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Perseverative Behaviour after Amphetamine; Dissociation of Response Tendency from Reward Association

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Abstract. Low doses of amphetamine were found to alter the ability of marmosets to take account of changes in reward values of object stimuli in a visual discrimination task. Under amphetamine, animals changed their motor responses and stimulus choice in order to preserve the acquired reward value or meaning of certain stimuli. These results suggest that the perseverative effect of amphetamine on behaviour is due to impaired cognitive flexibility rather than to an enhancement of motor habit.

Key words: Amphetamine – Reversal learning – Reward association – Marmoset

When an animal is faced with a decision, for example in a simultaneous two-choice visual discrimination problem, its response will be influenced by a variety of factors. If the discrimination has been learnt the animal will choose the stimulus which has become associated with reward, or avoid the object associated with punishment or non-reward. If the animal has had no previous experience of the stimuli, its choice may be based on the resemblance of these stimuli to previously rewarded objects (simple generalisation). Possession of certain preferred or non-preferred qualities (a more categorical form of generalisation) may also have an important effect; for example, animals may consistently prefer the more brightly coloured or the larger stimulus. Choice in terms of qualities is the result of a complex interaction of innate factors and experience. Neonatal animals approach sources of weak stimulation and withdraw from strong ones (Schnierla 1965). Subsequent experience alters the range of stimuli approached or avoided such that a complex mosaic of preferences emerges (Hinde 1970). Apparently idiosyncratic responses may be based on this pattern of preferences, or they may be random, or may be based on factors unrelated to the objects' appearance e.g. an animal may choose the object nearest itself. All these factors must be considered when analysing an animal's choice behaviour.

We have previously observed (Ridley et al. 1981b) that marmosets treated with amphetamine were severely impaired on visual discrimination reversal performance, and that this impairment consisted almost entirely of perseverative errors at the beginning of reversal training. It was not possible, however, to determine whether this perseveration resulted from an inability to alter the reward association of the stimuli or from an inability to break the motor habit of responding to one stimulus.

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In another experiment (Ridley et al. 1981a) we observed that marmosets perseverate their initial object preference in a two-choice simultaneous visual discrimination under amphetamine. However, since these animals indicated their preference by choosing one of the objects on the first trial, it could not be determined whether this perseveration consisted of an enhancement of the object preference (or aversion for the alternative object) or of a consolidation of the response choice i.e. that a random choice, once made, was maintained. In this experiment we have attempted to establish a preference or aversion to particular stimuli (relative to novel stimuli) by associating them with reward or non-reward but to induce the animal to respond on all of these stimulus presentations. In this way we have been able to dissociate reward-association from response and to demonstrate that amphetamine causes a perseveration of the reward-association of the stimuli rather than increasing the animal's tendency to repeat its response choice.

Materials and Methods

Subjects and Apparatus. Six laboratory born common marmosets (*Callithrix jacchus* 5 female, 1 male), each weighing 250–350 g were used. Two animals had received extensive training, including choice perseveration testing (Ridley et al. 1981a); two animals had received considerable training on many object discrimination tasks to five consecutive correct responses each (Ridley et al. 1981c) and two animals had received only shaping and one preliminary discrimination task. Animals were housed individually or in groups of two or three (with other animals) and were fed their normal daily diet of bread, fruit and pellet chow after training each day and at weekends. Strict food deprivation was not required to maintain performance since banana, which was used for reward, is a preferred choice for this species. Animals were trained in a miniature Wisconsin General Test Apparatus (Harlow 1958) consisting of a lighted chamber containing three small food wells (2.0 cm diameter), one being 6.0 cm to the left and the other 6.0 cm to the right of a centrally positioned food well. On each trial either the central food well or both the lateral food wells were covered with stimuli made from small junk objects mounted on white plastic discs. The junk objects were selected randomly from several hundred such objects. On central stimulus trials the central food well was sometimes baited with a 3 mm cube of banana (see design – Table 1), while on lateral stimulus trials only one of the two food wells was baited. Unused food wells were always uncovered and unbaited. On each trial the animal could reach through the bars of the test cage when

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Table 1. Design of experiment

Task	Designation[a]	Number of trials	Wells used	Junk object	
				Thimble	Button
A	++	5	Central	Rewarded	Not used
		10	Left/Right	Rewarded	Not rewarded
				Bottle top	Pen top
B	+−	5	Central	Rewarded	Not used
		10	Left/Right	Not rewarded	Rewarded
				Cotton reel	Doll
C	−−	5	Central	Not rewarded	Not used
		10	Left/Right	Not rewarded	Rewarded
				Toy car	Knob
D	−+	5	Central	Not rewarded	Not used
		10	Left/Right	Rewarded	Not rewarded

[a] The first symbol refers to the reward value of the first presented object and the second symbol to the reward value of the same object in the second part of each task

the screen was raised, displace one object and retrieve the banana piece if that object covered a reward. The experimenter could observe the animal's performance through a one-way viewing screen and could load the food wells through a hatch at the back of the apparatus between trials.

Experimental Design and Behaviour Testing. Training consisted throughout of presenting one object in the central position for five trials followed by ten trials on which that object was placed in the left or right position [according to a pseudorandom Gellermann (1933) schedule] while a new object was placed over the other food well. New objects were used for each of the 15-trial tasks for all animals. There were four types of task depending on whether the object presented in the first part of the task was rewarded or not, and which of the two objects was rewarded in the second part (Table 1). Thus for two tasks the object presented on the first five trials was rewarded; on one of these tasks this object was rewarded in the subsequent ten trials while for the other of these tasks the new object was rewarded on the subsequent ten trials. For the remaining two tasks the object presented on the first five trials was not rewarded (but the animal was required to displace it in order to complete the trial); on one of these tasks this object was rewarded in the next ten trials while on the other task the new object was rewarded.

On each week day each animal performed between one and five tasks (usually three) in a different order each time. *d*-Amphetamine sulphate (Sigma) or saline was administered by IM injection into the thigh in a volume of 0.05 − 0.1 ml, 20 − 30 min before testing. Doses of 0.0, 0.3, 0.6 mg/kg were administered in ascending and then descending order across days until each animal had completed four repetitions of each task at each dose. Scores on the four repetitions of each task at each dose were summed for each animal before subsequent analysis. In this way it was hoped that the effect of intrinsic object preference (as opposed to acquired preference determined by reward in the first five trials) would be counteracted.

All animals were required to respond on all of the first five trials of each task. These responses were not used in analysis. On the ten two-choice trials of each task a response was scored correct if it was rewarded and incorrect if it was unrewarded, irrespective of the reward condition of the first five trials.

In a supplementary experiment the same animals were trained at each dose on four two-choice visual discrimination tasks using novel junk objects, to a criterion of five consecutive correct responses per task. Two tasks were given each day and animals were pretreated with saline, 0.3 or 0.6 mg/kg amphetamine IM in a balanced design as before. The first ten trials of each of these tasks can be compared to the ten trial two-choice stage of the main experiment, so that the effect of pre-exposure of one object (either rewarded or unrewarded) can be compared to the initial trials of learning a discrimination between completely novel objects.

Results

Scores were compared, where indicated, using a matched-pairs *t*-test with 5 *df*.

If the animals attached a positive or negative reward association to the first encountered object and maintained this association during the two-choice trials of each task, they would perform better on those tasks on which the reward value was preserved (tasks A and C) than on those tasks on which the reward value was changed (tasks B and D). Alternatively, if the animals persisted in responding to the previously encountered object, they would perform better on those tasks on which such a response was correct (tasks A and D) than on those tasks on which such a response was incorrect (tasks B and C). Figure 1 illustrates these two hypotheses. Figure 1 A shows that performance was worse on tasks (B + D) (scores combined) than on tasks (A + C) ($P < 0.05$, saline; $P < 0.01$, 0.3 mg/kg; $P < 0.001$, 0.6 mg/kg *d*-amphetamine). Performance on tasks (B + D), where reward value was changed, was significantly worse after amphetamine than after saline ($P < 0.01$, 0.3 mg/kg; $P < 0.05$, 0.6 mg/kg). No effect of amphetamine occurred where reward value was unchanged (tasks A + C). Figure 1 B shows that there was no tendency for response-choice (habit) to be maintained under amphetamine. This suggests that perseveration under amphetamine reflects the animals' inability to change reward-association rather than to abandon a response tendency or habit.

When comparing performance on individual tasks it was found that there was no significant difference between saline and amphetamine conditions. There was, however, a tendency for performance to be worse on task B (+ −) than on task A (+ +) which attained significance under amphetamine ($P < 0.01$, 0.3 mg/kg; $P < 0.05$, 0.6 mg/kg), and a tendency for performance to be worse on task D (− +) than on task C (− −) which also attained significance under amphetamine ($P < 0.01$, 0.3 mg/kg; $P < 0.05$, 0.6 mg/kg). This suggests that prior experience of reward or non-reward are both effective in determining subsequent choice behaviour.

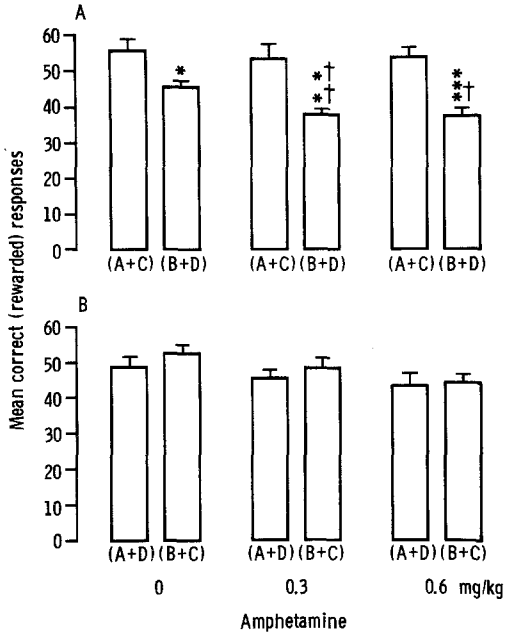

Fig. 1. A The effect of amphetamine on combined scores on tasks $(A + C)$ (meaning retained) and $(B + D)$ (meaning changed) $+ P < 0.05$, $++ P < 0.01$ comparing amphetamine with saline on each task combination. $* P < 0.05$, $** P < 0.01$, $*** P < 0.001$ comparing scores on $(A + C)$ with scores on $(B + D)$ at each dose. **B** The effect of amphetamine on habit or response perseveration determined by the combined scores on $(A + D)$ and $(B + C)$. See text for fuller explanation

Performance in the main experiment can also be compared to performance on the first ten trials of the supplementary tasks with no prior experience where mean total correct scores per animal were 23.8 ± 1.5, saline; 25.5 ± 1.4, 0.3 mg/kg; 22.5 ± 0.7, 0.6 mg/kg amphetamine. Performance was worse on task B $(+-)$ and on task D $(-+)$ where reward value changed when compared to the no prior experience condition, under amphetamine [$P < 0.01$ $(+-)$, $P < 0.02$ $(-+)$, 0.3 mg/kg; $P < 0.02$ $(+-)$, 0.6 mg/kg] but not under saline. Similarly comparing mean performance on tasks where reward value was changed (B + D) or maintained (A + C) with the no prior experience condition, it was found that performance under amphetamine (but not saline) was significantly worse on tasks (B + D) ($P < 0.01$, 0.3 mg/kg; $P < 0.02$, 0.6 mg/kg), but unchanged on tasks (A + C). This supports the suggestion that amphetamine impairs the animals' ability to change reward associations.

Other factors which may affect choice behaviour are (i) idiosyncratic preferences, (ii) a previously acquired preference for either novel or familar objects, (iii) response choice based on position rather than object preference and (iv) learning the two-choice discrimination part of each task on the basis of the then rewarded object independently of the reward condition in the first five trials. We have already shown that idiosyncratic preferences are enhanced by amphetamine (Ridley et al. 1981a). It is, however, not possible to determine an animal's initial preference without affecting the reward association of the stimuli. For this reason no attempt was made to assess initial preferences, but the effect of each drug dose was summed over four stimulus pairs, for each condition, for each animal, in an attempt to overcome preferences for individual stimuli. If the animals preferred the familar object at the two-choice stage of each task this would be seen as habit or response perseveration. Similarly, if the animals consistently chose the novel object a significant inverse effect on habit perseveration would have been seen. Animals might consistently prefer one of the lateral stimulus positions despite the initial central presentations of the first object. Considering the position at which each animal made most responses over all testing, it was found that there was no significant difference between amphetamine and saline conditions. It might be supposed, however, that animals may tend to respond at one stimulus position throughout any ten-trial task but to change position between tasks. Mean numbers of responses on the preferred side for each animal for each task were 5.9 (saline), 6.4 (0.3 mg/kg) and 6.3 (0.6 mg/kg). The difference from the saline condition just reached significance under 0.3 mg/kg amphetamine ($P < 0.05$). There is thus some suggestion that amphetamine may increase the tendency to respond in one position over short runs of trials. This effect, however, would tend to confound rather than exaggerate the effect of amphetamine on perseveration of reward association since, in each task, each object appeared five times on each side according to the Gellermann schedule.

It is possible that animals would learn the discrimination task on the basis of which object was rewarded at that stage irrespective of the reward value of the previously presented object. However, summed over all tasks, it was found that performance did not exceed chance except in the saline condition ($P < 0.005$, binomial test). This provides further evidence that information from the first five trials carries over to the two-choice trials more under amphetamine than saline, since it interferes with the animals' ability to learn the discrimination.

Discussion

The main finding of this experiment is that the perseverative effect of amphetamine on reversal tasks is due to an inability to alter the reward-value or meaning of stimuli rather than to a difficulty in relinquishing a motor habit.

If amphetamine were to act as a reinforcer such that all actions committed under amphetamine were "accidentally" rewarded (Ellinwood 1971), animals might be expected to show motor habit perseveration i.e. to continue responding to the familar object irrespective of its association with food reward. That motor habit perseveration did not occur argues against a simple reward theory of amphetamine action. If amphetamine were to potentiate the effect of reward (Stein 1964) then not only should acquired preference be more difficult to abandon (task B) but performance on the task where an acquired preference would be beneficial to subsequent performance (task A) should be improved. No such improvement was seen after amphetamine, suggesting that the results of this experiment cannot be described purely in terms of reward potentiation but that amphetamine acts directly on those processes which permit an alteration in an association rather than changing the level of incentive. Similarly, if amphetamine were to potentiate conditioned reinforcing properties of the originally encountered object (Hill 1970), then improved performance on task A as well as impaired performance on task B would be predicted.

The results of this and previous experiments described below lead us to suggest that amphetamine blocks a specific mechanism which normally inhibits or suppresses previously

acquired or prepotent cognitive set as a prerequisite visual change in behaviour. Amphetamine disrupts successive visual discrimination performance by increasing responses to unrewarded stimuli (Ridley et al. 1980a). Since monkeys invariably learn this task by initially responding to all stimuli and gradually suppressing responses to the unrewarded stimulus, this effect represents a release of behaviour suppressed by non-reward, i.e. extinction. Where non-responding is inhibited at the behavioural level by simple competition e.g. in simultaneous or "go her, go there" discrimination (Ridley et al. 1980b) amphetamine does not disrupt performance at comparable doses. The loss of a specific inhibitory mechanism after amphetamine is particularly evident on simple reversal learning (Ridley et al. 1981b). Undrugged animals were found to abandon an acquired association in two or three trials of reversal training, but then to learn the new disrimination at a similar rate to the original learning. After amphetamine no such rapid return to chance was seen and animals "learned their way" back to chance at the same rate as they learned the reversal and the original discrimination. Weiss and Laties (1971) have argued that many of the response-enhancing effects of amphetamine in animal experiments and improvement in performance on vigilance and monotonous tasks in human studies are best explained as a loss of active inhibitory processes mediating behavioural extinction. It is possible that stereotypy after higher doses of amphetamine results from failure of an inhibitory system which records that a motivated act has been completed and need not therefore be repeated. Several workers have demonstrated that stimulants enhance the capacity of conditioned reinforcing stimuli to sustain further acquisition learning (Beninger et al. 1980; Robbins 1976, 1978). While their experiments may indicate that stimulants potentiate the magnitude of conditioned reinforcing effects, they are also compatible with the suggestion that stimulants block inhibitory mechanisms which would normally permit extinction of conditioned reinforcement before acquisition learning could be established.

In view of the similarity between the amphetamine psychosis and schizophrenia (Connell 1958; Janowsky and Risch 1979) it is relevant to ask whether the cognitive changes occurring after amphetamine resemble those which are features of schizophrenia. The persistence of the assumed meaning of events in the face of subsequent evidence to the contrary may contribute to delusions, thought disorders and loss of reality orientation.

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