designed specificially to address this theory, Laties and his associates reported that the behavioral effects of three neuroleptics (chlorpromazine, promazine and haloperidol) were not influenced by the degree to which responding was controlled by external stimuli [12,14]. It is possible that the lack of compatibility between these two studies and those previously reviewed reflect (1) procedural differences or (2) specific effects associated with the various types of neuroleptics studied. For example, none of the neuroleptics employed by Laties are DA specific. CPZ and promazine have been shown to affect both noradrenergic and dopaminergic systems. Similarly, haloperidol also effects both systems. However, in comparison to CPZ it is much more selective in blocking dopaminergic receptors. Thus, Laties' results may reflect the involvement of non-dopaminergic systems. Consequently, the present study used pimozide, a neuroleptic which is reported to be a highly

specific DA receptor blocker [2,18], to further examine the relationship between stimulus control and dopamine.

Since it is well known that drug effects may be related to rates of responding [19], it is important to ensure that the introduction or presence of a discriminative stimulus does not change the rate of responding which occurs in the non-cued condition. This is particularly critical in the present study because of the extra-pyramidal effects associated with pimozide and related neuroleptics [1, 17, 18]. Consequently, a procedure was employed which ensured that comparable rates of responding would occur in the discriminative and nondiscriminative conditions. A fixed consecutive number (FCN) reinforcement schedule was selected which originally was designed by Mechner [16] and has since been extensively employed by Laties [12]. It requires the subject to emit a specified minimum number of consecutive responses to one response key (side key) before a response on a second key (center key) will be reinforced. If the subject switches to the center key prior to completing the required number of responses, reinforcement is withheld and the response requirement is reset to the beginning. This schedule results in a low degree of stimulus control since no external stimulus changes are directly associated with the task. It is possible, however, to increase the degree of stimulus control by presenting a salient cue, such as changing the color of the side key, whenever the response requirement on that key has been satisfied. Laties [12] reported that the addition of the discriminative stimulus did not change response rates suggesting that this paradigm may provide a useful tool for examining the relationship between pimozide and stimulus control.

METHOD

Subjects

Eight adult (2 years) White Carneaux pigeons (Palmetto Pigeon Plant, Sumter, SC) which had been previously trained to autopeck were used. All subjects were individually housed and reduced to 80% (±5%) of their free feeding weights. Water and grit were available in the home cage but not in the experimental chamber.

Apparatus

Four Lehigh Valley operant chambers were used. Each chamber was enclosed in a plywood box insulated with acoustical ceiling tile. Masking noise and ventilation were provided by two 100-CFM Dayton blowers. Three translucent (Perspex) response keys, 2.54 cm in diameter, were arranged horizontally. Only the center and left keys were used. Selected stimuli (red, green and a 0.15 cm wide black vertical line on a white background) could be rear-projected onto the keys by an In-Line Digital Unit. Directly below the center key was a 5.08 cm square aperature giving access to a mixed grain hopper. General illumination was provided by a houselight located above the center key. All experimental contingencies were programmed and recorded by a PDP-8I digital computer located in a separate room.

Training

Eight pigeons were trained on a continuous reinforcement schedule (CRF) to peck the center key which was transilluminated with a green light. Reinforcement consisted of 2.7 sec access to mixed grain (50% milo, 50% wheat) and presentation of the hopper was accompanied by the onset of the hopper light and the offset of the key light(s) and houselight. After this behavior was well-established a black vertical line superimposed on a white background was projected on the key located immediately to the left of the center key and a minimum of one response on this key (work key) was required before a response on the green center key (reinforcement key) would be reinforced. After three days the required number of consecutive responses on the work key was increased to two. All subjects were maintained on this "fixed consecutive number" (FCN) schedule for two days. The reinforcement contingency was then increased to five (four days), six (two days) and finally, to eight. Subjects were maintained on this schedule for five days at which time they were divided into two groups matched for percent of trials reinforced over the last two days of training. While the control group (FCN-8) continued to be maintained on the same FCN-8 schedule of reinforcement, the schedule was modified for the experimental group (FCN-SD) so that the eighth consecutive response on the work key changed the stimulus from white to red. The change in color served as a discriminative stimulus (SD) for responding to the reinforcement key where, as previously, a single response produced reinforcement.

For purposes of data analysis, a trial was defined as a response on the reinforcement key following at least one response on the work key. It is important to note that a response on the reinforcement key *before* completion of the required number of responses on the work key resulted in the non-reinforced termination of that trial. The next response on the work key marked the beginning of the next trial. Experimental sessions were conducted daily, seven days a week. Each session consisted of 125 trials or 45 min.

Testing

After a stable level of responding was obtained (percent trials reinforced) each bird received four intramuscular (pectoral) injections of pimozide (vehicle, 0.1, 0.3 and 0.5 mg/kg). Pimozide was dissolved in one to two drops of acetic acid and then a heated solution of 5.5% dextrose was added to make up a concentration of 0.25 mg/ml. The order of dose administrations was determined by a Latin Square design. Subjects were tested four hours following injection. Three days of stable performance were required prior to each injection. Each test session was separated by a minimum of eight drug free training sessions. For each test session the three days immediately preceding a test day served as baseline.

RESULTS

The effects of pimozide on two response rate measures, and percent of trials reinforced are summarized in Table 1 for individual FCN-SD and FNC-8 subjects. Overall rates of responding were computed by dividing the total number of responses emitted on the work key by the time (sec) required to complete the session, excluding hopper presentation time and time to complete the first trial. The second measure, response rate during runs, reflects the mean response rate which occurred between the first peck on the work key and a response on the reinforcement key. Baseline data demonstrate that FCN-SD and FCN-8 subjects responded at similar rates. Following the administration of pimozide decrements in response rates were observed for both FCN-8 and FCN-SD conditions. In most cases, 0.5 mg/kg produced greater suppression than either 0.1 or 0.3 mg/kg. However,

TABLE 1

OVERALL RESPONSE RATE, RESPONSE RATE DURING RUNS AND PERCENT TRIALS REINFORCED FOR INDIVIDUAL FCN-SD AND FCN-8 SUBJECTS AS A FUNCTION OF BASELINE, AND FOUR DOSES OF PIMOZIDE*

Measure	Cond/Subject		Baseline†	Dose: Vehicle	0.1	0.3	0.5
Overall Response Rate (r/sec)	FCN-SD	2	1.3	1.5	0.9	1.1	0.6
		4	1.5	1.0	1.1	1.4	1.3
		7	1.4	1.4	1.1	0.9	0.8
		8	1.9	2.1	1.6	1.2	1.4
	FCN-8	1	1.6	1.7	1.3	1.0	1.0
		3	1.4	1.4	1.4	1.1	0.8
		5	2.2	2.3	2.1	1.6	1.5
		6‡	1.6	1.5	1.1	1.3	0.2
Response Rate During Runs (r/sec)	FCN-SD	2	2.5	2.5	2.1	1.9	2.4
		4	2.6	2.7	2.2	2.0	2.1
		7	1.9	2.2	1.9	1.4	1.4
		8	2.5	2.4	2.2	1.5	2.0
	FCN-8	1	2.4	2.7	2.0	1.8	2.1
		3	2.3	2.5	2.1	1.9	1.4
		5	3.4	3.1	3.0	2.7	2.2
		6	2.3	2.2	1.7	2.0	1.6
Percent Trials Reinforced	FCN-SD	2	99	100	98	93	99
		4	98	98	98	98	100
		7	99	100	99	93	98
		8	99	100	100	97	100
	FCN-8	1	85	87	73	78	63
		3	80	64	60	30	50
		5	87	92	80	82	77
		6	91	93	63	87	43

*Test data were obtained from single administrations of each dose given to each individual subject.

†The mean level of performance was first calculated over each block of 3 sessions immediately preceding an injection. Baseline data represent the average of these 4 scores.

‡Test data for 0.5 mg/kg are based upon 58 trials for all dependent measures.

frequent inversions of scores were observed between consecutive doses.

Percent of trials reinforced (see Table 1) was calculated by dividing the number of trials having run lengths greater than seven (i.e., runs that produced reinforcement) by the total number of trials completed and multiplying this proportion by 100. The SD condition yielded a higher percentage of reinforced trials during baseline with performance relatively stable for all birds. The administration of pimozide differentially influenced the percent of trials reinforced for the two conditions. Performance of the FCN-8 subjects was affected such that increasing doses typically resulted in progressive decrements, while no systematic changes were observed in the performance of the FCN-SD subjects. In three of the four FCN-SD subjects a slight decrease in percent of reinforced trials was evident when injected with 0.3 mg/kg. However, when tested with 0.5 mg/kg, responding was not affected in any of the four birds. Decreases in percent of trials reinforced were evident in all four FCN-8 subjects, even when tested with the relatively small dose of 0.1 mg/kg. The seemingly low level of performance of Subject 3 reflects the failure of this bird to recover the original baseline following initial testing with 0.5 mg/kg. When responding under vehicle was compared to the mean performance on the three days immediately preceding the vehicle test session, no treatment effects were observed. It is important to note that although this subject never completely regained the original baseline level of responding, performance did stabilize at a new but lower level.

The degree to which stimulus control modulated the effects of pimozide is perhaps most clearly illustrated when one examines the frequency distributions of run lengths and conditional probability functions of responding to the reinforcement key. Figure 1 (FCN-SD) and Fig. 2 (FCN-8) show the distribution of run lengths for individual subjects. Data points were excluded if the run length occurred less than three times within a test session and/or less than two out of three baseline sessions. Run lengths less than three and

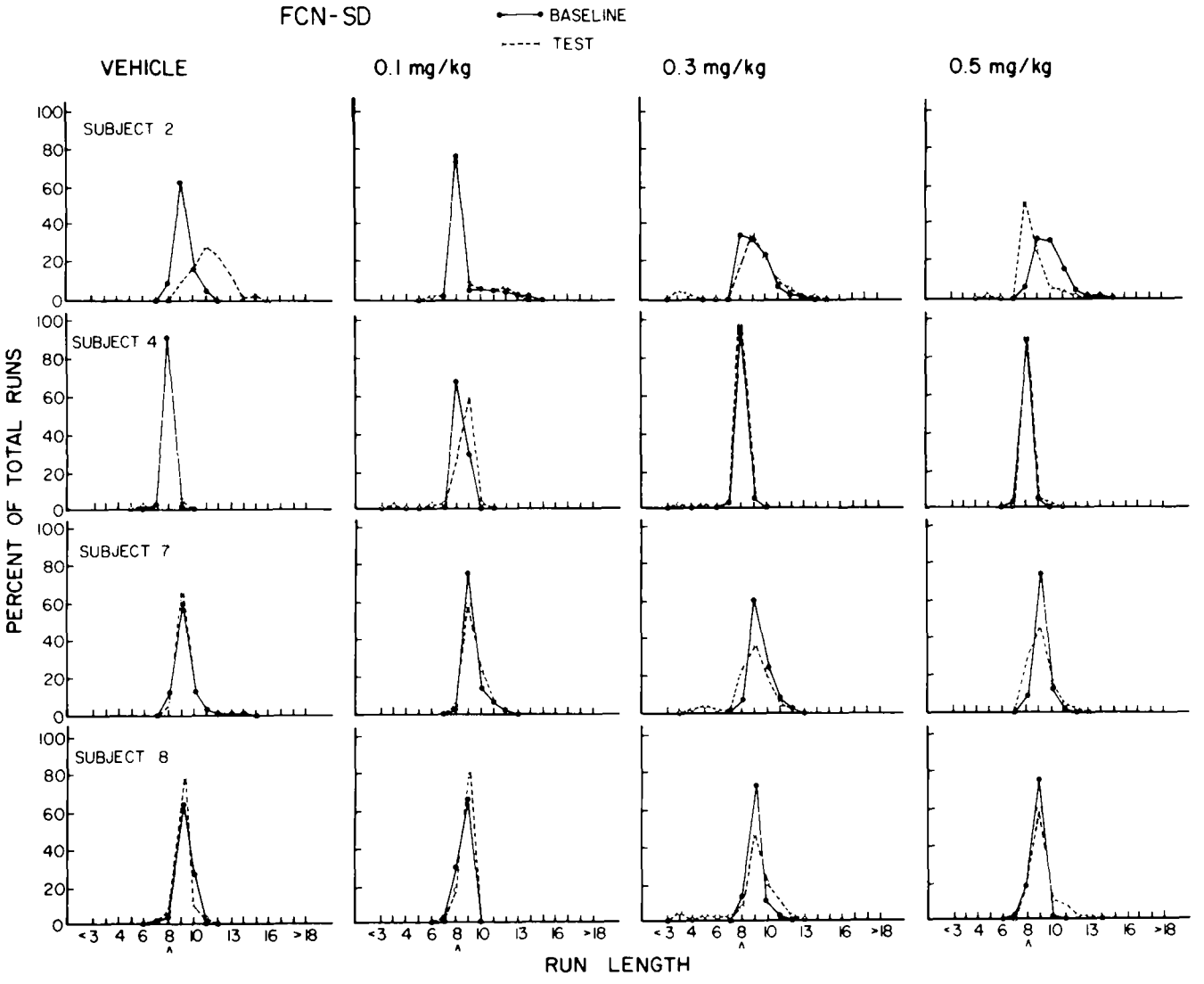

FIG. 1. Frequency distributions of run lengths as a function of dose of pimozide (vehicle, 0.1, 0.3 and 0.5 mg/kg) are presented for individual FCN-SD subjects. Baseline data represent the mean score of the three days immediately preceding a test day. Data points based on (1) less than two of three baseline sessions and/or (2) less than three trials within a session were excluded.

greater than eighteen were collapsed into two categories. Baseline gradients represent the mean of the three days immediately preceding the appropriate test session. A high degree of stimulus control is indicated in these figures by a steep gradient, with a peak occurring at a run length of eight. This shows that the majority of trials consisted of eight consecutive responses on the work key before a response to the reinforcement key was recorded. Decreasing degrees of stimulus control are depicted by a flattening of the gradients. Comparison of baseline gradients (solid lines) in Fig. 1 and 2 reveals that the two schedules of reinforcement exerted differential degrees of stimulus control. With the exception of Subject 2, FCN-SD subjects showed constant sharp baseline gradients, peaking consistently either at run lengths of eight (Subject 4) or nine (Subjects 7, 8). Baseline gradients for the FCN-8 subjects were much flatter possessing a greater number of run lengths less than eight and greater than ten. Pimozide-induced changes in distribution of run lengths were limited to the FCN-8 condition. While there was some tendency for pimozide to flatten the slope of FCN-SD gradients, these effects were predominantly due to an increase in the number of run lengths greater than nine, and hence did not decrease the number of reinforcements. Moreover, the increase in run lengths was not dose related. In contrast to the FCN-SD results, dose-dependent effects were observed with the FCN-8 condition. As the dose increased, the number of shorter run lengths (left of the peak) increased and the number of longer run lengths (right of the peak) decreased. When injected with 0.1 mg/kg all four subjects increased the number of occurrences of run lengths shorter than eight, this effect being more predominant with Subjects 3 and 6. There was also a slight tendency for the frequency of run lengths greater than eight to decrease. Again, this effect was more noticeable with Subects 3 and 6.

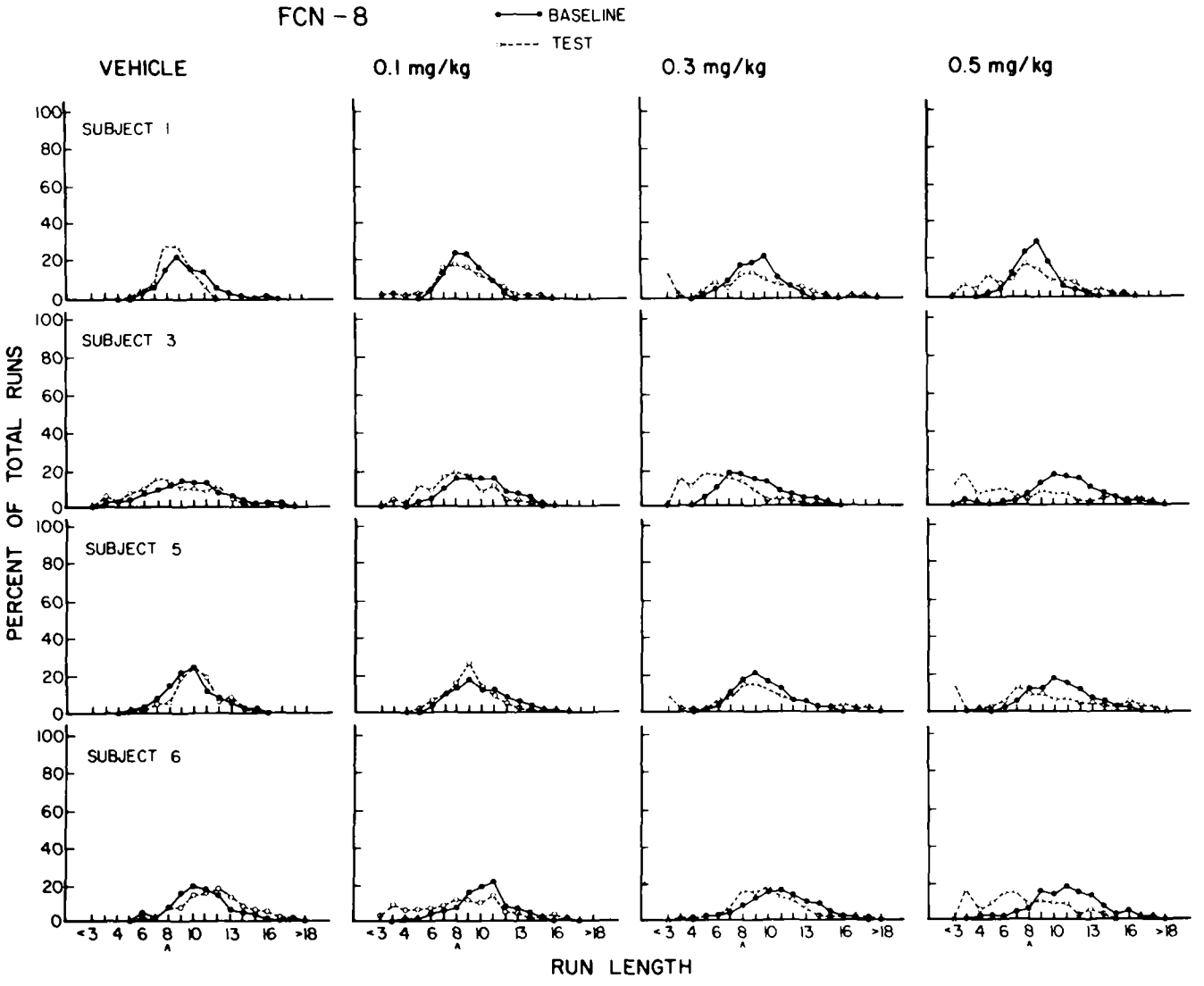

FIG. 2. Distribution gradients of run lengths as a function of pimozide (vehicle, 0.1, 0.3 and 0.5 mg/kg) are presented for individual FCN-8 subjects. Ordinate: percent of total trials. Abscissa: run lengths of (1) less than three; (2) three to eighteen, in steps of 1; and (3) greater than eighteen. Baseline gradients are based upon the mean of the three days immediately preceding an injection day. Data points based on (1) less than two of three baseline sessions and/or (2) less than three trials within a session were excluded. Test gradient for Subject 6 following administration of 0.5 mg/kg is based upon 58 trials.

With 0.3 mg/kg, the concurrent increase of shorter run lengths and decrease in longer runs became more evident, especially in Subject 3. Following administration of 0.5 mg/kg all four of the FCN-8 birds demonstrated a marked flattening of their distribution gradients, typically reflecting a pronounced increase in the number of short run lengths and a decrease in run lengths greater than eight.

The ability of the discriminative stimulus to attenuate pimozide-induced changes is further illustrated in the conditional probability functions shown in Fig. 3 (FCN-SD) and Fig. 4 (FCN-8). These curves reflect the probability that a subject will switch to the reinforcement key given that a particular run length has occurred. The conditional probability for specific run lengths (less than three, three-eighteen, greater than eighteen) was computed by dividing the frequency of a particular run length by the total number of trials completed minus the number of trials completed *before* the run length in question had been reached. Increases in the likelihood of switching to the reinforcement key are shown by increases in the conditonal probability. Again, data points based upon (a) less than three occurrences within a session, and/or (b) less than two out of three baseline sessions were excluded. Comparison of the baseline and treatment effects show that pimozide did not influence the probability of switching to the reinforcement key *before* the SD was presented (Fig. 3). While there were isolated instances of premature switching these were of a relatively small magnitude and not dose related. A fairly consistent decrease in the probability of switching following the presentation of the SD was observed on all test days in three out of the four sub-

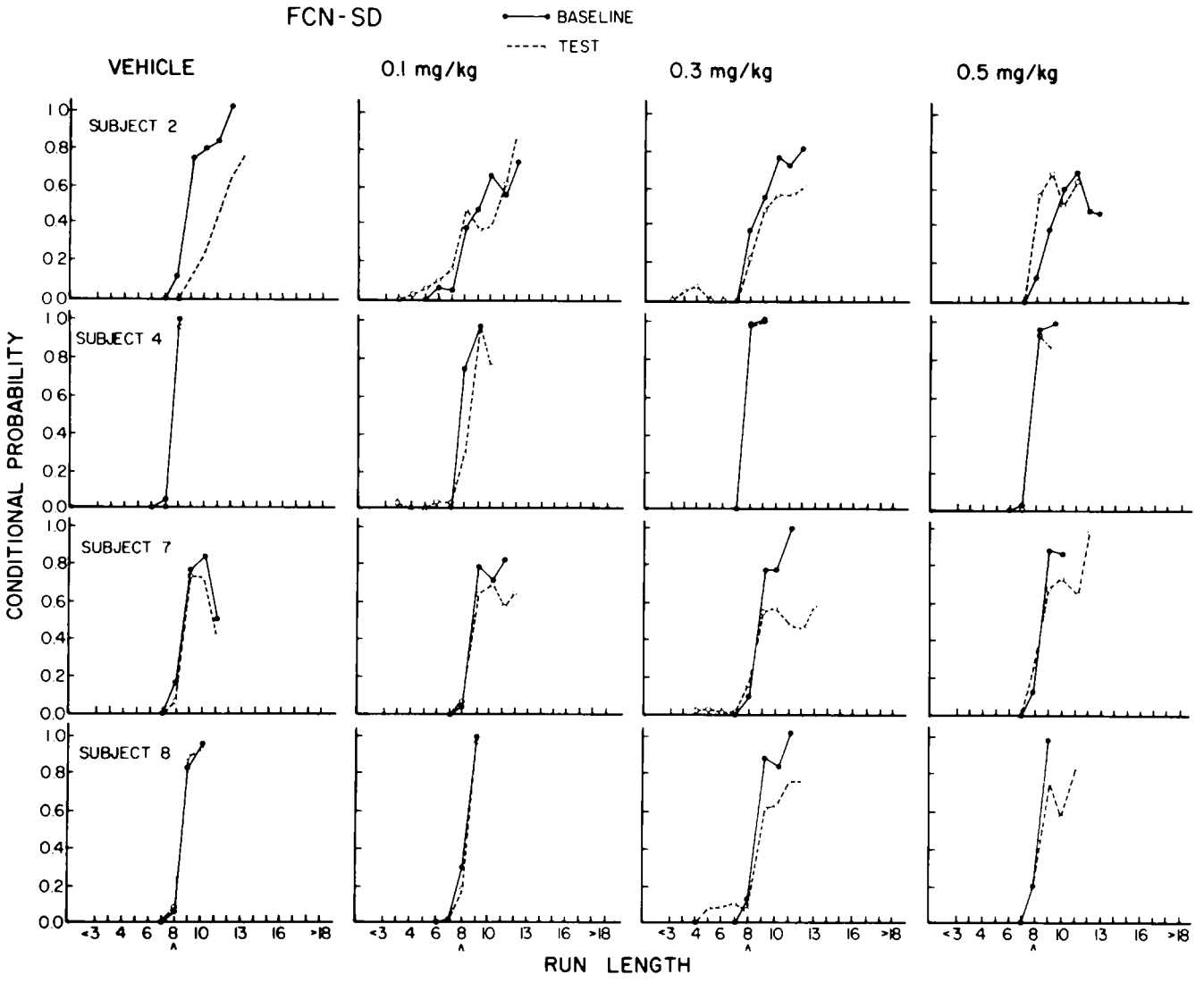

FIG. 3. Effects of pimozide (vehicle, 0.1, 0.3 and 0.5 mg/kg) on the conditional probability functions of individual FCN-SD subjects. The ordinate gives the probability that a bird will peck the reinforcement key after a consecutive number of responses have been emitted by the work key. Baseline gradients are based upon the mean of the three days preceding a test session. Data points based upon (1) less than two of three baseline sessions and/or (2) less than three trials within a session were excluded.

jects. This indicated that once the SD had been presented, FCN-SD subjects were as likely to respond nine, ten or eleven times on the work key before responding on the reinforcement key. It should be noted that such a change in response patterns does not influence the presentation of reinforcement. The effects of pimozide on the conditional probability for the FCN-8 subjects are as follows (see Fig. 4). A slight shift to the left of the gradient was observed in three of the four birds following the administration of 0.1 mg/kg. As the dose increased a pronounced increase in the probability of switching after short run lengths and a corresponding decrease following longer run lengths was apparent. When tested with 0.3 mg/kg this effect was most noticeable with Subject 1. Subjects 3 and 6 demonstrated an overall increase in probability of switching while Subject 5 had a slightly increased tendency to switch following shorter run lengths and a more marked decrease in the probability for longer runs. Finally, when injected with 0.5 mg/kg three out of the four subjects demonstrated increases in the likelihood of switching following fewer than eight or nine responses and concurrent decreases in the probability of switching for longer runs. These findings are similar to those previously observed with the distribution gradients of run length.

DISCUSSION

The finding that pimozide produced decrements in response rates under both schedules of reinforcement is consistent with results from previous research [17, 22, 25]. While these results suggest that blockade of DA receptors may produce some type of general motor impairment, the selective nature of this effect is illustrated by the finding that

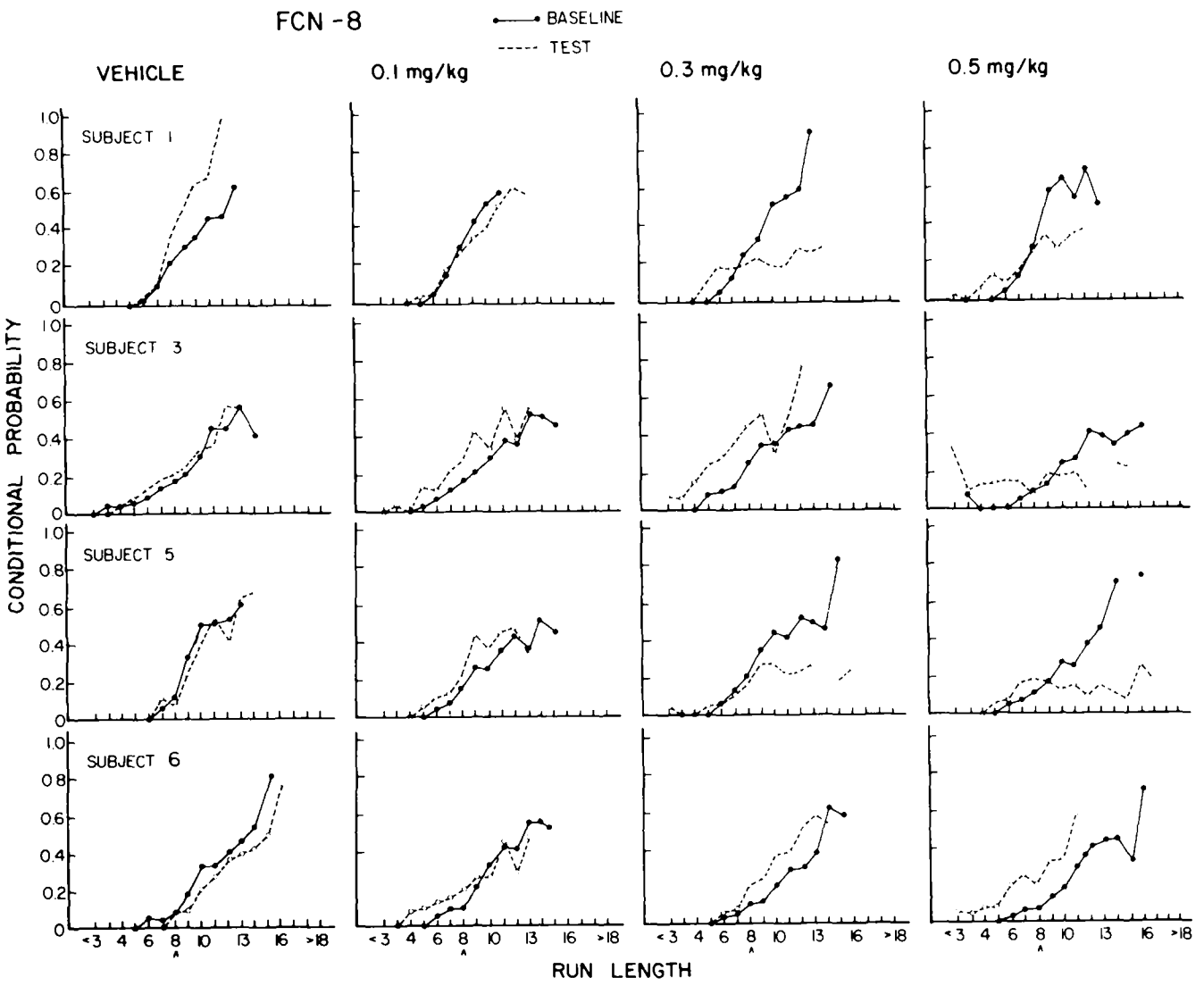

FIG. 4. Conditional probability functions for individual FCN-8 subjects as a function of dose of pimozide (vehicle, 0.1, 0.3 and 0.5 mg/kg). The ordinate indicates the probability that a bird will peck the reinforcement key after the number of consecutive responses have been emitted on the work key. Baseline data represent the mean of the three days prior to an injection. Points have not been plotted when they would have been based on (1) less than two out of three baseline days and/or (2) fewer than 3 runs within a session.

patterns of responding were only disrupted under the non-cued (FCN-8) condition. The differential effects which pimozide exerted on behavior maintained by the FCN-8 and FCN-SD schedules are congruent with the hypothesis that behaviors controlled by internal stimuli are more sensitive to pharmacological modification than behaviors maintained under strong external stimulus control [12, 14, 20]. In the current situation, birds in the FCN-8 condition may have been using some type of internal counter registering the number of responses or an internal clock whereby they continued responding until a specified period of time transpired. It is also possible that they were using some type of positional cues. In any case, pimozide disrupted the birds' ability to utilize these cues introducing a dramatic change in their performance. The addition of a discriminative cue provided a salient environmental event signalling when to peck the center key which reduced their dependence on internal cues and immunized them from the disruptive effects of pimozide.

The addition of discriminative cues apparently does not have a similar effect with all neuroleptics. Laties, using the same two schedules of reinforcement, reported that stimulus control did not substantially alter the effects which other neuroleptics (chlorpromazine, promazine, haloperidol) had on patterns on behavior measured by distributions of conditional probabilities and run lengths. Subjects treated with chlorpromazine or promazine, both members of the phenothiazine category of neuroleptics, showed similar alterations in patterns or responding with both FCN-8 and FCN-SD, with the latter schedule tending to reduce the magnitude of the effect. Haloperidol, a neuroleptic of the

butyrophenone family, was found to have little effect on either schedule other than producing decreased rates of responding and increased variability of response patterns. These results are contrasted to those obtained in the present study where pimozide, a diphenylbutylamine [2,18], was found to selectively influence performance on the FCN-8 schedule—even though similar decrements in overall rate of responding were observed under both conditions. While one might expect pimozide, chlorpromazine, promazine and haloperidol to produce similar effects because they are all classified as neuroleptics, the differential effects are, in fact, consistent with other research. For example, Bignami and Gatti [4] reported that chlorpromazine produced a marked increase in the proportion of responses emitted in the initial portion of a fixed interval schedule while haloperidol did not, even at doses that resulted in substantial decreases in overall rates of responding. It is thus possible that the differential behavioral effects of the four neuroleptics reflect differences in their pharmacological properties. Chlorpromazine and promazine are known to effect both dopaminergic and noradrenergic systems while haloperidol is reported to have fairly specific DA properties. Pimozide is also reported to have a high DA specificity, differing from haloperidol mainly in its lower degree of toxicity.

Several alternative explanations may be proposed to explain the effectiveness of the discriminative stimulus in attenuating pimozide-induced effects. First, Laties [13] postulated that external cues may exert their mediating effects by changing patterns of responding. This alternative may be discarded in the present experiment since FCN-8 and FCN-SD conditions yielded similar response rates. However, there is ample evidence showing that animals may use different response topology and body orientations to solve various behavioral problems [15, 24, 26], and it is possible that the two conditions promoted different types of response strategies. While systematic observation of animals' performance under drug and no-drug conditions was not undertaken, casual observation led us to believe that the response topology of the FCN-8 subjects changed as a function of pimozide. Second, the FCN-SD condition may have produced its effects by increasing the density of reward. That is, performance on the FCN-SD schedule resulted in a greater percentage of trials being reinforced which caused the SD to be associated with a higher frequency of reward. However, it is unlikely that the small differences in the percent of trials reinforced is responsible for the observed effects. The similar degree of reduction in the response rates that occurred for both conditions also argues against this possibility. Finally, the ability of the FCN-SD condition to overcome the effects of pimozide may be related to the fact that cues serving as discriminative stimuli can acquire reinforcing properties and thus, they may also function as conditioned reinforcers [9,11]. Because responding to the center key typically occurred in the presence of the SD, the presentation of the stimulus eventually served to reinforce responding on the work key. That is, the FCN-SD schedule is logically equivalent to a two component chained schedule consisting of a FR-8 component terminating with a change in the side-key hue and a FR-1 component on the center key. Since the signal terminating the first component was also associated with reward, it probably acquired secondary reinforcement properties which reinforced responding on the work key.

The ability of the SD to serve as a conditioned reinforcer is highly relevant for theories which assume that DA mediates reward processes. Originally arguing that pimozide blocks the reinforcing properties of various stimuli including food [25], it has since been postulated by Gray and Wise [10] that pimozide-induced performance deficits are, at least in part, due to a reduction in the effectiveness of the conditioned reinforcers present in the situation (e.g., general apparatus cues). Such a position would predict that higher doses of pimozide should progressively decrease the degree to which the secondary reinforcers are able to maintain responding on the work key. This prediction is not supported in the present experiment where performance of the FCN-SD group was not altered substantially by any of the doses of pimozide. Apparently, the cue had acquired such strong discriminative and secondary reinforcing values that even the largest dose used was not sufficient to interfere with the performance of the task. Although it may be argued that higher doses of pimozide could have disrupted performance, subsequent experimentation in our laboratory has indicated that this is not the case. Following injections of 1.0 mg/kg performance of the FCN-SD schedule remained relatively unaffected. Further testing with 2.0 mg/kg resulted in highly variable behavior. However, when responding occurred response profiles were consistent with baseline data. Because of the extensive variability observed across subjects these data are inconclusive without further systematic testing.

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