Independence of Memory Functions and Emotional Behavior: Separate Contributions of the Hippocampal Formation and the Amygdala

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ABSTRACT

Structures and connections in the medial temporal lobe of humans and nonhuman primates have long been recognized as important for normal memory and emotional behavior. The present study investigated memory and emotional behavior in normal monkeys and six groups of monkeys with lesions of the medial temporal lobe. Two groups had damage to the hippocampal formation (or adjacent perirhinal and parahippocampal cortex) but not the amygdaloid complex; two groups had either partial or complete damage to the amygdaloid complex but not the hippocampal formation; and two groups had damage to both the hippocampal formation and the amygdaloid complex. Memory was evaluated with three tasks sensitive to human amnesia: (1) delayed nonmatching to sample; (2) retention of object discriminations; and (3) concurrent discrimination learning. Emotional behavior was assessed by measuring the responsiveness of monkeys to 12 different stimulus situations. Damage to the hippocampal formation or anatomically related cortex impaired memory but did not affect emotional behavior. Partial or complete damage to the amygdaloid complex affected emotional behavior but not memory. These findings show that memory impairment and abnormal emotional behavior are anatomically dissociable and independent effects of damage to the medial temporal lobe.

Key words: memory, emotion, hippocampal formation, amygdala, monkeys

It is well established in both humans and nonhuman primates that bilateral damage to the medial temporal lobe can disrupt normal function within two broad categories of behavior: memory and emotion. Memory impairment was first linked to medial temporal lobe damage nearly a century ago as the result of neuropathological findings from a case of human amnesia (von Bechterew, 1900). Subsequently, several thoroughly studied cases of medial temporal lobe amnesia (including patient H.M., Scoville and Milner, 1957; patient D.R.B., Damasio et al., 1985; and patient R.B., Zola-Morgan et al., 1986) have provided information about the organization of memory and the anatomy of memory impairment (Squire, 1987). In addition, the successful development of an animal model of human amnesia in the monkey (for reviews, see Squire and Zola-Morgan, 1983; Zola-Morgan and Squire, 1991a) has led to the identification of structures and connections within the medial temporal lobe that, when damaged, produce memory impairment.

Impaired emotional behavior was first linked to temporal lobe damage in a report that described the effects of large bilateral temporal lobe lesions on emotional behavior in monkeys (Brown and Schafer, 1888). Systematic study of these effects began with the observations of Klüver and Bucy (1938; 1939), who reported a complex set of emotional and behavioral changes in monkeys following bilateral temporal lobectomy. Prominent among the observed emotional changes were tameness, a tendency to approach both animate and inanimate stimuli without hesitation, and a tendency to examine objects by mouth instead of by hand.

The finding that temporal lobe lesions can both impair memory and produce abnormal emotional behavior raises two kinds of questions. The first question is an anatomical one: Are the deficits in memory and emotional behavior caused by damage to the same structures or group of structures? That is, are the neural substrates for memory and emotional behavior similar, as suggested originally by Papez (1937), do they only partly overlap, or are they completely different? The second question is a behavioral one: Might damage to one system affect performance on tests intended to assess the status of the other system (even if memory and behavior are

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anatomically independent)? For example, it seems possible that emotional changes associated with the Klüver-Bucy syndrome could affect performance on memory tests (e.g., stimuli might acquire abnormal emotional meaning and, therefore, be remembered differently from normal). Similarly, it seems possible that memory impairment could change reactions to stimuli that ordinarily produce emotional reactions (e.g., the value of a stimulus might not be remembered accurately).

To answer the first question, attempts have been made to separate emotion and memory anatomically. The lesion in the monkey that first established an animal model of human medial temporal lobe amnesia was intended to approximate the removal sustained by amnesic patient H.M. The lesion involved the amygdala and the hippocampus (including the dentate gyrus and the subicular complex) as well as adjacent cortical regions, that is, perirhinal, entorhinal, and parahippocampal cortex. Monkeys with this lesion exhibited severe memory impairment on a number of tasks (Mishkin, 1978; Mahut et al., 1981; Zola-Morgan and Squire, 1984; 1985). Subsequent work has suggested that damage to the amygdala does not contribute to this memory impairment (Zola-Morgan et al., 1989b) and that the impairment results from damage to the hippocampus and adjacent, anatomically related cortex, that is, perirhinal, entorhinal, and parahippocampal cortex (Zola-Morgan et al., 1989c; Zola-Morgan and Squire, 1990; for a different view, see Murray and Mishkin, 1990).

Studies of abnormal emotional behavior have found that all the components of the Klüver-Bucy syndrome that involve emotional behavior can be produced by damage to the amygdaloid complex together with adjacent cortex, that is, perirhinal and entorhinal cortex (Pribram and Bagshaw, 1953; Mishkin and Pribram, 1954; Weiskrantz, 1956; Schwartzbaum, 1965; Meyers and Swett, 1970; Horel et al., 1975). More recently, most of these components of the Klüver-Bucy syndrome (tameness and excessive examination and mouthing of stimuli, including nonfood objects) were also observed following bilateral stereotaxic lesions of the amygdaloid complex that spared the cortical regions adjacent to the amygdala, that is, perirhinal and entorhinal cortex (Aggleton and Passingham, 1981; for a review of the neurobiology of emotion, including the effects of amygdala damage on emotional behavior in species other than nonhuman primates, see LeDoux, 1987).

These studies, taken together, suggest an anatomical dissociation of emotional behavior and memory: The integrity of the amygdaloid complex appears necessary for normal emotional behavior (LeDoux, 1987), while the integrity of the hippocampus and anatomically related cortex is required for normal memory (Squire and Zola-Morgan, 1988). This view is consistent with the significant differences that are found in the neuroanatomy of the amygdaloid complex and the hippocampal formation. Specifically, the amygdaloid complex, unlike the hippocampal formation, is directly innervated by many cortical and subcortical structures that have been implicated in species-specific aggression, defense, sexual behavior, and other kinds of emotional behavior (Amaral, 1987). Nevertheless, several questions remain. Does damage to the cortical regions that surround the amygdala and hippocampus (e.g., the perirhinal and parahippocampal cortex) affect only memory, or does damage to these regions affect emotional

behavior as well? Furthermore, because almost all previous studies have examined only emotion or memory separately, it remains unclear whether an impairment in one function might affect measures of the other. For example, one must consider the possibility that the severe memory impairment associated with large medial temporal lobe lesions could result in part from abnormal emotional behavior.

Quantitative studies of both memory and emotional behavior in monkeys with damage to different components of the medial temporal lobe are needed to answer these questions. Accordingly, several years ago, in conjunction with our ongoing studies of memory, we initiated formal assessments of emotional behavior in all surgical groups of monkeys who were undergoing postoperative tests of memory function (Alvarez-Royo et al., 1988).

Here, we present observations of memory and emotional behavior in normal monkeys and in 6 groups of operated monkeys who sustained surgical damage to the medial temporal lobe. Two lesion groups included the amygdaloid complex, but spared the hippocampal function; 2 groups included the hippocampal formation or related cortex, but spared the amygdala; the final 2 lesion groups included both the hippocampal formation and the amygdala. Emotional behavior was investigated by measuring the response of monkeys to 12 different stimulus situations. Seven of the stimuli (object stimuli) measured investigatory or consummatory behavior. The other five stimuli (social stimuli) measured interactive social behavior. Memory was tested on three tasks sensitive to human amnesia (Squire et al., 1988), that is, delayed nonmatching to sample, delayed retention of object discriminations, and 8-pair concurrent discrimination learning.

MATERIALS AND METHODS

Subjects

The findings from 43 adult cynomolgus monkeys (*Macaca fascicularis*) will be presented. All monkeys weighed between 3.5 and 6 kg at the beginning of the behavioral tests reported here. Based on weight-and-age tables (Szabo and Cowan, 1984; Hartley et al., 1984) these monkeys were estimated to be between 3 and 5 years of age (young adults).

Table 1 shows the number of animals in each group. Fifteen normal monkeys were studied, together with 28 monkeys in six different operated groups. Of the 15 normal monkeys, 9 were given the tests of emotional reactivity but not the memory tests, and 6 were given the memory tests but not the emotional tests (all described below). The monkeys in 4 of the operated groups (A⁻, A, H⁺A, and PRPH) were given both the memory and emotional batteries. The remaining 2 operated groups (H⁺A⁺ and H⁺) consisted of 7 monkeys each. Three monkeys from the H⁺A⁺ group and 4 monkeys from the H⁺ group were given the emotional battery, and the other monkeys in each group were given the memory battery.

Surgery

The surgical procedures used for all the operated groups except the A⁻ group have been described in detail elsewhere (see Table 1) and will be only summarized here. All lesions were made in a single stage under aseptic conditions. Intra-

Table 1. Tests of Emotional Reactivity and Memory

Group	n	Emotional Battery	Memory Battery	References to Behavioral and Neurohistological Findings
N	9	+ (2–10)	–	Salmon et al., 1987*
	6	–	+	Zola-Morgan et al., 1989c
A⁻	4	+ (4)	+	See text
A	3	+ (4)	+	Zola-Morgan et al., 1989b
H⁺A	3	+ (4)	+	Zola-Morgan et al., 1989b
H⁺A⁺	3	+ (10)	–	Salmon et al., 1987
	4	–	+	Zola-Morgan and Squire, 1984; 1985
H⁺	4	+ (2)	–	See text
	3	–	+	Zola-Morgan and Squire, 1986
PRPH	4	+ (4)	+	Zola-Morgan et al., 1989a Zola-Morgan et al., 1989c

Tests of emotional reactivity and tests of memory were given to 7 groups of monkeys (n = number of animals in each group). The emotional battery and the memory battery were sometimes given to the same animals in each surgical group and sometimes to different animals in each group (+, test administered; –, not tested). The numbers in parentheses indicate for each group the number of times that the emotional battery was administered after surgery. The references indicate where details of neurosurgery, neurohistology, and memory performance can be found. Nomenclature: N, normal; A⁻, bilateral incomplete lesions of the amygdaloid complex; A, bilateral complete lesions of the amygdaloid complex; H⁺A, bilateral complete lesions of the amygdaloid complex, the hippocampus proper, dentate gyrus, subicular cortex, posterior entorhinal cortex, and parahippocampal cortex; H⁺A⁺, bilateral conjoint hippocampus–amygdala lesions that were the same as the H⁺A lesions but which also involved the anterior entorhinal cortex and the perirhinal cortex; H⁺, the same as the H⁺A lesions, but with sparing of the amygdaloid complex; PRPH, bilateral conjoint lesions of the perirhinal and parahippocampal cortices. *Reference reports data for only 3 of the 9 normal monkeys who were given the emotional battery.

venous or intraperitoneal sodium pentobarbital (15–30 mg/kg) was used for anesthesia.

Group A⁻

Bilateral removal of the amygdala was accomplished through two separate entries, one on each side of the brain. Following a craniotomy overlying the dorsolateral frontal cortex, the amygdala was approached by elevating the frontotemporal junction, and the brain was entered at a point medial to the anterior tip of the rhinal sulcus. As described in the Results section, damage to the amygdala was incomplete. Accordingly, we have used the term A⁻ to designate this group.

Group A

Monkeys sustained bilateral radio frequency lesions of the amygdala (for detailed description of the procedure, see Zola-Morgan et al., 1989b). The removal was intended to damage all the components of the amygdaloid complex, while sparing

the adjacent cortical areas (i.e., anterior entorhinal cortex and perirhinal cortex).

Group H⁺A

Monkeys first sustained bilateral radio frequency lesions of the amygdala, as described above (for details, see Zola-Morgan et al., 1989b). The hippocampus was then removed by aspiration under direct vision. The removal was intended to include the amygdala (including periamygdaloid cortex), the hippocampus (including dentate gyrus and subicular complex), and the cortical regions adjacent to the hippocampus (i.e., posterior entorhinal cortex and parahippocampal cortex).

Group H⁺A⁺

For all monkeys, the removal was intended to include the amygdala (including periamygdaloid cortex), the hippocampus (including the dentate gyrus and the subicular complex), and the cortical regions adjacent to the hippocampus and the amygdala (i.e., perirhinal, entorhinal, and parahippocampal cortex). This lesion differed from the H⁺A lesion in that the cortical areas adjacent to the amygdala were also damaged. Detailed description of the surgical procedure can be found in Salmon et al. (1987) (for the monkeys that were tested on the emotional battery), and in Zola-Morgan and Squire (1984; 1985) (for the monkeys that were tested on the memory battery).

Group H⁺

The same surgical procedure was used for the monkeys tested on the emotional battery and the monkeys tested on the memory battery (see Zola-Morgan and Squire, 1986). The removal was intended to include the hippocampus (including the dentate gyrus and the subicular complex) and the cortical regions surrounding the hippocampus (i.e., posterior entorhinal cortex and parahippocampal cortex).

Group PRPH

This lesion was intended to include all of the perirhinal cortex (PR) and parahippocampal cortex (PH) that together provide the major source of cortical input to the hippocampal formation. The anterior portion of the removal was intended to involve approximately 3–4 mm of cortex lateral to the rhinal sulcus (for details, see Zola-Morgan et al., 1989c). The ablation expanded caudally so as to encompass the TH and TF fields (Bonin and Bailey, 1947) of the parahippocampal cortex. Additionally, projections from other cortical regions to the hippocampal formation that traverse the PRPH region were interrupted in order to disconnect the hippocampus from its cortical input.

Housing

All monkeys were housed in individual cages that measured 27 cubic feet in volume (3' × 3' × 3'). The fronts of the cages were made of bars spaced at 2.5-cm intervals. The cages were positioned to provide tactual, visual, and auditory stimulation. That is, each monkey could touch at least one other monkey by reaching through the cage bars, could see at least four other monkeys, and could hear and vocalize with all the monkeys in the room. Room illumination consisted of over-

head fluorescent lighting and was automatically controlled using a schedule of 12 hours of light and 12 hours of darkness (7 A.M.—7 P.M. and 7 P.M.–7 A.M., respectively). Room temperature was maintained at 72°–74° F (22°–23° C) and relative humidity at 50%. The diet consisted of Purina monkey chow, supplemented daily with fruit and chewable vitamin C tablets. Monkeys were fed each afternoon after completion of the day's behavioral testing.

Testing of emotional behavior

The test battery consisted of a total of 12 items, which belonged to two categories. One category (object stimuli) consisted of 7 inanimate stimuli that had the potential to elicit investigatory or consummatory behavior. The other category (social stimuli) consisted of 5 animate stimuli that had the potential to elicit interactive social behavior. The stimuli were always presented in the same mixed order (Table 2). Testing always took place between 12 noon and 6 P.M.

The first groups to be studied (3 of the normal monkeys and 3 of the H^+A^+ monkeys, all of whom were tested only on the emotional battery; Table 1) were tested on 10 different occasions during a period of 5 months. Because performance was quite stable (see Results), most of the other groups were tested on only 4 occasions, at approximately 3, 5, 9, and 17 weeks after surgery. The exceptions were 5 normal monkeys, who were tested on either 2, 3, or 6 occasions during a period that ranged from 3 to 20 weeks; the 4 H^+ monkeys who were tested on only 2 occasions, at 3 and 5 weeks after surgery; and the 3 H^+A monkeys and 1 A monkey, who were tested on 4 occasions over a period of 15 weeks beginning approximately 2 years after surgery.

Each item in the battery was presented individually to all the monkeys in a room before the next item was introduced. Following the initial presentation of the stimulus, the response of the target monkey was monitored for a period of 15 or 30 seconds (Table 2). Preliminary studies were used to determine the optimal time period after stimulus presentation

Table 2. Order of Stimulus Presentation and Duration of Scoring Interval

Stimulus	Category	Duration (in seconds)
M&M candy	Object	15
Boot	Object	30
Tape	Object	30
Monkey	Social	30
Finger	Object	15
Airpuff	Social	15
Keys	Object	15
Lip-smack	Social	15
Stare	Social	15
Mirror	Object	30
Rubber snake	Object	30
Lunge	Social	15

Twelve stimuli (7 object and 5 social stimuli) were presented to all monkeys in the order shown. The last column (Duration) indicates the time during which responses were recorded, which in most cases corresponded to how long the stimulus was exposed. The airpuff, lip-smack, and lunge stimuli involved only a few seconds of presentation time, but responses were recorded during the time period indicated.

during which to observe behavior. The same two experimenters administered all the test sessions to each monkey. One of the experimenters always presented the stimuli, and the other always recorded the behavior of the monkeys.

The object stimuli consisted of: (1) a brown, sugar-coated chocolate candy (an M&M); (2) a black rubber boot; (3) a roll of white masking tape; (4) a set of keys; (5) a small mirror; (6) a rubber model of a snake in a coiled position; and (7) the experimenter's gloved index finger. The objects were either placed on a small ledge attached to the front of the cage (tape, M&M), hung on the front of the cage (keys, mirror), placed on a small cart in front of the cage (boot, snake), or placed just in front of the cage (finger). The monkeys were allowed to reach through the bars of the cage to touch, manipulate, smell, or bite each stimulus. The gloved finger could also be touched, but it was too far from the front of the cage to be bitten. The finger could have been classified as a social stimulus, but monkeys appeared to treat it like one of the other objects. Overall results were the same, regardless of how this stimulus was classified. Except for the M&M candy, which monkeys were allowed to eat, the objects were retrieved by the experimenter at the end of the test.

The social stimuli consisted of: (1) Monkey: Another monkey, unfamiliar to the monkey being tested, was placed in a wire-mesh cage directly in front of the home cage. The two monkeys could interact visually and vocally, but could not touch each other. For each monkey tested, the same stimulus monkey was used in all test sessions. (2) Airpuff: From a position directly in front of the cage, the experimenter waited until the monkey was not moving and then blew a puff of air directly at the monkey. (3) Lip-smack: The experimenter protruded his lips and smacked them rapidly together in imitation of the lip-smacking behavior characteristically exhibited by macaques. (4) Stare: The experimenter stood directly in front of the cage and attempted to maintain eye contact with the monkey. (5) Lunge: The experimenter stood facing the monkey, took two steps back from the front of the cage and then took a sudden, loud step toward the front of the cage while looking directly at the monkey.

Scoring of emotional responses

A monkey's response to each stimulus in the battery was assigned a score of 0, 1, 2, or 3. A 3 was intended to designate behavior characteristic of the Klüver-Bucy syndrome (Klüver and Bucy, 1939; Rosvold et al., 1954; Masserman et al., 1958) and included a tendency to approach and examine the stimuli, especially by mouth, or to exhibit tameness. A score of 0 was intended to designate behavior characteristic of normal monkeys, and included avoidance of contact with stimuli or marked aggressiveness (e.g., lunging or vocalizing) or fear (e.g., retreating or grimacing). To make the scoring as objective as possible, the following system was adopted:

Object stimuli

M&M candy: 3, retrieve in 0–5 seconds; 2, retrieve in 6–10 seconds; 1, retrieve in 11–15 seconds; 0, no retrieval
Boot, Tape, Finger, Keys, Snake: 3, manually and orally contact stimulus; 2, manually or orally contact stimulus; 1, approach, sniff, or visually inspect stimulus; 0, no response, avoidance

Mirror: 3, reach for reflection or approach with facial expression; 2, approach or make facial expression at mirror; 1, visually inspect reflection; 0, no response, avoidance

Social stimuli

Monkey: 3, contact transport cage; 2, facial expression at monkey; 1, approach and visually inspect monkey; 0, no response or avoidance

Airpuff, Lunge, Lip-smack: 3, no avoidance and no retreat; 2, any one of the following behaviors—vocalization, facial expression, or locomotor activity associated with fear or aggression; 1, any two of behaviors just listed; 0, all three of these behaviors

Stare: 3, continuous eye contact; 2, eye contact for a period of at least 8 seconds; 1, sporadic eye contact; 0, no eye contact or avoidance

Memory testing

As described in the Subjects section, all the operated monkeys were also involved in studies of memory function. Table 1 indicates (with a " + " in the Memory Battery column) the monkeys that were administered a standard battery of tasks used in our laboratory to evaluate memory. Some monkeys (designated with a " − " in the Memory Battery column) were given other memory tasks to evaluate retrograde amnesia that will not be considered here.

Memory testing was carried out in a Wisconsin General Test Apparatus (Harlow and Bromer, 1938). All monkeys were tested according to the same schedule beginning 6–8 weeks after surgery: (1) trial-unique delayed nonmatching to sample; (2) pattern discrimination; (3) delayed retention of object discriminations; and (4) concurrent discrimination learning. Some groups also received additional testing. Because none of the groups was impaired on pattern discrimination learning, the data for this task will not be considered further.

Trial-unique delayed nonmatching to sample task Monkeys first displaced an object covering the central food well of a 3-well tray (this portion of the task is referred to as the sample trial). An opaque door was then lowered to block the monkey's view of the food wells. After 8 seconds, monkeys saw 2 objects, the original object and a new one, which covered the 2 lateral food wells. They were required to displace the new object to obtain a raisin reward (this portion of the task is referred to as the choice trial). Each trial used a new pair of objects selected from a pool of 300 objects. Twenty trials per day were presented with an intertrial interval of 20 seconds. After training on the 8-second task was completed (learning criterion was 90 correct choices in 100 trials), monkeys were tested with successively longer delays of 15 seconds, 60 seconds, and 10 minutes between the sample and the choice trials. One hundred trials were given at the 15-second and 60-second delays with 50 trials at the 10-minute delay.

Retention of object discrimination For retention of object discriminations, monkeys were given 20 trials of training on a 2-choice discrimination problem, 20 trials on the second day, and 20 more trials on the fourth day. This same sequence was then repeated until a total of 4 different discrimination problems had been presented.

Concurrent discrimination learning For concurrent discrimination learning, 8 pairs of objects were learned simultaneously. Forty trials were given daily (each of the 8 pairs was presented 5 times) until a learning criterion of 39 correct responses in 40 consecutive trials was achieved during one test session. (For detailed descriptions of this task and the previous task, see Zola-Morgan and Squire, 1985).

RESULTS

Histological findings

After completion of behavioral testing, operated monkeys were administered an overdose of Nembutal and perfused with 0.9% saline followed by 10% buffered formalin. Frozen sections were cut at 50 μm, and every fifth section was stained with thionin for Nissl substance. For most of the operated groups, detailed histological descriptions of the lesions have already been published (see Table 1 for references). Accordingly, only brief descriptions will be provided here. Neurohistological analyses for the A^- group and the 4 monkeys in the H^+ group that were tested only on the emotional battery have not appeared elsewhere.

Group A^-

The amygdaloid lesions in all 4 animals were incomplete and involved on the average approximately 40–70% of the amygdaloid complex (Figs. 1 and 2). In general, the basal nucleus (especially the parvocellular part) suffered severe bilateral damage, and the lateral nucleus suffered moderate bilateral damage. Each animal also sustained some damage to the surrounding cortical regions (i.e., the periamygdaloid, perirhinal, and entorhinal cortex). This damage was only moderate (30–50%) and asymmetrical in all cases.

A^-1

This animal had the most complete lesion of the amygdaloid complex. Damage was symmetrical and involved at least two-thirds of the amygdaloid complex on both sides over most of its rostrocaudal extent. The lateral nucleus rostrally and the medial and central nuclei at more caudal levels were partially spared on both sides. There was moderate bilateral damage to the piriform and entorhinal cortex anterior to the amygdala. The perirhinal cortex was spared bilaterally. Damage to the entorhinal cortex was nearly complete on the left side. On the right side, the entorhinal cortex sustained slight damage anteriorly, but the posterior two-thirds was spared. There was slight damage to the most rostral portion of the hippocampus on the left side and to the tail of the caudate nucleus on the right side.

A^-2

The lesion moderately damaged the rostral third of the amygdaloid complex bilaterally, partially sparing the dorsal portions of the accessory basal, lateral, and basal nuclei. Most of the middle third of the amygdala was destroyed on the left side, but damage to the amygdala on the right side was limited to its ventral half. Damage to the caudal third of the amygdala was slight and limited to its ventral portions bilaterally. Damage to perirhinal cortex was slight and limited to the right side, involving mainly the region adjacent to the
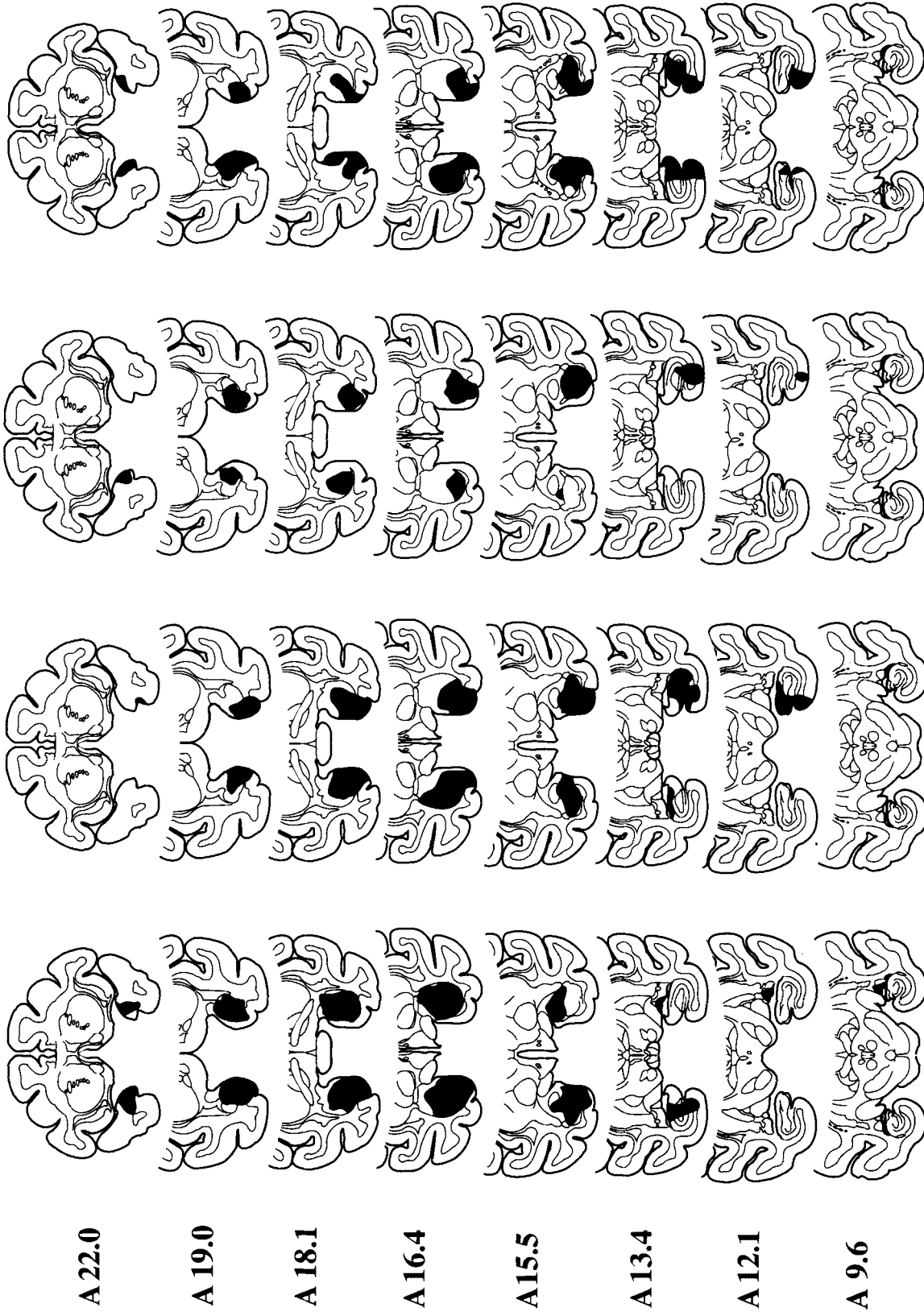
Fig. 1. Representative coronal sections through the temporal lobes, showing the extent of damage (black) in the 4 monkeys with partial lesions of the amygdala (A⁻). Numerals to the left indicate the approximate distance (mm) from the interaural plane (atlas drawings based on Szabo and Cowan, 1984).
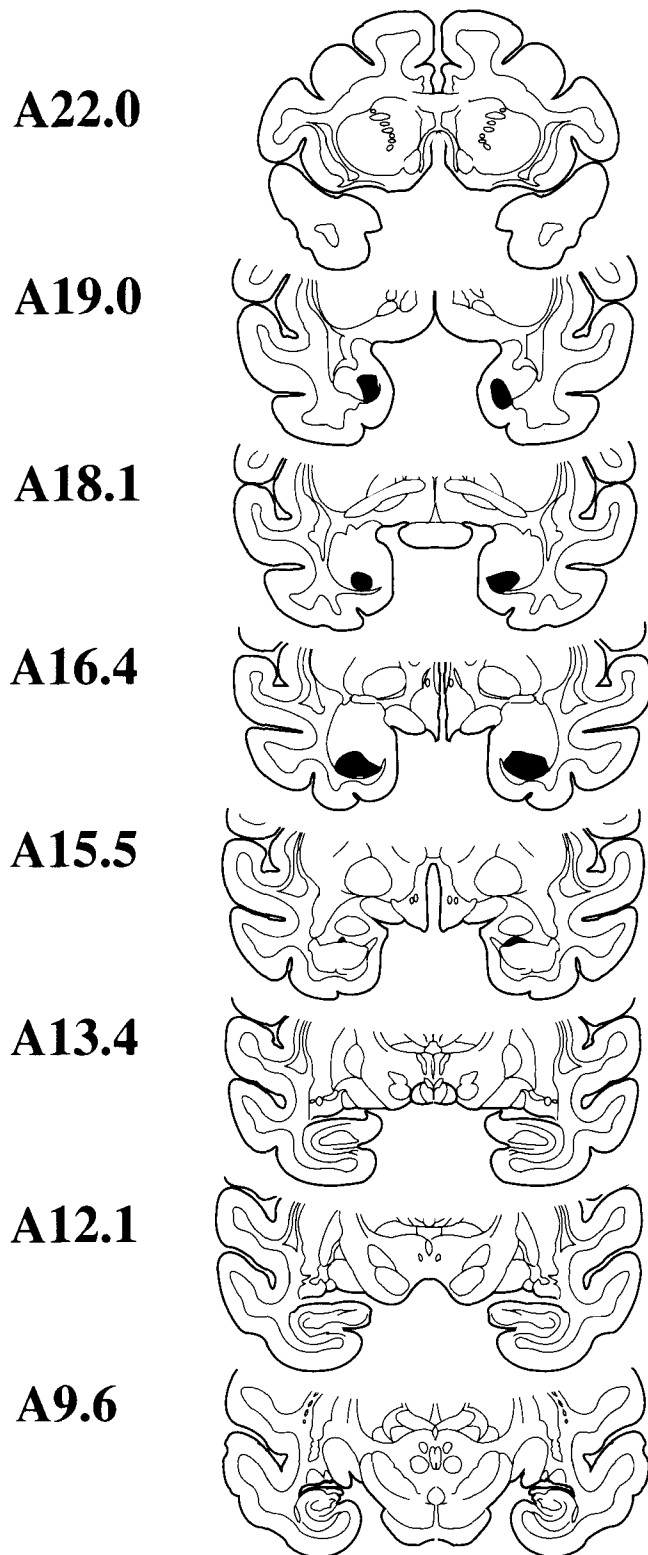
A22.0

A19.0

A18.1

A16.4

A15.5

A13.4

A12.1

A9.6

Fig. 2. Representative coronal sections through the temporal lobes, showing in black the damage common to the 4 monkeys with A⁻ lesions. Bilateral damage was ventral and involved mainly the basal and lateral nuclei. Numerals to the left indicate the approximate distance (mm) from the interaural plane (atlas drawings based on Szabo and Cowan, 1984).

posterior amygdala and the anterior hippocampus. Damage to the entorhinal cortex was nearly complete on the right side, but only a portion of the anterior entorhinal cortex was damaged on the left side.

A⁻ 3

The amygdaloid complex sustained moderate bilateral damage over its rostral third. The accessory basal nucleus and dorsal portions of the lateral and basal nuclei were largely spared bilaterally. Over its middle third, only the ventral half of the amygdala was damaged bilaterally, and the posterior third of the amygdala was largely spared bilaterally. The perirhinal cortex was moderately damaged on the right side at levels adjacent to the anterior hippocampus and was entirely spared on the left side. Damage to the entorhinal cortex was substantial on the right side, but on the left side the entorhinal cortex was almost completely spared.

A⁻ 4

The lesion destroyed much of the rostral third of the amygdala on the left side, but there was less damage on the right. On both sides, damage was moderate in the middle third of the amygdala, sparing the cortical nucleus and dorsal portions of the lateral, basal, and accessory basal nucleus. The caudal third of the amygdala was largely spared on both sides. The perirhinal cortex was spared bilaterally. The anterior half of entorhinal cortex was moderately damaged on both sides.

Group A

Two of the 3 animals in this group (A1 and A2) had extensive bilateral damage to the amygdaloid complex (Zola-Morgan et al., 1989b). In the third animal (A3), the lesion was more posterior and medial so that the anterior third of the amygdala was spared. There was minimal damage to the perirhinal and entorhinal cortex, to the laterally adjacent inferotemporal cortex (area TE, von Bonin and Bailey, 1947), and slight damage to the rostral pole of the hippocampal formation. The parahippocampal cortex was completely spared in all cases. The damage sustained by monkeys in the A group was more extensive than the damage sustained by monkeys in the A⁻ group (Fig. 3).

Group H⁺A

Two of the 3 animals had extensive damage to the amygdala and to the hippocampus bilaterally (Zola-Morgan et al., 1989b). The third animal sustained extensive bilateral damage to the hippocampus, but the lesion involved only the posterior third of the amygdala. The entorhinal cortex was either damaged directly, or the cells in layer II were nearly completely depopulated through retrograde degeneration as a result of the elimination of their terminal field in the dentate gyrus. The parahippocampal cortex was nearly completely damaged bilaterally in 1 animal and incompletely damaged in the other 2 animals.

Group H⁺A⁺

The extent of damage in the monkeys given the emotional battery (n = 3) and the monkeys given the memory battery (n = 4) was comparable. All 7 monkeys sustained extensive bilateral removals of the amygdala and the hippocampus (de-
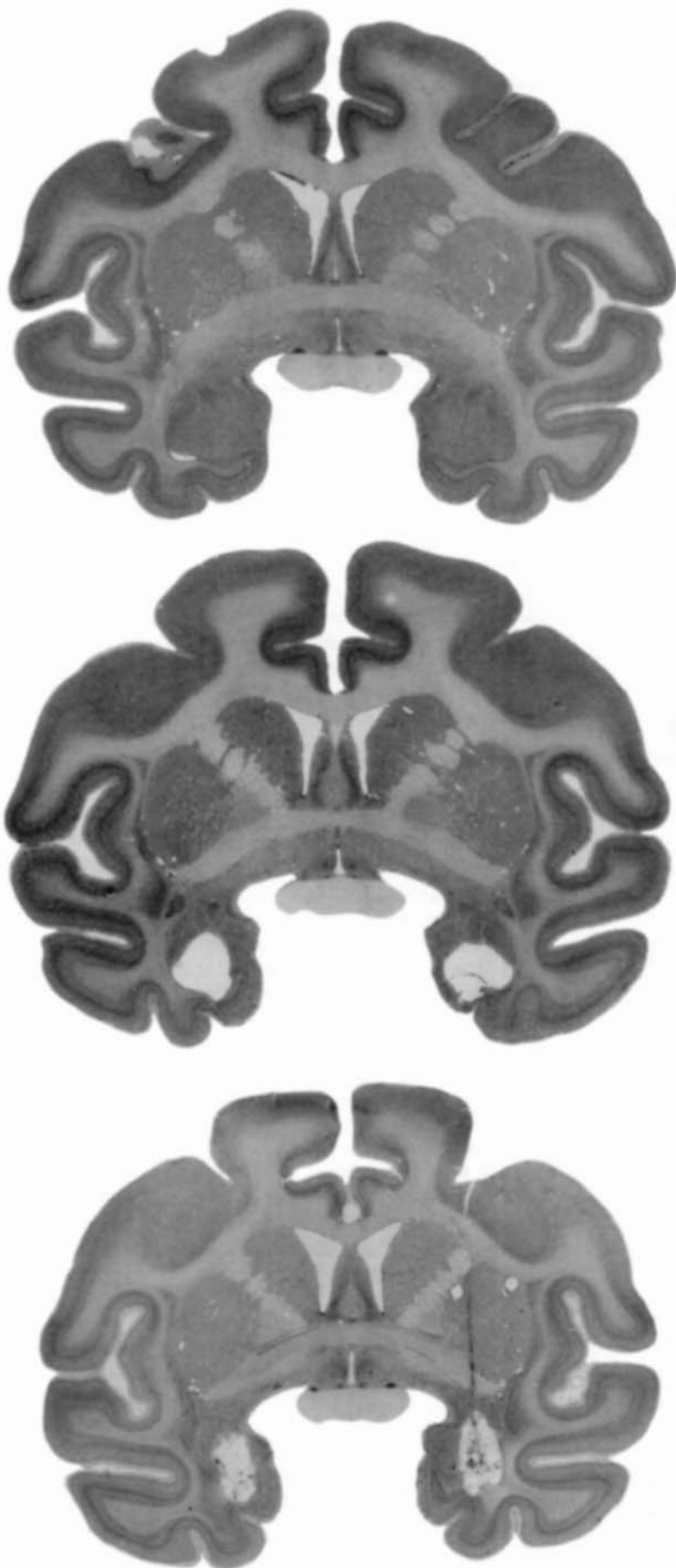
Fig. 3. Representative Nissl-stained sections at equivalent levels through the amygdaloid complex of a normal monkey (top), 1 of the 4 monkeys with partial damage to the amygdaloid complex (the A⁻ lesion; middle), and 1 of the 3 monkeys with extensive damage to the amygdaloid complex (the A lesion; bottom). Monkeys with the A⁻ lesion had considerable sparing of the amygdaloid complex on both sides. As shown in this section, the lesions in this group were incomplete and limited to the ventral amygdala. The lateral and accessory basal nuclei were only partially damaged, and the magnocellular portion of the basal nucleus was almost entirely spared. Periamygdaloid cortex was spared in 3 of the 4 monkeys. There was variable damage to anterior entorhinal cortex and to the underlying white matter. In the section shown, there was extensive damage to entorhinal cortex on the right side but almost none on the left side. The A lesion involved most of the amygdaloid complex bilaterally. In the section shown here, a small amount of the accessory basal nucleus was preserved on the right side. The entorhinal cortex was not damaged by the lesion.

tailed descriptions of these lesions have been published elsewhere; see Table 1). The extent of damage to perirhinal cortex ranged between 30% and 70% (with the exception of 1 monkey in the emotional battery group that sustained damage to less than 10% of the perirhinal cortex). The lesions in all monkeys included bilaterally most of the entorhinal and the parahippocampal cortex. Inadvertent damage to inferotemporal cortex occurred in all 7 animals but generally involved less than 15% of area TE. One monkey given the memory battery and one monkey given the emotional battery each sustained bilateral damage involving approximately 30% of area TE.

Group H⁺

In the monkeys given the emotional battery (n = 4) and in the monkeys given the memory battery (n = 3), the extent of damage was comparable for all brain regions with the exception of the entorhinal cortex (see below). All 7 monkeys sustained moderate to extensive bilateral damage to the hippocampus (see Zola-Morgan et al., 1989a, for histological illustrations of brains from monkeys given the memory battery). In all animals the perirhinal cortex was either entirely spared or only minimally damaged. Bilateral damage to the parahippocampal cortex ranged from moderate (30%) to extensive (70% or more). The posterior entorhinal cortex was extensively damaged in 2 of the 3 monkeys given the memory battery. In the third, the entorhinal cortex was not directly damaged by the lesion. In the 4 monkeys given the emotional battery, the entorhinal cortex sustained only slight direct damage. However, in all cases, there was partial to complete loss of layer II cells as a result of retrograde degeneration following elimination of the dentate gyrus. Slight direct damage to the amygdaloid complex occurred in 1 monkey given the emotional battery and 1 monkey given the memory battery.

Group PRPH

The ablations in 3 of the 4 monkeys were extensive and quite similar (Zola-Morgan et al., 1989c). The fourth monkey sustained a lesion that was also similar but somewhat smaller in extent. The most anterior portion of the perirhinal cortex (the temporal polar portion) was largely spared in all cases. However, the more ventral portion of the perirhinal cortex that lines the rhinal sulcus under the amygdala and adjacent to the entorhinal cortex was nearly completely removed in all cases. While the lateral aspect of the parahippocampal cortex was extensively damaged in all cases, the ablation did not extend as far medially as intended, and area TH was directly damaged in only one case.

BEHAVIORAL FINDINGS

The findings from the emotional battery will be described first, followed by a summary of the findings from the memory battery. The final section compares the effects of the lesions on emotion and memory.

Emotional Battery

A 2-way ANOVA (group × stimulus type) compared the reactivity scores for object and social stimuli across the 7 groups. There was a significant effect of group

$(F[6,23] = 12.5,\ P < .001)$ and stimulus type $(F[1,6] = 90.24,$ $P < .001)$ and a significant interaction of group and stimulus type $(F[6,23] = 24.31,\ P < .001)$. Because results differed for the 2 types of stimuli (object and social), the data were evaluated further in separate analyses.

Object stimuli

For each animal, an overall score for the 7 object stimuli was obtained by averaging the scores for all stimuli across all testing sessions. Figure 4A shows the reactivity scores to the object stimuli for each group. A 1-way analysis of variance revealed a significant effect of group $(F(6,23) = 27.5,$ $P < .001)$. Post-hoc pair-wise comparisons using the Scheffe F-test showed that all 4 groups with amygdala damage (A, A⁻, H⁺A, and H⁺A⁺) obtained significantly higher scores than the 3 groups without amygdala damage (N, H⁺, PRPH) (All $P < .05$). In addition, all 4 animals with partial amygdala lesions (A⁻ group) had lower reactivity scores than all 3 animals with complete amygdala lesions (A group; $t[5] = 3.4,$ $P < .05$).
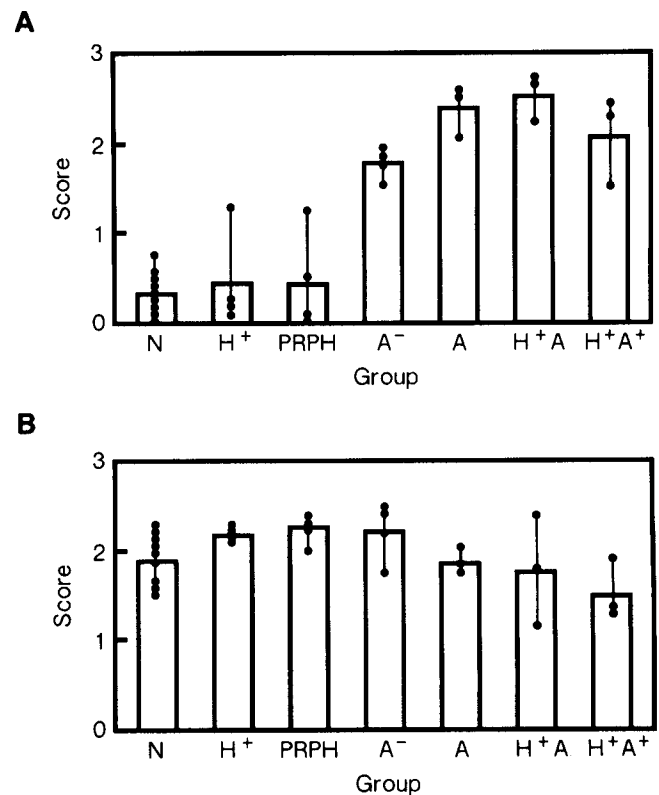
Fig. 4. Mean emotional reactivity scores for all groups. The scores were averaged across all test sessions. Filled circles show scores for individual monkeys. For abbreviations of operated groups, see Table 1. (A) Reactivity to object stimuli. Groups with lesions that included the amygdala (A, A⁻, H⁺A, or H⁺A⁺) obtained significantly higher scores (i.e., exhibited abnormal emotional reactivity) than the groups without amygdala damage (N, H⁺, and PRPH). (B) Reactivity to social stimuli None of the groups differed from normal.

Social stimuli

For each animal, an overall score for the 5 social stimuli was obtained by averaging the scores for the stimuli across all testing sessions. Figure 4B shows the reactivity scores to the social stimuli for each group. A 1-way analysis of variance showed a significant effect of lesion group $(F[6,23] = 2.78$, $P<.05)$. This effect seems to be due mainly to the fact that the H^+A^+ scores were lower than the H^+ and PRPH scores. However, post-hoc analyses using the Scheffe F-test revealed no significant differences between any of the groups (all $P >$ .10). Because the operated groups did not respond abnormally to the social stimuli, and because there were no changes across the period of testing, the social stimuli will not be considered in subsequent analyses.

Stability of test scores across time

To determine whether reactivity to object stimuli was stable across time, we compared the scores across test sessions for each monkey (Fig. 5). A 2-way analysis of variance involving 6 groups (the H^+ group was not included in this statistical analysis because only 2 test sessions were given) and 4 test sessions revealed a significant effect of group $(F[5,16] = 27.0$, $P<.001)$ but no effect of session $(F[3,15] = 0.60$, $P>.10)$ and no interaction $(F[15,48] = 0.94$, $P>.10)$. Separate 1-way analyses of variance confirmed that there were no measurable changes across sessions for any of the 7 groups (all $P>.10)$.

Three normal monkeys and the 3 H^+A^+ monkeys given the emotional battery were tested for a total of 10 sessions. Their scores were stable across all of the sessions (the mean score for the normal group was 0.25 over the first 4 sessions and 0.25 over the subsequent 6 sessions; the corresponding
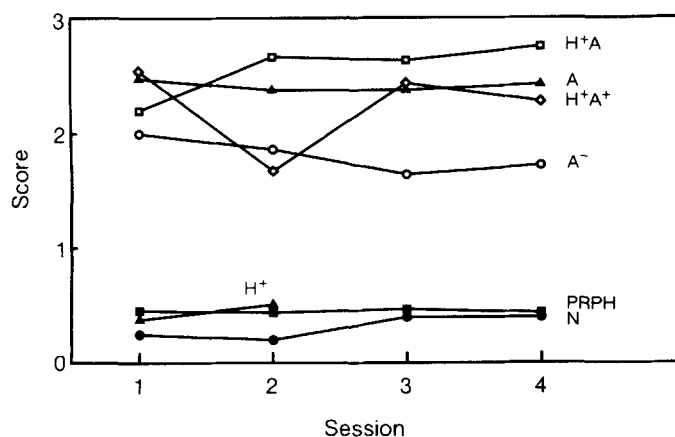

Fig. 5. Mean emotional reactivity scores for all 7 groups on the object stimuli portion of the emotional battery. Scores are for the first 4 sessions given to each group, in most cases 3–17 weeks after surgery (the H^+ group was tested only twice, 3 and 5 weeks after surgery; the H^+A group and 1 animal in the A group were tested on 4 occasions beginning 2 years after surgery). The normal data are for the 5 normal animals that received 4 or more test sessions. For abbreviations, see Table 1.

Table 3. Mean Performance Scores

Group	DNMS	Delayed Retention of Object Discrimination	Concurrent Discrimination
N	88	85	507
A⁻	84	85	595
A	84	85	420
H⁺A	75*	72*	653
H⁺A⁺	61*	70*	1100*
H⁺	78*	76*	787*
PRPH	72*	73*	1200 + *

Mean performance scores for all 7 groups on the 3 memory tests: delayed nonmatching to sample (DNMS), retention of object discriminations, and concurrent discrimination. The score for DNMS is the percent correct score averaged across 3 delays (15 seconds, 60 seconds, and 10 minutes). The score for object retention is the percent correct score for 4 different discriminations averaged across 3 test days. The score for concurrent discrimination is the number of trials required to reach the learning criterion. * indicates performance significantly different from Group N, $P < .05)$. +, training was discontinued after the indicated number of trials without reaching the learning criterion. Although the H^+A group was not significantly different from the normal group on the concurrent task, this group did perform significantly more poorly than the A group $(P < .05)$. Abbreviations same as in Table 1.

scores for the H^+A^+ group were 2.22 and 2.02; all $P>.10)$. Moreover, the length of time after surgery at which testing was started did not appear to affect the scores. The scores of the H^+A monkeys (initially tested 2 years after surgery) were not significantly different from those of the H^+A^+ monkeys (initially tested 2 weeks after surgery; $t[4] = 1.5$, $P>.10)$. Finally, the monkey in the A group that was tested 1.5 years after surgery obtained a mean reactivity score for objects (2.60) that was similar to the scores of the other 2 monkeys in that group (2.17 and 2.61).

Memory battery

The performance scores of all the groups are presented in Table 3. Except for the A^- group, the behavioral data for these groups have been presented previously (see Table 1 for references). The A and A^- groups performed similarly to normal monkeys on all 3 memory tasks. In contrast, with one exception, all 4 groups with lesions that included the hippocampal formation or anatomically related cortical areas (groups H^+A, H^+A^+, H^+, and PRPH) performed significantly worse than the normal group on all 3 tasks. The exception was that, on the concurrent discrimination task, the difference between the H^+A group and the normal group did not reach statistical significance $(P = .11)$. However, the H^+A group did perform significantly more poorly than the A group $(P<.05)$.

Comparison of the effects of lesions on the emotional battery and the memory battery

To compare directly the effects of lesions on both emotional behavior and memory performance, the lesion groups were arranged into 3 sets. Set A and H (n = 10) included

groups with damage to both the hippocampal formation and the amygdala (groups H^+A and H^+A^+); set A (n = 7) included groups with damage to the amygdala but not the hippocampal formation (groups A^- and A), and set H (n = 10) included groups with damage to the hippocampal formation and/or associated cortical areas, but not to the amygdala (groups H^+ and PRPH; one of the PRPH animals was unable to learn the DNMS task, so this animal's data are not included in this comparison).

Two scores were used for comparison, the overall object reactivity score from the emotional battery (averaged across all stimuli and all test sessions) and the 10-minute delay score from the delayed nonmatching to sample test. Some monkeys (n = 29) were tested on only 1 of the 2 batteries and contributed scores to only 1 measure. Other monkeys (n = 14) were given both the emotional and the memory batteries and contributed to both measures. The top panel (Normal) in Figure 6 shows the performance of 15 normal monkeys (9 were given the emotional battery and 6 were given the memory battery). The middle panel (A and H) shows that the 10 animals in set A and H (3 were given the emotional battery, 4 were given the memory battery, and 3 were given both batteries) had abnormal scores on both measures (All $P<.01$). The bottom

panels show that the 7 animals in set A (all 7 were given both batteries) had abnormal scores only on the emotional reactivity measure (emotion: $P<.01$; memory: $P>.10$). In contrast, the 10 animals in set H (4 were given the emotional battery, 3 were given the memory battery, and 3 were given both batteries) had abnormal scores only on the memory measure (emotion: $P>.10$; memory: $P<.01$).

In summary, a double dissociation was observed between site of lesion and performance. Specifically, damage to the amygdaloid complex caused abnormal emotional reactivity but did not affect memory, while damage to the hippocampal formation and associated cortical areas impaired memory but did not affect emotion. Importantly, this dissociation was not limited to delayed nonmatching to sample. Table 4 summarizes the results for reactivity to objects and for all 3 memory tasks and shows that the dissociation extends across all the memory tasks.

DISCUSSION

The purpose of the present study was to assess the effects of medial temporal lobe damage on emotional behavior and on the kind of memory that is impaired in human amnesia. Damage to the hippocampal formation or the adjacent, ana-
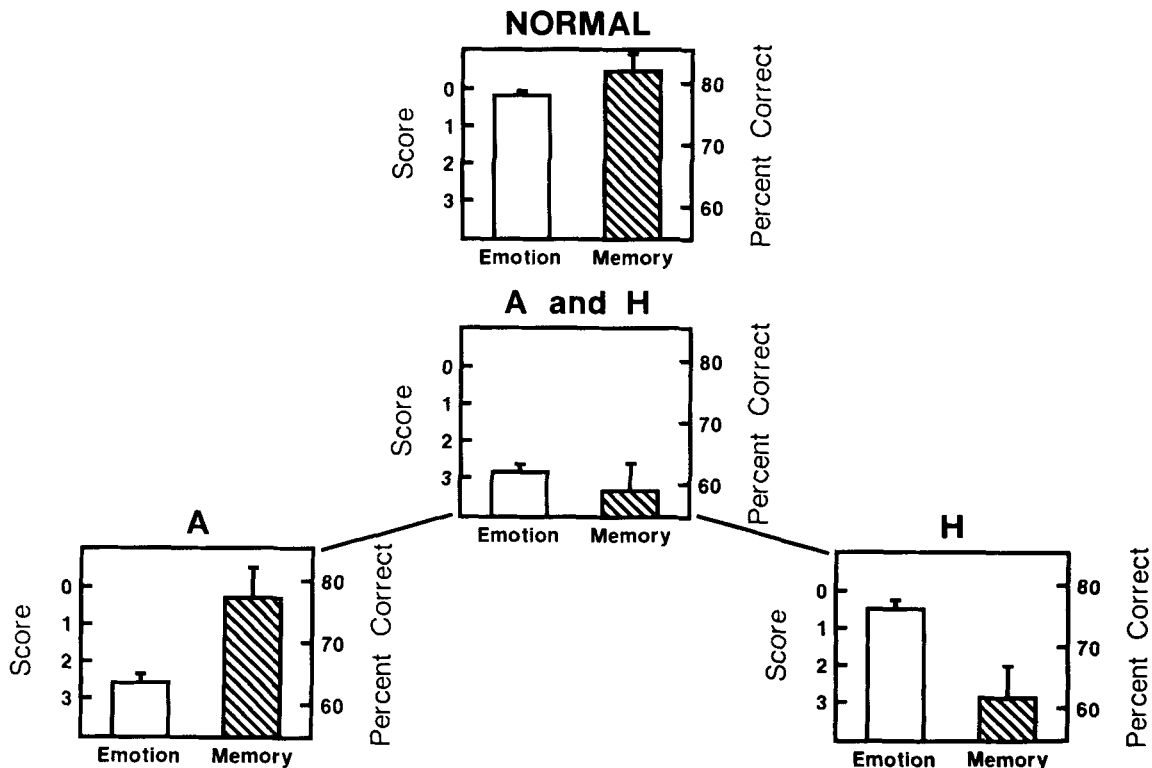

Fig. 6. Comparison of emotional reactivity and memory performance. The score for emotional reactivity is the score on the object stimuli portion of the emotional battery averaged across all test sessions. The score for memory is the performance score on the delayed nonmatching to sample task at a delay of 10 minutes. In both cases, high bars indicate normal performance. The H, the A, and the A and H categories are defined in the text above. Brackets show standard errors of the mean. For the numbers of animals contributing to each measure, see Table 1. The data show that lesions of the amygdala impaired emotional reactivity, lesions of the hippocampal formation or related cortex impaired memory, and combined lesions produced both kinds of impairment.

Table 4. Summary of Performance on the Emotional Battery and 3 Memory Tasks

	Emotional Battery	Memory Battery		
	Reactivity to Object Stimuli	Delayed Non-matching	Object Reten-tion	Concur-rent Dis-crimina-tion
A and H	+	+	+	+
H	−	+	+	+
A	+	−	−	−

Data from Fig. 4 and Table 3, according to whether the hippocampal formation or related cortex was damaged but not the amygdala (H), the amygdala was damaged but not the hippocampal formation (A), or both regions were damaged (A and H). The H category includes the H$^+$ and PRPH groups, the A category includes the A and A$^-$ groups, and the A and H category includes the H$^+$A$^+$ and the H$^+$A groups. + indicates that performance was significantly impaired relative to normal monkeys; − indicates normal performance.

tomically related perirhinal and parahippocampal cortex impaired memory but did not affect emotional behavior. Damage to the amygdaloid complex affected emotional behavior but not memory. Importantly, conjoint damage to the amygdaloid complex and the hippocampal formation had no greater effect on memory or emotion than damage to either region alone. Specifically, the memory scores of the A and H monkeys (Fig. 6, middle panel) were not significantly different from the memory scores of the H monkeys (Fig. 6, lower right panel; $t[11] = 0.62$, $P > .10$), and the emotion scores of the A and H monkeys were not significantly different from the emotion scores of the A monkeys (Fig. 6, lower left panel; $t[11] = 1.1$, $P > .10$). Taken together, the results show that memory impairment and abnormal emotional behavior are independent and dissociable effects of medial temporal lobe damage.

The abnormal emotional behavior associated with amygdala lesions was expressed as increased reactivity to the object stimuli, specifically as an increased tendency to examine and manipulate objects. This same abnormality has been observed consistently in studies of monkeys with lesions of the amygdaloid complex (Klüver and Bucy, 1939; Thompson et al., 1969; Horel et al., 1975; Aggleton and Passingham, 1981). In contrast to increased reactivity to the object stimuli, reactivity to the social stimuli was not affected by amygdala damage in our study. In view of the fact that all the monkeys in the present study had extensive daily contact with humans, including the experimenters, it is possible that the animals became habituated to human interaction prior to being tested. If so, the social stimuli used in the study may not have been strong enough to discriminate between normal and operated monkeys. Indeed, our impression based on informal observations is that the animals with amygdala lesions were in fact more "tame" and easier to work with than normal monkeys. Also, monkeys with amygdala lesions have often been reported to exhibit abnormal emotional reactivity in social situations (Klüver and Bucy, 1939; Aggleton and Passingham, 1981). Our formal tests with social stimuli used here may not

have been sufficiently sensitive to detect this feature of abnormal emotional behavior.

The present study provided the opportunity to compare directly the effects on emotional reactivity of partial damage to the amygdala (group A$^-$) with the effects of complete amygdala damage (group A). Figure 2 shows that the focus of amygdala damage in group A$^-$ involved two nuclei. The parvocellular portion of the basal nucleus sustained near total bilateral damage, and the lateral nucleus sustained moderate bilateral damage. The periamygdaloid cortex as well as the dorsal nuclei of the amygdala (i.e., the anterior and posterior cortical nuclei, the anterior amygdaloid area, and the central nucleus of the amygdala) were largely spared in most animals in the A$^-$ group. The behavioral findings were that the 4 animals with partial amygdala lesions were abnormal; they investigated the object stimuli to a significantly greater extent than normal monkeys, but they were not as abnormal in this respect as animals with complete amygdala lesions (group A).

A previous study in rhesus monkeys (*Macaca mulatta*; Aggleton and Passingham, 1981) reported that severe emotional changes and altered food preferences were seen only after total amygdalectomy, but less severe changes (i.e., an abnormal tendency to investigate objects) were observed consistently with partial lesions. As in the present study, this less severe effect was associated with damage to the basolateral portion of the amygdala. Thus, damage limited to the basal and lateral nuclei is sufficient to increase the tendency to approach and manipulate objects. More complete damage to the amygdaloid complex further increases the reactivity to objects and can produce other emotional changes.

To summarize, partial lesions of the amygdala produced significant and enduring changes in emotional behavior but did not impair memory. Complete lesions of the amygdala produced even greater effects on emotional behavior and also did not impair memory. Damage to the hippocampal formation and anatomically related cortex produced a severe memory impairment but did not affect emotional behavior. In a previous study, even partial damage to the hippocampus was found sufficient to produce significant and enduring memory impairment (Zola-Morgan and Squire, 1990). These findings, taken together, lead to the conclusion that the amygdala is important for normal emotional behavior and that the hippocampal formation together with adjacent cortex is important for the kind of memory impaired in amnesia. Importantly, the present findings also suggest that the amygdala is not part of the medial temporal lobe memory system (also see Zola-Morgan et al., 1989b; 1989c), although it is involved in other cognitive functions (Mishkin and Aggleton, 1981; Murray and Mishkin, 1985; Gaffan and Harrison, 1987). Finally, this conclusion in no way discounts the possibility of considerable interaction between affect and the storage and recall of memory. Within the medial temporal lobe, however, emotional reactivity and memory appear to be separately organized.

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