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Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes

(*d*-amphetamine/hippocampus/striatum/learning)

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ABSTRACT **These experiments investigated the effects, on memory, of injections of *d*-amphetamine (10 μg/0.5 μl) administered into the amygdala, hippocampus, or caudate nucleus immediately after training in cued or spatial water-maze tasks. In experiment 1, rats received an eight-trial training session on one of the two tasks followed by injections of *d*-amphetamine or saline. Retention was tested 24 hr later. On the spatial task, intrahippocampal, but not intracaudate, injections of *d*-amphetamine facilitated retention. In contrast, on the cued task intracaudate, but not intrahippocampal, injections of *d*-amphetamine facilitated retention. Posttraining intraamygdala injections of *d*-amphetamine enhanced retention of both tasks. In experiment 2, lidocaine (2% solution; 1.0 μl) injected intraamygdally prior to the retention test did not block the memory enhancement induced by posttraining intraamygdala injections of *d*-amphetamine. The findings (*i*) provide further evidence of a dissociation between the roles of the hippocampus and caudate nucleus in different forms of memory, (*ii*) indicate that the modulatory role of the amygdala is not limited to either of the two different forms of memory represented in spatial and cued discriminations in a water maze, and (*iii*) are consistent with previous findings indicating that amygdala influences on memory storage are not mediated by lasting neural changes located within the amygdala.**

Studies investigating brain systems and memory in rats (1–6), monkeys (7–9), and humans (10–13) provide evidence suggesting that different forms of memory are mediated by different brain systems. In rats, findings of double-dissociation experiments using brain lesions (2, 4, 6) and posttraining brain stimulation (5) suggest that the hippocampal system and the caudate nucleus are involved in different forms of memory. Within the theoretical framework of various dual-memory theories, it might be suggested that the hippocampus is critically involved in cognitive (1, 8), spatial (3), or declarative (10) memory, whereas the caudate nucleus is involved in habit (1, 8), taxon (3), or procedural (10) memory.

Extensive evidence indicates that memory storage is influenced by posttraining intraamygdala injections of drugs affecting several different neuromodulatory and neurotransmitter systems (cf. ref. 14). Moreover, the memory-modulating effects of many peripherally administered drugs and hormones require a functionally intact stria terminalis, a major amygdala afferent/efferent pathway, suggesting that posttraining activation of the amygdala influences memory storage occurring in other brain regions innervated by the amygdala (15, 16).

The amygdala is known to project to both the hippocampus and caudate nucleus (17–20), and the finding that c-fos is expressed in hippocampus and caudate nucleus following intraamygdala injections of the excitatory amino acid *N*-methyl-D-aspartate (21) indicates that the amygdala is functionally connected with both of these structures. Such evidence suggests the possibility that the amygdala may influence both hippocampal- and caudate-dependent memory.

To investigate this implication, experiment 1 examined the effects of posttraining intraamygdala injections of *d*-amphetamine on memory for two different types of water-maze tasks—a spatial task and a cued task—that are known to differentially involve the hippocampus and caudate nucleus, respectively (4, 22, 23). *d*-Amphetamine was used in these experiments because of extensive evidence that *d*-amphetamine enhances retention of a variety of tasks when administered either centrally (5, 24) or peripherally (25, 26).

In the spatial task, rats were trained to swim to an escape platform placed in a constant spatial location. As the top of the platform was 1.0 cm below the water surface, and rats were trained to approach the platform from different start points, the platform could be located only by learning spatial relationships among distal extramaze cues. In the cued task, rats were trained to swim to a visible cue mounted on a platform, which was placed in a different spatial location on each trial.

Experiment 2 was designed to determine whether the amygdala was involved as a locus of changes mediating the amygdala influences on memory in these two tasks. Rats were trained on one of the two tasks, given posttraining intraamygdala injections of *d*-amphetamine or saline, and then, shortly before testing, given an intraamygdala injection of lidocaine to inactivate the amygdala.

MATERIALS AND METHODS

Subjects. Subjects were 143 male Sprague–Dawley rats (250–275 g; Charles River Breeding Laboratories) individually housed in a temperature-controlled environment on a 12-hr light/12-hr dark cycle with the lights on from 7 a.m. to 7 p.m. Behavioral testing occurred between 1 p.m. and 4 p.m.

Apparatus. The water maze was a black circular galvanized steel tank (diameter, 1.83 m; height, 0.58 m) filled with water (25°C) to a depth of 20 cm. Four starting positions (north, south, east, west) were equally spaced around the perimeter of the tank, dividing the pool into quadrants. The rectangular Plexiglas escape platform used for the spatial task (11 × 14 × 19 cm) was submerged at a depth of 1 cm. For the cued task, a black and white striped rubber ball (diameter, 8 cm) was attached to the top of the submerged platform and protruded above the water surface. The platform could be used as a step to mount the ball and escape the water.

Surgery. Animals were anesthetized with sodium pentobarbital (50 mg/kg). Unilateral guide cannulae were implanted on the left side by standard stereotaxic techniques. For the posteroventral caudate placements, coordinates for

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the guide cannulae were as follows: anteroposterior (AP) = −0.3 mm, mediolateral (ML) = 4.0 mm from bregma, and dorsoventral (DV) = −4.0 mm from the skull surface. Coordinates for the dorsal hippocampal placements were as follows: AP = −3.1 mm, ML = 1.5 mm from bregma, and DV = −1.0 mm from the skull surface. Coordinates for the amygdala placements were as follows: AP = −2.2 mm, ML = 4.4 mm from bregma, and DV = −6.3 mm from skull surface. Behavioral testing began 1 week after surgery.

Drugs/Injection Procedures. *d*-Amphetamine (Sigma) was dissolved in physiological saline (experiments 1 and 2). A 2% lidocaine hydrochloride solution (Western Medical Supply, Arcadia, CA) was used in experiment 2. Injections (0.5 μl) were administered intracerebrally via guide cannulae using 30-gauge injection needles connected by polyethylene tubing to 10-μl Hamilton microsyringes. The injections were delivered over 37 sec with a syringe pump (Sage Instruments, Boston), and the injection needles (extending 2 mm from the end of the guide cannulae) were left in place an additional 60 sec to allow for diffusion of solution away from the needle tip. In experiment 2 lidocaine injections (1.0 μl) were administered over a period of 75 sec and the injection needles were left in place an additional 60 sec to allow for diffusion of solution. All injections were administered unilaterally (left side).

Histology. The animals were anesthetized with a 1-ml injection of sodium pentobarbital and perfused with saline followed by a 10% formal saline solution. The brains were removed and sectioned at 20 μm through the cannulae tract region and stained with cresyl violet. The slides were examined for verification of cannulae placement and injection needle tip location using the atlas of Paxinos and Watson (27).

Results of the histological examination for the caudate nucleus placements indicate that the cannulae needle tips were located in the posteroventral caudate, ranging from −0.2 to −0.6 mm from bregma. Hippocampal placements were located in the dorsal hippocampus, ranging from −2.6 to −3.3 mm from bregma. Amygdala placements were located primarily within the basolateral nucleus, ranging from −1.80 to −3.4 mm from bregma.

Behavioral Procedures. In both the spatial and the cued tasks, the animals received one training session consisting of eight trials (i.e., swims). On each trial, the animal was placed in the tank facing the wall at one of the four designated start points (north, south, east, and west) and allowed to escape onto the hidden or cued platform. A different starting point was used on each trial such that each starting point was used twice within the eight trials. If an animal did not escape within 60 sec, it was manually guided to the escape platform. After mounting the platform the rats remained there for 20 sec and were then removed from the maze and placed in a holding cage for a 30-sec intertrial interval. The latency to mount the escape platform was recorded and used as a measure of acquisition of each task.

In the spatial task, the submerged escape platform was located in the same quadrant on every trial. In the cued task, the escape platform was placed in a different quadrant on each trial, such that each of the four quadrants contained the escape platform on two of the eight trials. The locations of the start points for the cued task were arranged so that distance to the escape platform (i.e., proximal or distal) and location of the platform relative to the start point (i.e., left or right) were counterbalanced across the eight trials.

For experiment 1, the animals were randomly assigned to treatment groups (n = 7–10 per group) and received an injection of either *d*-amphetamine (10 μg) or physiological saline into the hippocampus, caudate nucleus, or amygdala immediately after training in the spatial or cued tasks. For experiment 2, the rats were randomly assigned to treatment groups (n = 8 per group) and received a posttraining injection of either *d*-amphetamine (10 μg) or physiological saline into the amygdala on the first day and an injection of either lidocaine or physiological saline into the same amygdala 5 min before the retention test on the 2nd day.

Retention was tested 24 hr after completion of training. The retention test on the spatial task consisted of one trial. The submerged escape platform was located in the same quadrant of the maze as during training. A starting point located distal to the escape platform was used. The retention test for the cued task consisted of four trials. As during training, the visible escape platform was placed in a different quadrant of the maze on each trial. On each of these four trials a different start point located distal to the visible escape platform was used. In both tasks, the latency to mount the escape platform was recorded on all retention test trials and used as a measure of memory for the previous day's training session.

RESULTS

Experiment 1

Experiment 1 examined the effects of posttraining intracerebral injections of *d*-amphetamine on retention of training in the spatial and cued tasks.

Training Day Escape Latencies. Two-way ANOVAs with one repeated measure (trial) were computed on the escape latencies on the training day (i.e., prior to injections). There were no significant differences among the groups in training escape latencies (data not shown). In the spatial task, all groups improved over the eight training trials, obtaining mean escape latencies of 15–20 sec on trials 7 and 8. In the cued task, all groups obtained mean escape latencies of 10–15 sec on trials 7 and 8.

Spatial Task. The effects of posttraining intrahippocampal, intraamygdala, and intracaudate administration of *d*-amphetamine on retention test performance in the spatial task are shown in Fig. 1 *a*, *b*, and *c*, respectively. A one-way ANOVA of retention test escape latencies revealed that retention was significantly enhanced by injections of *d*-amphetamine into the hippocampus ($F_{(1,14)} = 5.4$; $P < 0.05$) and amygdala ($F_{(1,14)} = 7.08$; $P < 0.01$). Intracaudate injections of *d*-amphetamine did not affect retention test escape latencies in the spatial task ($F_{(1,14)} = 0.35$; not significant).

Cued Task. The effects of posttraining intrahippocampal, intraamygdala, and intracaudate administration of *d*-amphetamine on retention test performance in the cued task are shown in Fig. 2 *a*, *b*, and *c*, respectively. Two-way ANOVAs with one repeated measure (trial) computed on the retention test escape latencies revealed significant effects of *d*-amphetamine for both the caudate ($F_{(1,14)} = 9.72$; $P < 0.01$) and amygdala ($F_{(1,17)} = 10.51$; $P < 0.01$) injections. Scheffe post hoc tests showed that in comparison with saline controls, *d*-amphetamine-treated caudate rats had significantly shorter escape latencies on retention test trials 1 ($F = 4.85$; $P < 0.01$), 3 ($F = 11.5$; $P < 0.01$), and 4 ($F = 10.36$; $P < 0.01$). Similar post hoc tests showed that in comparison with saline controls, *d*-amphetamine-treated amygdala rats had significantly shorter escape latencies on retention test trials 1 ($F = 7.65$; $P < 0.01$) and 4 ($F = 4.49$; $P < 0.01$). Intrahippocampal injections of *d*-amphetamine did not affect retention test escape latencies in the cued discrimination task ($F_{(1,14)} = 0.96$; not significant).

The findings of experiment 1 indicate that intrahippocampal and intracaudate injections of *d*-amphetamine had different effects on retention of these two water-maze tasks; intrahippocampal administration selectively enhanced memory on the spatial task, whereas intracaudate administration selectively enhanced memory on the cued task. These findings are consistent with previous findings of a double dissociation obtained in an experiment examining the effects of

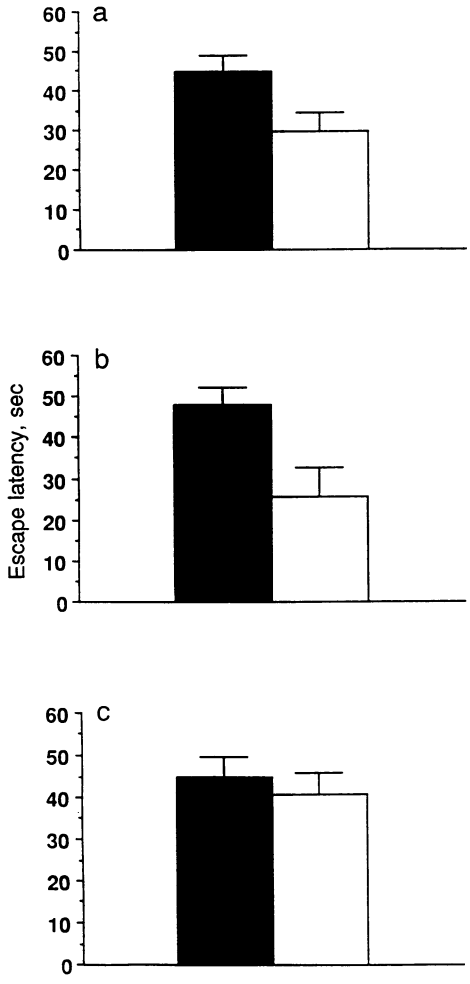

FIG. 1. Mean (±SE) escape latencies of *d*-amphetamine (10 μg) (□) and saline-treated (■) rats on the retention test trial in the spatial task. (*a*) Hippocampal injections. (*b*) Amygdala injections. (*c*) Caudate nucleus injections.

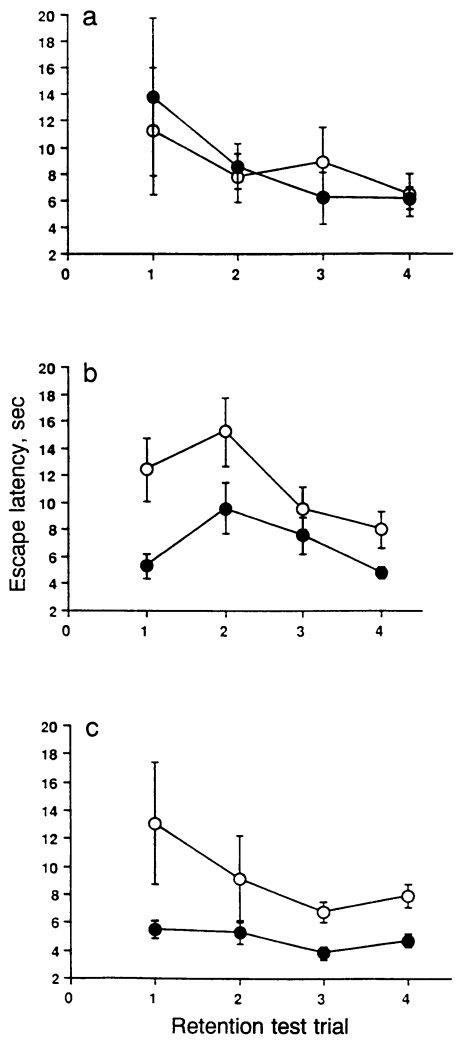

FIG. 2. Mean (±SE) escape latencies of *d*-amphetamine (10 μg) (●) and saline-treated (○) rats on the retention test trial in the cued task. (*a*) Hippocampal injections. (*b*) Amygdala injections. (*c*) Caudate nucleus injections.

posttraining intracaudate and intrahippocampal injections of *d*-amphetamine on retention of cued and spatial learning in appetitively motivated radial maze tasks (5).

In contrast to the differential effects of hippocampal and caudate injections of *d*-amphetamine on the spatial and cued tasks, intraamygdala administration of *d*-amphetamine enhanced memory in both water-maze tasks. That is, the modulatory role of the amygdala in memory did not depend on the type of learning task used to assess memory. The extensive evidence from lesion studies implicating the amygdala in the acquisition and retention of aversively motivated tasks (e.g., see refs. 28 and 29) suggests the possibility that the intraamygdala injections of *d*-amphetamine may have had comparable effects on retention in the two tasks simply because both tasks used aversive motivation (escape from water). However, as lesions of the amygdala do not impair acquisition of spatial (30) or cued (unpublished data) water-maze tasks, the use of aversive motivation does not appear to provide a basis for the common effect of the intraamygdala injections of *d*-amphetamine on memory in these two water-maze tasks.

Experiment 2

The findings of experiment 1 indicate that posttraining activation of the amygdala enhanced memory on both hippocampal-dependent and caudate nucleus-dependent learning tasks. There are at least two possible hypotheses concerning the locus of the effects of intraamygdala injections of *d*-amphetamine on memory. First, the injections may have acted to influence the consolidation of memory traces located within the amygdala. Alternatively, the injections may have acted to modulate memory processes occurring in or regulated by other brain structures, possibly the hippocampus and caudate nucleus, two brain sites that appear to selectively mediate the acquisition of spatial and cued discriminations in a water maze (4) and that have anatomical (17–20) and functional (21) connections with the amygdala.

Experiment 2 was designed to examine these two hypotheses. As in experiment 1, rats received training in either the spatial or cued tasks followed by a posttraining intraamygdala injection of *d*-amphetamine or vehicle. Prior to the retention test session, half of the animals trained on each task received intraamygdala injections of a 2% lidocaine solution, a local anesthetic that produces a functional blockade of neural activity. If *d*-amphetamine enhances memory in both tasks by consolidating memory traces located exclusively within the amygdala, such enhancement should not be expressed in the absence of a functional amygdala. Alternatively, if posttraining intraamygdala *d*-amphetamine enhances memory in both tasks by modulating memory processes occurring in other brain structures, such enhancement should still be expressed in the absence of a functional amygdala.

Training Day Escape Latencies. A two-way ANOVA with one repeated measure (trial) computed on the escape laten-

cies on the training day revealed no significant differences between the groups that were to receive posttraining intraamygdala injections of saline or *d*-amphetamine (F values; data not shown). In the spatial task, all groups improved over the eight training trials, obtaining mean escape latencies of 15–20 sec on trials 7 and 8. In the cued task, all groups obtained mean escape latencies of 10–15 sec on trials 7 and 8.

Spatial Task. The effects of intraamygdala posttraining injections of *d*-amphetamine and preretention test injections of lidocaine on retention test performance in the spatial task are shown in Fig. 3*a*. A one-way ANOVA computed on the retention test escape latencies revealed a significant group effect ($F_{(2,21)} = 10.96$; $P < 0.01$). Scheffe post hoc tests showed that the retention test escape latencies of rats given posttraining *d*-amphetamine and preretention test saline injections were significantly shorter than those of rats given posttraining saline and preretention test saline injections ($F = 8.03$; $P < 0.01$). This finding replicated the memory-enhancing effect of *d*-amphetamine observed in experiment 1. Furthermore, the retention test escape latencies of rats given posttraining *d*-amphetamine and preretention test lidocaine injections were significantly shorter than those of rats given posttraining saline and preretention test saline injections ($F = 8.41$; $P < 0.01$). This finding indicates that lidocaine administration did not prevent expression of the memory-enhancing effects of posttraining intraamygdala injections of *d*-amphetamine.

Cued Task. The effects of intraamygdala posttraining injections of *d*-amphetamine and preretention test injections of lidocaine on retention test performance in the cued task are shown in Fig. 3*b*. A two-way ANOVA with one repeated measure (trial) computed on the retention test escape latencies revealed a significant group effect ($F_{(2,21)} = 10.18$; $P < 0.01$). Scheffe post hoc tests showed that the escape latencies of rats given posttraining *d*-amphetamine and preretention test saline injections were significantly shorter on trials 1 ($F = 3.56$; $P < 0.05$), 2 ($F = 9.02$; $P < 0.05$), and 3 ($F = 6.40$; $P < 0.05$) than those of rats given posttraining saline and preretention test saline injections. Similar post hoc tests showed that the trial 1 escape latencies of rats given posttraining *d*-amphetamine and preretention test lidocaine were significantly shorter ($F = 3.52$; $P < 0.05$) than those of rats given posttraining saline and preretention test saline injections. The differences in escape latencies for these groups on trials 2 and 3 showed only a trend toward significance; trial 2 ($F = 2.23$; $P < 0.12$), trial 3 ($F = 2.48$; $P < 0.08$). However, as escape performance on the first retention test trial represents the most sensitive measure of memory for the previous day's training, the findings indicate that lidocaine administration did not prevent expression of the memory-enhancing effects of *d*-amphetamine.

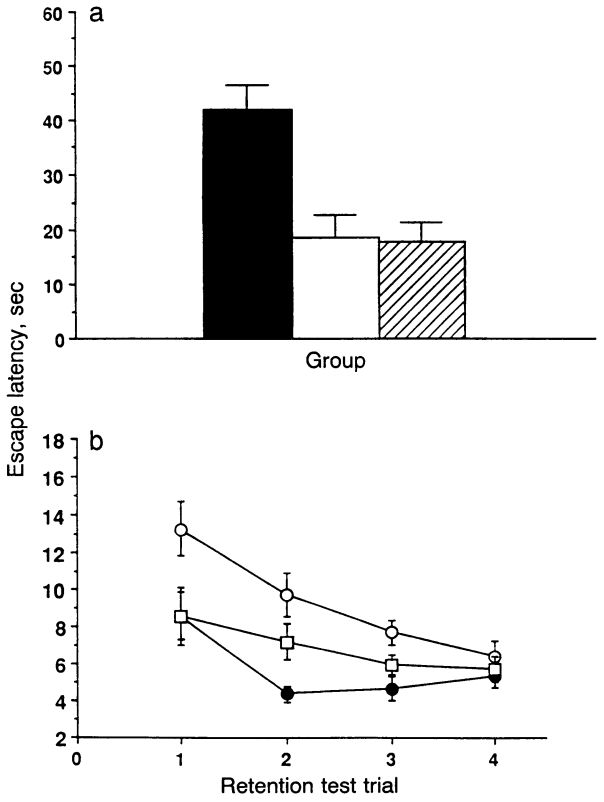

FIG. 3. Mean (±SE) escape latencies of rats receiving intraamygdala posttraining *d*-amphetamine or saline and rats receiving preretention test lidocaine or saline on the retention test trial(s) in the spatial task (*a*) and cued task (*b*). Posttraining/preretention: ■ (*a*) and ○ (*b*), saline/saline; □ (*a*) and ● (*b*), *d*-amphetamine/saline; ▨ (*a*) and □ (*b*), *d*-amphetamine/lidocaine.

The findings of experiment 2 indicate that intraamygdala administration of lidocaine prior to the retention test did not prevent expression of the memory-enhancing effects of posttraining intraamygdala injections of *d*-amphetamine on either the spatial or cued water-maze tasks. The findings indicate that an intact amygdala is not required for the expression of memory in these tasks and suggest that the retention enhancement produced by *d*-amphetamine was not mediated by modulation of memory traces located within the amygdala. Rather, the findings are consistent with the hypothesis that the memory enhancement produced by *d*-amphetamine resulted from modulatory influences on memory processes in other brain structures activated by the amygdala.

Evidence from lesion studies indicates that the hippocampal system and caudate nucleus selectively mediate the acquisition of spatial and cued discriminations, respectively, in a water maze (4), and the results of experiment 1 indicate a double dissociation following posttraining injections of *d*-amphetamine into the hippocampus and caudate nucleus on these two tasks. Thus, although the findings of the present experiments do not directly identify the structure(s) receiving a modulatory influence from the amygdala on memory, the hippocampus and caudate nucleus would appear to be strong candidates.

DISCUSSION

The present findings support the general hypothesis that the amygdala serves to "modulate" memory storage rather than as a "permanent site" of plastic changes underlying memory for the kinds of tasks used in the present experiments as well as memory for other aversively motivated tasks (14). We have tentatively proposed (31) several defining characteristics of a memory modulatory system, three of which are pertinent in the context of the present experiments: (*i*) A modulatory memory system is not essential for learning to occur. Removal of such a system may not prevent learning, but it may prevent the memory-impairing or enhancing effects of posttraining treatments. (*ii*) A modulatory memory system is not essential for the expression of learned behavior. (*iii*) A modulatory memory system can affect memory independently of the type of memory involved in a task. Evidence for the first characteristic comes primarily from studies indicating that although lesions of the stria terminalis prevent the memory-enhancing and impairing effects of posttraining drug treatments on retention in inhibitory avoidance tasks, such lesions do not prevent learning in otherwise untreated animals (15, 16). These findings suggest that the functional integrity of the amygdala is a necessary cofactor for the expression of posttraining treatment effects. Similarly, al-

though posttraining intraamygdala administration of *d*-amphetamine enhanced memory in both spatial and cued discriminations in a water maze, the acquisition of each of these tasks is unaffected by amygdala lesions (ref. 30; unpublished data).

Evidence in support of the second characteristic of a memory modulatory system comes from findings indicating that lesions (32) or reversible inactivation (33) of the amygdala induced a week or longer after training, do not prevent the expression of memory. Similarly, in experiment 2, functional inactivation of the amygdala prior to a retention test given 24 hr after training did not prevent the expression of the memory-enhancing effects of posttraining intraamygdala injections of *d*-amphetamine.

The present findings also provide evidence in support of the third characteristic—namely, that a modulatory system can affect memory independently of the type of memory involved in acquiring a task. This characteristic appears to distinguish a memory modulatory system (e.g., amygdala) from other brain systems (e.g., hippocampus, caudate nucleus), which appear to directly mediate acquisition of tasks involving specific forms of memory.

It should be noted that findings of amygdala lesion studies suggest that, in some learning situations, the amygdala is the locus of an "essential circuit" underlying acquisition and storage of memory. This view is primarily supported by studies examining the role of the amygdala in fear-motivated learning (28, 29) and acquisition/retention of second-order stimulus–reward associations (34, 35). However, while the modulatory and essential circuit views of the role of the amygdala in memory may not appear to be compatible, we have no *a priori* reason to believe that they are mutually exclusive for all tasks. It is possible that both functions involve initial activation of similar anatomical circuitry within the amygdala and that the ultimate expression of a modulatory or circuit role of the amygdala in memory may depend on the specific learning situation. Alternatively, with regard to fear-motivated learning, it is possible that the fear component related to aversive training may be stored in the amygdala. Given that the two water-maze tasks do not require memory of the aversiveness of the water, the present findings may demonstrate the modulatory function of the amygdala in different forms of memory independently of the possible involvement of the amygdala as a locus of storage for learned fear. Finally, experiments examining the effect of functional manipulations of discrete amygdala nuclei and their target structures may help determine whether these two hypothesized roles of the amygdala in memory are mediated by a differential involvement of specific amygdala nuclei.

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