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The role of dopamine in the timing of Pavlovian conditioned keypecking in ring doves☆

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Abstract

The effect of dopaminergic drugs on the timing of conditioned keypecking in ring doves was studied in two experiments. Subjects were given pairings of a keylight with food and the temporal distribution of keypecks was obtained during unreinforced probe trials. Experiment 1 demonstrated that injections of pimozide before each session immediately decreased response rates but shifted timing distributions gradually to the right over several days of treatment. Experiment 2 showed similar results using a longer interstimulus interval (ISI). No shifts were observed when the drug was injected after training sessions, or when a delay, identical to each subject's average latency to eat during the drug condition, was inserted between keylight offset and food presentation. Consequently, the shifts in timing were mediated neither by mere accumulation of the drug nor a delay from keylight offset to food presentation resulting from the drug's ability to slow motor processes. The results suggest that pimozide modulates response rate through its effect on motor processes or incentive value, and response timing through a conditioned response (CR) to injection-related cues established via their repeated pairings with the drug.

Keywords: Amphetamine; Conditioning; Dopamine; Pimozide; Timing

1. Introduction

Interval timing refers to the ability of animals to perceive and respond on the basis of time intervals in the seconds to hours range (Church, 1984; Gibbon, 1991; Gibbon et al., 1997a; Meck, 1996). The functional properties of interval timing have been studied extensively in a number of paradigms (Church, 1984; Gibbon, 1977; Killeen and Fetterman, 1988). In the commonly used peak procedure (Catania, 1970; Gibbon, 1991; Roberts, 1981), an animal is sometimes presented with a signal and is reinforced for responding after a criterion time since its onset (fixed-interval (FI) trials). At other times, the signal extends well beyond the criterion time but is not reinforced (peak trials), and the average rate of responding in these trials is plotted as a function of the time since the onset of the signal. The resulting function is nearly symmetrical, and the time at which the animal responds most frequently (commonly called peak time) mirrors the FI value.

An influential account of timing behavior, scalar timing theory, assumes clock, memory, and decision processes (Church, 1984; Gibbon, 1991; Gibbon and Balsam, 1981; Gibbon et al., 1984, 1997b; Balsam, 1984; Gallistel and Gibbon, 2000; Malapani et al., 1998). The clock is composed of a pacemaker, gate, and accumulator, and is thought to represent time intervals by the number of pulses that are gated from the pacemaker to the accumulator during stimulus presentation. These representations of time are processed in working memory and transferred to reference memory whenever the interval ends in reinforcement. The decision process involves a rule that determines behavioral output, and differs depending on the timing paradigm. In the

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peak procedure, animals are assumed to compare the currently elapsing time in working memory with the memory for reinforced time, and respond only if their relative discrepancy is below some threshold value. This yields the near-symmetrical functions observed during peak trials.

The neurobiological bases of clock, memory, and decision processes have not been established so clearly. Initial studies attempted to pharmacologically manipulate clock and memory processes. In the peak procedure, the formal model of Gibbon et al. (1984) predicts an immediate shift in peak time upon the administration of a drug that selectively increases or decreases the rate of a pacemaker without affecting memory storage. This is because performance is determined only by a comparison between the currently elapsing time and a memory of the reinforced time. If a drug only changes the rate of a pacemaker, then it should immediately shift the time at which the comparison threshold is reached, and immediately shift the peak time. (To the extent that new ''distorted'' memories are stored under the new pacemaker rate, peak times should eventually return to the reinforced time.) In contrast, if a drug produces a distortion in memory storage without affecting the rate of the pacemaker, then the change in timing should occur gradually as repeated trials would be required to establish a distorted memory distribution dense enough to affect performance. These predictions, together with the finding that dopaminergic drugs produce immediate but transient shifts in measures of timing, whereas cholinergic drugs induce sustained shifts that develop gradually with repeated testing under the drug (Meck, 1983; Meck and Church, 1987a), have led to the suggestion that dopaminergic drugs selectively affect the speed of the pacemaker while cholinergic drugs distort the storage of temporal memories (Meck, 1996). Specifically, the dopamine (DA) agonist methamphetamine and DA antagonist haloperidol respectively appear to increase and decrease the rate of the pacemaker (but see Altman et al., 1979; Rapp and Robbins, 1976; Stubbs and Thomas, 1974), while the cholinergic agonist physostigmine and antagonist atropine respectively appear to increase and decrease the stored time of reinforcement. This pattern of shifts has been obtained in both the peak procedure (Meck and Church, 1987a; Meck and Angell, 1992) and the temporal bisection procedure (Meck, 1983) for cholinergic drugs. However, the complete pattern of shifts for dopaminergic drugs has been reported only in the temporal bisection paradigm (Maricq and Church, 1983; Maricq et al., 1981; Meck, 1983, 1996; Meck and Church, 1987b), and only with the DA agonist methamphetamine using the peak procedure (Maricq et al., 1981). Furthermore, all of these prior studies used rats as their subjects. The pattern of shifts has yet to be reported in birds, though a sensitivity of response timing to amphetamine has been demonstrated in pigeons (Kraemer et al., 1997). Lastly, all of the work cited above on the neuropharmacology of timing have employed instrumental procedures. Timing is fundamental both to the acquisition (Gibbon and Balsam, 1981; Gallistel and Gibbon, 2000) and production of Pavlovian conditioned responses (CRs) (Bitterman, 1964; Brown and Hemmes, 1997; Davis et al., 1989; Desmond and Moore, 1988; Gibbon et al., 1980; Gormezano, 1972; Mauk and Donegan, 1997; Moore and Choi, 1997; Ohyama et al., 1999), but we do not know if the neuropharmacological basis of timing in Pavlovian conditioning is related to that of instrumental conditioning.

The present set of experiments sought to study the pattern of changes in the timing of keypecking in ring doves induced by administration of a DA antagonist and its subsequent removal. We used a Pavlovian analogue of the peak procedure (Bitterman, 1964; Ohyama et al., 1999) to investigate the effects of dopaminergic drugs on CR timing. It has previously been shown that the functional properties of timing behavior in Pavlovian conditioning procedures are similar to those found in instrumental timing paradigms (Brown and Hemmes, 1997; Gibbon et al., 1980; Ohyama et al., 1999; Gallistel and Gibbon, 2000). Similar functional properties suggest similar underlying mechanisms. Consequently, dopaminergic manipulations in a Pavlovian timing procedure would provide some evidence about whether there is a common neural substrate for response timing in all conditioning procedures (Gallistel and Gibbon, 2000; Meck, 1996).

2. Experiment 1

Ring doves (*Streptopelia risoria*) were trained and maintained on a Pavlovian conditioning procedure in which unreinforced probe trials extending beyond the usual interstimulus interval (ISI) were interspersed among standard reinforced trials, so that timing of conditioned keypecking could be assessed. If an increase in DA levels increases the speed of the internal pacemaker, then administration of amphetamine should shift timing distributions during probe trials to the left. Conversely, if a decrease in DA levels slows the speed of the pacemaker, then administration of pimozide should shift CR timing distributions to the right. In addition, if DA levels directly affect the speed of the pacemaker, then the change in the timing should be immediate rather than gradual. In Experiment 1, subjects were trained with an 8-s ISI, and the effects of systemic injections of amphetamine or pimozide on the timing of keypecking were assessed.

2.1. Method

2.1.1. Subjects

Eight ring doves, bred and housed in our own laboratory and kept at 85% of their free-feeding weight, served as the subjects. All subjects had prior experience with autoshaping. Both Experiments 1 and 2 were conducted in accord with the guidelines of the Institutional Animal Care and Use Committee at Columbia University.

2.1.2. Apparatus

The experimental apparatus consisted of two identical Lehigh Valley conditioning chambers connected to a computer. The dimensions of the enclosure in each chamber were $30 \times 30 \times 26$ cm. The sides and top wall were painted flat black, and the floor consisted of wooden panels. The front wall panel was comprised of four No. 1829 lights situated at the top that provided the ambient illumination, a circular panel (keylight) 2.5 cm in diameter that was activated by 0.18 N of force, and a food aperture that provided access to grain. The center of the keylight was located 7 cm to the left of the midline of the front panel, 13 cm above the floor. The keylight was illuminated amber from behind by an IEE stimulus projector. The food aperture (6.5×7.0 cm) was centered with respect to the midline of the front panel and situated 2 cm above the floor. Located behind the aperture was a food hopper, which, when activated, moved into a position that allowed the animal access to the grain. Simultaneous with hopper activation, the food aperture was illuminated by a hopperlight. A photocell was situated such that the first head thrust at the food by the subject would interrupt the photobeam, and record the latency to eat. A specified time after this interruption, the hopperlight turned off and the food hopper was deactivated. If no interruptions occurred, the hopperlight and hopper activation terminated after 15 s. A computer was used to control stimulus presentations and record data.

2.1.3. Drugs

The drugs used in the experiment were amphetamine and pimozide (Research Biochemical, Natick, MA). The doses for each drug, 2.0 mg/kg for amphetamine and 0.6 mg/kg for pimozide, were chosen on the basis of previous experiments employing similar methods (Kraemer et al., 1997; Maricq et al., 1981; Meck, 1986; Tombaugh, 1981). The drugs were dissolved in a 0.3% lactic acid solution and injected in a volume of 1 ml per kg of body weight.

2.1.4. Procedure

An experimental session consisted of 20 pairings of the keylight as the conditioned stimulus (CS) and presentation of grain as the unconditioned stimulus (US). The ISI, or the duration from the onset of the CS to the presentation of the US, was 8 s (equal to the duration of the CS). In addition, there were 12 unreinforced presentations of the CS and eight unreinforced presentations of probe trials during which the keylight persisted for 48 s. Trials occurred in a semirandom order, in which a trial type was sampled without replacement from a collection of five CS–US, three CS–noUS, and two probe trials, for every block of 10 trials. The mean intertrial interval (ITI) was 96 s. Each session lasted approximately 80 min. Subjects were trained 5 days a week at the same time of day, and were fed at least 1 h after the session ended. Any change in treatment condition began on a Tuesday so as to avoid coincidence of treatment changes with the end of the weekend rest period.

On Days 1–20, all subjects received daily sessions of the standard training described above. The subjects were then divided into two groups equated for their average response rate distributions during probe trials. Injection treatments began on Day 21. All injections occurred 1.5–2 h before the beginning of a session. On Days 21–25, all subjects were given 1 ml/kg of intramuscular injections of the vehicle solution. On Days 26–30, half of the subjects received injections of 0.6 mg/kg of pimozide, while the remaining subjects received 2.0 mg/kg of amphetamine.

On Days 31–40, subjects were given vehicle injections. On Days 41–50, half of the subjects that had received amphetamine during the first drug treatment were given injections of 0.6 mg/kg pimozide. The animals that had received pimozide during the first treatment were injected with 2.0 mg/kg of amphetamine. Finally, on Days 51–60, subjects were once more given vehicle injections. (The second series of injections was continued for 10 days, because the effects during the first 5 days appeared weaker than during the initial series. However, as described below, only data from the first half of the second injection series were pooled with data from the first injection series. Thus, data from the latter half of the injection series were not included in the analysis.)

2.1.5. Data analysis

To avoid any effects of weekend rest periods, Monday data were excluded; only data from the four other days (Tuesday to Friday) are reported. Average response rate distributions during the eight unreinforced probe trials were calculated daily in 1-s bins for each subject. As reported previously, the obtained response distributions in this procedure peaked prior to the reinforced time and reached a minimum around twice the duration of the ISI (Ohyama et al., 1999). The peak time of responding was calculated based on a truncated distribution consisting of data limited to the portion of probe trials from the onset of the CS to twice the duration of the ISI (16 s for Experiment 1 and 32 s for Experiment 2). The middle time was defined as the midpoint of the interquartile range of the truncated distribution, and was obtained only for days on which responding occurred on at least four CS trials and a total of at least 20 responses were made during the eight probe trials. This criterion was chosen because when subjects responded at very low rates, all measures were unstable. The maximum response rate during probe trials was obtained daily for each subject by examining the average response rate during each second of the probe trials. A discrimination ratio was also calculated by dividing the maximum rate in the probe by the overall response rate during the probe to index the degree of temporal discrimination. If the distribution of responses is uniform during a probe trial, then the discrimination ratio is 1. The discrimination ratio in both experiments was typically near 2. A decrease in this ratio

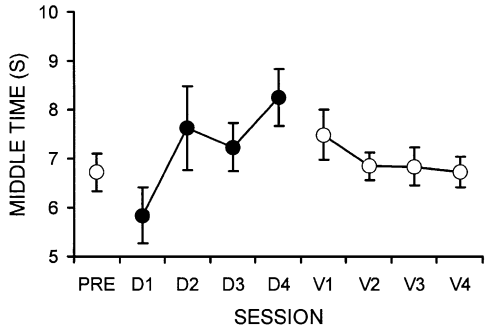

Fig. 1. Mean middle times during predrug (PRE), drug (D1–D4), and postdrug vehicle (V1–V4) phases of pimozide treatment in Experiment 1. Filled circles indicate days with a drug injection and open circles indicate those with a vehicle injection. Bars indicate the standard error of the mean.

indicates deterioration in the temporal discrimination, whereas an increase in the ratio indicates an enhancement in the discrimination. Latencies to eat were also recorded on each reinforced trial. If a subject missed a food presentation that trial was not included in the computation of average latencies.

To assess changes in behavior during drug treatment and during its subsequent removal, for each behavioral measure, medians across the four vehicle injection days preceding the treatment condition were obtained for each subject. Medians were used because the four vehicle injection days preceding a particular drug condition corresponded to postdrug days of the alternative drug condition. For example, for animals first treated with pimozide and then treated with amphetamine, the four vehicle injection days preceding amphetamine treatment corresponded to the Days 6–9 of vehicle injections after removal of pimozide. For each behavioral measure, the median of the four pretreatment days was compared to the mean of each drug or postdrug day using one-tailed, paired-sample t tests to test the specific hypothesis that pimozide would increase middle times, increase eating latencies, and lower response rates and the specific hypothesis that amphetamine would decrease middle times, decrease eat latencies, and increase response rates. Because we had no other specific hypotheses to test, two-tailed tests were used for comparing all behavioral measures between prevehicle and the first vehicle injection condition, as well as comparing discrimination ratios and coefficients of variation (see next section) between the predrug and drug or postdrug conditions.

2.2. Results

2.2.1. Effect of vehicle

Paired-sample t tests revealed no significant differences between middle times, maximum response rates, and discrimination ratios before and after vehicle injections, t's(7) < 1. The mean median middle time was 7.06 s, the mean maximum rate was 2.29 pecks/s, and discrimination ratios averaged 1.75.

2.2.2. Effect of pimozide

Pimozide produced a shift in the average timing distribution to the right. Fig. 1 shows the middle times for the predrug, drug, and postdrug conditions pooled across all subjects. The first point shows the 4-day median of the predrug condition. Middle times increased across successive days of pimozide treatment, and returned gradually to pretreatment values when subjects were returned to the vehicle. One subject was dropped from the analyses because response rates were so low that a middle time could be obtained only on the first treatment day. The response rate was so low for a second subject on the fourth day of pimozide treatment that a middle time could not be calculated. In analyzing middle times, the mean middle time across Days 1–3 was substituted for that subject's missing data point (Winer, 1971). All other subjects responded enough to compute middle times on all drug treatment days. Paired-sample t tests between the middle time on each day of the drug condition and for the predrug condition revealed that the difference was significant on Day 4, $t(6) = 2.09$, $P < .05$, but not on Days 1–3, t's(6) < 1.1. The middle times during the postdrug condition did not differ from the predrug condition on any day, t's(7) < 1. Discrimination ratios increased slightly during pimozide treatment. The mean median discrimination ratio ± S.D. during the 4 days of vehicle treatment before pimozide treatment was 1.78 ± 0.36, while the values for the 4 days of pimozide treatment were 2.64 ± 1.04, 2.07 ± 0.31, 2.05 ± 0.35, and 2.09 ± 0.19, respectively. Paired-sample t tests revealed that discrimination ratios were greater on Days 2–4 of the drug condition compared to the predrug condition, t's(6) > 3, $P < .05$, but not on Day 1, $t(6) = 2.22$. The discrimination ratios during the postdrug condition did not differ from the predrug condition on any day, t's(7) < 1.3.

Fig. 2 shows the maximum rate of responding in probe trials during predrug, drug, and postdrug conditions, pooled across all subjects. Response rates decreased immediately upon pimozide treatment. Upon removal of the drug, the response rates returned quickly to their pretreatment values. Paired-sample t tests revealed that the maximum response rates were lower on all 4 days of the drug condition compared to the predrug condition, t's(7) ≥ 3, P's ≤ .01.

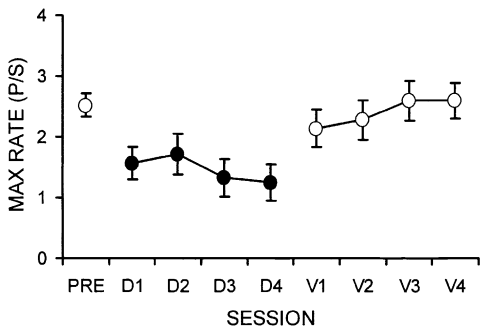

Fig. 2. Mean maximum response rates during predrug, drug, and postdrug vehicle phases of pimozide treatment in Experiment 1.

The rates during the postdrug condition did not differ from the predrug condition on any day, t's(7) < 1.8.

The latency to eat increased during pimozide treatment. The mean median latency ± S.D. during the 4 days of vehicle treatment prior to pimozide treatment was 1.61 ± 0.87 s, and the values for the 4 days of pimozide treatment were 2.36 ± 1.24, 2.27 ± 1.05, 3.16 ± 1.56, and 3.11 ± 1.65 s, respectively. Paired-sample t tests revealed that latencies were greater on all 4 days of the drug condition compared to the predrug condition, t's(7) > 2.9, P's < .05. When subjects were returned to the vehicle condition, the latency returned gradually to predrug values. The latencies during the postdrug condition were greater on Day 1 compared to the predrug condition, $t(7) = 1.99$, $P < .05$, but did not differ from the predrug condition on any other day, t's(7) < 1.8.

2.2.3. Effect of amphetamine

There was no systematic effect of amphetamine on any of the behavioral measures. Paired t tests on middle times, maximum rates, discrimination ratios, and latencies to eat revealed no systematic differences between predrug, drug, and postdrug phases, t's(7) < 1.8.

2.3. Discussion

2.3.1. Effects of amphetamine

Amphetamine had little effect on the timing of key-pecking. Neither middle times nor discrimination ratios were affected by the drug treatment. While it is possible that the lack of effect may have been due to species or procedural differences as compared to other studies (Kraemer et al., 1997; Maricq and Church, 1983; Maricq et al., 1981; Meck, 1983), it is also possible that the animals were already responding to the CS with a minimal latency and at maximal rates (Ohyama et al., 1999). Thus, the lack of an amphetamine effect may have been due to a floor effect. The use of a relatively short ISI in the present experiment (8 s) is likely to have made it difficult to detect increases in response rates and a leftward shift in response distributions.

2.3.2. Effects of pimozide

Injections of pimozide increased middle times. The shift in timing did not occur immediately but emerged gradually, becoming maximal on the fourth day of pimozide treatment. This gradual change is inconsistent with the pattern reported for drugs affecting pacemaker speed, but is consistent with the pattern for drugs affecting temporal memory (Meck, 1983, 1996; Meck and Church, 1987a; Meck and Angell, 1992). An alternative account of the gradual change in middle times is based on the idea that stimuli associated with drug administration can come to evoke CRs (Eikelboom and Stewart, 1982; Ramsay and Woods, 1997; Siegel, 1989). It is possible that it takes several pairings of the injection procedure with the pimozide before a CR is evoked that then affects timing.

When subjects were returned to the vehicle condition after drug treatment, the middle times returned to their pretreatment values. Although the middle times appeared to decrease gradually across postdrug days, the difference between the middle time on the first postdrug day and the predrug days was not significant. This indicates that the return to baseline was rapid. It is possible that the learning that underlies the shift in timing is state dependent (Maricq et al., 1981; Overton, 1984). Consequently, when subjects are returned to the nondrug state, the baseline memories are more likely to be retrieved than are the memories stored during the drug phase.

The maximum response rate in probe trials decreased immediately upon administration of pimozide. This finding is consistent with the literature showing the detrimental effect of neuroleptics on appetitive instrumental responses (Tombaugh et al., 1979; Wise, 1982). There was a small decline in rate across successive days of pimozide treatment. This resembles previous findings in which administration of neuroleptics to rats after acquisition of a lever-pressing response results in a successive decrease in responding across training sessions (Wise, 1982). In the present experiment, there was an immediate change in response rate, while the change in middle time appeared only gradually. This suggests that the drug affected each measure independently. Such independence is consistent with findings in the timing literature, in which it has been shown that the peak rate and peak time can be manipulated independently. Using rats, Roberts (1981) found that peak time could be changed by manipulating the scheduled time of reinforcement on standard FI trials without changing peak rate. He also found that peak rate could be changed by manipulating the probability of reinforcement on FI trials without changing peak time. In addition, extinction has been shown to decrease peak rate without changing peak time (Ohyama et al., 1999; Roberts and Holder, 1984). Collectively, these findings suggest that the systems determining response rates and those determining CR timing are independent.

The latency to eat increased during treatment with pimozide. This is consistent with evidence showing that neuroleptics increase the latency to initiate feeding while having little effect on the continuation of feeding once it is initiated (Blackburn et al., 1992). An increase in eat latency may have affected the timing of the CR, by delaying reward. It is not known whether increasing a trace interval produces a rightward shift in the timing of the CR after acquisition, but the duration of the trace interval can have large effects on acquisition speed and asymptotic response levels during initial learning (Balsam, 1984; Kamin, 1965). It is certainly possible that imposing a delay between CS-offset and the US might lead to a shift in CR timing, by increasing the time of reinforcement stored in reference memory.

3. Experiment 2

Experiment 1 showed that systemic injections of pimozide shifted CR timing distributions to the right. The shifts during pimozide treatment occurred gradually across days, suggesting that the drug may have affected memory storage rather than the speed of an internal pacemaker. The present experiment sought to replicate the effects of pimozide at a longer ISI. The ISI was 16 s, while the duration of the probe trials was maintained at 48 s. In the Pimozide Condition, subjects received presession injections of pimozide. It was expected that if pimozide changed some aspect of the timing system (i.e., the speed of the pacemaker or memory for time), the shift in CR timing would be proportional to the ISI (Maricq et al., 1981). Subsequently, the subjects were run through two separate control conditions. The Home Cage Condition controlled for the timing of pimozide injections by giving postsession injections of the drug. If subjects must experience the timing procedure under the influence of the drug for timing to shift, then postsession pimozide injections should not change middle times. If accumulation of the drug over days is sufficient for producing the timing change, then this condition should also show a change in middle times. The Trace Condition was designed to examine how drug-induced changes in the latency to eat might affect middle times. We attempted to yoke each subject to its own performance during the Pimozide Condition. A trace interval that approximately matched the increase in eat latencies under pimozide was introduced from the end of the CS presentation until grain was presented. This condition controlled for the possibility that changes in eat latency mediated the change in timing produced by pimozide injections.

3.1. Method

3.1.1. Subjects

The eight ring doves used in Experiment 1 served as the subjects. All subjects were maintained at 85% of their free-feeding weight.

3.1.2. Procedure

The apparatus and method of drug preparation were identical to Experiment 1. The ISI in the present experiment was 16 s. In addition, the color of the keylight was changed from amber to red in order to attenuate transfer effects from the original training with the 8 s ISI. All other aspects of the training situation were identical to Experiment 1. As in Experiment 1, a change in condition usually occurred on a Tuesday and data from the first 4 days after the change were used for analyses. (This was true except for the Trace Condition, which began on Thursday, continued for 3 days until Saturday, and resumed for 1 more day the following Tuesday.)

After Experiment 1, the subjects were given food ad lib for a few weeks, after which they were returned to a restricted diet. Training began once all subjects were at 85% of their free-feeding weight. On Days 1–20, subjects were trained under the protocol described above. On baseline Days 21–25, the subjects were given an injection of vehicle solution 1.5 h before the daily session began. The subjects were then divided into the two groups by equating for their averaged temporal gradients during probe trials on the last 5 days of baseline training. In addition, the groups were constructed such that two subjects in each had a different order of training in Experiment 1 from the other two subjects.

On Days 26–30, animals in one group were given an injection of 2.0 mg/kg amphetamine 1.5 h before the session began, while subjects in the other group were injected with 0.6 mg/kg of pimozide before the session. On Days 31–35, all subjects were returned to the vehicle condition. On Days 36–40, the group given amphetamine during the first drug treatment was now injected with pimozide, and the group treated with pimozide during the first drug condition was now injected with amphetamine. On Days 41–50, all subjects were returned once more to the vehicle condition. As there were no systematic effects of amphetamine, only the data obtained during treatment with pimozide is reported. Subjects were exposed to a lower dose of pimozide (0.3 mg/kg) on Days 51–55 in an unsuccessful attempt to maintain greater responding during pimozide treatment. (The data are not reported here as subjects responded even less to the CS during their third exposure to the drug, albeit at a lower dose.) All subjects were returned to the vehicle condition on Days 56–60.

Days 61–65 constituted the Home Cage Condition, during which subjects were injected with 0.6 mg/kg of pimozide within 5 min after the end of a daily training session. The condition thus served as a within-subject control for the timing of drug injection. After this phase, subjects were returned to the vehicle condition on Days 71–95.

Days 96–100 constituted the Trace Condition, in which subjects continued to be injected with vehicle solution 1.5 h prior to the session. The purpose of this condition was to directly examine the effects of introducing a delay from the offset of the keylight until grain presentation. The aim was to make the value of that delay equal to the delay from CS offset until each subject ate during the Pimozide Condition. We attempted to match each subject's delays in the Trace Condition to delays in the Pimozide Condition by adding trace intervals from CS offset until grain presentation that were approximately equal to the difference between each subject's latency to eat in the baseline condition and the latency to eat on each day of the Pimozide Condition. Because latencies to eat depend on the subjects' behavior, the yoking between conditions was not exact. During Days 1–4 of the Pimozide Condition, the latencies to eat were 2.42, 2.92, 3.56, and 4.19 s. During the Trace Condition, the delays from CS offset until subjects ate were 1.67, 2.77, 3.43, and 4.68 s. The yoking procedure mirrored the

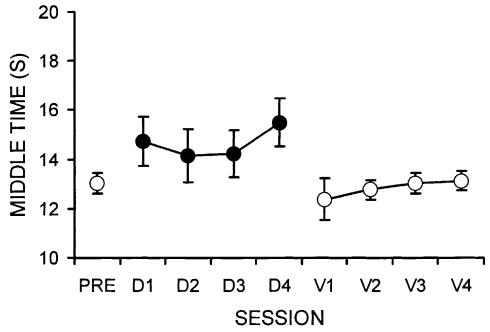

Fig. 3. Mean middle times during predrug (PRE), drug (D1–D4), and postdrug vehicle (V1–V4) phases of pimozide treatment in Experiment 2.

changes in delay over days and spanned the range of delays that subjects experienced in the Pimozide Condition. There was no significant difference between the two conditions in this interval, $F(1,7) < 1$. Finally, on Days 101–105, subjects were returned to the standard protocol with vehicle injections.

3.2. Results

3.2.1. Effects of vehicle

Response distributions during probe trials for 4 days of training before the vehicle injections began were similar to the distributions obtained during 4 days of initial vehicle training. The mean median middle time ± S.D. across the 4 prevehicle days was 13.21 ± 0.57 s and that for the 4 vehicle days was 12.23 ± 0.32 s. The mean discrimination ratios ± S.D. during the corresponding days were 2.08 ± 0.20 and 1.90 ± 0.12, respectively. Paired-comparison *t* tests on each of these measures showed that the measures did not differ before and after vehicle injections, t's(7) < 2.3.

3.2.2. Effects of pimozide

As in Experiment 1, pimozide shifted CR timing to the right. Fig. 3 shows middle times plotted for the predrug, drug, and postdrug conditions, pooled across all subjects. Each point represents data from all subjects that satisfied the response criteria as in Experiment 1. The first point shows the mean of the median middle time across the 4 days of the predrug condition. Middle times showed a systematic increase during pimozide treatment. When returned to vehicle, the middle times returned immediately to predrug values. One subject was dropped from the analyses because response rates were so low that middle times could not be obtained on any treatment day. Another subject did not respond on the first day of pimozide treatment and that point was not included for that subject. In analyzing middle times for the remaining subjects, means on surrounding days were substituted for any days in which responding was too suppressed to compute the standard measures (Winer, 1971). Substitutions for missing data were made for a single day for each of two subjects. Paired-sample *t* tests revealed a difference in middle times during the drug condition compared to the predrug condition on Day 4, $t(6) = 2.13$, $P < .05$, but not on Days 1, 2, or 3, t's(6) < 1.44. There were no significant differences in middle time between each day of the postdrug condition and that during the predrug condition, t's(7) < 1.1. Paired-sample *t* tests on discrimination ratios revealed that compared to the predrug condition (1.86 ± 0.15), discrimination ratios were greater on the first day of the drug condition (2.28 ± 0.21), $t(5) = 2.77$, $P < .05$, and on the first day of the postdrug condition (2.12 ± 0.21), $t(7) = 2.37$, $P = .05$, but not on any other day.

Fig. 4 shows the maximum response rate in the probe trial during the predrug, drug, and postdrug conditions, pooled across all subjects. The maximum response rate decreased immediately upon pimozide administration. Upon removal of the drug, response rates quickly returned to predrug rates. Paired-sample *t* tests revealed that the differences between maximum response rates in the drug condition and the rate during the predrug condition were significant on all four days of the drug condition, t's(7) > 5.8, P's < .01. The differences between rates in the postdrug condition and the rate in the predrug condition were significant on Day 1, $t(7) > 3.65$, $P < .01$, and Day 3, $t(7) = 6.45$, $P < .01$, but not on Days 2 or 4, t's(7) < 1.

The latency to eat on reinforced trials increased gradually during treatment with pimozide. The average latencies across the first 4 treatment days were 2.42, 2.92, 3.56, and 4.19 s. Upon removal of the drug, latencies immediately returned to predrug values. Paired-sample *t* tests revealed that the latency to eat was greater during the drug condition compared to the predrug condition on Days 2–4, t's(7) > 2.4, P's < .05, but not on Day 1, $t(7) < 1$. There were no differences in latency between the postdrug and predrug conditions on any day, t's(7) < 1.2.

3.2.3. Home cage condition

Pimozide injections in the home cage had no effect on CR timing. Middle times, response rates, and latencies were unaffected during the treatment condition, and remained unchanged during the posttreatment condition, t's(7) < 1.5. There were no differences in discrimination ratios between the pretreatment condition and the treatment or posttreatment conditions on any day, t's(7) ≤ 1.8.

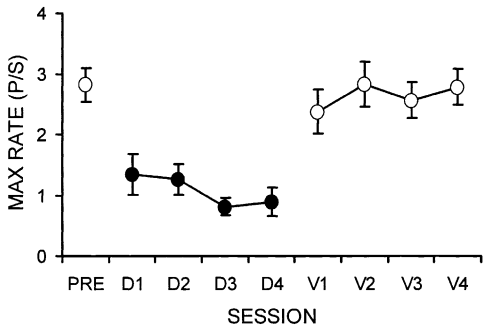

Fig. 4. Mean maximum response rates during predrug, drug, and postdrug vehicle phases of pimozide treatment in Experiment 2.

3.2.4. Trace condition

Imposing a delay between the termination of the CS and the access to food also had no effect on CR timing. Middle times, response rates, latencies (timed from feeder presentation), and discrimination ratios did not differ significantly from baseline values during the treatment condition, and remained unchanged during the posttreatment condition.

3.3. Discussion

Pimozide treatment shifted the CR timing distribution to the right. As in Experiment 1, this shift occurred gradually. In contrast, there was no change in CR timing in either the Home Cage or Trace Condition. The performance during the Home Cage Condition suggests that the increase in middle time during the treatment condition was not due to cumulative exposure to the drug across days, but depends on injections occurring prior to training sessions. The performance during the Trace Condition suggests that the shift in timing was not due increases in eat latency induced by pimozide.

A closer look at individual subject data revealed that not all subjects exhibited the same pattern. Of the five subjects that responded on all of the 4 days during pimozide treatment, three showed a gradual increase across days — consistent with a memory effect — and two showed an immediate increase on Day 1 — consistent with a clock speed effect. A hypothesis consistent with all of the data is that a CR to drug injection causes the shift in timing. The gradual increase in middle times across days raises the possibility that a CR, perhaps to the cues accompanying drug administration, mediates the effect on the clock (see Ohyama et al., 2000). Several exposures to the drug might have been necessary for the CR to be evoked, which would account for the gradual change in timing seen in all subjects in Experiment 1. The immediate increase seen in some subjects in Experiment 2 may have been mediated by a CR that had become established in Experiment 1. For other subjects, reconditioning trials may have been necessary, which would explain why the increase in middle times was gradual for those subjects.

When subjects were returned to the vehicle condition after drug treatment, middle times returned immediately to their pretreatment values. Again, this immediate change in timing may reflect state-dependent learning (Maricq et al., 1981; Overton, 1984). When not on the drug, the animals may have been more likely to retrieve the temporal memories acquired during the baseline phase.

The maximum response rate during probe trials showed an immediate decline upon administration of pimozide. As in Experiment 1, this finding is consistent with the literature on the effects of neuroleptic drugs on instrumentally CRs (Tombaugh et al., 1979; Wise, 1982). When subjects were returned to the vehicle condition after treatment with pimozide, response rates immediately recovered to their pretreatment levels. The maximum response rates were unaffected in the Home Cage and Trace Conditions.

As in Experiment 1, there was no effect of amphetamine on CR timing. One likely explanation is that in contrast to the peak procedure there is persistent responding during the early portion of the CS in the current Pavlovian procedure (Ohyama et al., 1999). This early responding would have masked any shift under amphetamine (see below).

4. General discussion

Together, the above experiments suggest that DA does not affect CR timing simply by modulating the speed of a pacemaker. In two experiments, the DA antagonist pimozide produced a gradual shift in the CR timing distribution during probe trials, suggesting a possible effect of pimozide on temporal memory. A few subjects in Experiment 2 showed an immediate shift in CR timing under pimozide, consistent with a clock-speed effect. In both experiments, the middle times showed an immediate return to predrug values when pimozide was removed, consistent with a clock-speed effect. The overall pattern of results is inconsistent with the notion that pimozide selectively slows a pacemaker.

One explanation for the gradual change in CR timing observed during pimozide treatment is that the drug distorted the storage of temporal memories (Meck, 1983, 1996; Meck and Church, 1987a; Meck and Angell, 1992). The gradual increase in middle times in Experiment 1 could reflect the gradual increase in the proportion of distorted temporal memories from which the animal subsequently samples to make a response. The immediate decline back to baseline values upon removal of the drug may reflect state-dependent learning (Maricq et al., 1981; Overton, 1984). Animals may have acquired different temporal memories under the vehicle and pimozide states, and retrieved the appropriate temporal memory based on the state at the time of testing. The gradual increase seen for some subjects in Experiment 2 and the immediate decline to baseline values is explained similarly. The immediate shift for some subjects in Experiment 2 is harder to reconcile with a memory account. One might have expected animals to show an immediate leftward shift in Experiment 2 had they retrieved state-dependent temporal memories from Experiment 1 in which the CS was only 8 s in duration. However, this may not have occurred because the color and duration of the keylight was changed between experiments. Nevertheless, the immediate rightward shift in CR distributions during the drug phase poses a difficulty for the memory account.

An alternative possibility is that the gradual shift in CR timing seen in Experiments 1 and 2 reflects the acquisition of a CR to the drug injection. That is, pairings of cues associated with the injection and the unconditioned effect of the drug may have resulted in the development of a CR (Eikelboom and Stewart, 1982; Ramsay and Woods, 1997;

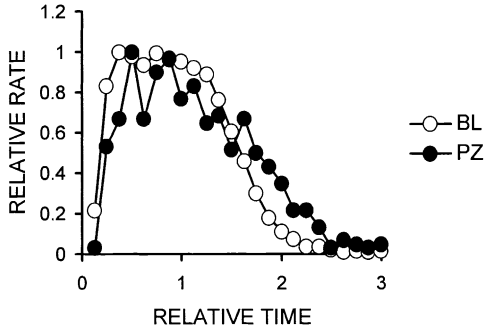

Fig. 5. Temporal distribution of CRs during probe trials in Experiment 1. The average rate of responding relative to the maximum average rate is plotted as a function of the time into the probe trial relative to the ISI, up to a value of 3. The data are plotted for the four baseline days prior to pimozide treatment (BL) and the fourth day of pimozide treatment (PZ).

Siegel, 1989). Such an explanation seems plausible, because previous studies have shown drug conditioning effects for various behaviors after repeated administration of substances that increase or decrease DA levels (Beninger and Hahn, 1983; Carey, 1986, 1992; Chinen and Frussa-Filho, 1999; Lindenblatt and Delius, 1987; Mazurski and Beninger, 1987; Poulos and Hinson, 1982; Schiff, 1982). The gradual increase in middle times may therefore reflect the gradual strengthening of a CR with repeated pairings. In this view, the effect of pimozide on the timing mechanism is indirect, being mediated by a CR to cues associated with the injection of the drug. The immediate decline in middle times when animals are returned to vehicle injections is explained by assuming that the CR becomes associated not only with cues related to any injection, but also with sensory states induced by the drug. Therefore, removal of the drug results in a rapid recovery of baseline performance under vehicle, since the internal sensory cues produced by the drug are also removed. That some subjects in Experiment 2 showed an immediate shift is explained by assuming that the CR had been well established in these subjects, whereas reconditioning was necessary for others.

A recent study in our laboratory with rats using the peak procedure also supports the hypothesis that a CR elicited by drug injection is mediating the change in timing (Ohyama et al., 2000). When rats trained on the peak procedure were given repeated presession injections of pimozide, a shift in the timing of lever-pressing during peak trials emerged gradually, whereas rats given either presession vehicle or postsession pimozide injections showed no shift in timing. This shift was sustained in subsequent extinction sessions preceded by vehicle injections, consistent with both the memory distortion and CR hypotheses. A shift during extinction sessions was also observed, however, in rats given postsession injections of pimozide during the treatment phase but given presession vehicle injections prior to the extinction test. Such a shift could only have occurred because a CR had developed to the cues associated with the drug administration procedure. It should not have been observed if pimozide were simply distorting the memory for reinforced time, since rats in the latter groups were never given the opportunity to perform the timing task under the presence of pimozide. It should be noted that in the present study, there was neither a sustained shift in timing upon return to vehicle after the drug condition (Experiments 1 and 2) nor a shift upon return to presession vehicle injections after the Home Cage Condition (Experiment 2). One likely reason for this is that subjects in the present study were exposed to the vehicle prior to pimozide, and, thus, had acquired state-dependent discriminations.

If the shift in timing is in fact mediated by a CR to the drug administration then the pattern of results reported here suggest that this response produces a change in pacemaker rate or clock speed. The initial slow change in timing would reflect the acquisition of the CR. The immediate shifts in timing after initial training would be dependent on the reinstatement of the training cues. Additionally, a shift in pacemaker rate implies that the change in timing should be proportional to the duration of the event being timed (Maricq et al., 1981). In other words, if the clock was slowed by 10% then timing of all intervals would be delayed by 10%. The data of the current experiments are consistent with this view. Figs. 5 and 6 show the temporal distribution of CRs for Experiments 1 and 2, where the average rate of responding as a proportion of the maximum average rate is plotted as a function of the time elapsed in the probe trial relative to the ISI, for 4 days of baseline prior to pimozide treatment and the fourth day of pimozide treatment. It can be seen that the shifts timing on Day 4 were approximately proportional to the ISI. The average peak time on the fourth treatment day shifted 20% in Experiment 1 (8 s cue) and 16% in Experiment 2 (16 s cue). There was no significant difference in the percentage of change, $t(6) < 1$.

Our findings raise the possibility that the effects of dopaminergic drugs on timing are mediated by CRs that gradually develop to cues associated with drug administration. Although the timing shifts in early studies were reported to be consistent with the hypothesis that DA directly modulates the speed of a pacemaker (i.e., relatively "immediate"), the specific data pooling procedure in these studies may have masked a gradual shift that would have

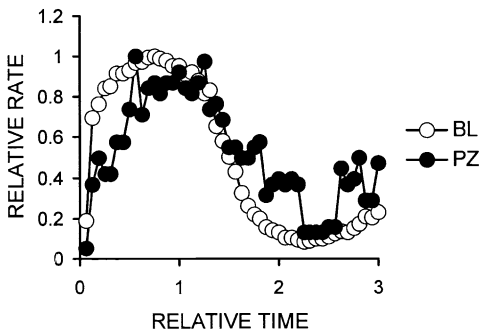

Fig. 6. Temporal distribution of CRs during probe trials in Experiment 2. Data are plotted as in Fig. 5.

been observed had the data been pooled in smaller blocks of trials (Kraemer et al., 1997; Maricq and Church, 1983; Maricq et al., 1981; Meck, 1983). Another factor that may have contributed to the apparent difference between previous results and the current findings is that in earlier studies subjects were given prior exposure to the drug to be tested (Maricq and Church, 1983; Meck, 1983). That some shifts in Experiment 2 were also immediate suggests that prior exposure to dopaminergic drugs may be a necessary condition for the immediate shift in timing to occur. The results, then, are consistent with the notion that an experience-dependent process (e.g., conditioning) mediates the effects of dopaminergic drugs on timing. If this interpretation is correct, the notion that response timing in Pavlovian key-pecking in ring doves and instrumental lever-pressing in rats is mediated by a common neural substrate gains considerable plausibility.

It should be reemphasised that the middle time and response rates were dissociated by our experimental manipulation. The results of Experiments 1 and 2 showed that while the maximum response rate declines immediately upon the administration of pimozide, the change in CR timing does not occur until after repeated testing under the drug. These data suggest that the mechanisms underlying CR timing and those determining the maximum rate of responding to the CS are independent (see Ohyama et al., 1999; Roberts, 1981; Roberts and Holder, 1984). Recent evidence suggests that such mechanisms may involve the basal ganglia (Gibbon et al., 1997b; Malapani et al., 1998). We have suggested that the effects of DA on CR timing may be mediated by slow experience-dependent changes induced in the nigrostriatal DA pathway, while the relatively immediate effects on response rate are mediated by changes in the mesolimbic DA pathway (Ohyama et al., 2000). It is of interest to note that studies of rabbit eyelid conditioning also suggest independent neural sites within the cerebellum (a structure also implicated in timing; Ivry, 1996) that code for the timing of the CR, as well as its expression (Raymond et al., 1996). It remains to be seen how the basal ganglia and cerebellum respectively generate CR timing and how they jointly function in various types of timing tasks (Gibbon et al., 1997b). Regardless, our data provide further support for the view that the mechanisms underlying the learning of "when" to respond, are somewhat independent of those underlying the learning of "whether" to respond (Bouton, 1997; Gallistel and Gibbon, 2000).

In contrast to pimozide, the indirect DA antagonist amphetamine had no effect on CR timing. A recent study showed that amphetamine produced a dose-dependent leftward shift in the CR timing distributions of pigeons trained on the peak procedure, with a maximal shift at 2.0 mg/kg (Kraemer et al., 1997). Given the similarity of CR timing in ring doves trained on the current procedure and pigeons trained in the peak procedure (Kraemer et al., 1997; Ohyama et al., 1999), we anticipated that the same dose of amphetamine would affect CR timing in a similar manner. In two experiments, however, amphetamine had no systematic effect on CR timing. One likely explanation is that compared to the peak procedure, there is less suppression of behavior during the early portions of the non-reinforced probe trials in the current Pavlovian procedure (compare distributions from Kraemer et al., 1997; Ohyama et al., 1999). To detect a significant shift, there must be enough suppression early in the trial to allow for the CR distribution to move left. In the current procedure, there was substantial responding early in the trial regardless of the ISI (Ohyama et al., 1999; Figs. 5 and 6). Thus, the lack of an amphetamine effect was probably in part due to a floor effect. Casual observation of the truncated portion of the probe trials showed that amphetamine substantially elevated responding during this segment in Experiment 2 (data not shown), similar to a previous study in rats (Maricq et al., 1981; Kraemer et al., 1997; Poling and Thompson, 1977). Such an elevation would have further masked a leftward shift in CR timing.

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References

Altman JL, Appel JB, McGowan WT. Drugs and the discrimination of duration. Psychopharmacology 1979;60:183–8.

Balsam PD. Relative time in trace conditioning. In: Gibbon J, Allan LG, editors. Timing and time perception. New York: New York Academy of Sciences, 1984. pp. 211–27.

Beninger RJ, Hahn BL. Pimozide blocks the establishment but not expression of amphetamine-produced environment-specific conditioning. Science 1983;220:1304–6.

Bitterman ME. Classical conditioning in the goldfish as a function of the CS–US interval. J Comp Physiol Psychol 1964;58:359–66.

Blackburn JR, Pfaus JG, Phillips AG. Dopamine functions in appetitive and defensive behaviours. Prog Neurobiol 1992;39:247–79.

Bouton ME. Signals for whether versus when an event will occur. In: Bouton ME, Fanselow MS, editors. Learning, motivation, and cognition: the functional behaviorism of Robert C Bolles. Washington, DC: American Psychological Association, 1997. pp. 385–409.

Brown BL, Hemmes NS. Timing of the CS–US interval by pigeons in trace and delay autoshaping. Q J Exp Psychol 1997;50B:43–50.

Carey RJ. A conditioned anti-parkinsonian drug effect in the hemi-parkinsonian rat. Psychopharmacology 1986;89:269–72.

Carey RJ. Pavlovian conditioning of L-dopa induced movement. Psychopharmacology 1992;107:203–10.

Catania AC. Reinforcement schedules and psychophysical judgements: a study of some temporal properties of behavior. In: Shoenfeld WN, editor. The theory of reinforcement schedules. New York: Appleton-Century-Crofts, 1970. pp. 1–42.

Chinen CC, Frussa-Filho R. Conditioning to injection-procedures and repeated testing increase SCH 23390-induced catalepsy in mice. Neuropsychopharmacology 1999;21:670–8.

Church RM. Properties of the internal clock. In: Gibbon J, Allan LG, editors. Timing and time perception. New York: New York Academy of Sciences, 1984. pp. 566–82.

Davis M, Schlesinger LS, Sorenson CA. Temporal specificity of fear conditioning: effects of different conditioned stimulus-unconditioned stimulus intervals on the fear-potentiated startle effect. J Exp Psychol: Anim Behav Processes 1989;15:295–310.

Desmond JE, Moore JW. Adaptive timing in neural networks: the conditioned response. Biol Cybern 1988;58:405–15.

Eikelboom R, Stewart J. Conditioning of drug-induced physiological responses. Psychol Rev 1982;89:507–28.

Gallistel CR, Gibbon J. Time, rate, and conditioning. Psychol Rev 2000;107:289–344.

Gibbon J. Scalar expectancy theory and Weber's Law in animal timing. Psychol Rev 1977;84:279–325.

Gibbon J. The origins of scalar timing. Learn Motiv 1991;22:3–38.

Gibbon J, Balsam PD. Spreading association in time. In: Locurto CM, Terrace HS, Gibbon J, editors. Autoshaping and conditioning theory. San Diego (CA): Academic Press, 1981. pp. 219–51.

Gibbon J, Farrell L, Locurto CM, Duncan HJ, Terrace HS. Partial reinforcement in autoshaping with pigeons. Anim Learn Behav 1980;8: 45–59.

Gibbon J, Church RM, Meck WH. Scalar timing in memory. In: Gibbon J, Allan LG, editors. Timing and time perception. New York: New York Academy of Sciences, 1984. pp. 52–77.

Gibbon J, Fairhurst S, Goldberg B. Cooperation, conflict and compromise between circadian and interval clocks in pigeons. In: Bradshaw CM, Szabadi E, editors. Time and behaviour: psychological and neurobehavioural analyses. Advances in psychology, vol. 120. Amsterdam, Netherlands: North-Holland/Elsevier, 1997a. pp. 329–84.

Gibbon J, Malapani C, Dale CL, Gallistel C. Toward a neurobiology of temporal cognition: advances and challenges. Curr Opin Neurobiol 1997b;7:170–84.

Gormezano I. Investigations of defense and reward conditioning in the rabbit. In: Black A, Prokasy WF, editors. Classical conditioning: II. Current research and theory. New York: Appleton-Century-Crofts, 1972. pp. 151–81.

Ivry RB. The representation of temporal information in perception and motor control. Curr Opin Neurobiol 1996;6:851–7.

Kamin LJ. Temporal and intensity characteristics of the conditioned stimulus. In: Prokasy WF, editor. Classical conditioning: a symposium. New York: Appleton-Century-Crofts, 1965. pp. 118–47.

Killeen PR, Fetterman JG. A behavioral theory of timing. Psychol Rev 1988;95:274–95.

Kraemer PJ, Randall CK, Dose JM, Brown RW. Impact of d-Amphetamine on temporal estimation in pigeons tested with a production procedure. Pharmacol, Biochem Behav 1997;58:323–7.

Lindenblatt U, Delius JD. Apomorphine-induced pecking in pigeons classically conditioned to environmental cues. Psychopharmacology 1987;93:223–5.

Malapani C, Rakitin B, Levy C, Meck WH, Deweer B, Dubois B, Gibbon J. Coupled temporal memories in Parkinson's Disease: a dopamine-related dysfunction. J Cognit Neurosci 1998;10:316–31.

Maricq AV, Church RM. The differential effects of haloperidol and methamphetamine on time estimation in the rat. Psychopharmacology 1983;79:10–5.

Maricq AV, Roberts S, Church RM. Methamphetamine and time estimation. J Exp Psychol: Anim Behav Processes 1981;7:18–30.

Mauk MD, Donegan NH. A model of Pavlovian eyelid conditioning based on the synaptic organization of the cerebellum. Learn Mem 1997;4: 130–58.

Mazurski EJ, Beninger RJ. Environment-specific conditioning and sensitization with (+)-amphetamine. Pharmacol, Biochem Behav 1987; 27:61–5.

Meck WH. Selective adjustment of the speed of internal clock and memory processes. J Exp Psychol: Anim Behav Processes 1983;9:171–201.

Meck WH. Affinity for the dopamine D_2 receptor predicts neuroleptic potency in decreasing the speed of an internal clock. Pharmacol, Biochem Behav 1986;25:1185–9.

Meck WH. The neuropharmacology of interval timing. Cognit Brain Res 1996;3:227–42.

Meck WH, Church RM. Cholinergic modulation of the content of temporal memory. Behav Neurosci 1987a;101:457–64.

Meck WH, Church RM. Nutrients that modify the speed of internal clock and memory storage processes. Behav Neurosci 1987b;101:465–75.

Meck WH, Angell KE. Repeated administration of pyrithiamine lead to a proportional increase in the remembered durations of events. Psychobiology 1992;20:39–46.

Moore JW, Choi JS. The TD model of classical conditioning: response topography and brain implementation. In: Donahoe JW, Dorsel VP, editors. Neural-network models of cognition: biobehavioral foundations. Advances in psychology, vol. 121. Amsterdam, Netherlands: North Holland/Elsevier, 1997. pp. 387–405.

Ohyama T, Gibbon J, Deich JD, Balsam PD. Temporal control and maintenance of autoshaping in the ring dove. Anim Learn Behav 1999;27:89–98.

Ohyama T, Horvitz JC, Drew M, Gibbon J, Malapani C, Balsam PD. Conditioned and unconditioned behavioral–cognitive effects of a dopamine antagonist. Behav Neurosci 2000;114:1251–5.

Overton DA. State-dependent learning and drug discriminations. In: Iverson LL, Iverson SD, editors. Handbook of psychopharmacology, vol. 18. New York: Plenum, 1984. pp. 59–127.

Poling A, Thompson T. The effects of d-amphetamine on the automaintained key pecking of pigeons. Psychopharmacology 1977;51:285–8.

Poulos CX, Hinson R. Pavlovian conditional tolerance to haloperidol catalepsy: evidence of dynamic adaptation in the dopaminergic system. Science 1982;218:491–2.

Ramsay DS, Woods SC. Biological consequences of drug administration: implications for acute and chronic tolerance. Psychol Rev 1997; 104:170–93.

Rapp DL, Robbins TW. The effects of d-amphetamine on temporal discrimination in the rat. Psychopharmacology 1976;51:91–100.

Raymond JL, Lisberger SG, Mauk MD. The cerebellum: a neuronal learning machine? Science 1996;272:1126–31.

Roberts S. Isolation of an internal clock. J Exp Psychol: Anim Behav Processes 1981;7:242–68.

Roberts S, Holder MD. What starts an internal clock? J Exp Psychol: Anim Behav Processes 1984;10:273–96.

Schiff SR. Conditioned dopaminergic activity. Biol Psychiatry 1982; 17:135–54.

Siegel S. Pharmacological conditioning and drug effects. In: Goudie AJ, Emmett-Oglesby MW, editors. Psychoactive drugs: tolerance and sensitization. New Jersey: Humana Press, 1989. pp. 115–80.

Stubbs DA, Thomas JR. Discrimination of stimulus duration and d-amphetamine in pigeons: a psychophysical analysis. Psychopharmacologia 1974;36:313–22.

Tombaugh TN. Effects of pimozide on nondiscriminated and discriminated performance in the pigeon. Psychopharmacology 1981;73:137–41.

Tombaugh TN, Tombaugh J, Anisman H. Effects of dopamine receptor blockade on alimentary behaviors: home cage food consumption, magazine training, operant acquisition, and performance. Psychopharmacology 1979;66:219–25.

Winer BJ. Statistical principles in experimental design New York: McGraw-Hill, 1971.

Wise RA. Neuroleptics and operant behavior: the anhedonia hypothesis. Behav Brain Sci 1982;5:39–87.