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Schedule-dependent effects of haloperidol and amphetamine: multiple-schedule task shows within-subject effects

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Abstract

A two-lever, multiple-schedule task was used to evaluate the effects of haloperidol (HA) and amphetamine (AM) on responding controlled by continuous reinforcement (CRF) and progressive ratio (PR) schedules of reinforcement. Rats were trained to press one lever for food delivered on a CRF schedule and the other lever for food delivered on a PR schedule. The operative schedule was signaled by the illumination of a cuelight mounted above the appropriate lever. Following 30 sessions of training, dose–response functions were determined for HA (0.0075, 0.015, 0.03, and 0.06 mg/kg) and AM (0.0625, 0.125, 0.25, 0.50, 0.75, and 1.00 mg/kg). Both drugs produced dose- and schedule-dependent effects. For example, administration of 0.03 mg/kg HA did not affect responding under the CRF schedule but did reduce responding during PR components, whereas administration of 0.06 mg/kg reduced responding under both schedules of reinforcement. Some doses of AM produced increased responding under the CRF schedule and, within the same session, decreased responding under the PR schedule. The results with HA are consistent with the view that interfering with dopaminergic function affects the allocation and maintenance of responding and that this effect depends on properties of the schedule of reinforcement. The results with AM emphasize that statements about the effects of the drug on positively reinforced behavior cannot be made without reference to specific schedules of reinforcement.

Keywords: Amphetamine; Haloperidol; Continuous reinforcement; Progressive ratio; Multiple schedule; Schedules of reinforcement

The effects of altering dopaminergic function on operant responding in laboratory animals have been widely studied. Such work is important given the use of dopamine (DA) antagonists in antipsychotic medications (Swerdlow and Koob, 1987) and the role of DA in modulating behavior maintained by positive reinforcement (for reviews, see Berridge, 1996; Berridge and Robinson, 1998; Ettenberg, 1989; Salamone, 1987; Salamone et al., 1997; Wise, 1982, 1985).

Although antagonism of DA receptors reduces responding in many test situations, there are conditions under which this effect is not observed. A thorough evaluation of both of these cases is important to understanding the mechanism(s) by which DA modulates reinforced behavior. The results of a series of studies by Salamone et al. (1999) support the view that nucleus accumbens DA affects processes that regulate the initiation, allocation, and maintenance of responding by being sensitive to the response cost in energy relative to the benefit derived from reinforcement (for review, see Salamone et al., 1999). Using a task developed by Salamone et al. (1991), Cousins et al. (1994) gave animals a choice between earning preferred food each time they made five responses on a lever and consuming a less-preferred food that was freely available. Injections of haloperidol (HA), *cis*-flupenthixol, or SCH23390 prior to testing in this concurrent fixed-ratio (FR) 5/free-feeding task, produced both dose-related decreases in lever pressing and increases in free food consumption. The shift from lever pressing to free feeding produced by HA has been consistently reported (Salamone et al., 1991, 1996). This same pattern of behavioral change has been produced by injections of the neurotoxin 6-hydroxydopamine (6-OHDA) into the nucleus accumbens (Cousins and Salamone, 1994; Salamone et al., 1991) and, more

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specifically, into the core of the nucleus accumbens (Sokolowski and Salamone, 1998).

One purpose of the present study was to evaluate the conclusions reached by these studies by testing the effects of HA on behavior using a multiple-schedule task. The usefulness of multiple-schedule tasks for assessing the behavioral effects of manipulations of dopaminergic function have been well documented (e.g., Caine and Koob, 1994; Schuster et al., 1966; Villanueva and Porter, 1993). By this procedure, the element of choice present in the FR 5/free-feeding procedure is eliminated and the impact of drug on behavior can be assessed during discrete components that differ in terms of the response effort required to earn reinforcement. Although free feeding, as used in the studies cited above, may represent the case of minimal response effort for reinforcement (Egli et al., 1992), the low-effort components of the present study involved reinforcement on an FR 1, continuous reinforcement (CRF) schedule. (Aberman and Salamone, 1999) have reported that the effects of nucleus accumbens DA depletion following 6-OHDA treatment on behavior maintained by FR schedules depend on the value of the ratio. No effect of DA depletion was observed in the group of subjects that was reinforced under an FR 1, CRF schedule. However, for groups reinforced on FR 4, FR 16, and FR 64 schedules, DA depletion produced response deficits that increased as the ratio requirement increased. The effect of DA depletion as a function of the ratio value of FR schedule is consistent with the view that DA is involved in mediating response output as a function of response cost.

A progressive ratio (PR) schedule of reinforcement was used in the high-effort components of our multiple-schedule task. PR schedules of reinforcement systematically increase the ratio requirement for successive reinforcements within an experimental session. Although the use of such schedules was originally proposed as a measure of reinforcer efficacy that is relatively independent of response rate (Hodos, 1961; Hodos and Kalman, 1963), it is clear that the behavior maintained by these schedules is sensitive to manipulations of response effort (Skjoldager et al., 1993). In addition, (Aberman et al., 1998) have reported reductions in responding on a PR schedule in rats by injections of the D1 antagonist SCH23390, and the D2 antagonists HA and raclopride.

In the (Aberman et al., 1998) study, the lowest dose of HA that was evaluated (0.0375 mg/kg, ip, 60 min prior to testing) produced a marked reduction in the highest ratio completed during the 30-min test session. It may be, however, that some low dose of HA would enhance responding on a PR schedule. This possibility is suggested by the recent finding by Smith et al. (1997a) that, at low doses, some DA antagonists increased operant responding for a conditioned reinforcer in rats. Thus, the present study evaluated the effects of a wide range of doses of HA.

The second purpose of the present study was to use our multiple-schedule task to assess the behavioral effects of amphetamine (AM) over a wide range of doses. In the Smith et al. (1997a) study cited above, it was found that operant responding for a conditioned reinforcer was also enhanced by the administration of moderate doses (0.25 and 0.5 mg/kg) of AM. This finding raises the possibility that in our task, at some doses, AM might enhance responding. In addition, it was anticipated that assessment of the effects of AM over a wide range of doses on behavior in this task would help in understanding the apparent contradictions in the literature concerning the effects of AM on responding on PR schedules (Gentry et al., 1995; Gylys, 1967; Poncelet et al., 1983; Schulze and Paule, 1990; Smith et al., 1997b; Thomas, 1976; Thompson, 1972).

1. Method

1.1. Subjects

Twenty-eight male Sprague–Dawley rats, 500–515 days old at the beginning of this study, served as subjects. The animals were purchased from Harlan Sprague–Dawley, Indianapolis, IN, and had been previously trained to lever press for food reinforcement in different operant boxes as subjects in a drug-discrimination study that involved the discrimination of AM (2.0 mg/kg maximum dose) from vehicle. Sixty days elapsed between the end of the drug-discrimination study and the beginning of the research reported here.

Over a 14-day period, the animals' weights were reduced to 85% of their free-feeding body weight. Deprivation weights were maintained by supplementing the food pellets earned during experimental sessions with powdered food in the home cage immediately following the experimental sessions. On days when experimental sessions were not conducted, animals were weighed and given the appropriate amount of powdered food. Subjects were housed individually in a colony room on a 12-h light/dark cycle (lights on at 07:00 h). Water was available without restriction.

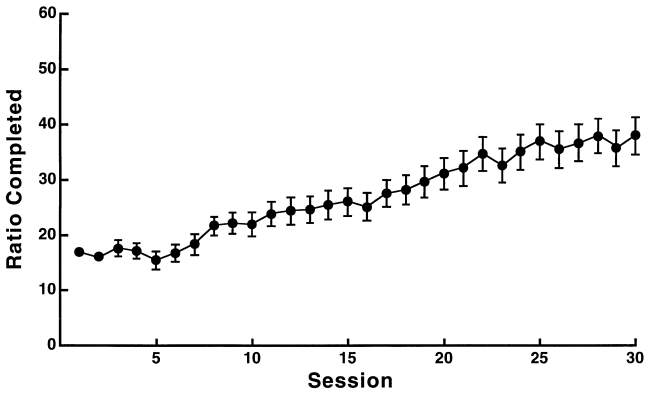

Fig. 1. Mean (±S.E.M.) highest ratio completed during PR responding for the 30-session training period.

The procedures used in this research were approved by the Institutional Animal Care and Use Committee of Vanderbilt University.

1.2. Apparatus

Six operant boxes (BRS/LVE model RTC-022) were housed in sound-attenuating chambers (BRS/LVE model SEC-002) supplied with white noise. Each box contained two levers and a food hopper that was located centrally between the levers. A white cuelight was located 4.6 cm above each lever. A house light in each box was located near the ceiling above the food hopper and was illuminated at the beginning of each session and extinguished when the session ended. All sessions were controlled and data collected by a computer and interface equipment located in an adjacent room.

1.3. Preliminary training

Two weeks after the onset of food deprivation, preliminary training sessions of 10-min duration were started.

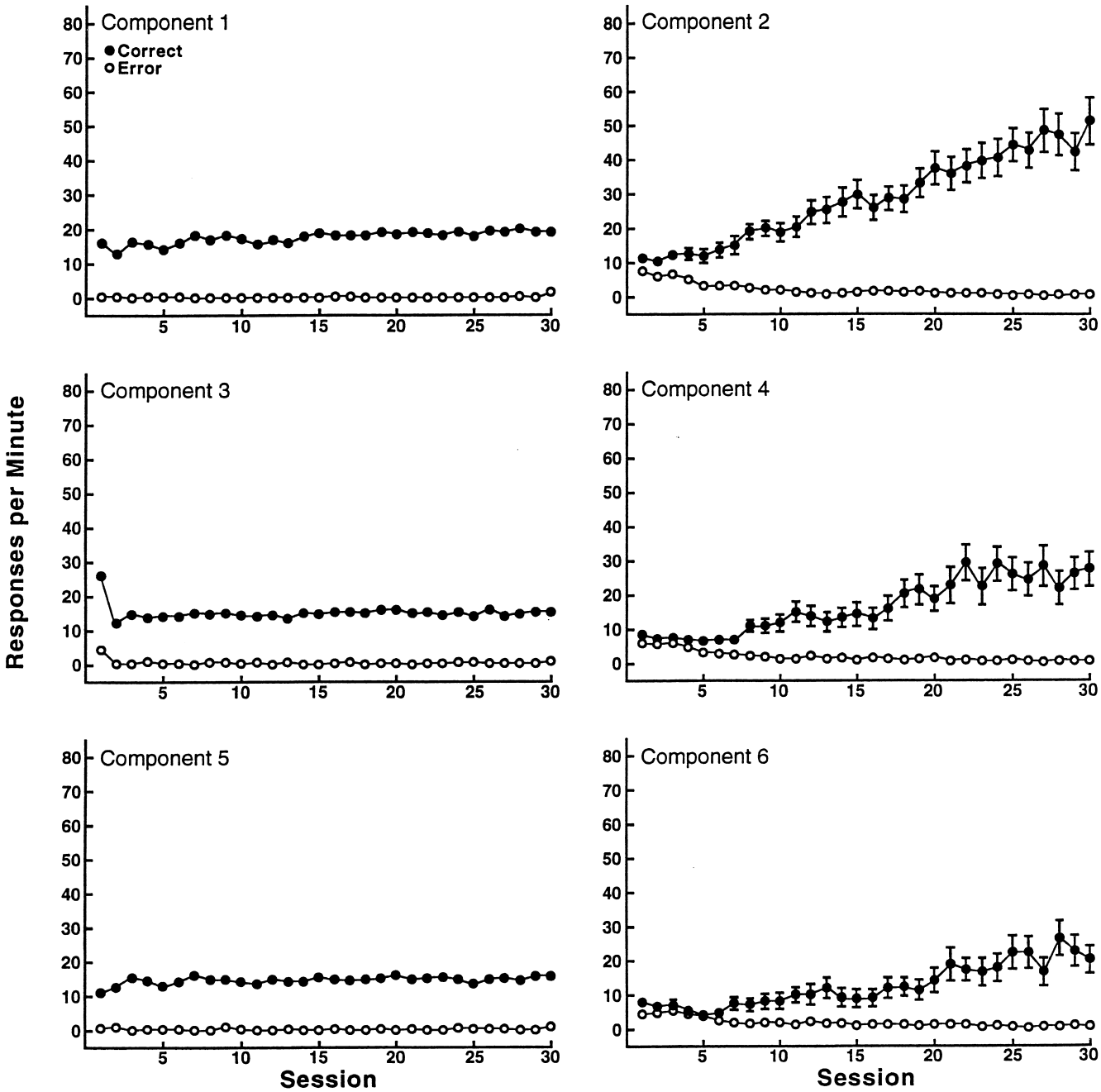

Fig. 2. Mean (±S.E.M.) correct and error responses per minute during each component for the 30-session training period. The left column shows the data from components 1, 3, and 5 (CRF). The right column shows the data from components 2, 4, and 6 (PR).

During the initial sessions, the cuelight above the left lever was turned on for the entire session and responding on the left lever was shaped and reinforced on a CRF schedule with food pellets (45 mg; P.J. Noyes). Responses on the right lever were recorded but had no programmed consequences. After animals made at least 25 responses on the left lever during one of these sessions, subsequent 10-min sessions were used to shape and reinforce responding on the right lever while the right cuelight was on. During these sessions, responses on the left lever had no consequences. After animals made at least 25 responses on the right lever during one of these sessions, subsequent sessions were used to train the animals to discriminate between the active and inactive lever based on the illumination of the cuelight above the active lever. These 10-min sessions consisted of four 2.5-min components during which responding on the correct lever was reinforced on a CRF schedule. The left cuelight was on and responses on the left lever were reinforced during the first and third components, whereas the right cuelight was on and responses on the right lever were

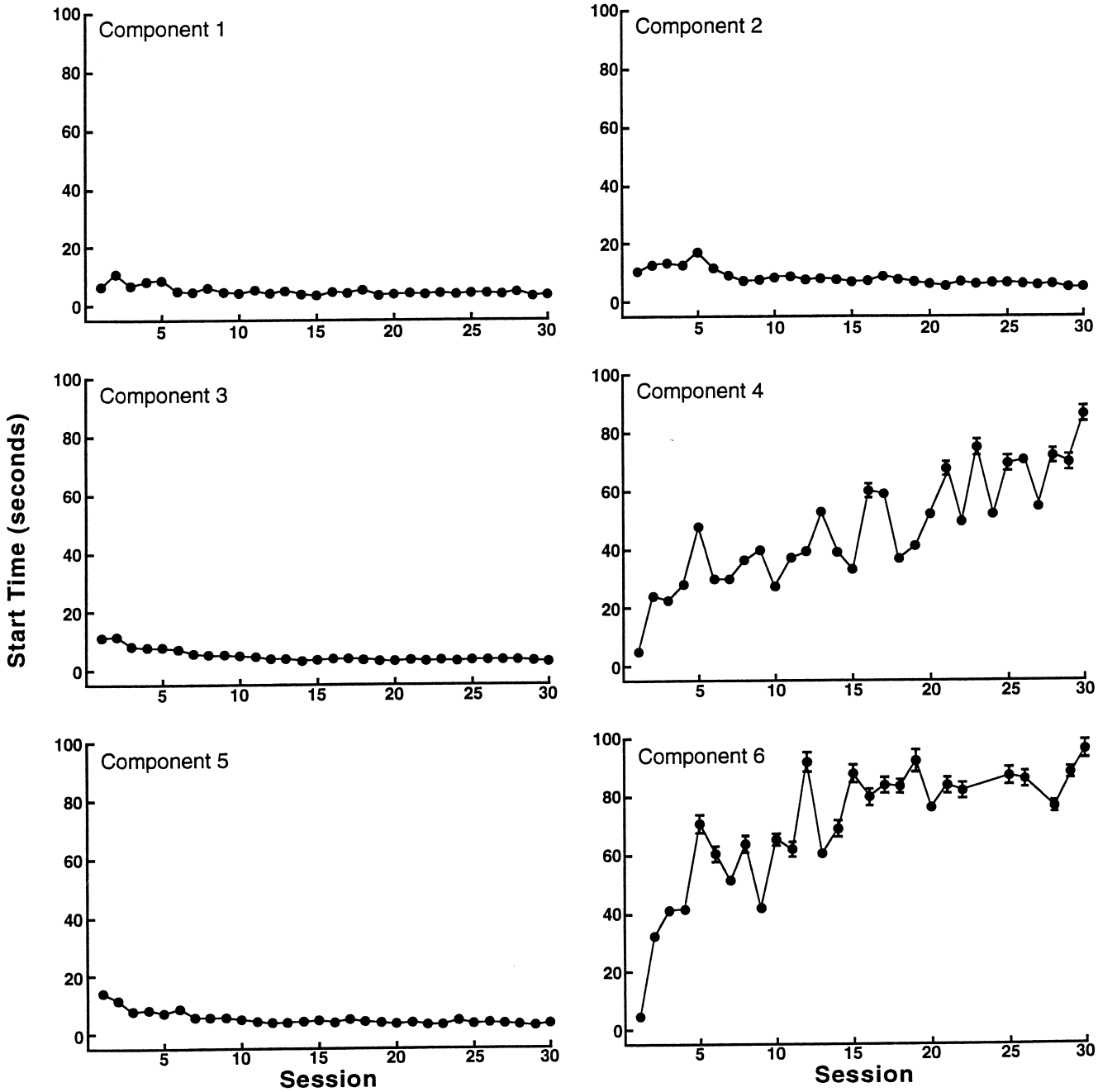

Fig. 3. Mean (±S.E.M.) start time for each component for the 30-session training period. The left column shows the data from components 1, 3, and 5 (CRF). The right column shows the data from components 2, 4, and 6 (PR).

reinforced during the second and fourth components. The criterion of less than five responses on the inactive lever, i.e., error responses, during one session was met by each animal within five sessions.

1.4. Training with a multiple schedule of reinforcement

Thirty sessions were conducted under a multiple schedule of reinforcement during which a CRF schedule was operative for responding on the left lever when the left cuelight was on, and a PR schedule was operative for responding on the right lever when the right cuelight was on. Under the PR 1+2 schedule, the first response was reinforced and the ratio increment was 2. Thus, the response requirement for reinforcement progressed from one to three to five to seven, etc. Training sessions lasted 18 min and consisted of six components. Components 1, 3, and 5 (CRF) were 1 min in duration and were signaled by illumination of the left cuelight. Components 2, 4, and 6 (PR 1+2) were 5 min in duration and were signaled by illumination of the right cuelight. At the beginning of components 4 and 6, the PR schedule resumed at the ratio value that was in effect at the end of the previous PR component. The task was designed to assess performance controlled by both CRF and PR 1+2 schedules of reinforcement during 18-min sessions beginning 20 min after drug administration.

The results of pilot work suggested that stable performance under these conditions could be achieved in about 30 sessions. No injections were given prior to the first 16 training sessions. Twenty minutes prior to each of the final 14 sessions, however, all animals were injected with distilled water (DW) (1 ml/kg, sc).

1.5. Dependent variables

During acquisition and all subsequent phases of the experiment, four dependent variables were measured during each session. The highest ratio completed was measured across PR components. The other three measures were determined for each component: correct responses per minute, error responses per minute, and the time of the first response of a component, i.e., start time.

1.6. Dose–response assessment

Subjects were rank-ordered according to the highest ratio completed during the final day of training and then randomly assigned within pairs to either the control group (Group DW, $n=14$) or the experimental group (Group Drug, $n=14$). Animals in Group Drug were tested once with each dose of each drug while animals in Group DW were injected with DW prior to every test session. Dose–response functions were determined first for HA (DW, 0.0075, 0.015, 0.03, and 0.06 mg/kg), and then for D-amphetamine sulfate (DW, 0.0625, 0.125, 0.25, 0.50, 0.75, and 1.0 mg/kg). HA (Haloperidol Injection USP, SoloPak Laboratories) and AM solutions were prepared with DW and were administered subcutaneously in 1 ml/kg volume 20 min prior to test sessions.

DW was administered to both groups of animals prior to the first session of dose–response assessment for each drug. Sessions with drug, during which Group Drug was given drug and Group DW was given DW, were always preceded by a DW session for all animals, and were always followed by a day off during which no injections were given and animals remained in their home cages. Within each dose–response assessment, the order of doses tested was haphazard.

1.7. Design considerations and statistical analyses

Two related concerns determined the procedures used. First, because we were unsure how a test session with drug might affect performance on CRF and/or PR components of the next session, a day off and a DW session were inserted between each drug test, essentially adding eight DW training sessions for all animals. Second, even though pilot work suggested that performance on this task might stabilize by 30 training sessions, our uncertainty about this suggested the need for Group DW that was run every session without drug exposure. Thus, the performance of this group allowed assessment of potential performance changes over the entire experiment and provided the appropriate comparison group for assessing drug effects.

These procedures produced a Group × Dose mixed design for each dose–response assessment with Group being a between–subject variable and Dose being a within–subject variable. A two-way repeated-measures analysis of variance (ANOVA) and subsequent *t* tests were used to analyze highest ratio completed. The ANOVAs of correct responses per minute, error responses per minute, and start time also included the within-subject factor of component.

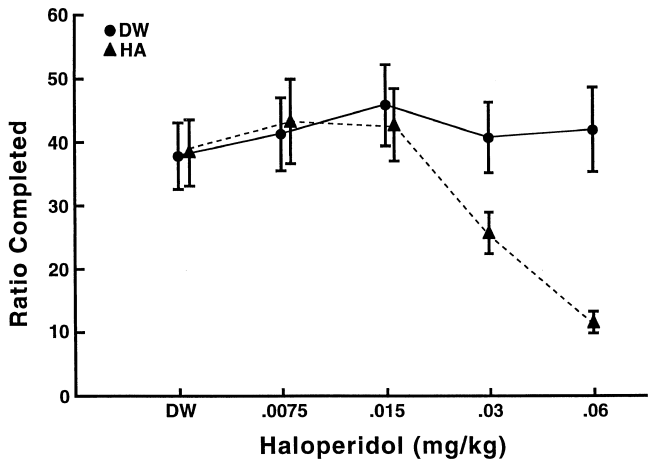

Fig. 4. Mean (±S.E.M.) highest ratio completed for Group Drug as a function of dose of HA and for Group DW that was administered DW prior to every session.

CRF components 1, 3, and 5, were analyzed separately from PR components 2, 4, and 6.

2. Results

2.1. Training sessions

The data presented for the training sessions are means for all 28 animals. Fig. 1 shows that the mean highest ratio completed over components 2, 4, and 6 increased gradually throughout the 30-session period.

In Fig. 2, mean correct and mean error responses per minute are plotted for each component throughout training. Mean error responses per minute reached very low and stable levels early in the training period for all components. Mean correct responses per minute in the CRF components (1, 3, and 5) also reached stable levels early in training. In the PR components (2, 4, and 6), however, mean correct responses per minute increased gradually throughout train-

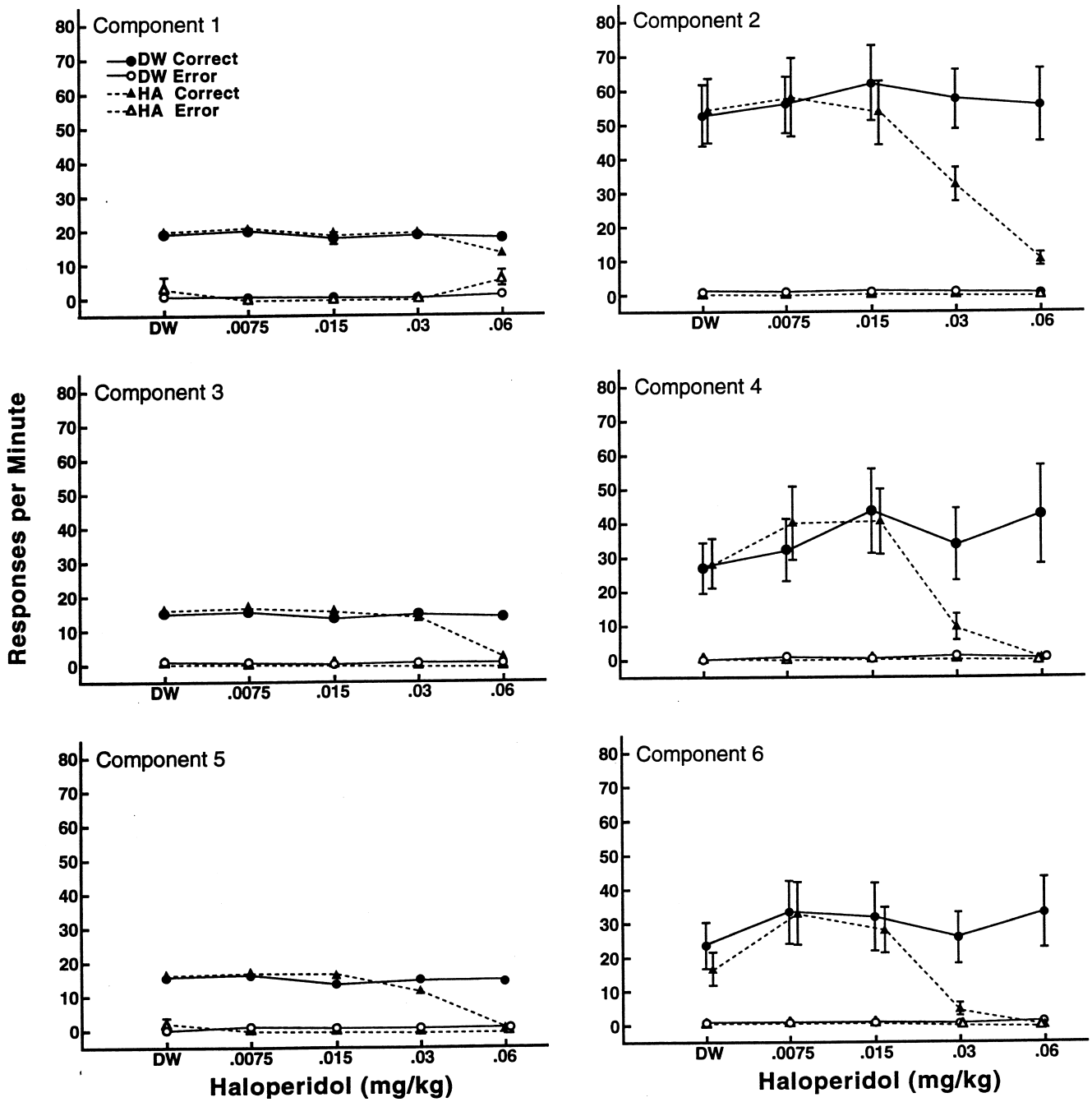

Fig. 5. Mean (±S.E.M.) correct and error responses per minute for each component for Group Drug as a function of dose of HA and for Group DW that was administered DW prior to every session.

ing. This increase was most pronounced in component 2, which was the initial PR component during each session. During component 2 of the final training session, the mean ratio completed was 28.2 (14 pellets earned). During component 4, the mean ratio completed was 34.4 (two pellets earned). During component 6, the mean ratio completed was 38.0 (two pellets earned).

Fig. 3 shows mean start time values for each component throughout training. Start times for the CRF components 1, 3, and 5 became short and stable early in training. For PR components, start times were also short and stable for the initial PR component, whereas, for components 4 and 6, start times increased over the entire training period and were more variable both within days and across days.

2.2. HA dose–response

Fig. 4 shows the effects of HA on mean highest ratio completed during PR components. The overall ANOVA of these data revealed a significant Group × Dose interaction, $F(4,100) = 21.76$, $P < .001$. Further analyses showed no significant differences between groups at doses of DW, 0.0075 and 0.015 mg/kg ($t < 1$ in each case). HA significantly decreased ratio completed, however, at 0.03 mg/kg (mean DW = 40.7, mean HA = 25.6), $t(26) = 5.54$, $P < .05$, and 0.06 mg/kg (mean DW = 41.9, mean HA = 11.6), $t(26) = 59.96$, $P < .001$.

Fig. 5 shows mean correct and mean error responses per minute for each component for both groups plotted as a function of HA dose. Error responding remained very low for each group across all components.

ANOVA of correct responses per minute across components 1, 3, and 5 showed that response rate decreased across these CRF components, $F(2,50) = 104.76$, $P < .001$. The significant Group × Dose × Component interaction, $F(8,200) = 4.46$, $P < .001$, resulted from the effects of HA at the highest dose tested, i.e., 0.06 mg/kg. A similar analysis excluding the 0.06 mg/kg dose revealed no such three-way interaction, $F(6,150) = 1.22$, $P = .30$. ANOVA of correct response rate for the group given 0.06 mg/kg HA vs. the group given DW produced a significant difference between Groups, $F(1,26) = 42.24$, $P < .001$, a significant effect of Component, $F(2,52) = 80.32$, $P < .001$, as well as a significant Group × Component interaction, $F(2,52) = 23.00$, $P < .001$. Thus, 0.06 mg/kg HA decreased correct response rate during CRF components: an effect seen predominantly during components 3 (mean DW = 13.6, mean HA = 2.4) and 5 (mean DW = 14.0, mean HA = 0.6).

During PR components, mean correct responses per minute decreased across components 2, 4, and 6 [Component: $F(2,50) = 51.80$, $P < .001$], and decreased as a function of dose of HA [Group × Dose interaction: $F(4,100) = 12.81$, $P < .001$]. Both the 0.03 and 0.06 mg/kg dose reduced response rates relative to controls [$F(1,26) = 5.90$, $P < .05$ and $F(1,26) = 12.14$, $P < .01$, respectively]. When given 0.03 mg/kg HA, animals completed a mean ratio of 22.1 (11 pellets earned) during component 2, a mean ratio of 24.1 (one pellet earned) during component 4, and a mean ratio of 25.1 (one pellet earned) during component 6. When given 0.06 mg/kg HA, Group Drug completed a mean ratio of 11.6 (six pellets earned) during component 2. No additional ratios were completed during components 4 and 6.

2.3. AM dose–response

In Fig. 6, the mean highest ratio completed for both groups are plotted as a function of the dose of AM. ANOVA confirmed the apparent Group × Dose interaction, $F(6,150) = 18.81$, $P < .001$. Further analyses showed no significant differences between groups at doses of DW, 0.0625, 0.125, and 0.250 mg/kg ($t < 1$ in each case). However, the reduction in ratio completed approached significance for animals given 0.5 mg/kg AM (mean DW = 40.4, mean AM = 27.4), $t(25) = 3.80$, $P < .06$, and was significant at 0.75 mg/kg (mean DW = 46.9, mean AM = 16.1), $t(26) = 22.74$, $P < .001$, and 1.0 mg/kg dose (mean DW = 47.7, mean AM = 11.8), $t(26) = 39.26$, $P < .001$. Fig. 7 presents mean correct and error responses per minute for each component for both groups plotted as a function of AM dose. Error responding remained very low for both groups over all doses of drug and all components.

Analysis of correct responses per minute for CRF components 1, 3, and 5 showed that while there was a small but significant decrease in overall rate of correct responding across components, $F(2,50) = 17.14$, $P < .001$, there was also a significant Group × Dose × Component interaction, $F(12,300) = 1.92$, $P < .05$. This interaction is attributable to the increase in rate of correct responding over the lowest five doses of AM (0.0625–0.75 mg/kg) (overall mean

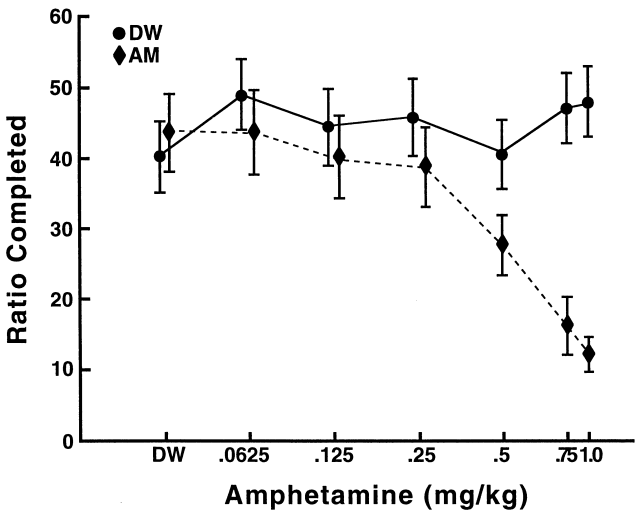

Fig. 6. Mean (±S.E.M.) highest ratio completed for Group Drug as a function of dose of AM and for Group DW that was administered DW prior to every session.

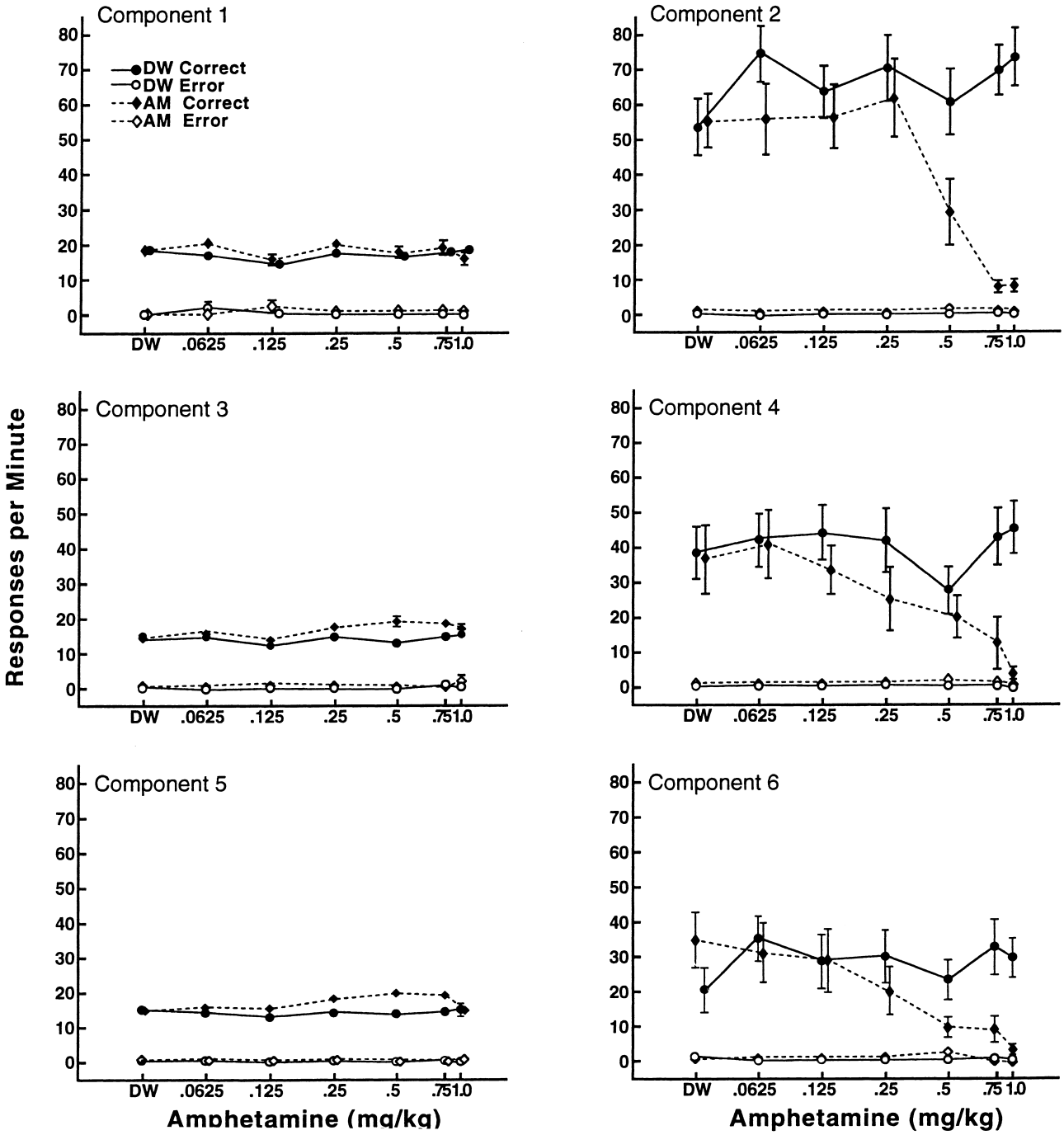

Fig. 7. Mean (±S.E.M.) correct and error responses per minute for each component for Group Drug as a function of dose of AM and for Group DW that was administered DW prior to every session.

DW = 14.7, overall mean AM = 17.7) that was most pronounced in components 3 and 5, and the lack of a group difference at the 1.0 mg/kg dose (mean DW over components = 16.2, mean AM over components = 16.0), $F(1,26) < 1$.

ANOVA of correct responses per minute across PR components 2, 4, and 6 revealed a significant decrease in response rate as a function of Component, $F(2,50) = 2.83$, $P < .001$, and a significant Group × Dose interaction, $F(6,150) = 2.57$, $P < .05$. Further analyses failed to show a Group effect at AM doses of 0.0625, 0.125, and 0.250 mg/kg, $F(1,26) < 1$ in each case. The apparent effect of 0.5 mg/kg AM to decrease rate of correct responding during PR components approached significance (mean DW = 35.9, mean AM = 19.6), $F(1,26) = 3.23$, $P = .08$, while correct response rate was significantly reduced by the 0.75 mg/kg (mean DW = 46.9, mean AM = 9.8), $F(1,26) = 19.30$, $P < .001$, and 1.0 mg/kg dose (mean DW = 47.7, mean

AM = 5.1), $F(1,26) = 31.96$, $P < .001$ When given 0.50 mg/kg AM, animals completed a mean ratio of 19.0 (10 pellets earned) during component 2, a mean ratio of 24.9 (two pellets earned) during component 4, and a mean ratio of 27.4 (two pellets earned) during component 6. When given 0.75 mg/kg AM, Group Drug completed a mean ratio of 8.2 (four pellets earned) during component 2, a mean ratio of 13.1 (three pellets earned) during component 4, and a mean ratio of 16.1 (one pellet earned) during component 6.

3. Discussion

The multiple-schedule task with alternating CRF and PR components was effective in yielding stable, schedule-dependent behavior with little variability among animals. After about 10 training sessions, the animals made very few error responses as they discriminated between the levers and their associated schedules of reinforcement. Response rate on the correct lever during CRF components 1, 3, and 5 stabilized very early in training and response rates during PR components 2, 4, and 6 increased gradually over much of the 30-session training period. This increased responding during PR components is also reflected in the gradual increase in the highest ratio completed. Although asymptotic performance is suggested during sessions 25–30, the gradual increase in PR responding persisted throughout the experiment for both groups. During the 30th session of acquisition, which is also presented on Fig. 4 as the first session of HA testing, when both groups received DW, the mean highest ratio completed was 37.71 for Group DW and 38.29 for Group Drug. During the 38th session, which was the DW day of the AM testing sessions (Fig. 6), the mean highest ratio completed was 40.14 for Group DW and 43.57 for Group Drug. Finally, during the 50th session (not shown), which was conducted after completion of AM evaluation and included DW administration to both groups, the mean highest ratio was 45.71 and 44.29 for Group DW and Group Drug, respectively. The equivalent responding by the two groups on these sessions, when both groups were tested after receiving DW, indicates that the gradual increase in responding under the PR schedule was not affected by the 4 days of testing with HA and the 6 days of testing with AM experienced by Group Drug. This gradual and persistent increase in PR responding over sessions, while it does not compromise the results presented here, is an important consideration in the design of experiments using a PR task. It also suggests the need to better understand the behavioral effects of parameters of PR schedules (Stafford and Branch, 1998).

A dose-dependent effect of HA on the highest ratio completed on the PR schedule was observed. While the lowest two doses had no effect, the highest ratio completed was reduced by administration of 0.03 mg/kg HA and was reduced further by 0.06 mg/kg. The dose-dependent effects of HA were schedule dependent as well. In terms of responses per minute, the 0.03 mg/kg dose had no effect during CRF components 1, 3, and 5, but markedly reduced responding during PR components 2, 4, and 6. Only at the 0.06 mg/kg dose were reductions of responding observed during both CRF and PR components. These results are consistent with the view developed by Salamone et al. (1999) that interfering with dopaminergic function with HA affects the allocation and maintenance of responding and that this effect depends on the properties of the schedule of reinforcement (Cousins et al., 1994; Salamone et al., 1996). In the concurrent FR 5/free-feeding task developed by Salamone et al. (1991), animals are given the choice between lever pressing for preferred food and free feeding on less-preferred food. In the present study, responding was monitored under both high-effort (PR) and low-effort (CRF) schedules of reinforcement within every session. The dose-dependent effects of HA as a function of the schedule of reinforcement cannot be confused with effects that might depend on the time since injection, duration of the test session, or the ability of the animal to respond.

The possibility that low doses of HA and AM might increase responding on this task was suggested by the results of a study on conditioned reinforcement by Smith et al. (1997a). In this study, a compound conditioned stimulus was paired with food reward during twelve training sessions. During test sessions, two levers were present. Responses on one of them produced the conditioned stimulus, whereas responses on the other lever had no consequences. It was found that low doses of AM, as well as the D2 antagonists sulpiride, pimozide, and raclopride, selectively increased responding on the lever that produced the conditioned reinforcer and that a low dose of HA increased responding on both levers. The results for highest ratio completed presented in Fig. 4, and for response rate seen in Fig. 5, however, offer no suggestion of increased responding for food in either CRF or PR components. It seems unlikely that this is due to differences between the studies in HA dose. Smith et al. (1997a) reported increased responding with 0.01 mg/kg, administered intraperitoneally 30 min prior to test, whereas no effects were seen in the present study with 0.0075 and 0.015 mg/kg, administered subcutaneously 20 min prior to test.

The effects of AM were also schedule dependent and dose dependent. The measures of highest ratio completed and response rate both decreased as a function of increasing dose of AM. This result is consistent with (Schulze and Paule's 1990) report of the effects of AM on these same measures of PR responding in monkey. Ten-minute sessions of PR performance, reinforced on PR 1 + 1 or PR 2 + 2 schedules, were included in a battery of complex food-reinforced tasks. AM, administered intravenously at least 15 min prior to testing, had no effect at 0.01, 0.03, and 0.10 mg/kg, whereas both the highest ratio completed and response rate were decreased at doses of 0.30 and 1.0 mg/kg. However, a very different dose–response pattern for the effects of AM on PR behavior in rats has been reported by

Poncelet et al. (1983). This study found a dose-dependent increase in PR responding in rats over the range of 0.25–1.0 mg/kg (administered intraperitoneally 30 min prior to session). The measure used was the cumulative number of responses made in a 30-min PR test period. The PR test period was preceded by a 2-min period during which responding was reinforced on a CRF schedule. The number of responses required for a pellet doubled every second minute during the PR period. Although only one dose of drug was evaluated by Smith et al., (1997b), they also found that 0.5 mg/kg of AM (administered intraperitoneally 30 min prior to session) increased PR responding. The measures used in this study were response rate and break point, defined as the final ratio completed prior to a 30-min period during which no additional ratio was completed. In addition, two studies report bidirectional effects of AM as a function of dose. Thomas (1976) presents patterns of responding on a PR 5+5 schedule for individual rats that show increased responding from 0.025 mg/kg to a maximum dose of 1 to 2 mg/kg, followed by a marked reduction of responding at 4.0 mg/kg (administered intraperitoneally 30 min prior to session). A similar result was observed in pigeons by Thompson (1972). Because of the differences among these studies in procedure, parameters of the PR tasks, and measures used, it is not clear how to account for the apparently inconsistent results.

The analyses of responses per minute during CRF and PR components as a function of dose of AM support three conclusions. First, discrimination of the components remained very good over all doses of drug evaluated. Second, the reduction in responding at higher doses of AM occurred during the initial PR component. Third, the reduced responding during PR components produced by AM was independent from the drug's effects on responding during CRF components. In fact, doses of 0.25, 0.50, and 0.75 mg/kg increased response rates during CRF components 3 and 5, while decreasing rates during PR components.

In conclusion, the present study has extended the usefulness of a multiple-schedule task to evaluating drug effects on responding under a PR schedule of reinforcement. Within-subject, schedule-dependent, dose-dependent effects were found for both HA and AM. The effects of HA on behavior on this task are consistent with the generalization that interfering with dopaminergic function affects the allocation and maintenance of responding and that this depends on the properties of the schedule of reinforcement (Aberman et al., 1998; Hamill et al., 1999; Salamone et al., 1999). It is important to note that this generalization is derived from converging evidence generated by behavioral studies in which DA antagonists were administered peripherally, and studies in which nucleus accumbens DA was depleted (Aberman et al., 1998; Salamone et al., 1999). Even so, it is necessary to recognize that the behavioral effects of systemic DA antagonists may involve interactions between neurochemical systems (Harper, 1999; Salamone, 1987), and that precisely identifying the functional significance of depleting DA in specific sites in the brain is a complex endeavor (Hamill et al., 1999; Le Moal and Simon, 1991). The effects of AM reported here, in conjunction with the results of relevant studies in the literature on behavior controlled by PR schedules of reinforcement, do not establish a consistent pattern of the drug's effects. However, it is clear that statements about the effects of AM on positively reinforced behavior cannot be made without reference to specific schedules of reinforcement (Barrett and Katz, 1981; Dews and DeWeese, 1977; Sanger and Blackman, 1976).

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