Pharmacology, Biochemistry and Behavior 100 (2012) 616–623

Contents lists available at SciVerse ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Tolerance to cocaine's effects on schedule-controlled behavior: Role of delay between pause-ending responses and reinforcement☆

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ARTICLE INFO

Article history:
Received 16 April 2011
Received in revised form 21 October 2011
Accepted 27 October 2011
Available online 4 November 2011

Keywords:
Tolerance
Schedule parameter
Delay to reinforcement
Cocaine
Key peck
Pigeons

ABSTRACT

The schedule of reinforcement under which behavior is maintained is an important contributor to whether tolerance to the behavioral effects of cocaine develops. Schedule parameter value (for example, fixed-ratio size) has been shown to affect the development of tolerance under some schedule types but not others, but the specific procedural variables causing this effect remain to be identified. To date, schedule-parameter-related tolerance has developed when a longer pause after reinforcement does not lead to a shorter delay between the response that ends the pause and reinforcement. The current study investigated the importance of this variable in pigeons using a multiple chained Fixed-Ratio 1, Fixed-Time x schedule, in which the first key peck in a trial produced a stimulus change and initiated a delay at the end of which food was presented regardless of whether or not additional pecks were made during the delay. Dose–response curves were assessed before, during and after chronic (daily) administration of cocaine. Tolerance to the pause-increasing effects of cocaine occurred to a similar degree regardless of the scheduled time between the end of the pause and reinforcement. Therefore, the relationship between pause length and delay to reinforcement does not provide an explanation for schedule-parameter-related tolerance.

1. Introduction

When a drug is administered repeatedly, later administrations of a given dose often have smaller effects on behavior than did earlier administrations, an effect referred to as tolerance (e.g., Branch, 1991; Rang et al., 2011). Tolerance is reported by most cocaine addicts (e.g., Carroll et al., 1994). That is, they report needing larger doses to achieve a given psychological effect than they did when they first began to use the drug. This may suggest that understanding the processes through which drug tolerance develops may clarify why some people who are exposed to a given drug develop a substance abuse or addiction problem, while others do not. This possibility is consistent with research demonstrating that repeated administrations of a drug alone are not always sufficient for the development of tolerance, but rather environmental variables also contribute to whether and how much tolerance develops. A full understanding of the development of tolerance requires an understanding of how these environmental variables function, and of how they interact with features of the drug-administration regimen to produce the presence or absence of tolerance to a particular behavioral effect of a drug.

These environmental contributors to drug tolerance can be investigated using animal models where environmental factors and drug administration can be controlled. In such animal models it is often tolerance to the behavioral effects of a drug that is studied (Stewart and Badiani, 1993). For example, acute administration of a sufficiently high dose of cocaine increases post-reinforcement pause (a period of time without responding that occurs immediately following the presentation of a reinforcer). Behavioral tolerance would be observed if following repeated administrations pause lengths under cocaine shortened and became more similar to those observed when cocaine had not been administered.

One environmental factor that has been shown to contribute to whether or not an animal exhibits tolerance to behavioral effects of cocaine is the type and parameter of reinforcement schedule under which behavior is maintained. These schedule effects can be studied within-subject using multiple schedules of reinforcement. In a multiple schedule, one of a set of simple schedules is presented during each segment of the session, and each is associated with a unique stimulus.

For example, Hoffman et al. (1987) trained pigeons to respond under a multiple fixed-ratio (FR) schedule of reinforcement. Ratio sizes were 5, 25 and 125. That is, one light color signaled that every fifth response was reinforced, another that every twenty-fifth was reinforced, and a third that every one-hundred and twenty-fifth was reinforced. After daily pre-session (chronic) dosing Hoffman et al. observed more tolerance to the response-rate-reducing effects

☆ The research reported here was supported by USPHS Grant DA004074 from the National Institute on Drug Abuse (NIDA), and cocaine hydrochloride was provided by NIDA. The authors thank Mary Rupp, Matt Weaver, Dave Maguire, Brian Kangas, and Julie Marusich for assistance in conducting sessions.

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doi:10.1016/j.pbb.2011.10.022

of cocaine in the two components with the smaller FRs than in the component where the large FR was in effect. That is, Hoffman et al. observed schedule-parameter-related tolerance. This effect has also been observed with squirrel monkeys (Hughes and Branch, 1991) and rats (Van Haaren and Anderson, 1994).

Subsequent research found schedule parameter affected tolerance under some schedule arrangements but not others, which led to a line of research attempting to identify the procedural characteristics consistently associated with schedule-parameter-related tolerance. Schama and Branch (1989) found tolerance regardless of parameter value under fixed-interval schedules. Reinforcement rate differs among components in this procedure as it does in a multiple FR schedule. Therefore, Schama and Branch's finding indicated that reinforcement rate differences between components do not explain the differences in levels of tolerance that Hoffman et al. (1987) observed (see also Branch, 1990).

Similarly, Yoon and Branch (2004, studying cocaine), and Hughes et al. (2005, studying morphine) demonstrated that differences in the number of responses required for each second of access to reinforcement between components are not required for parameter differences in tolerance to occur. This was done using multiple FR schedules; the amount of food presented upon the completion of each ratio was adjusted in such a way that the number of seconds of food per response was identical in each component. Schedule parameter affected tolerance in both studies even though this variable (often referred to as unit price) was held constant.

In summary, previous research has ruled out differences in reinforcement rate and unit price among components as explanations for schedule-parameter-dependent tolerance. Therefore, the current study investigated an additional procedural feature that has been consistently associated with the development of schedule-parameter-related tolerance in previous studies. This variable relates to the (post-reinforcement) pause in key-pecking that occurs at the beginning of each ratio requirement. Schedule-parameter-dependent tolerance has developed in schedules where the length of the pause has no systematic relationship to the delay from the pause-ending response to reinforcement. In fixed-interval schedules long post-reinforcement pauses lead to shorter delays between the first response and reinforcement. This is not the case however, with ratio schedules where delays to reinforcement from the end of the pause depend on the subject's run rate (response rate excluding pause time) and the ratio size, but not the pause length. Therefore, it may be that multiple FR schedules have produced parameter-related tolerance while multiple FI schedules have not because only in the latter case did longer pauses result in shorter delays to reinforcement.

Weaver and Branch (2008) found results consistent with this proposal using a response-initiated FI schedule. In this schedule, the first response after reinforcement started the fixed interval, and the first response that occurred after the interval had elapsed resulted in reinforcement. This schedule was similar to an FR schedule in that the delay from pause termination to reinforcement was independent of pause lengths (depending primarily on the component's interval length), but similar to interval schedules in that the response requirement (two responses) was identical across components. Therefore, the fact that schedule-parameter-related tolerance was observed under this arrangement indicated that an inverse relation between pause and delay to reinforcement may contribute to the development of tolerance regardless of parameter value.

In FR schedules, one consequence of this lack of a relationship between pause length and delay to reinforcement is that delays between the pause-ending response and food remain long in the largest-parameter component, even when pauses are lengthened by drug administration; Weaver and Branch (2008) speculated that this might be an important contributor to schedule-parameter-related tolerance. Conversely, under multiple fixed-interval schedules, short delays to food are possible in the large-interval component if pause lengths are increased (a known effect of cocaine). These short experienced delays in the large component might contribute to the re-establishment of responding in that component under drug, and therefore to the development of tolerance. It may also be important that when delays from pause termination to food depend primarily on schedule parameter value, a consequence is that differences between components are preserved even when drug administration has markedly disrupted baseline response patterns. This preservation of the distinctness of a subject's experience during different components after drug administration may in turn increase the likelihood that different performance will develop in different components following chronic drug administration. Under a multiple fixed-interval schedule, by contrast, if pauses were long enough reinforcement would be relatively immediate in all components and the subject's experience therefore relatively similar regardless of programmed schedule parameter value.

The current study focused on the role of delay differences between components by using a multiple schedule of delayed reinforcement. The onset of the delay was associated with a stimulus change, and therefore, this schedule can also be described as a chained FR1–FTx schedule (where the value of x varied across the components of the multiple schedule). On each repetition of a schedule, the first (and only required) response produced a stimulus change (a flashing house-light), and started a delay timer. Food was delivered after that delay had elapsed regardless of whether the pigeon had responded during the delay. If schedule-parameter-related tolerance arises under arrangements in which the subjects' pause length does not affect the time from the first response to reinforcement in a given component then this effect should arise under the current schedules of reinforcement.

2. Method

2.1. Subjects

Six experimentally naive White Carneau pigeons served. Pigeons were maintained at 85% of their pre-experiment-determined free-feeding weight, were kept in a colony room with a 16:8-hour light: dark cycle, and had free access to water with vitamins and to health grit. Protocols describing the care and use of these pigeons were approved by the university animal care and use committee.

2.2. Apparatus

The pigeon chamber used had internal dimensions of $35 \times 31 \times 35$ cm, and a row of three 2.5 diameter circular keys set into the right wall 8 cm from the ceiling. Only the center key was used in this experiment, and was lit red, green, or white to signal the active component. There was a 6×3.5 cm opening located 9 cm below this center key through which mixed grain could be presented using a solenoid-operated feeder. Food presentations were accompanied by the illumination of a light set into the top of this opening. The house-light was located directly above the center key. The house-light was illuminated (either continuously or flashing, see below) except when a reinforcer was being presented and during the inter-component intervals (when the chamber was dark). White noise at 95 dB was used to mask extraneous sounds in the room containing the operant-conditioning chamber. The experimental apparatus was controlled and data were recorded using EC-BASIC software (Walter and Palya, 1984).

2.3. Procedure

Training began with reinforcement of successive approximations to key pecking, until all pigeons pecked the center key reliably when it was lit white. Reinforcement was then presented following every key-peck for one, 45-reinforcer session. The three key colors

(red, green, and white) used in the final procedure were then introduced under this FR1 schedule, which continued for three sessions, each consisting of 15 consecutive exposures to each key color.

When key-pecking was established in the presence of each of the three key colors, the multiple schedule was introduced with FR1 schedules operative in all three components. Each key color was presented for four food presentations (a component), and each component was followed by a 30-s inter-component-interval, during which the chamber was dark. The three components were presented in a random-without-replacement sequence three times. Therefore, in summary, a session consisted of three presentations of each of three four-reinforcement components, for a total of 36 reinforcers per session.

When reliable responding was established under this arrangement, delays from the first peck to food were introduced. The shortest delay was signaled by the white key color, the medium delay by the red key color, and the longest delay by the green key color. When the delays were introduced the shortest was 3 s, the medium 5 s, and the longest 10 s. Delays were then increased, according to the following sequence: 5, 10, 15; 5, 10, 20; 5, 15, 30; and 5, 20, 40 (where all delay lengths are in seconds).

Increases in delay length were implemented for a given pigeon when that pigeon was responding consistently in all three components, and the median pause for each component was stable from day to day. Stability was defined as five sessions in which neither the longest nor the shortest pause in the condition was present, and there were neither upward nor downward trends. For one pigeon, 553, it was necessary to reduce the delays at one point in this training sequence (from 5, 15, 30 s, to 5, 10, 20 s) in order to maintain reliable responding. After pigeon 553s responding had stabilized under these shorter delays, the delays were raised again using the procedure described above.

With the delays held at 5, 20, and 40 s a flashing house-light (500 ms off, 500 ms on) was added after the first peck in each interval. This was done because pecking occurred at relatively high rates and differed among components, and adding this additional stimulus was expected to reduce pecking during the delay, which would in turn have the effect of isolating delay to reinforcement as the primary difference between the components to the extent possible. A reversal design was used to confirm that the presence of the flashing house-light reliably reduced run rates. That is, the flashing house-light was initially absent, and then introduced, and then removed and, finally, introduced again. This confirmed that its presence reliably decreased responding during the delay. Importantly, this reversal also demonstrated that the presence of this delay signal did not have a consistent effect on pause duration, the key dependent variable in this study. Following the introduction of this signal, the delays were raised once again to final values of 5, 20, and 80 s.

Sessions occurred at approximately the same time of day, seven days a week. Each session began with a five-minute blackout. In this final procedure, components ended if either four reinforcements had been presented, or a time limit was reached. Time limits were 1 min for the chained FR1, FT 5 component, 3 min for the chained FR1, FT 20 component, and 12 min for the chained FR1, FT 80 component. After the time-limit had elapsed (or four reinforcers had been presented), the component ended, the inter-component interval occurred, and the next component began. These time-limits were included in anticipation of lengthened pauses caused by cocaine. Adding them meant that even when pauses were long pigeons would experience all three key light colors and that the session would be completed within the duration of action of the drug. It also meant that the maximum possible session length was 57 min (including one five-minute blackout and eight inter-component intervals) if the pigeon did not respond at all; however, sessions with typical pause lengths were generally between 35 and 40 min long.

2.4. Pharmacological procedures

All doses of cocaine hydrochloride were delivered in a 0.9% saline vehicle, in mg/kg (in terms of the salt), and dose volumes were 1 ml/kg of the pigeon's 85% weight. Doses were injected into the pectoral muscle immediately before the relevant session.

2.5. Pre-chronic determination of dose–response functions for pause length

Doses were administered every fifth day. On the intervening four days sessions occurred without drug administrations. All pigeons received two administrations of saline, and two administrations of each of 1.0, 3.0, 5.6, 7.4, and 10.0 mg/kg of cocaine. For three pigeons (553, 842, and 873) these six doses were administered in ascending order twice; for the remaining three pigeons (847, 936, and 776) they were delivered in descending order. No effects of order of administration were observed on pause, pecking rate, or the development of tolerance during any phase of the study. Additional administrations of these doses, and/or administrations of 4.2, 13.0 and 17.0 mg/kg, were given when they were needed to characterize fully the dose–response curve for each pigeon.

2.6. Chronic dosing procedure

After the pre-chronic assessment of the dose–response functions, each pigeon received a fixed dose each day for at least thirty days, and until the median pause in each component was stable across five consecutive sessions. Stability was defined as described above. It took 44 sessions to reach stability for 553, 35 for 847, 42 for 842, 42 for 873, 45 for 936, and 40 sessions for 776.

Pigeons did not receive the same absolute dose during the chronic phase; rather, they received individualized doses that had approximately similar behavioral effects during the pre-chronic determination of the dose–response functions. Specifically, the chronic dose selected for each pigeon was the smallest one that had reduced, but had not completely eliminated, responding during the pre-chronic determination of that pigeon's dose–response function. Pigeons 553, 873, 936, and 842 received 7.4 mg/kg daily during this phase, while 776 received 4.2 mg/kg, and 847 received 10.0 mg/kg.

2.7. During-chronic determination of dose–response functions for pause length

After the pause lengths in all three components were stable, dose–response functions for pause length were assessed a second time. Stability was defined as described above. This occurred using the same procedure as for the pre-chronic determination, except that the chronic dose was administered on days between probe doses.

2.8. Post-chronic determination of dose–response functions for pause length

After each pigeon's dose–response function had been fully characterized while a chronic dose was given on intervening days, no drug administration occurred for forty days. During this time all pigeons completed daily sessions as usual. After forty days, dose–response functions were characterized for a third time using the procedure that was employed during the two previous determinations.

2.9. Data analysis

The main dependent variable was session median pause, defined as the length of time between the beginning of a component or the end of a grain presentation and the pigeon's next key peck. If a component ended because the time-limit had elapsed, the time from

Table 1
Mean session median pause, in seconds, by component (columns) and pigeon (rows), during the last five sessions of baseline. Standard deviations are in parentheses.

Pigeon	FR1, FT 5	FR1, FT 20	FR1, FT 80
553	1.1 (0.0)	4.0 (0.8)	29.1 (17.1)
776	2.1 (0.3)	4.7 (1.4)	10.5 (2.2)
842	0.9 (0.1)	4.9 (1.0)	99.9 (88.2)
847	1.3 (0.1)	3.1 (1.7)	11.7 (1.0)
873	1.1 (0.1)	3.1 (0.9)	21.1 (4.3)
936	1.2 (0.2)	3.5 (0.5)	21.5 (4.9)
Mean	1.28 (0.13)	3.88 (1.05)	32.6 (19.62)

either the beginning of the component or the end of the last food presentation until the component ended was taken as a measure of the pause. Given that it was known only that the pause was at least this long, this had the effect of underestimating pause length. The relationship between pause length and dose of cocaine administered was assessed by constructing dose–response curves for each pigeon for each component and phase.

Additionally, the area under each of these dose response curves was calculated for each pigeon in each component using the software package GraphPad Prism™. The area under the curve (AUC) is the area of the space bounded by the section of the *x*-axis on which those doses are plotted, two vertical lines from the highest and lowest dose that intersect with the curve, and lines joining the data-points themselves. A decrease in AUC values from the acute to the during-chronic determinations of the pause dose–response functions would indicate tolerance to the pause-increasing effects of cocaine. Different ranges of doses were given during different phases of the study (acute, during-chronic, and post-chronic) and the number of doses given affects the range of AUC values that can occur. Therefore, to take account of these variations in dose ranges, these areas under the curve were normalized by dividing them by the total available area. The total available area is the AUC if maximum-possible pause lengths were observed for every dose administered. Therefore, this also normalized for differences in pause lengths across components. Presenting AUC in this manner therefore allowed for the cross-phase comparisons of drug effects to be made easily.

3. Results

The effects of cocaine on median pause lengths did not differ across blocks of the session, therefore, session medians were used to characterize behavior and drug effects.

3.1. Baseline performance

Baseline pause lengths (presented in Table 1) were affected by delay length for all pigeons, with longer pauses in components with longer delays. Run rate was also affected by delay length with faster rates in components with shorter delays (Table 2). For clarity, the right hand side of Table 2 presents the same data as mean absolute number of pecks per reinforcer. The smallest achievable response requirement was one, but pigeons often produced more pecks than were required.

3.2. Pause lengths during chronic administration

Fig. 1 presents mean median pause length as a proportion of control pause length for blocks of ten sessions for 40 sessions (35 sessions for pigeon 847) in the chronic administration period. The control period was the five sessions immediately before chronic dosing began (during which no drug was administered). In order to provide an indication of whether or not responding during chronic dosing was outside the range of this control period, the error bars on three points on the left hand side of each pigeon's figure present the range of the session median pause lengths observed during this control period.

There was no consistent overall pattern observed in pigeons' pause lengths during the chronic-dosing period; rather a range of patterns was observed across pigeons and across components. In general, however, in cases where there was an initial increase in pause (see 873, 776, 842 in the FT5 component, 936 in the FT80 component), pause lengths shortened across the initial chronic-dosing period, and were at or near baseline lengths by the fourth block of ten sessions of chronic administration indicating that tolerance to these effects had developed. In cases where the initial effect of the chronic dose of cocaine was to shorten the pause (553 and 842 in the larger two components, most notably), tolerance to these pause shortening effects did not develop during the initial chronic-dosing period.

3.3. Tolerance and schedule parameter

Acute administrations of larger doses of cocaine increased pause duration (Fig. 2, filled symbols). After chronic administration of a single dose of cocaine, higher doses were required to produce a given pause-increasing effect. For some pigeons the extent of this tolerance was such that the longest pauses observed during the acute determination were not produced by any of the doses administered after chronic administration had occurred (for example, see 553). This tolerance developed to approximately the same extent for a given pigeon regardless of schedule parameter; that is, schedule-parameter-related tolerance did not develop under the current procedure. When injections of saline were given during the chronic phase, performance closely approximated baseline performance (control), indicating that a baseline shift had not occurred during the chronic-dosing period.

Following the chronic dosing period no drugs were given for forty days and dose–response functions then re-determined. Fig. 3 presents these post-chronic dose–response functions for pause length with the during-chronic dose–response functions presented in Fig. 2 provided for reference. The dose required to increase a pigeon's pause by a

Table 2
Left hand section: run rate during the delay in responses per second, by component, mean of last five sessions of baseline, with standard deviations in parentheses. Right hand section: absolute number of pecks per reinforcer, by parameter value, mean of last five sessions of baseline, with standard deviation in parentheses (includes the peck that begins the delay and all subsequent pecks until reinforcement).

	Mean-run rate during delay			Mean pecks per delay period		
Pigeon	FR1, FT 5	FR1, FT 20	FR1, FT 80	FR1, FT 5	FR1, FT 20	FR1, FT 80
553	1.00 (0.17)	0.01 (0.01)	0.00 (0.00)	6.36 (0.85)	1.39 (0.22)	1.28 (0.26)
776	0.36 (0.12)	0.04 (0.02)	0.00 (0.00)	2.80 (0.59)	1.83 (0.44)	1.08 (0.06)
842	3.78 (0.13)	0.18 (0.11)	0.01 (0.01)	20.10 (0.64)	4.68 (2.11)	1.50 (0.48)
847	1.82 (0.13)	0.21 (0.09)	0.00 (0.00)	10.18 (0.67)	5.12 (1.74)	1.08 (0.14)
873	0.63 (0.06)	0.20 (0.02)	0.02 (0.01)	4.20 (0.32)	5.00 (0.41)	2.40 (0.57)
936	0.37 (0.07)	0.14 (0.04)	0.01 (0.03)	2.87 (0.33)	3.87 (0.75)	2.19 (2.36)
Mean	1.33 (0.11)	0.13 (0.48)	0.02 (0.01)	7.75 (0.57)	3.65 (0.95)	1.59 (0.65)

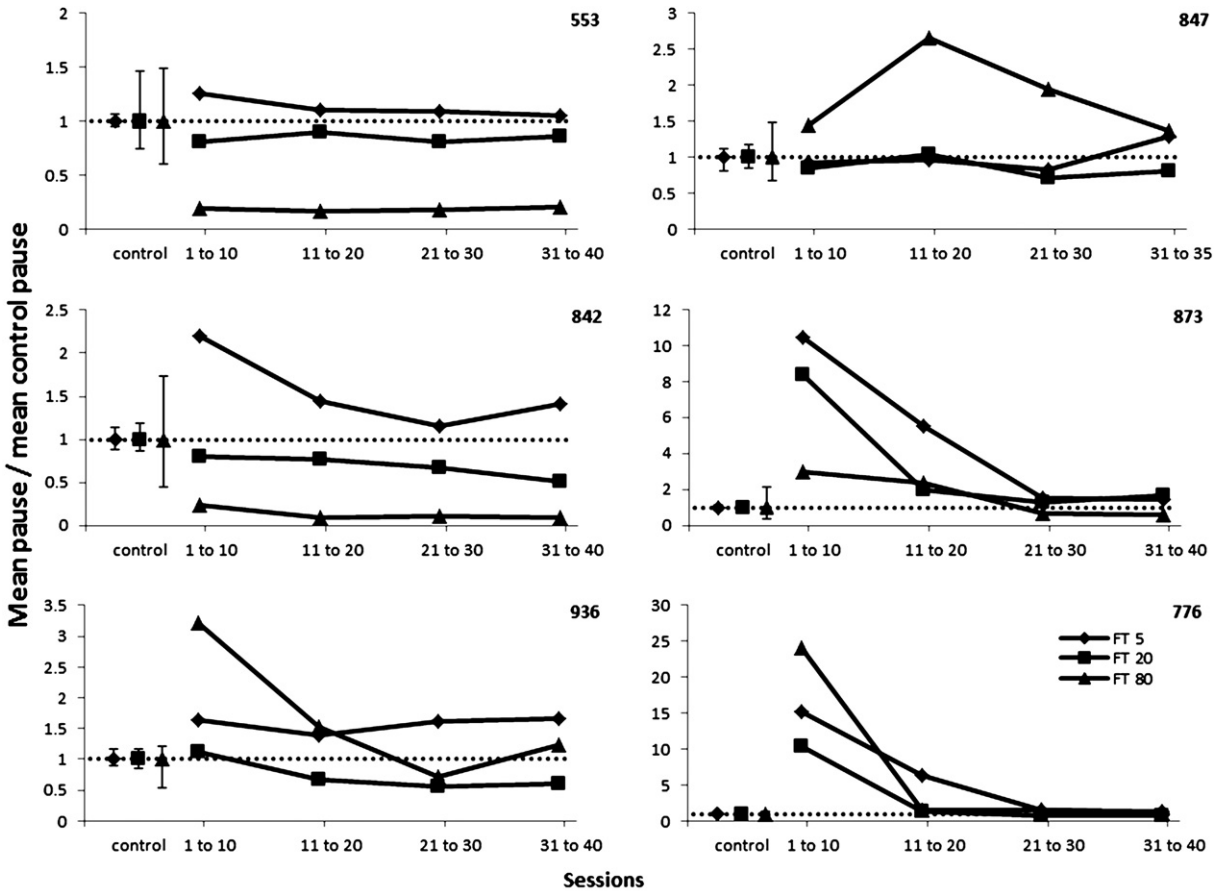

Fig. 1. Mean pause length, in blocks of ten sessions, during the chronic administration period. Note that for 847 only five sessions contributed to the mean for the final block, and that the *y*-axis range varies across pigeons. The dashed horizontal line and the three points on the left of each graph represent that pigeon's control performance. The control period was the five sessions immediately before chronic dosing began during which no doses were administered. The error bars on the three control points on each graph present the range of session-median pause lengths observed in each component during this control period.

given amount was lower after chronic administration had ceased than during chronic administration; this reduction in tolerance from the during-chronic to post-chronic phases indicated that tolerance had not occurred simply due to the passage of time, but rather due to the pigeons having experienced recent, repeated drug administrations.

Within a given component and phase, the greater the extent to which cocaine increased pause, the larger the area under the dose–response curve for pause. Therefore, a reduction in AUC from the acute to the during-chronic dose–response-functions indicated tolerance. This was the effect observed for all pigeons in all three components (See Fig. 4). In addition, the level to which chronic cocaine reduced the AUC was typically similar across components, i.e. independent of fixed-time parameter. The rightmost bar of each grouping shows that for every subject, areas under curve increased from the during-chronic to post-chronic phases in every component of the multiple schedule, indicating a change in pause lengths toward those that were observed during the acute determination of the dose response function for pause, and therefore a reduction in tolerance.

4. Discussion

There was no evidence of schedule-parameter-related tolerance to the effects of cocaine under the chained FR1, FT x schedule arranged here. Rather, in general, tolerance occurred to the pause-lengthening effects of cocaine regardless of schedule parameter value. This indicated that pause length being unrelated to the delay from the pause-ending response to reinforcement is not sufficient to create schedule-parameter-related tolerance. This is in spite of the fact that pause length has been unrelated to delay to reinforcement in previous procedures that have produced schedule-parameter-dependent tolerance. Weaver and Branch (2008) suggested that this variable might be important because more tolerance may develop in components where short delays from the first response in a trial to food are possible. The current study did not support this suggestion, however, because reinforcement was never presented after a short delay from the pause-ending response in the chained FR1, FT80 component, yet tolerance developed in that component for all pigeons. The procedural feature or features that have produced such parameter relatedness in some previous studies but not others remain to be experimentally identified.

The response-initiated fixed-interval arrangement used by Weaver and Branch (2008), which did produce parameter-dependent tolerance, is the procedure that has been previously studied that is most similar to the current one. The most salient performance difference between that study and the current one was that run rates were lower under the current chained FR1, FT schedule. In the current study, a stimulus change was added to decrease responding during the delay, and for some pigeons in some components responding was eliminated entirely by the introduction of this signal. This is contrast to Weaver and Branch's subjects' run rates, which were approximately two responses per second in the components with the two smaller response-initiated fixed intervals, and approximately one response per minute in the large interval component. Run rates of the pigeons in the current study were also substantially lower than those typical of both previous studies that have found parameter

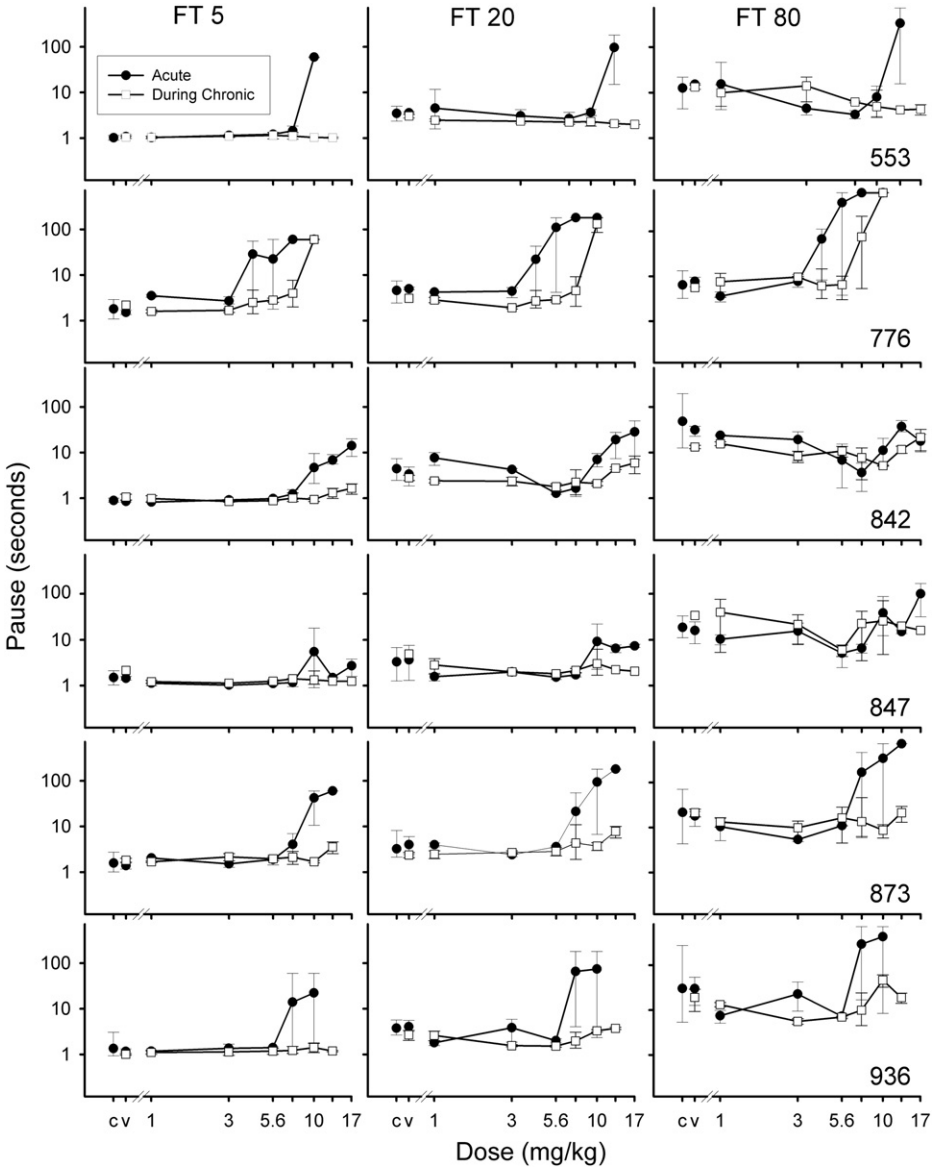

Fig. 2. Dose–response functions for session median pause, by component (columns) and pigeon (rows). Pauses during acute administrations are indicated with filled circles, and during chronic administration with open squares. Points are means of all administrations, and bars are ranges. Note the two log axes. On the left hand end of the *x*-axis, c indicates control sessions, which were those immediately before days on which a probe dose was administered during the acute determination; v indicates vehicle (saline) administration. During chronic administration, points for the chronic dose were collected by taking days immediately before probe doses were given; there are therefore more determinations for the chronic dose included in the mean than for other doses.

dependent tolerance (e.g., Hoffman et al., 1987), and those that have not (e.g., Schama and Branch, 1989). For example, the current run rates during the large component in the current study were well under ten percent of the rates observed by Schama and by Branch and Hoffman Branch and Sizemore. There is a possibility, therefore, that it is a combination of run rates above some threshold, and a link between pause termination and delay to reinforcement that creates the necessary conditions for schedule-parameter-related tolerance to emerge. A replication of the current study with the stimulus change removed so that response rates are not suppressed would be informative with regard to this possibility; an alternative approach would be to use a response-initiated fixed-interval schedule with such a signal added.

Although overall run rates above some threshold may be a precondition for parameter values to affect tolerance, it does not appear that run rate differences between components directly create differences in tolerance levels. Rather, this study is consistent with previous research suggesting that between-component differences in response rates likely do not contribute to relative levels of tolerance observed across components. The stimulus change presented after the first response in the current study resulted in low run rates generally. The baseline run rates differed across pigeons, and differed across components to different extents for different pigeons. None of these differences in patterns of run rates, however, produced parameter-related tolerance. This is consistent with previous research, where there has not been a link between run rate patterns and parameter effects. Rather, components have differed in response rate in studies that have observed schedule-parameter-related tolerance, and those that have not. Hughes et al. (2005), and Weaver and Branch (2008) found schedule-parameter-related tolerance in pigeons that responded the fastest in the component with the medium parameter value indicating that, while run rates are typically fastest in the short component when parameter-related tolerance is observed, this is not necessary for parameter-related tolerance to be

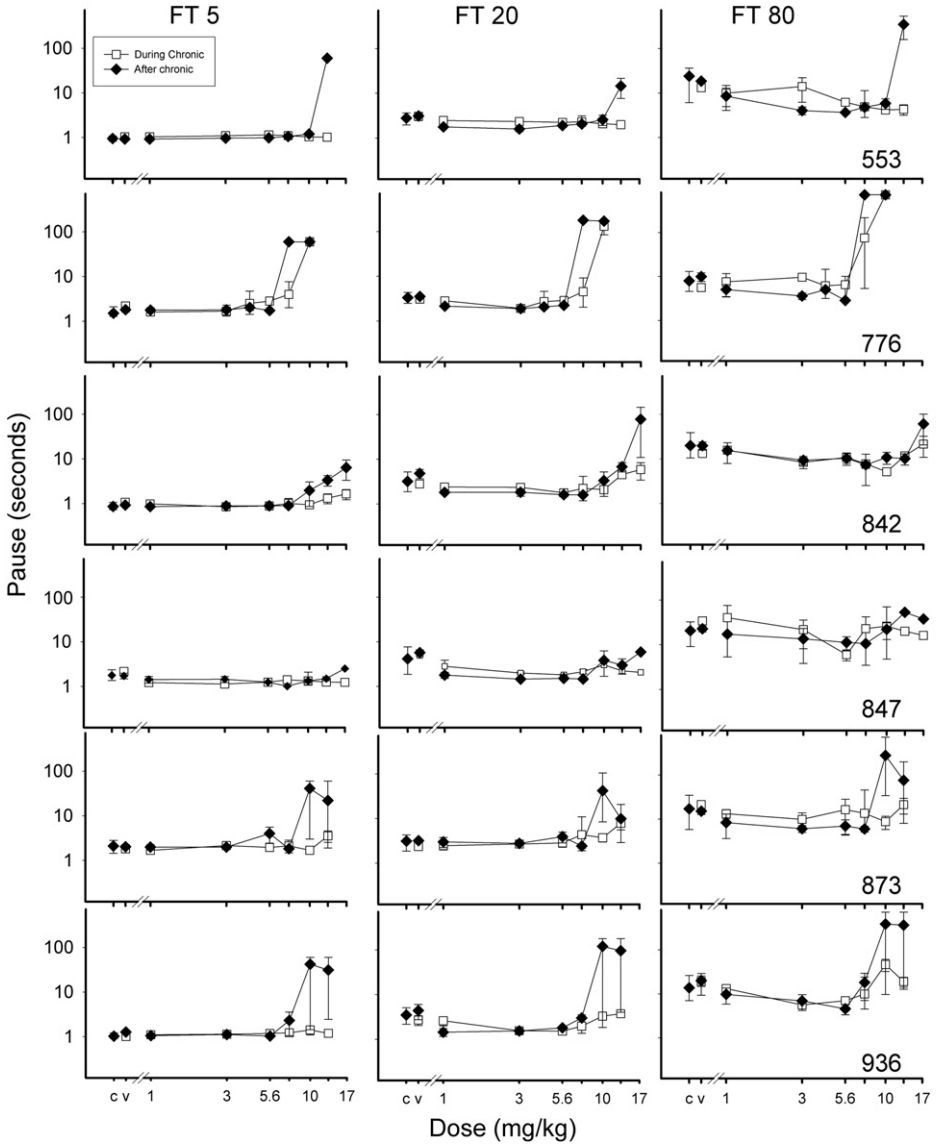

Fig. 3. Dose–response functions for session median pause, by component (columns) and pigeon (rows). Pauses during after-chronic administrations are indicated with filled diamonds, and during chronic administration with open squares. Points are means of all administrations, and bars are ranges. Note the two log axes. On the left hand end of the *x*-axis, c indicates control sessions, which were those immediately before days on which a probe dose was administered during the after-chronic determination; v indicates vehicle (saline) administration. During chronic administration, points for the chronic dose were collected by taking days immediately before probe doses were given; there are therefore more determinations for the chronic dose included in the mean than for other doses.

observed. Additionally, any contribution of run rate to the emergence of tolerance would have to be complex, given that lower run rates usually occur in larger ratio components in which tolerance is less likely to be observed, whereas the low run rates in the current study were associated with the development of tolerance in all three components.

An additional possible explanation for the differences between our results and previous studies is the change in dependent variable necessitated by the current procedure. That is, Hoffman et al. (1987), and Weaver and Branch (2008) focused on the development of tolerance to reductions in overall rate produced by cocaine. The results in those studies do suggest, however, that such pause increases were present and that tolerance did develop to them. The cumulative records presented by Hoffman, Branch and Sizemore indicate that this was the case, and that this tolerance was influenced by parameter size in the same way that tolerance to the rate-reducing effects of cocaine was. Additionally, pause-lengths are a component of overall rate, and it is likely that changes in overall rate in part reflect changes in pause length. Therefore, the difference in result observed here cannot be attributed to this difference in dependent variable.

5. Conclusion

The schedule-parameter-related tolerance observed under ratio and response-initiated FI schedules is a striking instance of an interaction between the effects of drug dose and behavioral processes. It is therefore of interest that the current chained FR1, FT schedule arrangement, which shares many features with response-initiated-FI, schedules did not produce such effects. The variables contributing to this difference remain to be identified. The current study suggested that the relationship between pause termination and delay to reinforcement alone does not provide an explanation for whether schedule-parameter-related tolerance develops. The potential importance of relatively high response rates in combination with a link between when pause termination occurs and when reinforcement is presented should be addressed by additional research, however.

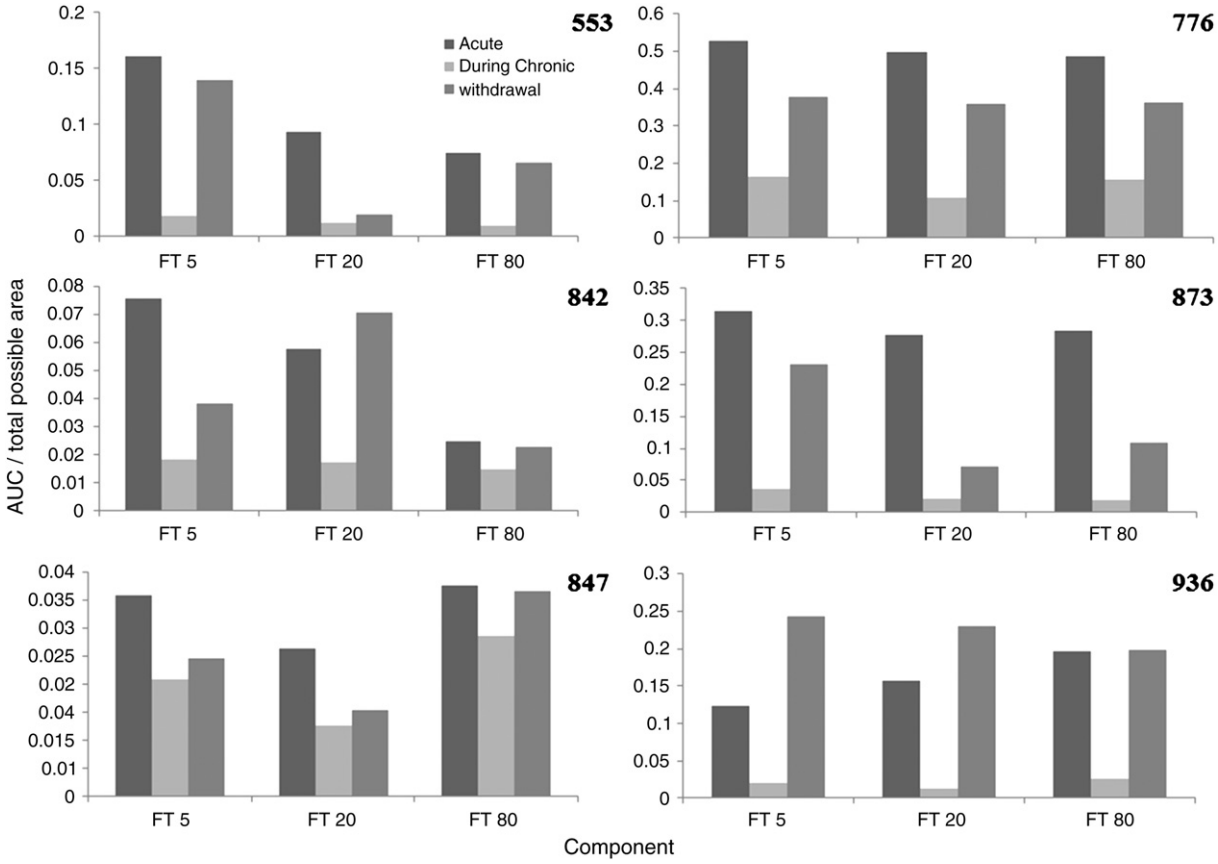

Fig. 4. Areas under the curve (mg/kg s) for each pigeon, by delay length and phase of drug treatment. Areas are presented as a proportion of the total available area for that curve. Note the differences in *y*-axis scale across pigeons.

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