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The Differential Effects of Haloperidol and Methamphetamine on Time Estimation in the Rat

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Abstract. Forty rats were trained to make a left lever response if a signal (white noise) was 2.5 s and to make a right lever response if the signal was 6.3 s. When seven intermediate signal durations, to which responses were not reinforced, were randomly interspersed the probability of a right-lever ('long') response increased as a function of signal duration. Methamphetamine shifted this psychometric function leftward and decreased its slope: haloperidol also decreased the slope but shifted the function rightward. A combination of haloperidol and methamphetamine led to a function similar to the saline control function. The leftward shift probably reflects an increase in the speed of an internal clock, and the rightward shift probably reflects a decrease in its speed. Since methamphetamine releases several catecholamines, including dopamine, and haloperidol blocks dopamine receptors, it is plausible that the horizontal location of the psychometric function (the speed of the clock) is related to the effective level of dopamine.

Key words: Haloperidol – Methamphetamine – Time estimation

There is evidence that administration of methamphetamine (M) increases the speed of the internal clock (Maricq et al. 1981). In one experiment, 28 rats were trained to press the left lever following a signal (light termination) of one duration and to press the right lever following a signal of a longer duration. When five intermediate signal durations to which responses were not reinforced were added, the probability of a right-lever ('long') response increased as a function of signal duration. As in a previous experiment (Church and Deluty 1977), the psychometric function was fairly symmetrical on a logarithmic time scale. The point of indifference (PI, the duration that the animals were equally likely to classify as short or long) was at the geometric mean between the two extreme signals to which responses were reinforced, and the difference limen (DL, one-half of the difference between the duration that was classified as long on 75% of the trials and on 25% of the trials) was a constant proportion of the PI. Thus, the Weber fraction (WF, the DL divided by the PI) was a constant at various ranges of signal durations (1 s versus 4 s, 2 s versus 8 s, 3 s versus 12 s, 4 s versus 16 s).

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Administration of M (1.5 mg/kg) produced a leftward shift in the psychometric function relating the probability of a long response to the duration of the signal. The shift occurred at all signal ranges used (1 s versus 4 s, 2 s versus 8 s, 4 s versus 16 s), and it was a fairly constant percentage rather than a constant number of seconds. The leftward shift in the PI was about 10%. This is presumably due to an increase in clock speed of about 10% produced by M.

Although there has been substantial previous research on the influence of M and related drugs (e.g., *d*-amphetamine) on the performance of animals on schedules in which time is a relevant variable, particularly differential reinforcement of low rate (DRL) and fixed-interval (FI) responding, the basis for the influence of the drugs on these schedules is difficult to interpret. For example, Maricq et al. (1981) present the argument that the leftward shift in the distribution of interresponse times produced by amphetamine in a DRL schedule (Sanger et al. 1974) could have been produced by either an increase in clock speed or an overall increase in response tendency. Others have provided evidence that the apparent disruption of temporal discrimination in DRL schedules by amphetamine is due to changes in response rate, not change in sensitivity to temporal cues (Robbins and Iversen 1973; Segal 1962). Similarly, the typical effect of amphetamine on FI performance is to increase the response rate early in the interval and leave it relatively unaffected later in the interval (Branch and Gollub 1974). This rate-dependent result might have occurred as a result of an increase in clock speed or a general disruption of schedule control. The two procedures used by Maricq et al. (1981), the temporal bisection method described above, and a peak procedure developed by Roberts (1981) were designed to isolate clock speed from other factors, such as overall responsiveness. Both procedures led to the conclusion that M increased clock speed.

The purpose of the present experiment was to attempt to narrow the range of possible neurotransmitter systems that might be responsible for the increase in clock speed produced by M. The predominant effect of M is to enhance the release of neuronal catecholamines, primarily dopamine (DA) and norepinephrine (NE) (Carlsson 1970; Glowinski 1970). One method to attempt to isolate the relevant neurotransmitter system is to employ a selective blocker. Using such blockers, Yokel and Wise (1976) found DA to be an important factor in the effectiveness of amphetamine as a reinforcement, while NE had a much smaller role. Ridley et al. (1981) found DA to be an important factor in the perseverative responding following administration of amphetamine.

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A similar conclusion was found with respect to the discriminative function of amphetamine, using the drug as a discriminative stimulus in an operant task. The stimulus properties were decreased after pretreatment with a DA receptor blocker (haloperidol), but were undisturbed if a NE receptor blocker (phenoxybenzamine) was used instead (Schechter and Cook 1975): also, in this study, a drug that specifically stimulates DA receptors (apomorphine) was used instead of amphetamine and was found to mimic its discriminative cue properties. Similarly, apomorphine failed to act as a discriminative cue if the animal was pretreated with haloperidol. Therefore, the discriminative property of amphetamine seems to be mainly mediated by DA.

In the present experiment, the same logic for drug selection was used. The problem was to determine whether the leftward shift in the psychometric function produced by M, which presumably reflects an increase in the speed of an internal clock, is due to an increase in the effective level of DA. To test the DA explanation of clock speed, we selected M (1.0 mg/kg) as a releaser of various neuronal catecholamines, and haloperidol (0.12 mg/kg) as a blocker of DA receptors. The design of the experiment was simple. Each of the 40 rats received each of the following treatments: M alone (M treatment); both haloperidol and M (B treatment); haloperidol alone (H treatment). Half the subjects received the treatments in the M-B-H order and half received them in the H-B-M order. Each session was separated by four sessions of nondrug training to minimize the development of tolerance.

Materials and Methods

The subjects were 40 experimentally naive male albino rats (Charles River). They were about 100 days old, and about 300 g in weight at the start of drug testing. Throughout the experiments, each rat received 14 g ground rat chow mixed with about 25 ml water daily.

Ten lever boxes (23 × 20 × 22 cm) were used in the experiment. Each box had two retractable levers, a food tray, and a speaker. A time-shared PDP-12 computer controlled the experimental equipment and recorded the responses.

Two-Signal Training (Days 1–16). After four sessions of combined magazine and lever press training, the rats were trained to press the left lever following a 2 s signal and to press the right lever following an 8 s signal. The signal was white noise. Each signal duration was presented with a probability of 0.5 on each trial. At the end of the signal both levers were inserted. If the rat made the correct response, a pellet of food was delivered immediately after the response. If the rat made the incorrect response, no pellet was delivered and the same stimulus duration was presented again on the next trial (correction method). In both cases the levers were withdrawn 0.5 s after the first response. After a 30-s intertrial interval another trial was begun. Daily sessions lasted for 1 h 50 min. Each animal received 16 days of two-signal training.

Nine-Signal Training (Days 17–24). The conditions of training were maintained except that each of the two extreme signal durations (2 and 8 s) was presented with a probability of 0.25 on each trial. On trials when an extreme signal was not presented, an intermediate signal was presented with a probability of 0.5; all of the seven intermediate signals were used once before being repeated. Five of the signal durations were spaced at equal logarithmic intervals between the two extremes used in training. The other two signals were placed at the logarithmic mean of the signals 3 and 5 and signals 5 and 7, respectively (2.0, 2.5, 3.2, 3.6, 4.0, 4.5, 5.0, 6.3, and 8.0 s). In the case of the seven intermediate signals, neither the left or right response was followed by food and there were no correction trials. Each rat had eight sessions of nine-signal training.

Seven Signal Training (Days 25–35). The conditions were identical to those in nine-signal training except that the 2-s and 8-s signals were no longer used so that the 2.5-s and 6.3-s signals were the new extremes and the only signals that were followed by reinforcement. This reduction in the number of signals increased the number of trials with signal durations in the range where the response choice varied with small changes in signal duration. Correction trials now occurred only following errors on 2.5-s or 6.3-s signals. Each rat received 11 sessions of seven-signal training before the drug-testing sessions. On the last 5 days each rat received 0.15 ml SC physiological saline approximately 15 min prior to testing. Daily sessions lasted for 1 h 50 min.

Drug Testing (Days 36–60). The effects of two drugs haloperidol and M were tested in this experiment. This phase began after 20 preliminary sessions, four with drugs (data not shown). Each drug session was separated by four nondrug sessions on which each rat received 0.15 ml physiological saline 15 min prior to testing. Group M-B-H received M, then both haloperidol and methamphetamine (B), then haloperidol (H). Group H-B-M received the three treatments in the opposite order. The drug treatments were as follows: group M-B-H received 0.15 ml physiological saline followed 1 h later by 1.0 mg/kg M on days 40 and 45, 0.12 mg/kg haloperidol followed 1 h later by 1.0 mg/kg M on day 50, and 0.12 mg/kg haloperidol followed 1 h later by 0.15 ml physiological saline on days 55 and 60; group H-B-M received 0.12 mg/kg haloperidol followed 1 h later by 0.15 ml physiological saline on days 40 and 45, 0.12 mg/kg haloperidol followed 1 h later by 1.0 mg/kg M on day 50, and 0.15 ml physiological saline followed 1 h later by 1.0 mg/kg M on days 55 and 60.

All drug injections were given in a volume of 0.15 ± 0.01 ml. All injections were SC in the flank, and testing began 15 min after the last injection.

Results

Seven-Signal Training. The mean percentage long response increased as a function of signal duration. A PI was estimated from the mean psychophysical function of each individual (excluding the two extreme signals) as follows: (1) the straight line with the greatest slope, fitted by the method of least-squares, relating the percentage of long responses to three adjacent signal durations was identified, and from this straight line (2) the signal duration that was associated with 50% long response was calculated and reported as PI. A DL was also estimated from the individual psychophysical functions. From the same straight lines used to estimate PI we found the signal duration associated with 75% long response and the signal duration associated with 25% long response. One-half of the range between these two signal durations was defined as the DL. The WF was defined as DL/PI.

When only responses with latencies greater than 5 s were used the resulting psychophysical function was fairly flat. When responses with latencies less than or equal to 5 s were used the resulting psychophysical function was much steeper and the function was approximately symmetrical when plotted against the logarithm of signal duration. The mean WF was 0.10 and the mean PI was 4.13. The PI was close to the geometric mean between the two extreme signals (4 s). The figures use only responses with latency less than or equal to 5 s.

Drug Testing. The most striking effect of M was the leftward shift in PI. This is shown as the mean psychophysical function of 37 animals in the left panel of Fig. 1, which omits two animals because they did not respond under M treatment and a third animal because of a procedural error. The mean PI were 3.83 s and 4.05 s for the M and saline conditions respectively [t (36) = 3.44, $P < 0.01$]. PI was lower on the M injection days than on the saline days for 28 of 37 animals. The crossing of the functions is due to the disruption in timing caused by the drug, e.g., the rats had a larger WF and made fewer correct responses at the extremes. The mean WF were 0.12 and 0.09, and the mean percent incorrect on the extremes were 16% and 9% for the methamphetamine and saline conditions, respectively [t (35) $\geq$ 4.15, $P < 0.001$]. The WF was higher on M injection days than on the saline days for 29 of 36 animals: one animal's WF was omitted from the analysis because it was greater than 3.3 SD above the mean. Six of the seven animals that had a decreased WF also had a leftward shift in PI.

The mean psychophysical function of the 38 animals that received 0.12 mg haloperidol plus 1.0 mg M was similar to the function on saline days (center panel of Fig. 1, which omits one animal because of insufficient responding on the preceding control days and another animal because its PI was greater than 3.3 SD from the mean). The most obvious discrepancy is that the percentage of incorrect responses on the extremes was increased from 10% under the saline condition to 17% under the drug condition [t (37) = 4.75, $P < 0.001$]. However, PI and WF were affected little by the drugs. The mean PI were 4.11 and 4.06 for the drug and saline conditions, respectively (20 rats had an increased PI, 18 had a decreased PI, binomial test, NS). The mean WF were 0.10 and 0.09 for the drug and saline conditions, respectively (22 rats had higher WF, 17 had lower WF, binomial test, NS).

When haloperidol alone was administered to the animals, there was disruption of timing, i.e., a decreased percentage correct on the extremes and an increased WF, and a rightward shift of PI (Fig. 1, right panel). The mean PI were 4.47 and 3.98 under the drug and saline conditions, respectively. Of the 37 animals, 31 had a rightward shift in the PI [t (36) = 6.86, $P < 0.001$]: three rats were omitted because of lack of responding during the drug days. The change in WF and percent incorrect on the extremes was also clear: the mean WF were 0.16 and 0.10, and the mean percent incorrect on the extremes were 28% and 10% under the drug and saline conditions, respectively [t (35) $\geq$ 5.50, $P < 0.001$]. Of 36 rats, 31 had an increased WF (one rat's WF was not included because it was greater than 3.3 SD above the mean). Only two of the five rats that had a lower WF on the drug day had a rightward shift in the PI.

For each drug condition, PI was calculated for each animal on the drug and saline control days. The difference between the drug and saline value was obtained: the mean decrease in PI in the M condition was 0.22 s, which was significantly different from zero change [t (36) = 3.44, $P < 0.01$]. The mean increase in PI for the haloperidol plus M condition was 0.06 s, which was not significantly different from zero change [t (37) = 0.70, NS] but was significantly different from the mean decrease in PI under the M conditions [t (36) = 2.54, $P < 0.05$]. The mean increase in PI for the haloperidol condition was 0.48 s, which was significantly different from zero change [t (36) = 6.86, $P < 0.001$]. The variability in the change in PI was greater for the combined drug group than for either drug alone [F (37,36) = 2.07 and F (37,36) = 1.73, $P < 0.05$].

For each drug condition, WF was calculated for each animal on the drug and control days and the difference between the drug and saline value was obtained: the mean increase in WF for the M condition was 0.034, which was significantly different from zero change [t (35) = 4.25, $P < 0.001$]. The mean increase for the haloperidol plus M condition was 0.004, which was not significantly different from zero change [t (38) = 0.44, NS] but was significantly different from the mean increase in WF under the M conditions [t (35) = 2.39, $P < 0.05$]. The mean increase for the haloperidol condition was 0.059, which was significantly different from zero change [t (37) = 5.4, $P < 0.001$].

The left panel of Fig. 2 shows PI for the two groups of 20 animals. Group M-B-H was presented with drug conditions

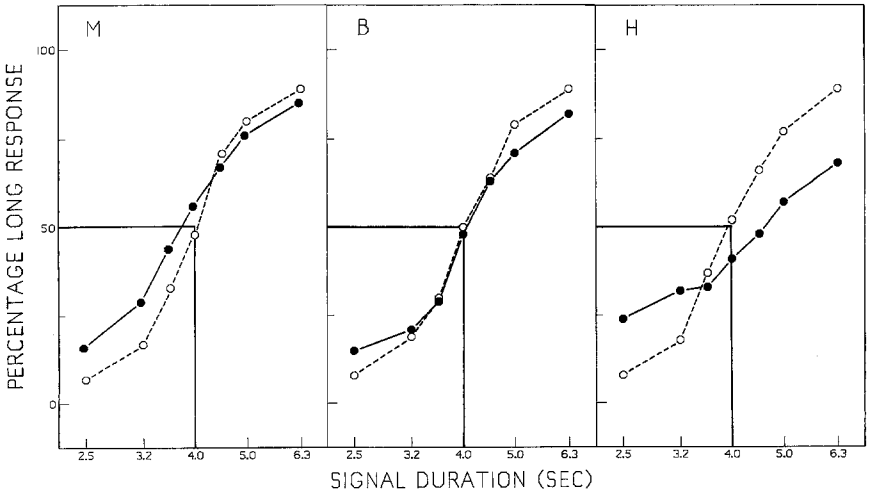

Fig. 1
Mean percentage 'long' response as a function of signal duration for sessions with methamphetamine (M, *left panel*), haloperidol plus methamphetamine (B, *center panel*) and haloperidol (H, *right panel*). Each of the drug functions (●) is shown with its saline control functions (○)

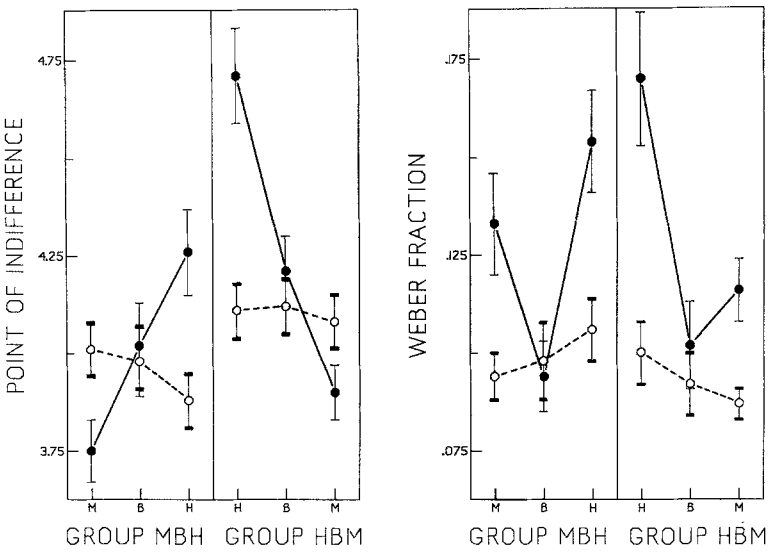

Fig. 2
Point of indifference (*left panel*) and Weber fraction (*right panel*) for the M-B-H group and the H-B-M group. The drug treatments are methamphetamine (M), haloperidol plus methamphetamine (B), and haloperidol (H). Each drug function (●) is shown with its saline control function (○)

in the following order: M; haloperidol plus M; haloperidol. Group H-B-M had the conditions in the reverse order. Both groups began and ended testing on the same days, differing only in the order of presentation. For either drug order the PI was lower with M than saline, higher with haloperidol than saline, and about the same as saline when both drugs were administered. Because of the order of presentation, this resulted in a rising PI function for the drug days in group M-B-H and a decreasing PI function for the drug days in group H-B-M. All differences between saline and drug PI values on single-drug injection days were reliable ($P < 0.05$), except for the M condition in group H-B-M. The difference between saline and drug PI values on the combination-drug days was not significant.

The right panel of Fig. 2 shows the WF for the two groups of 20 animals. For either drug order, WF was higher with either M or haloperidol alone than with saline, but it was about the same as the saline value on the combined-drug days. All single-drug WF values were reliably different from the corresponding saline values ($P < 0.05$). The difference between saline and drug WF values on the combination-drug days was not significant.

For each animal in group M-B-H a psychophysical function was constructed from the saline day following each M injection day. Unfortunately, this could not be done for group H-B-M since testing ended on the last M injection day. From each animal's psychophysical function a PI and WF were computed as described earlier. Compared to the saline days preceding M injection, on the saline days following M injection ten of 18 rats had a higher PI, eight had a higher WF, nine had a higher percentage of incorrect responses on the extremes, and 12 had a slower mean latency of response. The same analysis was applied to the 17 rats in group H-B-M that received haloperidol. Compared to the saline days preceding haloperidol injection, on the saline days following haloperidol injection 11 of the 17 rats had a higher PI, eight had a higher WF, eight had a higher percentage of incorrect responses on the extremes, and 11 had a slower mean latency of response. None of these values differed from values expected from chance alone. Therefore, we found no evidence for a rebound effect following either M or haloperidol injections, i.e., the saline days surrounding the injection days were indistinguishable.

For each animal, the mean latency of response for each signal duration under each drug condition and corresponding saline control condition was calculated, then the mean across animals was calculated (Fig. 3, where the procedure was identical to that used to generate the psychophysical functions in Fig. 1, except that latency of response rather than percentage long response was used).

The 37 rats that received M injections had fewer trials than under the saline control. The mean number of responses per signal per rat was 35 and 40 under drug and saline conditions, respectively [t (36) = 3.0, $P < 0.01$]. However, the rats responded much faster under the M condition (Fig. 3, left panel). The function for the saline days shows a clear peak at approximately the PI (4 s). The function for the animals under M conditions is below the saline function and shows no definitive maximum, although it appears to fall to the left of the saline peak. The mean latencies of response were 1.48 s and 1.74 s under the drug and saline conditions, respectively. This decrease in mean latency was reliably different from zero change [t (36) = 4.5, $P < 0.001$].

The 38 rats that received haloperidol plus M had 9 % fewer trials than under the saline control. The mean number of response per signal per rat was 21 and 19 under the drug and saline conditions, respectively [t (37) = 2.5, $P < 0.05$]. The latency function for these rats is shown in the center panel of Fig. 3. It is not as stable as the others since only 1 day of data was available. However, the saline function again rose to a maximum near the PI. The latency function for the drug condition did not reveal a clear maximum. The mean latencies of response were 1.61 s and 1.79 s under the drug and saline conditions, respectively. This decrease in mean latency was reliably different from zero change [t (37) = 3.9, $P < 0.001$], but was not significantly different from the change in latency in the M condition [t (37) = 1.0, NS].

The 37 rats that receiveved haloperidol injections had 32 % fewer trials than under the saline control. The mean number of responses per signal per rat was 29 and 42 under the drug and saline conditions, respectively [t (36) = 8.6, $P < 0.001$]. The latency function for these rats is shown in the right panel of Fig. 3: the saline function is similar to that shown in the other two panels, but the haloperidol function is generally above the saline function. The mean latencies of response were 1.97 s and 1.76 s under the drug and saline

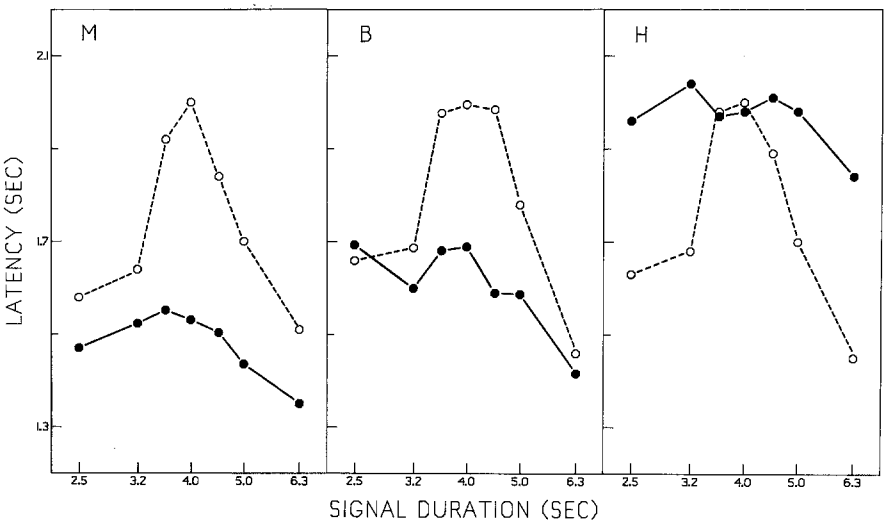

Fig. 3
Mean latency as a function of signal duration for sessions with methamphetamine (M, *left panel*), haloperidol plus methamphetamine (B, *center panel*), and haloperidol (H, *right panel*). Each of the drug functions (●) is shown with its saline control function (○)

conditions, respectively. This increase in mean latency was reliably different from zero change [t (36) = 3.9, $P < 0.001$]. The haloperidol function does not show a clearly defined maximum.

Discussion

The time estimation procedure used in this experiment led to evidence of excellent time discrimination, particularly when short-latency responses were observed. Responses with latencies over 5 s were only weakly related to the signal duration. Perhaps, on these trials the animal was not paying attention to signal duration or had forgotten the signal duration. Responses with latencies under 5 s were closely related to the signal duration. Consistent with earlier reports (Church and Deluty 1977; Maricq et al. 1981), the PI was close to the geometric mean of 4 s. In this experiment, the ratio between the longest and shortest signal was 2.5, while in previous experiments it has usually been 4.0. Thus, the PI appears to be located at the geometric mean between the two extremes, not relative to the shortest signal only. The function relating response latency to signal duration also had a maximum near the geometric mean. This is an independent measure of equality of psychological distance between the two extreme signal durations. Presumably, the animals respond slowly following this signal duration either because of conflict or because of the low probability of reinforcement.

The major result was that M produced a leftward shift in the psychometric function relating probability of a long response to signal duration, while haloperidol produced a rightward shift and the combination of haloperidol and M produced no shift in the psychometric function relative to saline control sessions. Both M and haloperidol alone, but not in combination, increased DL. In addition, M decreased response latencies and haloperidol increased response latencies, but the combination of haloperidol and M did not normalize response latencies. Although the drug effects were much larger than order effects, previous treatment with haloperidol attenuated the effects of M on subsequent sessions.

A tentative interpretation is that M releases DA that leads to an increase in clock speed that is reflected in the leftward shift of the psychometric function. Haloperidol, by blocking DA receptors, led to a decrease in clock speed that was reflected in the rightward shift in the psychometric function. Any change (i.e., either an increase or a decrease) in the normal effective level of DA interfered with maximal control by time as reflected in the increase in DL. When haloperidol and M were combined the effective receptor level of DA may have been close to normal. Thus, the PI and WF were restored to normal, although there are still measurable differences in response latency and response probability following extreme signal durations.

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