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A New Approach to the Role of Noradrenaline in Learning: Problem-Solving in the Marmoset After α-Noradrenergic Receptor Blockade

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RIDLEY, R. M., T. A. J. HAYSTEAD, H. F. BAKER AND T. J. CROW. *A new approach to the role of noradrenaline in learning: Problem-solving in the marmoset after α-noradrenergic receptor blockade.* PHARMAC. BIOCHEM. BEHAV. 14(6) 849–855, 1981.—Nine marmosets (*Callithrix jacchus*) were tested on a variety of visual discrimination learning tasks in a Wisconsin General Test Apparatus with or without α-noradrenergic receptor blockade achieved by the administration of aceperone. After aceperone, animals were found to be severely and consistently impaired at learning the first task of each test session and to be impaired on new and repeated reversal learning. They were, however, unimpaired on learning another similar task in each test session and on performance of a well-learnt task. Results are interpreted as evidence for defective association formation which can be compensated for by suitable priming or practice.

Noradrenaline Learning Aceperone Marmoset Discrimination Reversal

IT has been suggested that central noradrenergic neurones are involved in a variety of behavioural functions including learning [8,19], motivational drive [2], reward mechanisms [45], response inhibition [24] and selective attention [26], as well as in the phenomenon of intracranial self-stimulation [9]. The majority of studies of the role of noradrenaline (NA) in behaviour have focussed on the dorsal tegmental bundle (DNB) [21] of rodents which originates in the locus coeruleus, courses through the hypothalamus and terminates in the hippocampus and neocortex. Noradrenergic neurones in the locus coeruleus have been clearly identified in the common marmoset although NA neurones in the ventral tegmental area were found to be very diffuse [41].

The role of noradrenaline in behaviour remains controversial largely because of conflicting results from similar experimental procedures [27,33]. Intracranial self-stimulation has been reported in several studies [37,43] with electrodes in the region of the locus coeruleus but has not invariably been found [44]. Self-stimulation sites in or near the VNB have also been reported [38] although other workers have failed to find them [3,6]. Acquisition learning has been found to be unaffected by NA depletion in a variety of behavioural tasks in the rat (see [26]), although learning of complex tasks such as visual discrimination and visual discrimination reversal are impaired after depletion of forebrain NA [25].

In these experiments, using marmosets, we have studied the effect of reversible noradrenaline receptor blockade on learning in a variety of visual discrimination problems. Our results not only extend the study of noradrenaline function to the primate and to complex cognitive processing but also suggest that prior experience, immediately preceding training, and subtle differences in the type of task are of great importance in understanding the nature of the impairment of animals functionally deprived of noradrenaline.

Reversible α-noradrenergic blockade was achieved by the use of aceperone [18] (also known as acetabuton), a member of the butyrophenone group of drugs. When given peripherally to rats it produces a significant increase in brain levels of 3-methoxy-4-hydroxy-phenylglycol [5] and normetanephrine but not in 3-methoxy-tyramine [40] suggesting an action on central noradrenergic but not dopaminergic systems. Radioligand binding studies have indicated that aceperone is some 50–100 times less potent than haloperidol as a dopamine blocker [17,20]. On intramuscular injection in our studies, aceperone produced no immediately observable effect but a mild palpebral ptosis developed within a few minutes and lasted several hours. (Animals compensated for this by raising their eyebrows.) Previous studies in the marmoset [42] have demonstrated that 10 mg/kg IM aceperone has little effect on normal, directly observable behaviour with the exception of some decrease in locomotion during the first hour after injection. Aceperone was chosen in preference to the other well established α-noradrenergic blocking agents, phentolamine and phenoxybenzamine, since phentolamine is relatively short acting while phenoxybenzamine has a very long duration [30]. Pilot studies using propranolol [4,12], to produce β-noradrenergic blockade, did not yield a comparable effect on discrimination performance.

FIG. 1. Interior of W.G.T.A. showing marmoset retrieving the reward, having displaced the stimulus.

METHOD

Subjects and Apparatus

A total of 9 marmosets (*Callithrix jacchus*, 6 ♀, 3♂) weighing 170–300 g each, were used. Four marmosets had experienced considerable visual discrimination training under low doses of amphetamine and haloperidol [35,36], and were thus able to participate in this experiment without preliminary shaping. The remaining 5 animals were naive at the beginning of training. These animals were first shaped to displace a small object stimulus for food reward and then trained to a criterion of 90 correct responses in 100 consecutive trials (2–3 days training) on a simple discrimination task ('ballerina' versus 'soldier,' see below).

All animals were trained in a miniature Wisconsin General Test Apparatus (W.G.T.A.) [15]. Banana-flavoured pellets (BRS/LVE) or 3 mm cubes of fresh banana were used as reward. Motivational levels were maintained by giving the remainder of the animals' normal diet (bread, fruit and pellet chow) *after* training each day. Deliberate food deprivation was only required during the initial shaping. A variable number of trials was required to complete the learning tasks each day but typically an animal would not make more than ~80 responses in any training session.

Each trial commenced when the screen was raised to reveal 2 objects covering 2 small food wells, 12 cm apart (see Fig. 1). These objects were selected randomly from several hundred junk objects. Each object was less than 5 cm in its greatest dimension and mounted on a white plastic disc. Typical objects were bottle tops, broken plastic toys, etc. Two new, previously unseen, objects were used for each task for each animal such that by the end of an experiment each animal had experienced each pair of objects for only one task, but at a different stage of testing in each case. Reward was consistently placed in the food well under one of the two objects (designated positive), and the animal could obtain the reward by displacing that object. The left/right position of the positive object was varied according to a pseudorandom Gellermann schedule [11]. When one object had been displaced (and the reward obtained if the choice was correct) the screen was replaced and the objects positioned for the next trial. The intertrial interval was <15 sec.

Drug Administration

Aceperone was dissolved in saline acidified with a minimal amount of glacial acetic acid. The pH was adjusted with sodium hydroxide to ~6.8 (at which solubility was just maintained). A vehicle solution of comparable pH was used for control injections. One dose of aceperone was administrated in a volume of 0.1–0.2 ml into the thigh muscle 20–30 min before testing each week day. For each experiment aceperone was given in ascending followed by descending dosage (e.g., 0, 1.5, 3.0, 6.0, 6.0, 3.0, 1.5, 0 or 0, 6.0, 6.0, 0 mg/kg). The two days' performances at each drug dose were

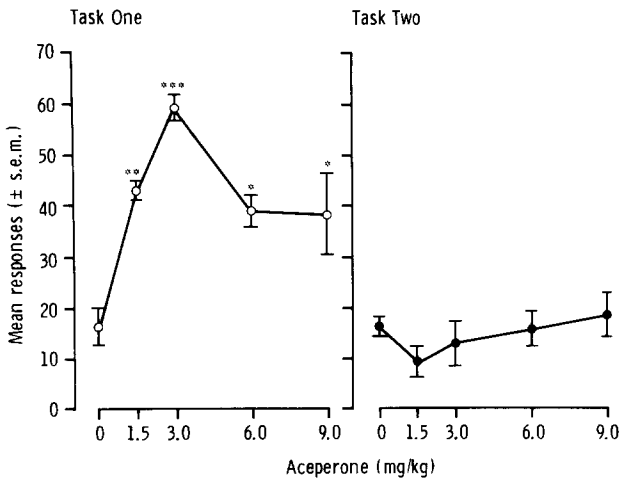

FIG. 2. Experiment 1. Effect of aceperone on learning two consecutive new object discriminations. Ordinate: mean responses (±s.e.m.) up to but excluding 5 consecutive correct. Abscissa: dose of aceperone (mg/kg). *$p<0.05$, **$p<0.01$, ***$p<0.001$ matched-pairs t-test, 4 df compared to vehicle condition (n=5). ○=task 1 ●=task 2.

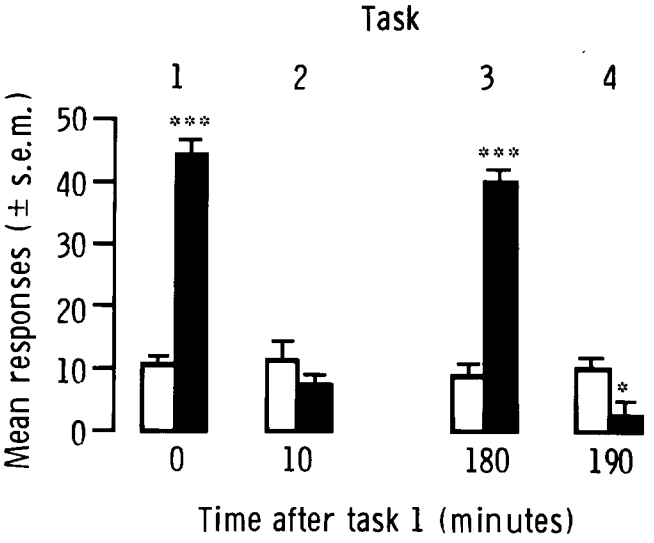

FIG. 3. Experiment 2. Effect of aceperone on learning four new object discriminations, tasks 3 and 4 being 3 hours after tasks 1 and 2. □=vehicle ■=6 mg/kg aceperone. *$p<0.05$, ***$p<0.001$ matched-pairs t-test, 4 df comparing aceperone with vehicle for each task (n=5).

summed for each animal in order to obviate the effects of any variation in daily conditions.

EXPERIMENTS AND RESULTS

Throughout this series of experiments animals were trained until they reached a criterion of 5 consecutive correct responses on each task. Learning scores for each task were calculated as the number of responses excluding those in criterion. A matched pairs t-test was used to compare animals' performances under different drug or training conditions. Examination of the data did not reveal any consistent difference between the effects of the two administrations of each experiment nor any consistent difference between experiments where the same types of task and conditions were repeated.

Experiment 1

The 5 previously inexperienced animals were used. On each day, each animal was trained on one object discrimination (task 1) followed immediately by training on another object discrimination (task 2). Figure 2 shows that there is a significant increase in learning scores on task 1 after all doses of aceperone. On task 2 there was no increase in learning scores after aceperone.

Experiment 2

In order to demonstrate that the lack of impairment on task 2 was due to a beneficial effect of learning a task 1 rather than, for instance, drug elimination, and to demonstrate the transience of this effect, the 5 animals were trained on a task 1 followed immediately by a task 2 and then, after 3 hours delay (spent in the home cage), on a task 3 followed immediately by a task 4. Animals were treated with vehicle or 6.0 mg/kg aceperone 20–30 min before task 1 only. Figure 3 shows the mean learning scores for each task. It can be seen that when the animals were treated with aceperone they had difficulty in learning task 1 but were unimpaired at learning task 2. After 3 hours they were impaired at learning task 3 but were then in fact significantly superior to the control condition in learning task 4.

Experiment 3

The four experienced animals were used to assess the effect of aceperone on discrimination performance using very familiar objects. As preliminary training, animals were first trained on a simple task using two small plastic toys ('guard' positive, 'soldier' negative) to 90 correct responses in 100 consecutive trials giving 50 trials/day. These animals had received 260–380 trials in a previous experiment where both of these objects were negative and paired with positive objects, 'Indian' and 'ballerina' [36] (see experiment 4 below). Learning scores (excluding the 100 trials in criterion) ranged from 90–170 trials. Animals were tested on performance of 50 trials/day of this task after vehicle or drug treatment on alternate week days. Performance remained at ⩾97% correct throughout testing at 0, 1.5, 3 and 6 mg/kg aceperone demonstrating that aceperone does not interfere with performance (including retention) of a well learnt task.

Experiment 4

On the intervening days during performance of experiment 3 the same animals were tested on re-learning and reversal learning of a task using the objects 'Indian' and 'ballerina.' The animals had previously experienced both these objects as rewarded (see above) and performed about

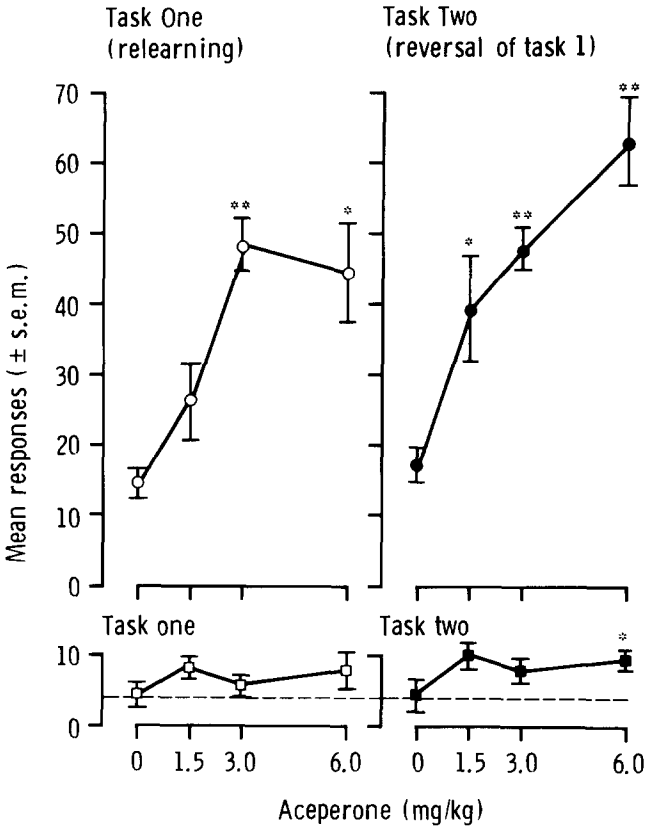

FIG. 4. Experiment 4. Effect of aceperone on re-learning and reversal learning and on perseverative (worse than chance) performance. $*p<0.05$, $**p<0.01$ matched-pairs t-test, 3 df comparing aceperone with vehicle for each task (n=4). ○ (re-learning), ● (reversal)=mean responses (±s.e.m.) to 5 consecutive correct. □ (re-learning), ■ (reversal)=mean responses (±s.e.m.) to 2 consecutive correct responses (perseveration). ---chance performance to 2 consecutive correct.

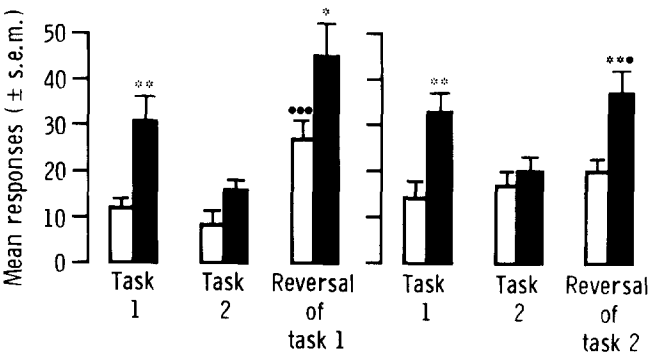

FIG. 5. Experiment 5. Effect of aceperone on a reversal of a task 1 or a task 2. □=vehicle ■=6 mg/kg aceperone. $*p<0.05$, $**p<0.01$ matched-pairs t-test, 8 df comparing aceperone with vehicle for each task. ● $p<0.05$, ●●● $p<0.001$ reversal compared to learning each task for aceperone or vehicle (n=9).

20 reversals of this task under amphetamine and haloperidol [35].

On each day the animals were required to relearn the discrimination which they had performed last 2 days previously (the previous day constituted part of experiment 3) followed immediately by the reversal of that task (i.e., objects reverse their reward value). Figure 4 shows that after aceperone animals were impaired both on re-learning this task and on learning its reversal.

Since after vehicle injection, animals required the same number of trials to re-learn the task as its reversal (see Fig. 4) animals showed no evidence of positive transfer (retention) on the re-learning task, or negative transfer (perseveration) on the reversal task. Initial performance on a task may also be used to assess the effects of transfer from a preceding task since initial performance which was better than chance would indicate positive transfer while worse than chance performance would indicate negative transfer. Computer simulation showed that the mean number of trials which would be performed before two consecutive correct responses occurred by chance is 4 (i.e., 2×2 days' testing, see method). Figure 4 shows that performance started at near chance levels on both re-learning and reversal under vehicle and drug conditions suggesting again that neither retention on the re-learning nor perseveration on reversal occurred to any important degree.

Initial performance on reversal in this study is consistent with the work of Cotterman *et al.* [7] who showed that performance on the second and third trials of repeated visual discrimination reversals by marmosets was already at chance level in the early stages of reversal learning but that complete reversal performance (*better* than chance on the second trial) was only achieved after more than 150 reversals.

Since doses of drug were given in ascending and descending order the 2 days' performance at each dose which were summed were preceded by different drug conditions. There is no evidence from individual day's scores of an influence on performance of the preceding drug condition.

Experiment 5

It was not clear from experiment 4 whether the high learning scores on reversal after aceperone were related to the high learning scores of the preceding task (i.e., that it takes as long to reverse a task as it takes to learn it) or whether animals treated with aceperone have an inherent difficulty in learning any reversal task. To distinguish these possibilities we studied the effect of aceperone on the reversal of a new task 1, (which they would be impaired at learning) and on the reversal of a new task 2, (which they would not be impaired at learning), using all nine animals. Figure 5 shows first that the predicted difference in learning task 1 and task 2 after aceperone was obtained and further that reversal learning for task 1 and task 2 was impaired after aceperone when compared to the equivalent reversal after vehicle. Comparing reversal scores with learning scores for each task, it can be seen that under aceperone reversal of task 2 is impaired. The reversal learning score on task 1 is 45% higher than the learning score on task 1 under aceperone although this difference does not reach significance ($p<0.1$). Thus an impairment on reversal learning occurs after aceperone irrespective of whether animals were impaired on the original learning of

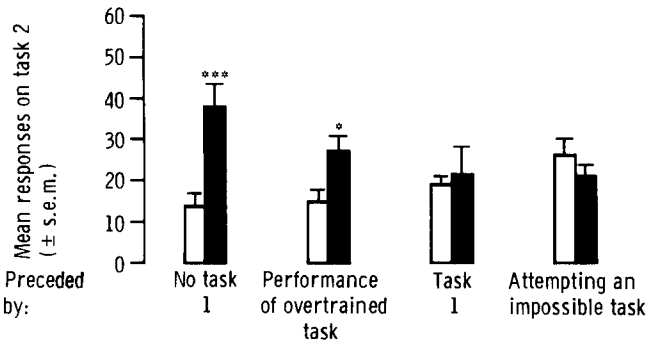

FIG. 6. Experiment 6. Effect of preceding training on learning under aceperone. □=vehicle ■=6 mg/kg aceperone. *$p<0.05$, ***$p<0.001$ matched-pairs t-test, 8 df comparing aceperone with vehicle for each condition (n=9).

that task. Unexpectedly, reversal of task 1 was impaired relative to learning task 1 after vehicle injection. Possibly task 1 had undergone some process of consolidation during the time spent learning task 2 rendering it more stable and thus more likely to interfere with reversal. Since reversal of task 1 was, however, significantly more impaired after aceperone than vehicle it would seem that some additional learning difficulty is involved after aceperone.

There was no significant difference after vehicle or aceperone on the reversal tasks between those animals from experiments 3 and 4 which had experiencd about 20 reversals of other objects and those animals from experiments 1 and 2 which had not previously been tested on reversal. This, again, is consistent with the work of Cotterman *et al.* [7] on reversal learning in the marmoset.

Experiment 6

In our final experiment we attempted to identify some of the aspects of learning a task which were beneficial in the subsequent learning of another task. All nine animals took part in this experiment. Training on a task 2 was preceded by:

1. another junk object task.
2. no training.
3. 30 trials performance of a previously well learnt task ('guard' vs 'soldier' for 4 animals and 'ballerina' vs 'soldier' for 5 animals) or
4. 30 trials of an impossible task using two identical objects 'sheep' vs 'sheep,' reward being distributed randomly between the two stimulus positions.

Figure 6 shows that, as previously, animals are impaired at learning a task under aceperone when there is no preceding task, but are unimpaired when they learn another task immediately after a first task (on which they were impaired, $p<0.02$). They were, however, impaired at learning a task 2 when it followed 30 trials of an over-trained task (where performance was ≥91%) but not when it followed 30 trials of attempting to solve an impossible task (where performance was between 46–56% rewarded trials for each animal).

DISCUSSION

Although aceperone may affect peripherally mediated levels of arousal it seems unlikely that this can explain the learning effects seen here since these depend largely on the animals' previous experience of the stimuli used. It is not clear how physiological arousal should interact with previous experience to produce a learning impairment on only certain tasks. Since animals were able to perform a well learnt task under aceperone (experiment 3) a general impairment such as an inability to see or move the objects, or a loss of motivation can be excluded. Similarly a loss of certain aspects of attention can be excluded; the animals must be able to attend to the stimuli within the context of the test box, to direct their responses towards the relevant object and to discriminate between familiar objects in order to perform the well learnt task.

All the occasions on which an impairment was observed after aceperone involved either new learning or reversal learning. This impairment could be attributable either to a difficulty in learning to distinguish between the two objects or in learning to associate only one with reward. The same discrimination, however, is required during learning and reversal, but the association with reward must be altered. Thus the impairment on reversal learning suggests that the defect is not one of perceptual discrimination but is more likely to consist of a difficulty in association formation. Not only must a new association be formed during reversal, but the old association must be abandoned. Failure to relinquish the old association would be demonstrated by perseverative responding, i.e., worse than chance performance. Since there is little evidence of perseveration in reversal after aceperone (Fig. 4) the impairment would appear to consist only of a failure of association formation, but not of association dissolution. In this respect reversal learning after aceperone differs markedly from that found in the same animals after amphetamine where the impairment could be attributed almost entirely to perseveration [35].

The ability of the animals in our study to abandon an association within the first two or three trials of reversal implies an almost immediate appreciation of the lost reward contingency. This makes a perceptual/attentional mechanism for the impairment unlikely. In so far as the results of this experiment can be compared to the effects of noradrenaline depletion by 6-OHDA lesions, our findings argue against an interpretation of the dorsal bundle extinction effect in terms of perseveration [23], loss of response inhibition [39] or a failure to notice either the lack of reward or any other changes in external conditions coinciding with the onset of extinction.

Experiment 6 attempts to analyse those aspects of learning a task which improve performance on a subsequent task. It would seem to be neither the perception of objects nor the performance of the response (which is required equally for *all* tasks including over-trained performance), finding the correct solution (which is required *only* for a conventional task 1), nor the number of rewards obtained (which is maximal for overlearnt performance) which bestows the greatest beneficial effect on subsequent learning. Rather, it would appear to be the cognitive analysis employed in actively *attempting* to solve a problem (demonstrated in isolation room *successful* solution during 'sheep' vs 'sheep') which is of most importance in overcoming the learning impairment produced by aceperone.

Experiment 2 demonstrates that the compensatory effect of learning a task on subsequent learning, is only temporary. This short term improvement resembles the 'warm-up' effects [13,16] seen in human learning. Since animals treated

with aceperone seem particularly sensitive to the beneficial effects of 'warm-up,' it seems probable that learning impairment following other forms of functional noradrenaline depletion e.g., dorsal bundle lesions may also be overcome by a very limited amount of preliminary practice or shaping and that subtle differences in the manner of training or of previous experience of the apparatus may produce large differences in subsequent performance.

'Warm-up' has been described as the "reinstatement of the appropriate perceptual-motor set" [34]. 'Set' has been shown to be an important aspect of discrimination learning in monkeys [14] including marmosets [29]. Since, without aceperone, learning scores on task 2 and task 1 are comparable (see Figs. 2–5) it would appear that animals with some previous training normally approach task 1 with the appropriate set and thus cannot show any improvement on task 2. Under aceperone, however, animals show a dramatic 'warm-up' effect suggesting that they previously lacked the appropriate set. The permanent retention of the benefits of past experience (as opposed to the specific retention of particular stimulus-response associations) is known as 'learning-to-learn' and has been amply demonstrated in monkeys [14]. Animals treated with aceperone may have impaired access to this learned set. This learned set, however, would appear to be of a cognitive rather than a simple perceptual or motor order because mere performance of an overlearnt task is less effective in restoring set than learning or attempting to learn. In the case of reversal learning it would appear that 'warm-up' is obliterated by negative interference from the stimuli of the preceding task. In other words, task 1 may act as a model for solving task 2 but in the case of reversal, specific information from the stimuli invites the animal to make the wrong response, rendering that particular task an unsatisfactory example. At this stage, we would suggest that the α-noradrenergic system is necessary to ensure access to cognitive skills in the absence of priming or 'warm-up' effects.

The discrete trial testing method used in this and numerous other primate studies has recently been applied to neuropsychological testing of brain damaged patients. Oscar-Berman and Zola-Morgan [31,32] have studied groups of patients with Broca's aphasia, Huntington's disease and Korsakoff's syndrome on a variety of learning and reversal tasks. The Korsakoff patients show a pattern of impairment which bears considerable resemblance to that seen in this experiment, i.e., an impairment on original new learning which shows a dramatic improvement on successive tasks within the same test session and an impairment on first reversal which is largely non-perseverative. In addition the Korsakoff patients showed an impairment on concurrent visual discrimination learning (which tests mainly association formation) and on spatial reversal tasks. By comparison the aphasic patients were not grossly impaired while the Huntington's group showed a more general difficulty on most of the visual tasks.

The major metabolite of NA, 3-methoxy-4-hydroxyphenylglycol (MHPG) has been found to be decreased in the c.s.f. of Korsakoff's patients [28], the extent of MHPG reduction being correlated with memory impairment across patients. A loss of NA from various brain areas [1] and of noradrenergic neurones from the locus coeruleus [22] has also been reported in post-mortem brains from patients with Alzheimer's disease. While the dementia of Alzheimer's disease may also be related to degeneration of the cholinergic system [10], the possible involvement of the NA system has clinical implications. Thus if learning impairments mediated by NA can be obviated by overlearning or 'warm-up,' therapeutic environments which concentrate on maintaining old habits and providing constant cues, reminders and examples should be particularly beneficial.

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