

Impaired Preference Conditioning after Anterior Temporal Lobe Resection in Humans

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Research with animals suggests that structures within the amygdaloid nuclear complex (ANC) are critical for acquiring associations between rewarding events and neutral stimuli, a form of conditioning often manifested in a subsequent preference for those (conditioned) stimuli. In this study, we investigated the relationship between the ANC and preference learning in humans. Three abstract monochrome patterns were presented to each subject over 180 trials in the context of a counting task requiring working memory. One pattern was paired with food reward on 90% of the trials in which it was presented and with no food reward on the other 10% of trials. The other patterns were similarly reinforced, but at ratios of 50:50% and 10:90% with reward and nonreward, respectively. Subsequently, a group of 21 normal participants preferred the pattern paired most often with reward to that paired least often

with reward, and they did not explicitly relate their preferences to the conditioning procedure, but instead attributed them to the characteristics of the patterns themselves. Unlike the normal controls, a group of patients with unilateral surgical lesions that included the ANC (15 left, 18 right) did not show conditioned preferences, but performed normally on a measure of working memory. In contrast, 13 patients with unilateral damage confined to frontal cortex exhibited normal conditioned preferences but were impaired on the working memory task. This double dissociation provides clear evidence that, in humans as in other animals, reward-related learning (conditioned reward) critically depends on a circuit involving inferotemporal cortex and the ANC.

Key words: amygdaloid body; conditioning; emotion; frontal lobe; reward; temporal lobe; working memory

An extensive body of research on animals has linked structures within the amygdaloid nuclear complex (ANC) to emotional associative learning. Much of this work has focussed on aversive phenomena such as fear conditioning (Gallagher and Chiba, 1996; Killcross et al., 1997; Rogan et al., 1997; Walker and Davis, 1997; Davis, 1998; LeDoux, 1998; Fanselow and LeDoux, 1999; Fendt and Fanselow, 1999). Studies of fear and aversive conditioning in humans have produced results consistent with the animal literature: patients with bilateral (Bechara et al., 1995) and even unilateral (LaBar et al., 1995) ANC lesions do not show normal fear conditioning responses. Functional neuroimaging studies also suggest a role for the ANC in fear conditioning in humans (Büchel et al., 1998; LaBar et al., 1998; Morris et al., 1998).

It has long been recognized in the animal literature that selective amygdala lesions can affect the ability of animals to associate stimuli with reward value (Weiskrantz, 1956; Jones and Mishkin, 1972; Speigler and Mishkin, 1981; Gaffan and Harrison, 1987; Cador et al., 1989; Robbins et al., 1989; Gallagher et al., 1990;

Everitt et al., 1991; Hiroi and White, 1991; White and McDonald, 1993) (for review, see Aggleton, 1993; McDonald and White, 1993; Gallagher and Holland, 1994; Ono et al., 1995; Hatfield et al., 1996; Gallagher and Chiba, 1996; Robbins and Everitt, 1996; Hitchcott et al., 1997; Hitchcott and Phillips, 1998; Everitt et al., 1999; Holland and Gallagher, 1999). Place-preference conditioning is one of the most common procedures for assessing conditioned reward associations (Carr et al., 1989; Schechter and Calcagnetti, 1993; Tzschentke, 1998). In this paradigm, a particular set of environmental cues is first paired with reward, and then an animal's tendency to approach and spend time in that environment, compared to a neutral one, is assessed. Place-preference conditioning procedures can be considered a special case of a more general conditioning paradigm (stimulus–reward association learning) in which biologically relevant stimuli (which normally elicit approach responses due to their rewarding affective significance) become associated with neutral stimuli that subsequently elicit approach on their own.

Conditioned preferences have been demonstrated previously in healthy human participants (Razran, 1954; Staats and Staats 1957, 1958; Levey and Martin, 1975, 1983; Martin and Levey, 1978; Kirk-Smith et al., 1983; Bierley et al., 1985; Rozin and Zellner, 1985; Stuart et al., 1987, 1991; Allen and Janiszewski, 1989; Niedenthal, 1990; Baeyens et al., 1993, 1995; Todorok et al., 1995), but the underlying anatomical substrates have not been examined in any detail. A few studies have investigated mechanisms of preference formation in brain-damaged populations, but these have focussed on the effects of exposure alone, rather than evaluating the effects of associative learning (Redington et al., 1984; Johnson et al., 1985).

Received Oct. 21, 1999; revised Jan. 12, 2000; accepted Jan. 20, 2000.

This work was supported by the Medical Research Council of Canada through a Career Investigatorship awarded to B. A. Milner. We gratefully acknowledge her assistance. I.S.J. was funded by the Wellcome Trust during the preparation of this manuscript. This work was conducted in the Neuropsychology/Cognitive Neuroscience Unit, Montreal Neurological Institute, McGill University, while I.S.J. and A.M.O. were working there. We thank the participants, the neurosurgeons A. Olivier, W. Feindel, and R. Leblanc, and numerous colleagues for helpful discussions.

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Table 1. Demographic information on participants in each group

Group	N	Sex		Handedness		Testing language		Age		Years of education		Time since surgery	
		M	F	R	L	English	French	Mean	Range	Mean	Range	Median	Range
LA	15	12	3	15	0	13	2	36	23–48	13	9–18	4 years	3 months–27 years
RA	18	7	11	15	3	8	10	38	22–55	12	6–18	1 year	3 months–16 years
FNTL	13	7	6	9	4	10	3	30	16–39	14	9–20	1 year	3 months–10 years
NC	21	10	11	20	1	15	6	37	23–58	13	11–18		

In a recent study (Johnsrude et al., 1999), conditioned preferences for novel, abstract, monochrome patterns were induced in young, normal volunteer participants using a method based on cue, or place, preference procedures originally developed for use with rats (Carr et al., 1989). Care was taken to minimize the subjects' awareness of the experimental contingencies and of the goal of the study by presenting the abstract patterns in the context of a cognitively demanding working memory task. Participants subsequently preferred the pattern paired most often with reward to that paired least often with reward. Importantly, participants did not attribute their preferences to the conditioning procedure, but instead attributed them to the physical characteristics of the patterns themselves, indicating that they were largely unaware of the effects of the conditioning procedure on their subsequent behavior.

In the present study, we used this procedure to assess preference conditioning in a group of neurosurgical patients with known damage to the amygdaloid region. In the majority of these patients, surgery was used to control pharmacologically intractable epilepsy. The resection always included the ANC and immediately surrounding tissue, as well as a variable amount of hippocampus, parahippocampal gyrus, and lateral neocortex in one hemisphere. The documented neuropsychological deficits after unilateral lesions of this type depend on the extent of the removal, but are generally mild and do not preclude the patient having a normal and productive life (Hermann et al., 1991; Eliashiv et al., 1997). We tested a matched group of normal volunteers and a group of patients with surgical lesions confined unilaterally to frontal cortex to evaluate the anatomical specificity of any resulting deficit.

MATERIALS AND METHODS

Participants. Thirty-three patients with unilateral anterior temporal lobe resections (15 left; 18 right) who had undergone surgery at the Montreal Neurological Institute for the relief of intractable epilepsy or for the removal of benign tumors were included in this study. In all of these patients, the lesion included the ANC and periamygdalar cortices, as described below. The study was approved by the Research and Ethics Committee of the Montreal Neurological Institute and Hospital, and all participants gave written consent. Patients with brain damage outside of the operated zone were excluded, and so were those who exhibited no improvement in their seizure frequency or intensity after surgery. All patients were either right-handed, or were left-hemisphere dominant for speech as determined by a preoperative sodium amobarbital test (Milner, 1997), and had full-scale intelligence quotient (IQ) ratings over 80 on the Wechsler Adult Intelligence Scale-Revised (WAIS-R).

Table 1 presents demographic information on participants in the four groups. The 15 patients with left ANC removals (LA) included one case of cortical dysplasia and one low-grade ganglioglioma. The pathology in the rest of the patients in this group was focal gliosis and sclerosis. Three of these patients were tested 3–4 months after surgery, two were tested 5 months to a year after surgery, three were tested between 1 and 5 years after surgery, and the rest were tested >10 years after surgery. Two of the 18 patients with removals of the right ANC (RA) were operated for neuroepithelial tumors, and one for a low-grade oligodendroglioma. The

pathology in the rest of the group was gliosis and sclerosis. Seven of these patients were tested 3–4 months after surgery, two were tested 5 months to a year after surgery, two were tested between 1 and 5 years after surgery, another two were tested between 5 and 10 years after surgery, and the rest were tested more than 10 years after surgery. A group of 13 surgical patients with lesions confined unilaterally to frontal cortex (FNTL; seven patients with left-sided removals, six patients with right-sided removals) were also tested. Pathology reports cited low-grade gliomas in five cases (two left, three right) a cavernous hemangioma in one left-sided case, an aneurysm and hematoma in another left-sided patient, an arteriovenous malformation (AVM) in a right-sided patient, and cortical dysplasia, gliosis, and/or sclerosis in the other five patients. The resection did not encroach on temporal lobe structures in any of these patients. Two of these patients were tested 3–4 months postoperatively, five were tested 5 months to a year after surgery, three were tested between 1 and 5 years after surgery, two others were tested 5–10 years after surgery, and one was tested more than 10 years after surgery. Twenty-one neurologically normal volunteers (NC) who were matched to the patients with respect to age and years of education were also tested. One-way ANOVAs demonstrated no difference in age or years of education among the four groups. Nonparametric (Kruskal–Wallis) ANOVAs did not reveal any significant differences in the distributions of handedness, sex, or testing language (English or French) across the four groups.

Imaging in patients with temporal lobe resections. For conclusions about functional specialization within the medial temporal lobe to be drawn, it was important to confirm the site and extent of the resections in the patients with temporal lobe resections, and quantify the degree of overlap. The resections were labeled on postoperative T1-weighted magnetic resonance (MR) images, acquired on each subject (Philips Gyroscan; 1.5 T). These images were linearly transformed into standardized stereotaxic space (Talairach and Tournoux, 1988), using DISPLAY, an interactive three-dimensional imaging software package (MacDonald et al., 1994; McConnell Brain Imaging Center, Montreal Neurological Institute). Postoperative MR images were not available for two patients in the LA group. The surgical reports for these two patients describe left anterior temporal lobe resections that include the amygdala and uncus, the pes of the hippocampus in one case, 3 cm of hippocampus in the other, and lateral neocortical resections in both extending to ~4.5 cm along the Sylvian fissure and along the base of the temporal lobe, measured from the temporal pole. A postoperative MR image was not available for one patient in the RA group. The surgical report for this patient describes a right anterior temporal lobe resection including the amygdala and uncus, 3 cm of the hippocampus, and a lateral neocortical resection extending to 4 cm along the Sylvian fissure and 6 cm along the base of the temporal lobe. The label volumes resulting from analysis of the 13 postoperative MRs in the LA group and the 17 MRs in the RA group were coregistered and averaged to produce probability volumes of lesion location, as shown in Figure 1. The area of maximal overlap in resection site (100%, resected in all patients) in each group is centered on the ANC (Talairach coordinates: LA, -24, -15, -18; RA, 24, -15, -19).

Materials and procedure. A computerized touch-screen task based on place-preference procedures used with rats was used. This task has been described in detail elsewhere (Johnsrude et al., 1999). Participants chose between raisins and fruit-flavored candy pellets (Dweebs; The Willy Wonka Candy Factory, Nestle, York, UK) before the start of the procedure, and they were always rewarded with that type of food. Raisins were chosen by 16 of 21 participants in the NC group, 12 of 15 patients in the LA group, 16 of 18 in the RA group, and 8 of 13 in the FNTL group. The rest chose candy pellets. These proportions are not significantly different across groups, as tested using χ^2 tests.

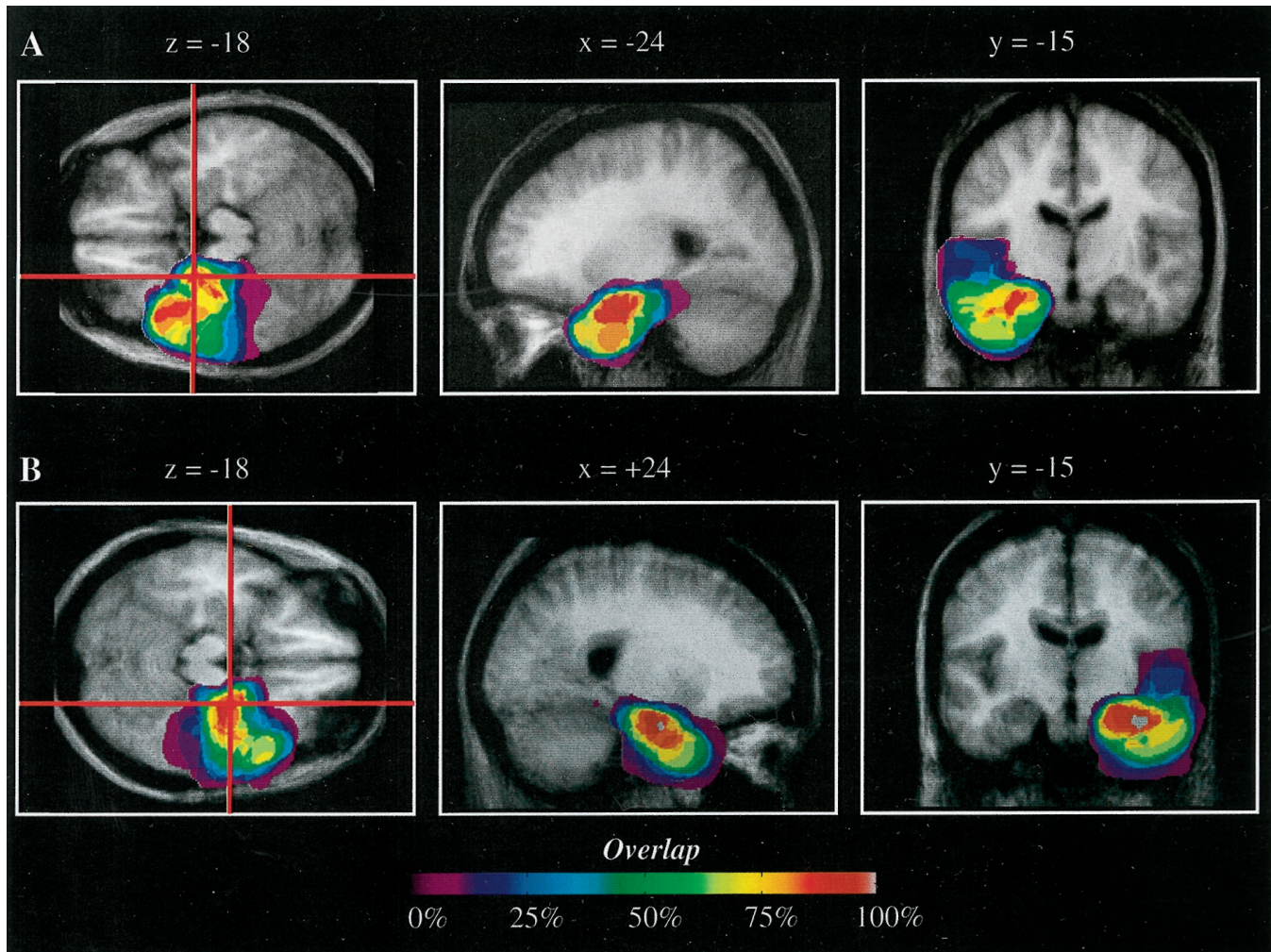


Figure 1. Overlap of lesions in patients with left (LA) or right (RA) anterior temporal lobe resection, as indexed by the color scale, superimposed on the averaged MR image for each group. *A*, $n = 13$ LA patients. *B*, $n = 17$ RA patients. In both LA and RA groups, the area of maximal overlap in lesion location includes the region of the amygdala.

There were three phases to the experimental procedure: formation of conditioned preferences, a test of preference expression, and an assessment of preference attribution. These are shown schematically in Fig. 2.

At the beginning of the formation phase, participants were presented with three black squares on the screen and were given the following instructions:

“You see three boxes on the screen. At any time, one of the boxes is hiding a red ball, and the other two are hiding black balls. What you have to do is guess where the red ball is. I would like you to find as many red balls as you can. You can choose a box by lightly touching the screen. Once you have touched a box, it will open up and show you which ball was hidden underneath. Every so often, you will be asked how many times you have found the red ball in a particular box. Thus, while you are choosing boxes you have also to try and remember how many times you have found a red ball in each of the three boxes. I would like you to eat one candy/raisin every time you find a red ball.”

The participants then proceeded to guess where the red “ball” was hidden by touching one of the three black “boxes.” After each guess, the selected box would “open” revealing one of three abstract black-and-white line drawings or patterns, and either a red or a black circle (or ball) superimposed on the center of that pattern (Fig. 2*A*). If the circle was red, the participants heard a melodic flourish and picked the chosen type of food reward (one candy or one raisin) from a bowl placed beside the computer screen. If the circle was black, they heard a buzzer and were not permitted to take a food reward. After 3 sec, the selected box returned to black, and the subject was required to make the next guess. This interval ensured that participants had sufficient time to taste the food in the presence of the stimulus patterns on the rewarded trials.

Unknown to the subjects, the stimulus pattern and circle color were predetermined for each trial, regardless of the location chosen.

A total of 180 trials were presented over six blocks. In total, each of the stimulus patterns was presented 60 times, together with either a red ball or a black ball according to the contingency relationship for that pattern (see below). At the end of each block, the participants were asked how many times they had found the red circle in each of the three boxes during the previous block of trials; this was the working memory task.

Three versions of the formation procedure were prepared. Each subject was tested using one of the three different versions, chosen pseudorandomly, in such a way that the distribution of the versions across the sexes and across the reward types (candy or raisins) was approximately equal. In each version, a different set of pattern–outcome contingency pairings was used. Thus, in one version, pattern A was accompanied by reward (red circle, melodic flourish, and food reward) on 90% of trials in which it appeared (i.e., 54 trials) and by nonreward (black circle, buzzer sound and no food) on 10% of those trials (i.e., six trials). Pattern B was accompanied by reward on 50% of trials in which it appeared and by nonreward on the other 50%. Pattern C was accompanied by reward on 10% of trials and by nonreward on the other 90%. In the second version of the task the ratios were: Pattern A, 10:90; Pattern B, 90:10; Pattern C, 50:50, whereas in the third version, the corresponding ratios were: 50:50; 10:90, and 90:10.

The trial order was pseudorandom and fixed. The rarest combinations were always presented just before or just after the more frequent combinations (e.g., for the first version described above, Pattern A paired with a black circle was presented just after Pattern A paired with a red circle). In addition, an identical pattern/outcome pair could not occur

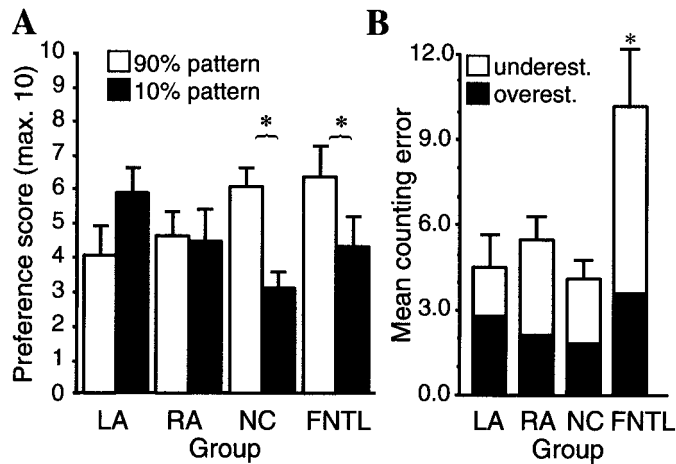


Figure 3. *A*, The mean preference scores (maximum = 10) and SEs for the 90 and 10% patterns in patients with left or right temporal lobe damage, including the amygdaloid body (*LA*, *RA*), normal control participants (*NC*), and patients with unilateral frontal lobe lesions (*FNTL*). Error bars indicate SEM. *LA* and *RA* participants fail to show a preference effect; see Results. *B*, Mean discrepancy scores on the working memory task in normal control participants (*NC*) and in patients with left (*LA*) or right (*RA*) anterior temporal lobe resection and frontal lobe resections (*FNTL*). The patients with frontal lobe lesions are impaired relative to all other groups. Error bars indicate SEM for the overall discrepancy scores. When the errors are categorized as overestimations or underestimations, the *FNTL* group is shown to produce significantly more underestimations relative to the other three groups; see Results.

value 5, which is the value expected if participants were choosing at random during the preference assessment phase, was within 1 SD of the cell mean preference scores for these patterns.

One-way ANOVA on the overall discrepancy scores revealed that *NC*, *LA*, and *RA* participants were equally able to keep track of the number of times they had found the red ball in each of the three boxes, whereas patients with frontal lobe damage were significantly impaired [Tukey's honestly significant difference (HSD) tests: main effect, $F_{(3,62)} = 5.22$; $p < 0.005$]. When the discrepancy values were categorized as overestimations and underestimations, it was apparent that patients with frontal lobe damage significantly underestimated the number of times they had found the red ball in each location (Tukey's HSD tests after one-way ANOVA: $F_{(3,62)} = 7.92$; $p < 0.0005$). There were no differences among the groups in overestimation (one-way ANOVA: $F_{(3,62)} = 1.35$; p , ns). This is shown in Figure 3*B*. Total discrepancy, overestimation, and underestimation scores for patients with left frontal ($n = 7$) and right frontal ($n = 6$) excisions were then examined separately to look for hemisphere effects. Mann-Whitney U tests were used to compare these two subgroups with normal participants and with each other. Both frontal groups differed significantly from normals on total discrepancy scores and underestimation scores (p values < 0.05), but not on overestimation scores, consistent with the F tests. Left frontal and right frontal groups did not differ on any measure.

DISCUSSION

In a previous experiment, a task based on place-preference conditioning procedures was used to induce conditioned reward associations in normal human volunteers (Johnsrude et al., 1999). The same task was used in the present study to investigate whether the ANC might be critically involved in conditioned reward learning in humans, as it is in other animals. Compared to

normal control subjects and patients with unilateral frontal cortex excisions, patients with unilateral anterior temporal lobe resections that included the amygdaloid complex showed severely impaired preference conditioning. In contrast, patients with anterior temporal lobe resections performed normally on the counting task, whereas patients with frontal cortex damage were severely impaired. This task, which required that subjects monitor the frequency of occurrence of red balls in each of the three boxes, places significant demands on aspects of working memory that are known to depend on the integrity of the prefrontal cortex rather than the medial temporal lobe structures (Petrides and Milner, 1982; Smith and Milner, 1988; Owen et al., 1990, 1996; Jonides et al., 1993; Smith, 1996; Owen, 1997). This double dissociation provides clear evidence that, in humans as in other animals, reward-related learning (conditioned reward) critically depends on a circuit involving inferotemporal cortex and the ANC.

Several features of the experimental design were included to minimize the participants' awareness of the conditioning procedure and the goals of the experiment. The subjects' attention was not explicitly drawn to the stimuli to be conditioned before or during conditioning, and these stimuli were irrelevant to performance of the counting task. Furthermore, the counting task was made quite demanding to minimize the subjects' opportunity to attend to anything but that task and the occurrence of reward or nonreward. The three patterns were paired with reward on 90, 50, and 10% of the trials in which they occurred. By avoiding the absolutes of 100 and 0%, and by including a pattern paired on equal number of trials with reward and nonreward, the experimental contingencies were made more difficult to discern. Participants were also asked, at the end of the study, why they showed the preferences they did, to determine whether preferences would be attributed to previous experience with the patterns. Without exception, participants attributed their preferences to the characteristics of the pattern itself. Because the patterns were randomly assigned to the different reward contingencies for each subject, these responses may be subjective rationalizations of a conditioned preference. This suggests that participants were largely unaware of the effect of their previous experience on their behavior. The patients with temporal lobe removals also attributed their preferences to the characteristics of the patterns themselves. They did show preferences, but their preferences were not consistently related to the frequency with which patterns were associated with reward in the conditioning procedure. They did not "learn to like", as the normal subjects and those with frontal lobe damage did.

All patients in the *LA* and *RA* groups had extensive damage to the amygdaloid region, including the perirhinal and entorhinal cortices, as well as white matter tracts passing through this area (Fig. 1). Both groups, particularly the *LA* group, also had significant damage to anterior temporal neocortex. Work in monkeys indicates that bilateral lesions of either the anterior part of inferior temporal cortex or the ANC (but not the posterior part of inferior temporal cortex or the hippocampus) produce impairments in object-reward association learning (Jones and Mishkin, 1972; Speigler and Mishkin, 1981; Gaffan and Harrison, 1987). The impairments seen in many of these studies may not be attributable to damage to the ANC per se, but may be caused by entorhinal and/or perirhinal cortex damage, or to damage to white matter tracts passing through the amygdalar region that normally connect rhinal and more lateral temporal cortex with ventral frontal cortex and medial thalamus (see, for example, Málková et al., 1997). However, considerable evidence from ex-

periments with rats does implicate the ANC, particularly the lateral and basolateral nuclei to the exclusion of other surrounding tissue, in conditioned reward (Peinado-Manzano, 1987, 1988; Cador et al., 1989; Everitt et al., 1989, 1991; Everitt, 1990; McDonald and White, 1993; White and Hiroi, 1993). The lesions in the patients we tested encompassed the amygdala and surrounding tissue and so we are unable to draw conclusions about functional specialization of structures within this region. A notable difference between the present study and the existing animal literature is that the amygdala is typically lesioned or inactivated bilaterally in animal studies of reward-related learning (Coleman-Meschers et al., 1996). The LA and RA participants tested in the present study had predominantly unilateral damage, although undiagnosed dysfunction in some structures contralateral to the site of the excised epileptic focus may have contributed to the impairment (Incisa della Rocchetta et al., 1995). LaBar et al. (1995) found significant impairments in fear conditioning in unilateral temporal lobectomy patients, also with no effect of side of excision.

The findings presented here of impaired preference conditioning in patients with even unilateral lesions of the medial temporal area contrast with those of Tranel and Damasio (1993), who found evidence for preserved learning of affective associations in Boswell, a patient with bilateral medial-temporal damage (including the ANC). In that study, three previously novel people were instructed to act toward Boswell in either a positive (e.g., giving compliments and treats), negative (e.g., requiring him to participate in tedious experiments), or neutral way, over a 5 d period. Boswell was subsequently unable to identify the stimulus persons, but when asked to “choose the person that you would go to for a treat” he consistently chose the positive stimulus person, suggesting that he was able to learn to associate faces with reward outcomes. However, Tranel and Damasio (1993) speculate that Boswell’s preserved learning might reflect the action of another learning system, that for reinforced stimulus–response associations. This type of learning appears to be mediated by a neural system that includes the dorsal striatum (e.g., Mishkin et al., 1985; McDonald and White, 1993), which is intact in Boswell. This learning system would also be expected to be intact in our patients with more restricted lesions. The apparent discrepancy in the results of the two studies therefore probably reflects the different requirements of the two tasks.

Because the anterior temporal lobe is considered to be the final stage in the cortical visual system, our results accord well with the idea that visual stimuli acquire affective significance through an interaction between high-level visual areas and the ANC. Temporal lobe excisions do not generally result in marked visual perceptual impairments, although patients with right temporal lobe lesions can show subtle deficits when normal stimulus redundancy has been reduced, by presenting items tachistoscopically, for example (Milner, 1990). The stimuli used in the present study were not degraded in any way, and all patients in both temporal lobe groups appeared able to discriminate them, judging from their physical descriptions of the patterns during the last phase.

The findings of the present study are also consistent with a body of literature demonstrating that aspects of working memory may be dependent on the integrity of the prefrontal cortex (Petrides and Milner, 1982; Funahashi et al., 1989; Owen et al., 1990, 1996; Jonides et al., 1993; Petrides et al., 1993; Wilson et al., 1993; Cohen et al., 1994; Courtney et al., 1996; Rao et al., 1997) (for review, see Owen, 1997; Rushworth and Owen, 1998). Thus, unlike the anterior temporal lobe group, the patients with exci-

sions of the frontal lobe were unable to maintain an ongoing record of how many red balls had been found in each location, a requirement that undoubtedly placed demands on aspects of working memory.

Smith and Milner (1988) and Smith (1996) presented series of words and abstract designs to normal volunteers and patients with unilateral frontal or temporal lobe excisions. The words and designs differed in the number of times that they were repeated within a series. Whereas normal participants and patients with anterior temporal lobe resections were equally able to estimate frequency of occurrence, patients with frontal lobe excisions, particularly the right frontal group, significantly underestimated the frequency of occurrence of either words or designs. Furthermore, Smith noticed a trend toward material-specificity in this deficit: patients with left frontal-lobe lesions were more impaired than patients with right frontal lobe lesions at estimating the frequency of occurrence of words, and the reverse pattern was observed for designs. No effect of side of excision was seen in the present study: patients with right and left frontal lobe resections appeared equally impaired. The lack of hemispheric asymmetry may be owing to the nature of the stimuli to be monitored in the present study: participants were required to monitor the conjunction of a particular event (red ball) with three distinct locations (left, top, or right). This is qualitatively different from monitoring the occurrence of words or abstract designs that are all presented in the same spatial position.

In conclusion, the results of this study suggest that working memory and stimulus–reward association learning are doubly dissociable in humans. Patients with unilateral frontal lesions were impaired at the working memory component of the task, but did show preference conditioning. Conversely, patients with anterior temporal lobe resections performed normally on the working memory component, but did not acquire stimulus–reward associations. To date, the work on mediation of emotional learning by the ANC in humans has focussed on negative affect, such as fear (Bechara et al., 1995; LaBar et al., 1995, 1998; Büchel et al., 1998; Morris et al., 1998; but see, Hamann et al., 1999). The results presented in this paper demonstrate that, in humans as in other species, structures in the region of the amygdala are required for cues to acquire affective significance through their association with rewarding events.

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