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The effects of *d*-amphetamine, chlordiazepoxide and alpha-flupenthixol on food-reinforced tracking of a visual stimulus by rats

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Abstract. Rats were trained to respond to one of two levers under a random ratio schedule of food reinforcement. Which of the levers was correct was redetermined before each response and signalled by a light. The effects of *d*-amphetamine (0.2–3.2 mg/kg), chlordiazepoxide (1–8 mg/kg), and the neuroleptic alpha-flupenthixol (0.03–0.33 mg/kg) on the efficiency of rats tracking this visual cue were examined. *d*-Amphetamine increased the proportion of responses made on the correct lever at low and intermediate doses, but reduced the proportion at 3.2 mg/kg. At the highest dose, chlordiazepoxide produced a small increase in this measure, together with a reduction in response rate, but alpha-flupenthixol had no effect, even at a dose reducing response rate. Low doses of amphetamine also increased switching between the levers, producing a proportionately greater increase in switching from the correct lever to the incorrect lever than vice versa. The results are interpreted as showing that *d*-amphetamine facilitates tracking performance as a result of its action of enhancing response switching, and supporting the hypothesis that facilitation of performance by amphetamine-like drugs depends on the effect of the drug on response output coinciding with task requirements.

Key words: Tracking – Visual discrimination – Switching – Perseveration – Attention – *d*-Amphetamine – Chlordiazepoxide – Alpha-flupenthixol – Rat

In some circumstances in which two separate incompatible responses are concurrently reinforced, animals will switch between them frequently. Evenden and Robbins (1983a and b) described a schedule in which switching was generated in rats by the random distribution of reinforcement across two levers in an operant chamber. The frequency of switching could be systematically altered both by environmental manipulations and by drug treatments. For example, *d*-amphetamine generally increased the relative frequency of switching at doses that did not affect the rate of responding, whereas chlordiazepoxide and the neuroleptic alpha-flupenthixol had no effect.

In the present experiment, we provided a visual cue (a light) to indicate on which of the two levers responses would result in reinforcement under a random ratio schedule. Behaviour under stronger exteroceptive stimulus control might be more resistant to the effects of *d*-amphetamine. For example, Laties (1972) and Laties et al. (1981) used a fixed consecutive number (FCN) schedule in which a switch between two levers was required after a fixed number of responses had been completed on the first lever. They found that introducing a visual stimulus to signal the completion of the response requirement on the first lever reduced premature switching produced by *d*-amphetamine in the unsignalled FCN condition.

In the present experiment, changing the location of the light and the availability of reinforcement from one lever to another during the completion of the schedule requirement caused the rats to switch between the levers, "tracking" the location of the light and providing a sensitive baseline for measuring drug-induced changes in performance.

This provides a way of evaluating how closely response switching coincides with the switching of the visual cue from one lever to another, and how drug effects under this schedule compare with those on response switching in the absence of the visual cue. For the purposes of comparison, in additon to *d*-amphetamine, we also examined the effects of chlordiazepoxide and alpha-flupenthixol, drugs with actions on response switching in the absence of visual cues that have already been studied (Evenden and Robbins 1983a).

This experiment is related to tracking experiments using human subjects, where amphetamine-like stimulants have been reported to facilitate performance under certain conditions (Weiss and Laties 1962). It may also help interpretation of both the facilitatory and disruptive effects of drugs on schedules of reinforcement in which animals are required to switch between responses to provide an assessment of discrimination (for example, Katz 1982), learning (Kulig and Calhoun 1972) and reinforcer efficacy (Valenstein and Myers 1964) independent of response rate.

Materials and methods

Subjects. The subjects were 12 naive male Sprague-Dawley rats (OLAC, Bicester, GB), aged 3 months and housed in pairs. Each rat was given 15 g laboratory chow each day in addition to the food obtained during testing, and had free access to water.

Apparatus. Two double-lever operant chambers, 26.5 × 22 × 20 cm high, were used (Model 4102, Campden Instru-

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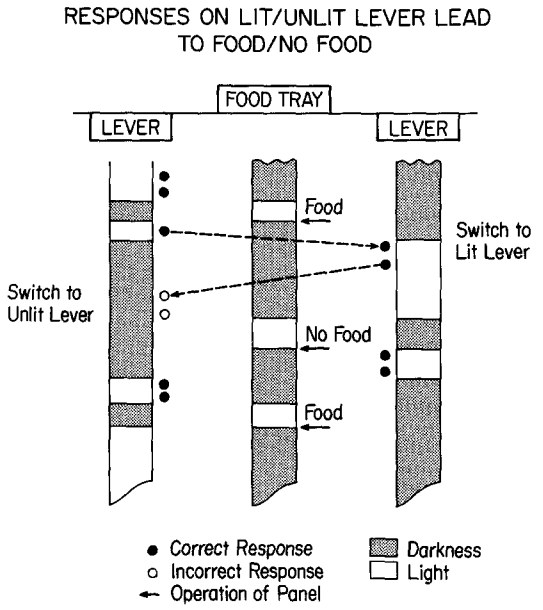

Fig. 1. Schematic diagram of the schedule, showing a short period of responding. The first two responses *(top of figure)* were made on the lit lever and the second resulted in the delivery of food. After opening the panel *(arrow)*, the subject made a single response on the lit, left lever before the light moved to the right. The animal then switched to the right lever and made two responses before switching back to the left, now unlit lever, where it responded twice, resulting in non-reinforcement. From the figure, the two measures of discrimination may be calculated. Response efficiency is the total number of filled circles divided by the total number of circles (here 81.8%), and switch efficiency is the total number of switches to the lit lever divided by the total number of switches (here 66%)

ments Ltd., London). Food pellets (45 mg, Campden Instruments Ltd.) were delivered to a tray placed centrally between the two levers. Access to the tray was by opening a hinged Perspex flap. The food-tray could be illuminated by a 2.8-W light, and a second 2.8-W light placed centrally in the roof of the chamber served as a houselight. Two additional lights were placed one above each of the levers. The apparatus was controlled and the data recorded by a single microcomputer (Acorn Computers Ltd., Cambridge).

Procedure. Figure 1 summarizes the procedure. Each session began with the non-contingent delivery of a food pellet. This pellet was obtained by opening the hinged panel, thereby closing a microswitch, after which one of the lights above the levers was turned on. The light turned on was selected at random with equal probability by the computer. Responses on this lit lever produced food pellets under a random ratio (RR) schedule. On completion of the ratio, the stimulus light was turned off, and the traylight turned on. The same schedule was in operation on the unlit lever, except that no food pellet was delivered. After the panel to the food tray was opened, the computer reselected which lever was to be correct, turned off the traylight and turned the houselight on, and the schedule recommenced.

Initial training began with a simple discrimination in which every response on the lit lever produced reinforcement (RR1), and every response on the unlit lever resulted in non-reinforcement. After 12 daily sessions, in which 100 correct responses were required, the experimental schedule was begun. Discrimination performance was excellent at the end of training (99.8% correct).

Two changes were made to the schedule at the end of initial training. First, the random ratio (RR) was increased to RR 6.67 (i.e., the probability of any response on the correct lever being reinforced was 0.15), and second, the possibility of the light moving from one lever to the other was introduced. Under the experimental schedule the light always indicated on which lever responses would result in food, but after each response there was a fixed probability (0.20) that the light would move to the other lever. For example, there was a probability of 0.5 that the left lever would be selected as correct after collection of the food, but after each response on either lever there was a probability of 0.2 that the other lever would then be selected as correct, this change being indicated by the extinguishing of the left lever light and the illumination of the right lever light. It should be emphasized that under this schedule it was possible for the subject to obtain all the reinforcements by responding on one lever, since even if that lever was incorrect at any time, it would eventually become the correct lever. However, on average, twice as many responses would be required, and would involve non-reinforcement as often as reinforcement.

Each session terminated when 100 reinforcers had been obtained or 30 min had elapsed, whichever occurred sooner.

Drugs. Injections of vehicle (0.9% saline solution) were started 4 days before the first drug injection. Thereafter, the experiment was conducted on a 4-day cycle (control vehicle injection, drug injection, no test, no injection). Thus, at least 3 days without drug preceded each injection of the drug. *d*-Amphetamine sulphate (0.2–3.2 mg/kg, Smith Kline and French, Welwyn Garden City, GB), chlordiazepoxide hydrochloride (CDP, 1.0–8.0 mg/kg, Hoffmann-La Roche, Basel, Switzerland) and alpha-flupenthixol hydrochloride (0.03–0.33 mg/kg, Lundbeck, Copenhagen, Denmark) were used. All drugs were dissolved in 0.9% saline solution and injected IP in a volume of 1 ml/kg. *d*-Amphetamine and CDP were injected 15 min before the session, and alpha-flupenthixol was injected 30 min before the session. All doses of each drug were administered in a balanced order and experiments with one drug were completed before the effects of the next were studied. Drugs were administered in the sequence of *d*-amphetamine, CDP, and alpha-flupenthixol. Approximately 1 week separated determinations with different drugs.

For drug treatments, each variable was subjected to analysis of variance with the factor, Dose, followed by Dunnett's *t*-test for comparing control values with a given dose. Inter-response times were subjected to a log transformation before analysis, and perseveration to an arcsine transformation to satisfy the assumptions of analysis of variance (Winer 1971). When subjects failed to respond, data points were estimated by the statistical analysis program GENSTAT (Rothamstead Experimental Station) to complete the ANOVA. For each estimated data point, one degree of freedom was subtracted from the error term in the analysis of variance. A 5% level of significance was used throughout.

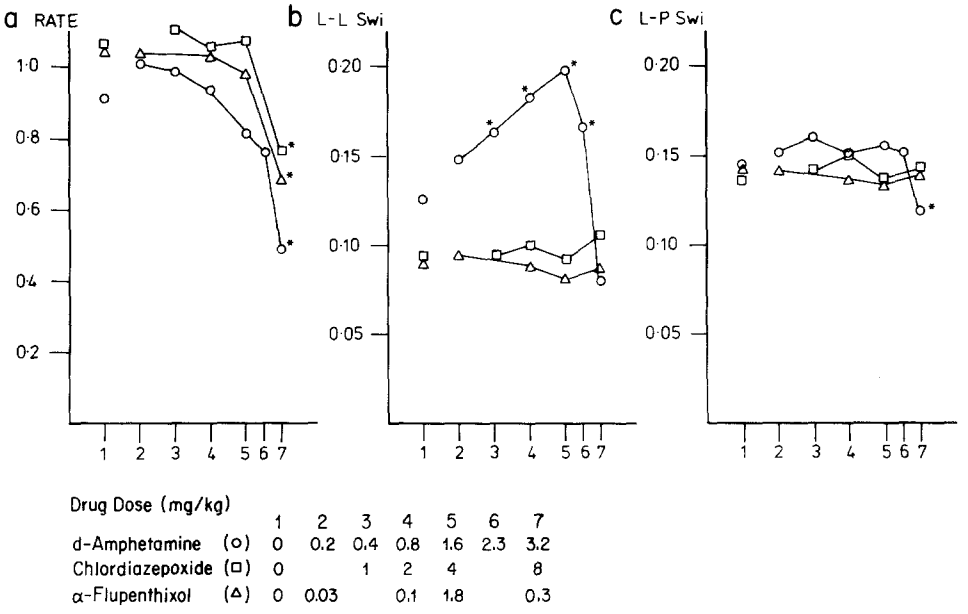

Fig. 2. The effects of *d*-amphetamine, chlordiazepoxide, and alpha-flupenthixol on **a** response rate (responses/s). **b** switching and **c** lever-panel switching. *Circles d*-amphetamine; *squares* chlordiazepoxide, and *triangles* alpha-flupenthixol. *Significantly different from control (Dunnett's *t*-test). Note that in panel **a** the doses of the three drugs have been plotted to equate their effects on response rate

Results

Response rate (Fig. 2a). Rate of responding was measured by summing the total number of responses on both levers and dividing by the session length (responses/s). Average rates under control conditions for the three drugs were (mean ± SEM) for amphetamine 0.91 ± 0.07, CDP, 1.04 ± 0.10 and alpha-flupenthixol, 1.07 ± 0.11, and were reduced by the highest dose of all three drugs studied [*d*-amphetamine, $F(6,66) = 8.48$, CDP, $F(4,44) = 5.85$, alpha-flupenthixol, $F(4,44) = 5.81$].

Lever-lever switching (L-L, Fig. 2b). Switching was defined by the frequency with which the subject switched between the two levers divided by the total number of switches + repeat responses. Under control conditions the relative frequency of switching (%) was for amphetamine 12.59 ± 1.06, CDP, 9.64 ± 0.99 and alpha-flupenthixol, 9.28 ± 1.01. Doses of *d*-amphetamine ranging from 0.4 to 2.3 mg/kg increased switching, but at the highest dose switching was slightly reduced compared to control [$F(6,62) = 15.11$]. Neither CDP nor alpha-flupenthixol affected switching.

Lever-panel switching (L-P, Fig. 2c). The probability of switching from the lever to the panel was calculated by dividing the number of such switches by the total number of responses. The percentage lever-panel switching under control for amphetamine was 14.6 ± 0.34, CDP, 13.8 ± 0.30 and alpha-flupenthixol 14.3 ± 0.78. Low doses of *d*-amphetamine produced small increases in lever-panel switching, while the highest dose (3.2 mg/kg) significantly decreased the probability of switching to the panel [$F(6,62) = 5.07$]. Neither CDP nor alpha-flupenthixol had any significant effect on lever-panel switching.

Response efficiency (R. Eff, Fig. 3a). Discrimination of response location was measured by the proportion of responses made on the correct (lit) lever (Response Efficiency, %). Response efficiency under control conditions for amphetamine was 81.5% ± 1.92, CDP 78.4% ± 1.96, and alpha-flupenthixol 78.1 ± 2.07. *d*-Amphetamine

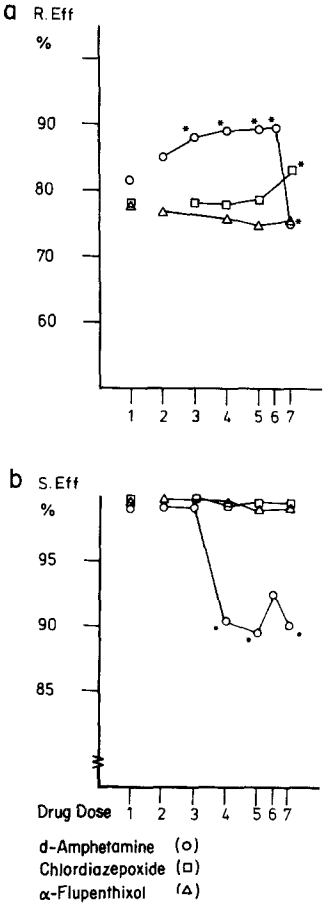

Fig. 3. The effects of the drugs on **a** response efficiency and **b** switch efficiency. *Circles d*-amphetamine; *squares* chlordiazepoxide; *triangles* alpha-flupenthixol. * Significantly different from control (Dunnett's *t*-test). The doses of drugs were the same as indicated in Fig. 2. Note the increase in response efficiency under *d*-amphetamine at doses at which switch efficiency (plotted on an expanded scale) was significantly reduced. Note also that response efficiency was reduced at the highest dose of amphetamine (3.2 mg/kg)

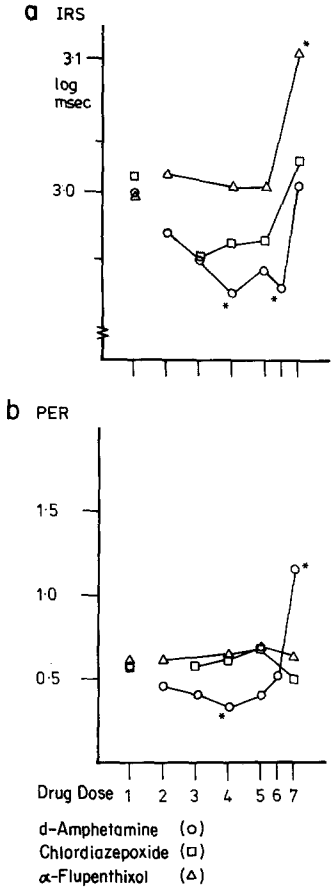

Fig. 4. The effects of the drugs on **a** inter-response time for switches and **b** perseveration. *Circles* *d*-amphetamine; *squares* chlordiazepoxide; *triangles* alpha-flupenthixol. * Significantly different from control (Dunnett's *t*-test). The doses of the drugs were the same as those shown in Fig. 2. Note that switches were performed faster than control at intermediate doses of *d*-amphetamine. At these doses, too, perseveration was reduced, but was increased compared to control at the highest dose of the drug (3.2 mg/kg)

significantly increased response efficiency at doses of 0.4–2.3 mg/kg, but significantly reduced it at 3.2 mg/kg [$F(6,62 = 13.56$]. All subjects showed increased efficiency at all doses up to and including 1.6 mg/kg. Low doses of CDP did not affect response efficiency, but it was significantly increased at the highest dose [$F(4,43) = 3.40$]. Alpha-flupenthixol had no significant effect on this measure.

Switch efficiency (S. Eff, Fig. 3b). Discrimination of the direction of response switching was measured by the proportion of switches made to the correct lever (Switch Efficiency, %); under control conditions, switch efficiency was very high, for amphetamine 98.1% ± 0.52, CDP, 99.2% ± 0.24 and alpha-flupenthixol, 99.1% ± 0.27. That is, almost all switches were from the unlit to the lit lever. Doses of *d*-amphetamine of 0.8 mg/kg and above reduced switch efficiency [$F(6,62) = 6.75$], although this reduction did not reach significance at the 2.3 mg/kg dose. Thus, switch efficiency was reduced at doses at which response efficiency was increased. The reduction in switch efficiency was a result of a proportionately greater increase in switching to the unlit, incorrect lever. Of course, in absolute terms, the number of switches to the unlit lever remained very small. Neither CDP nor alpha-flupenthixol had any significant effects on switch efficiency.

Inter-response time for switches (IRS, Fig. 4a). The inter-response times (IRT) for all switches were grouped into bins of 200 ms, and the modal bin was taken as the best estimate of the peak of the IRT distribution. This method was used in order to ensure that only IRTs for switches directly between the two levers, not involving lengthy bouts of other behaviour, contributed to the estimate. Under control conditions subjects took about 1 s to switch from one lever to the other. After log transformation the control means ± SEM were 2.998 ± 0.011 for amphetamine, 3.013 ± 0.012 for CDP, and 3.004 ± 0.015 for alpha-flupenthixol. Certain doses of *d*-amphetamine (0.8 and 2.3 mg/kg) significantly reduced IRS, but this reduction did not occur at the highest dose [$F(6,62) = 3.90$]. CDP did not significantly affect IRS whereas alpha-flupenthixol increased it at the highest dose [$F(4,44) = 4.02$].

Perseveration (Fig. 4b). Perseveration on the levers was indicated by the proportion of extra responses made after the traylight was turned on before the panel was opened (extra responses/total responses). Following saline, perseverative responding constituted approximately 9% of responding, mainly after non-reinforcement. After arcsine transformation the control mean ± SEM for amphetamine was 0.57 ± 0.05, CDP, 0.57 ± 0.05, and for alpha-flupenthixol, 0.62 ± 0.06. Amphetamine had a bimodal effect on perseveration [$F(6,62 = 29.3$]. Perseveration was significantly reduced compared to control at 0.8 mg/kg, but significantly increased at 3.2 mg/kg. CDP also had a significant effect following analysis of variance [$F(4,43 = 3.23$], but, at no dose did perseveration differ significantly from control. No dose of alpha-flupenthixol produced a significant change in perseveration.

Discussion

Figure 5 provides a summary of the significant effects of the three drugs on the various indices of performance measured in this experiment, and shows that the effects of the drugs were quite different.

Clearly, as in previous studies (Evenden and Robbins 1983a and Robbins and Watson 1981), amphetamine had much more marked effect on responding under this schedule than had chlordiazepoxide or alpha-flupenthixol. *d*-Amphetamine produced significant changes in perseveration and inter-response times for switches, as well as biphasic changes in switching and a reduction in response rate. Response switching was indeed brought under stimulus control, but this control was not very strong, since tracking of the stimulus was only moderately efficient. Thus, it is not surprising that the effect of amphetamine on the switching was little affected by the external discriminative stimulus. Evenden and Robbins (1983b) obtained a similar baseline of switching in the absence of discriminative stimuli by placing two Perspex walls inside the apparatus used in the experiments described here. Comparison with that experiment shows that the increases in switching brought about by *d*-amphetamine were quantitatively and qualitatively similar for the two conditions. The effects on both perseveration and the inter-response times for switches in the present study were also similar to those

SUMMARY

	Amph		CDP		α-Flu	
	Lo	Hi	Lo	Hi	Lo	Hi
Rate	-	▼	-	▼	-	▼
Switch	▲	-	-	-	-	-
L-P Switch	-	▼	-	-	-	-
Res. Eff.	▲	▼	-	▲	-	-
Switch Eff.	▼	▼	-	-	-	-
IRS	▼	-	-	-	-	▲
Per	▼	▲	-	-	-	-

▲ Increase
▼ Decrease
- No Change

Fig. 5. Summary of the effects of the three drugs. In general, *d*-amphetamine had a wider range of effects on this schedule than did chlordiazepoxide or alpha-flupenthixol. The effects of amphetamine at low doses (0.2–2.3 mg/kg) were different from those at the highest dose (3.2 mg/kg). The effects of all three drugs closely resembled those described by Evenden and Robbins (1983a)

obtained previously. Of course, this is not an explicit comparison as in Ksir (1975) in which the effects of amphetamine were found to depend upon the degree of stimulus control. Nevertheless, the data in these experiments do support the proposal of Evenden and Robbins (1983b) that the baseline relative frequency of switching may play a role in determining the effects of a drug independently of the contingency under which it was established.

Perhaps the most striking effect was the consistent increase in response efficiency brought about by amphetamine. This represents a real improvement in the performance of the discrimination, similar to the other rather infrequently reported improvements in discrimination produced by *d*-amphetamine in animals (e.g., Kulig and Calhoun 1972). However, the consistency of this effect should not prevent a critical examination of its relationship with the other changes in responding brought about by the drug, notably the concomitant increases in response switching and reductions in switch efficiency, in order to determine exactly how this improvement was effected.

Under control conditions, the subjects were switching between the levers at a sub-optimal level (i.e., 10% compared with the stimulus switching probability of 20%), and any improvement in tracking was likely to have been accompanied by an increase in switching. On the other hand, it is also true that any increase in switching would probably (although not necessarily) have resulted in improved tracking. Furthermore, the reduction in response efficiency at 3.2 mg/kg was accompanied by a reduction in switching. Therefore, it is impossible to ascertain whether increased switching leads to better tracking or vice-versa on the basis of this experiment alone. However, since it has previously been shown that amphetamine produces similar increases and decreases in the absence of any overt discriminative stimulus (Evenden and Robbins 1983b), the change in switching is most likely the primary effect of amphetamine and the apparent improvement in discrimination is only secondary. The effects of amphetamine generally result in decrements in performance, but clearly improvements can be obtained provided that the task requirements are compatible with the changes in performance produced by the drug (see also Lyon and Robbins 1975). Such coincidental compatibility may also account for other phenomena in which amphetamine appears to enhance the effects of external stimuli on responding; for example, the enhancement of the effects of conditioned reinforcement (Hill 1970; Robbins 1976) and in improving stimulus tracking in human subjects (Weiss and Laties 1962).

The reduction in switch efficiency at doses of amphetamine that increase response efficiency strengthens this conclusion, since it disposes of the possibility that the increases in switching in both experiments are actually a result of improved discrimination or control by conditioned reinforcers, either covert, in the experiments of Evenden and Robbins (1983b), or overt in the present experiment.

This conclusion also leads to a possibility entertained previously, that under these schedules *d*-amphetamine induces changes in response pattern largely independent of context, in this respect resembling drug-induced stereotyped behaviour (Randrup and Munkvad 1970). The results reported in this paper provide experimental support for anecdotal reports that amphetamine can produce stereotyped tracking behaviour in freely moving animals (Sahakian and Robbins 1975). They reported observations in guinea pigs of gnawing and licking directed towards particular cage-mates, which persisted despite the cage-mate's attempts to avoid pursuit. Stereotyped behaviour normally consists of an apparent focussing of attention together with a cessation of locomotor activity. Stereotyped tracking occurs when focussing is produced but locomotor or other activity is still possible. Examples of this type of behaviour have also been reported in Parkinsonian patients treated with L-dopa. Sacks (1973) reports the example of a patient who felt compelled to track one of her fellow patients with her gaze.

Finally, it should not be overlooked that whereas alpha-flupenthixol had no effect on tracking, chlordiazepoxide also improved response efficiency at the highest dose. Compared with amphetamine, this effect was much smaller and less consistent. Moreover, it too could be accounted for by other, coincidental changes in behaviour produced by the drug. For example, Evenden and Robbins (1983a) reported that CDP reduced ineffective perserverative responding, particularly after non-reinforcement, an effect which could reflect the effects of CDP on non-reinforcement rather than stimulus control (Evenden 1983; Gray 1977).

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