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The Effect of Amphetamine on Delayed Response Performance in the Monkey

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WEIGHT, M. L., R. M. RIDLEY AND H. F. BAKER. *The effect of amphetamine on delayed response performance in the monkey.* PHARMAC. BIOCHEM. BEHAV. 12(6) 861–864, 1980.—The effect of amphetamine on discrete-trial, visual discrimination where response was permitted simultaneously with stimulus presentations or 0, 1, or 3 sec after stimulus presentation, was assessed in the marmoset. An interaction between dose and delay was observed comprising significantly impaired performance after amphetamine under conditions of longer delay. Results are interpreted in terms of loss of response inhibition and increased distraction and are compared with frontal lobe function in the primate.

Amphetamine Delayed response Primate Frontal lobes

THE effects of amphetamine on motor activity and operant behaviour are well established in the rodent [10]. Studies using primates provide an opportunity to assess a wider range of behaviours which may be relevant to an understanding of the behavioural effects of psychoactive drugs in man. In dose range 1–10 mg/kg, amphetamine induces behavioural changes in the marmoset consisting principally of stereotyped head movements but no change in locomotion [15,16]. These effects bear a resemblance to those described in other primate species [5] although they are more reproducible and less idiosyncratic than those seen, for example, in macaques [4]. In order to measure the more subtle effects of low doses (less than 1 mg/kg) of amphetamine we employed the technique of discrete trial behavioural training and drug testing.

In a comparison of simultaneous and successive visual discrimination performance in the marmoset we have previously found that amphetamine did not disrupt simultaneous discrimination but performance was progressively disrupted by increasing doses of amphetamine in a successive visual discrimination task. In the simultaneous task the rewarded, positive stimulus appeared over one lever while the unrewarded, negative stimulus appeared over another lever on each trial; performance of the correct response precluded an incorrect response. In the successive task either stimulus appeared over only one lever; when the negative stimulus appeared the animal was required to refrain from responding (but was unable to do so after amphetamine). Thus stimulus control was only maintained under amphetamine where the presence of a stimulus indicated that a response was required 'there and then' while stimulus control of other behaviour, e.g., withholding a response, could be disrupted. To our knowledge the behavioural capacity of the marmoset has not been assessed using complex operant conditioning techniques. However, in the rodent, schedules requiring pauses in responding, e.g., differential reinforcement of low rate (DRL schedules) are easily disrupted by low doses of amphetamine [9] although performance can be maintained on this schedule if an external stimulus indicates the availability of reinforcement [7]. This suggests that amphetamine disrupts internally controlled behaviour, e.g., time estimation, but has less effect on behaviour directly controlled by an external stimulus. It seemed to us that stimulus control of behaviour separated in time from the stimulus might also be disrupted by amphetamine. We therefore attempted to assess the effects of amphetamine on delayed response performance where visual stimuli indicated which response was required after a short but obligatory delay. Overall we have found an interaction between dose of amphetamine and delay before response such that performance is most disturbed by amphetamine under conditions of the longest delay.

METHOD

A BRS/LVE rodent operant apparatus (Model No. RTC 027) and sound attenuating chamber (Model No. SEC 002) was controlled by compatible Digi-Bit logic systems (series 200) and a custom-built delay timing device. Figure 1 shows the operant box with side panel removed to reveal the stimulus lights, levers and reward dipper. One retractable lever was positioned 9.0 cm to the left and the other 9.0 cm to the right of the central food well which dispensed 0.05 ml homogenised banana as the reward by a dipper mechanism. (Banana was homogenised daily in a domestic blender.) Five

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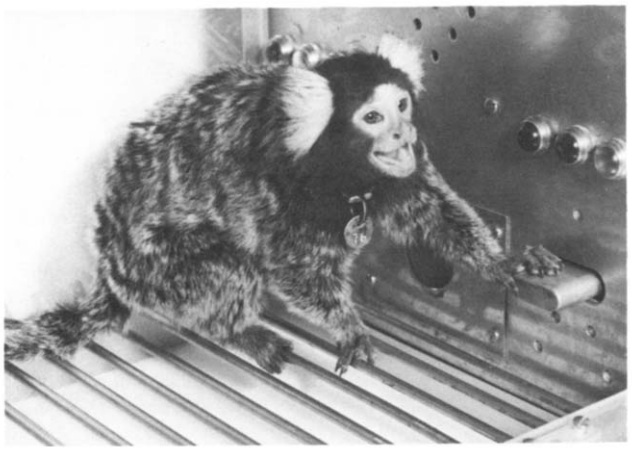

FIG. 1. Photograph of interior of operant chamber showing positions of stimuli, response levers, central banana reward dispenser and marmoset.

cm above each lever were two stimulus lights, one red and one white (and one green light which was not used).

Subjects and Training

Six individually housed adult marmosets (Callithrix jacchus, 4 females, 2 males) weighing 250–350 g each served as subjects. Three of these had previously been trained on simultaneous and successive versions of a red/white discrimination task (*Psychopharmacology*, in press) and tested on these tasks under 0.2 mg/kg d-amphetamine. The period between the end of this testing and drug testing on delayed response was 5–7 weeks. The remaining three animals were previously untrained and undrugged and were therefore (1) shaped to lever press and (2) trained to a criterion ≥80 correct responses in 100 trials on red versus white simultaneous discrimination before training on delayed response tasks began.

Throughout training and testing on delayed response, animals were fed a diet of 15 g chopped bread and fruit after training each weekday with 10 g extra pellet chow at weekends. The amount of food was adjusted to maintain motivational levels, being most stringently controlled during early training but stabilised at slightly less than would have been consumed ad lib during testing. With the addition of 0.5 g bone meal each week, animals can be maintained on this diet indefinitely. The animal colony was kept at 25°C on a 12-hr light, 12-hr dark cycle.

The Red vs White Delayed Response Task

Forty trials were given each weekday during training and testing. Each trial began with a 4 sec stimulus period when a red light appeared over one lever position and a white light appeared over the other lever position. During this time the levers were in a retracted state and hence were inoperable. The end of the stimulus period was followed by a delay of 0, 1 or 3 sec, after which the levers extended into the animal chamber (over a period of 2 sec).

The levers remained in position for up to 8 sec. When either lever was pressed a response was recorded and both levers began to retract, initiating a 9 sec inter-trial interval. If the lever below the position at which the red light had appeared was pressed, the response was scored correct and banana reward was dispensed. If the lever below the position at which the white light had appeared was pressed the trial was scored incorrect and no reward was dispensed. If no response was made during 8 sec the levers retracted and the 9 sec inter-trial interval commenced. The levers were sensitive to lever-press when they were extended or were advancing into the chamber but not when they were retracted or receding from the chamber. Thus only one lever press response could be made during the response period and lever pressing during the stimulus period or the inter-trial interval was impossible.

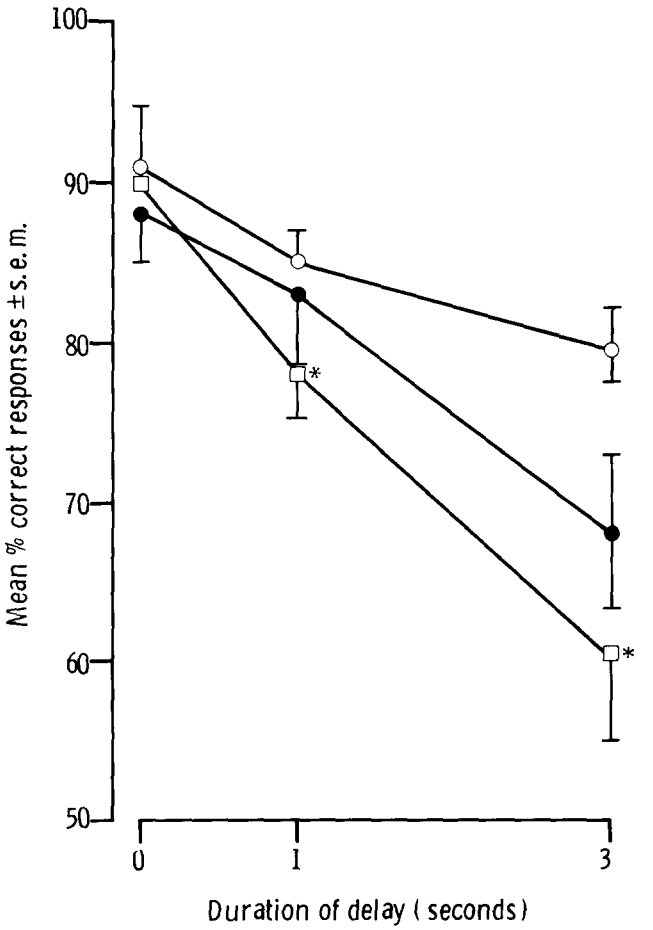

FIG. 2. The effects of amphetamine on delayed response visual discrimination. Ordinate shows mean % correct responses ± SEM in 80 trials. Abscissa shows duration of delay between end of stimulus period and beginning of response period. n=6 marmosets at 0 sec and 1 sec but n=4 at 3 sec. For each drug dose, performance at 1 sec and 3 sec was compared with performance at 0 sec delay using a 2-tailed matched pair *t*-test. *$p<0.02$, 5 *df* at 1 sec; 3 *df* at 3 sec. ○=saline, ●=0.2, □=0.4 mg/kg d-amphetamine sulphate IM.

The left/right position of the stimuli on each trial was determined by a pseudorandom schedule such that the stimuli appeared on equal number of times on each side on each day of training per animal.

Exeprimental Design and Drug Administration

Throughout the design animals were trained to criterion and then tested under all doses of amphetamine at one delay

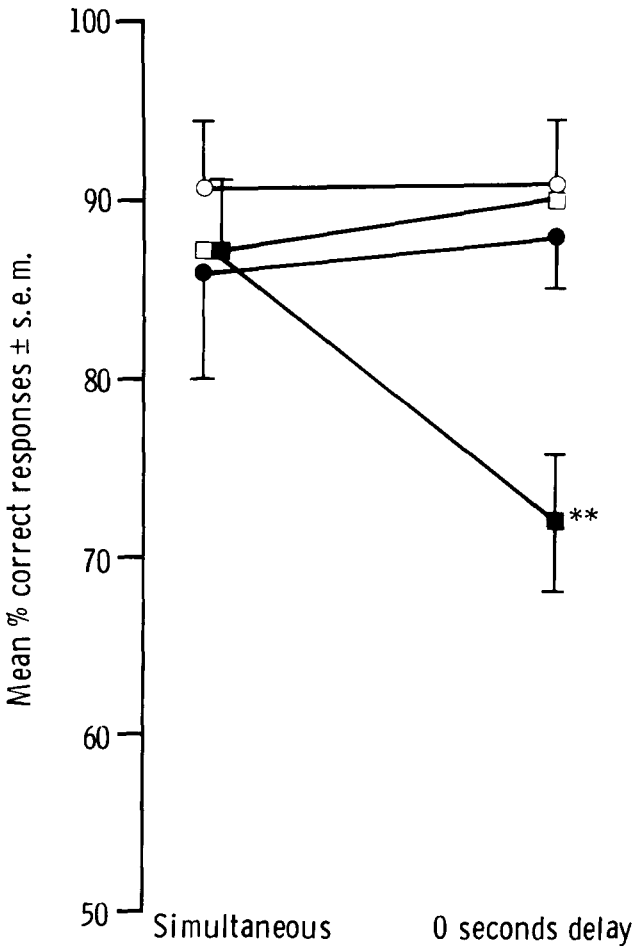

FIG. 3. The effect of amphetamine on visual discrimination where response could be made during (simultaneous) or immediately after (0 sec delay) stimulus presentation. Ordinate shows mean % correct responses ± SEM in 80 trials. n=6 marmosets except 0.8 mg/kg, 0 sec delay where n=4. Performance under each dose of amphetamine was compared to performance under saline for each condition using a 2-tailed matched pair *t*-test with 5 *df* at all doses except 0.8 mg/kg, 0 sec delay which had 3 *df*. $^{**}p<0.01$. ○=saline, ●=0.2, □=0.4, ■=0.8 mg/kg d-amphetamine sulphate IM.

before being trained and tested at another delay. Thus, initially, animals were trained to a criterion of >80% correct response in one day's performance at 0 sec delay without injections. Training was then continued at 0 sec delay to a criterion of >80% correct over two consecutive days when training was preceded each day by saline injection. The effect of amphetamine on performance at 0 sec delay was then determined by injecting amphetamine approximately 30 min prior to testing on consecutive days in the order: 0.0 (saline), 0.4, 0.2, 0.2, 0.4, 0.0 mg/kg d-amphetamine sulphate. (Thus the effect of saline in this part of the design was tested independently of the preceding criterion training after saline since performance at criterion is predetermined.) Scores on the 2 days of each drug dose were summed as a precaution against the effects of drug order, practice or daily variation, although subsequent analysis did not reveal consistent differences in performance between the two days at each dose. Drug doses were administered by IM injection into the thigh in volumes of 0.1–0.2 ml.

After training at 0 sec delay animals were trained and tested under amphetamine in the same manner at 1 sec delay then at 3 sec delay, 40 trials being given each day throughout.

Supplementary Experiment

After training on delayed response, all animals were rapidly retrained on red vs white simultaneous discrimination (3–4 days including criterion testing). In this task the levers were available during the presentation of the stimuli. Performing a response initiated a 9 sec inter-trial interval followed by a further stimulus period which continued until a response was made. Animals were trained and tested after amphetamine (0.0, 0.2, 0.4 mg/kg) in a balanced design as before using the same conditions of training.

The effect of 0.8 mg/kg amphetamine on simultaneous discrimination and 0 sec delayed response was then assessed.

RESULTS

For statistical comparisons the 2-tailed matched pair *t*-test was used throughout. The effects of 0.2 and 0.4 mg/kg d-amphetamine on visual discrimination with 0, 1 or 3 sec delayed response are shown in Fig. 2. All 6 animals learned to perform with 0 and 1 sec delay but only 4 animals reached criterion at 3 sec delay and were therefore tested after drugs at this delay; training for the other two animals was discontinued after >850 trials. After saline injection performance at 1 or 3 sec delay was not significantly different from performance at 0 sec ($t(5)=1.8775$, $p<0.2$ at 1 sec; $t(3)=2.2517$, $p<0.2$ at 3 sec). After 0.4 mg/kg amphetamine performance at 1 sec and 3 sec delay was significantly impaired relative to 0 sec delay ($t(5)=3.8924$, $p<0.05$ at 1 sec; $t(3)=4.6046$, $p<0.02$ at 3 sec). After 0.2 mg/kg amphetamine performance declined with increasing delay although this effect did not reach statistical significance ($t(5)=0.9537$, $p<0.4$ at 1 sec; $t(3)=2.0677$, $p<0.2$ at 3 sec).

Supplementary Experiment

The effects of 0.2, 0.4 and 0.8 mg/kg amphetamine on visual discrimination where the lever was available during (simultaneous) or immediately after the stimulus period (0 sec delay) are shown in Fig. 3. It can be seen that there is no effect of the lower doses of amphetamine on performance under either condition but 0.8 mg/kg amphetamine, compared to saline, disrupted performance only under the 0 sec delay condition ($t(3)=5.8974$, $p<0.01$). Two marmosets failed to perform under the high dose of amphetamine due to the appearance of incompatible stereotyped behaviour (comparable with the rapid head movements previously described at higher doses [15]). This behaviour also prevented assessment of performance at longer delays under this dose. At the lower doses of amphetamine used in this study, no behavioural changes (including locomotion) were evident by direct observation.

DISCUSSION

The delayed response task used in this study differs from the original delayed response task, which was performed in a Wisconsin General Test Apparatus, in that here coloured lights indicated where the response should be made whereas in Jacobsen's experiment [8] the animal watched the reward being hidden. Furthermore in our case response and stimulus

positions were slightly separated and there was only one reward site while in the original versions stimulus, response and reward positions were contiguous. These changes were made in order to facilitate automatic training. Delayed response is a task which can be performed to a comparable level by many primate species including New World and Old World monkeys as well as great apes [6] although marmosets may be inferior to macaques during initial training and at long delays [12]. Specific disruption of this task is characteristic of frontal lobe lesions in primates [8,14]. This has been ascribed [11] to increased effects of interference rather than to a memory deficit since minimising environmental stimuli (by extinguishing the lights during the delay period) improves performance after such lesions.

Similarities exist between the effects of amphetamines and frontal ablations [10,13]. Rosvold and Szwarcbart [14] have proposed the existence of a 'delayed response system' containing frontal cortex, caudate and subthalamic nuclei and substantia nigra. Lesions or electrical disruption of all of these areas has been found to impair delayed response performance [1, 2, 3]. That this system largely incorporates rising dopamine pathways from the substantia nigra to the caudate, mesolimbic and frontal areas may be of importance in understanding the relation between amphetamine action and frontal lobe function.

The results of this experiment suggest that amphetamine has a disruptive effect on performance where the response is separated in time from the stimulus even when time estimation per se is not required in the task. Thus the impaired performance under amphetamine on DRL schedules may not be due to an inability to estimate time [7] but may be due to a loss of stimulus control over time where the stimulus in this case is the previous response which initiated the DRL pause. Where external cues indicate the duration of the DRL pause, stimulus control is shifted to the time at which a response is required and adequate control is maintained.

Amphetamine may disrupt complex tasks by affecting response strategies. We have already suggested that a loss of response inhibition may produce failure on a go–no go successive task. An increased response rate may account for poor performance on DRL schedules even though it has been shown that direct stimulus control can counteract any such tendency. In this experiment changes in response choice are not compounded by changes in response rate since only one response is permissible on each trial. An increased propensity to respond after amphetamine would shorten the effective delay between the end of the stimulus and response performance and should not in itself disrupt response choice. A loss of response inhibition may, however, render an animal more likely to respond to extraneous events, i.e., to be more susceptible to distraction. In the simultaneous discrimination condition in this study responses were usually made promptly after stimulus onset or after the animal turned towards the stimulus whereas in the 0 sec delay condition response was postponed until stimulus offset which occurred up to 4 sec after the animal first saw and attended to the stimulus. Thus, despite the availability of the stimulus, impaired performance at 0 sec delay after the high dose of amphetamine may be due to distraction or interference occurring during the delay between first attending to the stimulus and being able to respond. Similarly, during delayed response trials amphetamine may impair performance by increasing distraction resulting in failure to maintain orientation towards the relevant lever. Observation of performing animals, however, suggested a lack of orientation strategies with or without amphetamine. Failure on the go–no go task is unlikely to be due to loss of relevant orientation since only one stimulus—and response—position was employed. Furthermore, amphetamine did not disrupt performance on another version of successive discrimination (go here–go there, *Psychopharmacology*, in press), which put considerable demand on orientation strategies but which did not require response inhibition. Thus, at the present time, the most comprehensive description of low dose amphetamine effects in the marmoset would seem to be a loss of response inhibition with possibly a concomitant increase in distraction which becomes evident under conditions of indirect stimulus control.

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