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Dissociable Effects of Cingulate and Medial Frontal Cortex Lesions on Stimulus–Reward Learning Using a Novel Pavlovian Autoshaping Procedure for the Rat: Implications for the Neurobiology of Emotion

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The effects of quinolinic acid-induced lesions of the anterior cingulate, posterior cingulate, and medial frontal cortices on stimulus–reward learning were investigated with a novel Pavlovian autoshaping procedure in an apparatus allowing the automated presentation of computer-graphic stimuli to rats (T. J. Bussey, J. L. Muir, & T. W. Robbins, 1994). White vertical rectangles were presented on the left or right of a computer screen. One of these conditioned stimuli (the CS+) was always followed by the presentation of a sucrose pellet; the other, the CS−, was never followed by reward. With training, rats came to approach the CS+ more often than the CS−. Anterior cingulate cortex-lesioned rats failed to demonstrate normal discriminated approach, making significantly more approaches to the CS− than did sham-operated controls. Medial frontal cortex-lesioned rats acquired the task normally but had longer overall approach latencies. Posterior cingulate cortex lesions did not affect acquisition.

Recent evidence has shown that selective lesions of subregions of the cingulate cortex produce contrasting effects on tests of discrimination learning. For example, it has been reported that lesions of the anterior cingulate cortex facilitate the acquisition of a visuospatial conditional discrimination task, in which rats learn a rule of the type, "If Stimulus A, then go left and if Stimulus B, then go right" (Bussey, Muir, Everitt, & Robbins, 1996). In attempting to explain this paradoxical result, it was suggested that the anterior cingulate cortex may be implicated in the acquisition of stimulus–reward associations, a process that may, under certain circumstances, compete with the acquisition of stimulus–response learning that is required in the conditional task (see Bussey et al., 1996; Muir, Bussey, Everitt, & Robbins, 1996). Further investigations have shown that although rats with anterior cingulate cortex lesions were unimpaired in the acquisition of a simple one-pair shape discrimination, they were significantly impaired in the acquisition of an eight-pair concurrent discrimination task, in which eight stimulus–reward associations had to be learned concurrently (Bussey, Muir, Everitt, & Robbins, 1997). Although this observation lends support to the hypothesis that the anterior cingulate cortex has a role in stimulus–reward learning, the eight-pair concurrent discrimination task has features that complicate the interpretation of the lesion deficit, such as a high degree of interitem interference, the complexity of the visual stimuli used, and long interstimulus intervals.

In the current study, we examined the effects of anterior cingulate, posterior cingulate, and medial frontal cortex lesions on stimulus–reward learning in a paradigm in which the contributions of such factors are minimized using an apparatus that allows the presentation of computer-graphic stimuli to rats (Bussey, Muir, & Robbins, 1994). The procedure capitalizes on the phenomenon of "autoshaping" (Brown & Jenkins, 1968) in which a stimulus predictive of reward (the CS+) comes to elicit responses, directed at that stimulus, that are normally elicited by the reinforcer alone. Pigeons, for example, will come to peck at a light presented on a peckable key, which is reliably presented just before the delivery of grain (Brown & Jenkins, 1968), presumably because of the acquisition of a Pavlovian association between the stimulus and the reinforcer. Similarly, rats will come to approach stimuli predictive of food reward (e.g., Boakes, 1977). There are, however, alternatives to the Pavlovian, stimulus–reinforcer learning account of autoshaping. Specifically, it has been suggested that because reinforcement reliably follows the animal’s response, the response is adventitiously reinforced and the animal learns an instrumental, response–reinforcer association. Of the several reasons for rejecting this account, one of the most compelling is the demonstration by Williams and Williams (1969) that if contingencies are altered such that responding prevents the delivery of reward, animals nevertheless continue to respond to the CS+. Because no adventitious reinforcement for responding could occur during this "omission schedule,” the persistent responding can be explained only by the
Pavlovian stimulus–reward pairings that occur on trials in which no response is made. In the current study, we applied this assay of stimulus–reward learning to our procedure.

In the autoshaping procedure used here, white vertical rectangles are presented on a variable interval (VI) 40-s schedule on either the left or the right side of a computer screen. One of these stimuli (the CS+) is always followed by a sucrose pellet. The other, the CS−, is never followed by reward. As a result of this training, rats come to approach the CS+ much more often than the CS− and with decreasing latency. Thus, the number of discriminative approaches to the CS+ and CS−, as well as latencies to approach these stimuli, serves as a measure of how well the animal has learned the association between the CS+ and the reward.

Method

Subjects

Thirty-four male Lister hooded rats (Olac, Bicester, England), weighing 320–350 g at the beginning of the experiment, were housed in pairs in a temperature-controlled room (minimum 22 °C) under 12:12-hr light–dark conditions. They were provided with free access to water and were maintained throughout the experiment at 90% of their free-feeding weight using a restricted feeding regimen.

Surgical Procedures

The rats received administration of an anesthetic (0.3 ml/100 g ip) with the following composition: 81 ml of Nembutal (Rhone Merieux Ltd., Harlow, England) containing 10% vol/vol alcohol plus 20% vol/vol propylene glycol, 21.25 g chloral hydrate, 10.63 g MgSO4, 198 ml of propane-1,2-diol, and 50 ml absolute alcohol and made up to 500 ml with distilled water. They were placed in a Kopf stereotaxic frame fitted withatraumatic ear bars. A dental drill was used to remove the bone directly above the injection sites, and the dura mater was broken using the tip of a hypodermic needle, avoiding damage to the superior sagittal sinus. Quinolinic acid (Sigma, Poole, England) was dissolved in 0.1 mol phosphate buffer (pH = 7.2–7.4) to a concentration of 0.09 mol. A volume of 0.5 μl of this solution was infused through a 30-gauge cannula attached to a 10-μl sampling syringe (SGE, Baton Rouge, LA). Bilateral lesions of the anterior cingulate cortex (ANT group) were made using the following injection coordinates (Paxinos & Watson, 1986): anteroposterior (AP) = +0.8, −3.0 and −2.0; AP mediolateral (ML) = ±0.5, and dorsoventral (DV) = ±0.5, DV = −2.5 and −2.0; and AP = −0.4, ML = ±0.5, and DV = −2.0 and −1.5 (incisor bar set at 2.3 mm below the interaural line). Bilateral posterior cingulate cortex lesions (POS group) were made in the same manner at the following sites: AP = −3.3, ML = ±0.5, and DV = −1.2; AP = −4.0, ML = ±0.5, and DV = −1.2; and AP = −5.0, ML = ±0.5, and DV = −2.0. Coordinates for the medial frontal lesion (MF group) were AP = +2.6, ML = ±0.5, and DV = −1.5; AP = +3.3, ML = ±0.5, and DV = −3.0 and −1.5; and AP = +3.8, ML = ±0.5, and DV = −1.5. After each infusion the injection cannula was left in place for another 2 min. Sham lesions of the anterior cingulate cortex (SHAMant; n = 3), posterior cingulate cortex (SHAMpos; n = 2), and medial frontal cortex (SHAMmf; n = 2) were made using the coordinates and procedures just outlined, except that no infusion was made after cannula insertion. The remaining animals were assigned to one of three lesion groups and the appropriate surgeries performed: ANT = 9, POS = 9, and MF = 9.

Histology

At the conclusion of behavioral testing, the animals were perfused transcardially with 0.9% saline followed by 10% formal saline. After dehydration by immersion in 30% sucrose, the brains were sectioned on a freezing microtome at 60-μm thickness. Every fourth section through the region of the lesions was collected, mounted on glass slides, and stained with Cresyl Violet. These sections were used to verify lesion placement and to assess the extent of lesion-induced neuronal loss.

Apparatus

The apparatus, shown in Figure 1 (built in the Department of Experimental Psychology, University of Cambridge), is a modification of an apparatus described by Bussey et al. (1994). It consisted of a testing chamber and video display unit (VDU) housed within a wooden sound-attenuating box and fitted with a fan for ventilation and masking of extraneous noise. The inner chamber measured 48 × 30 × 30 cm and consisted of a metal frame, clear Perspex walls, and an aluminum floor. A 3-W houselight was attached to the ceiling of the chamber. Located centrally in front of the VDU was a food magazine attached to a pellet dispenser (Campden Instruments, Loughborough, England) situated outside the sound-attenuating box. The magazine was not fitted with a standard magazine flap; this allowed the animal unrestricted access to the magazine, thus avoiding introducing into the task the requirement that animals perform the instrumental response of pushing open the flap to retrieve pellets. Pressure-sensitive areas of floor measuring 14 × 10 cm were located to the left and right of the magazine directly in front of the VDU screen. The floor panels were attached to microswitches to detect approaches to the left and right of the VDU screen. Another pressure-sensitive floor panel was located centrally at the other end of the chamber. The stimuli used were white horizontal rectangles displayed on the left and right of the VDU screen, and they measured 10 × 28 cm. The apparatus was controlled and monitored by a BBC Master series microcomputer using programs written by one of us in BBC BASIC.

Behavioral Procedures

Pretraining. Rats were initially given one 30-min session in which they were allowed to habituate to the testing chamber and to collect pellets from the magazine. The houselight was illuminated and pellets were delivered into the magazine on a VI 40-s schedule. Animals were observed during this session to ensure that they were successfully retrieving and consuming pellets.

Acquisition. On the day after pretraining, rats were trained to associate stimuli with the delivery of a 45-mg sucrose pellet (dustless pellets; Bioserve, Inc., Frenchtown, NJ) into the magazine. Stimuli were presented for 10 s. One of the stimuli was designated the CS+ and signaled the delivery of a sucrose pellet immediately after the offset of this stimulus; the other, designated the CS−, was never followed by food delivery. The left stimulus was designated the CS+ for half the animals in each of the experimental groups; for the other half, the right stimulus was designated the CS+. Both stimuli were presented on a VI 40-s schedule, and training consisted of 100 presentations of both the CS+ and CS− (two sessions of 50 presentations each, carried out on 2 consecutive days). When the rat stepped onto the floor panel in front of a stimulus, it was scored as an approach to that stimulus.
and no further approaches were scored during that stimulus presentation.

Presentation of stimuli and collection of response measures were subjected to the following restrictions: (a) Stimuli were not presented until the rat was centrally located at the rear of the chamber. This eliminated chance approaches to the stimuli, provided all rats on every trial with an equivalent opportunity for stimulus sampling, and allowed for the accurate calculation of approach latencies that were based on the time taken for rats to approach the stimuli starting from the same position in the test chamber on each trial. (b) The minimum time between presentations of the CS+ and CS− was 10 s. (c) The maximum number of consecutive presentations of either the CS+ or the CS− was two.

Several performance measures were calculated: (a) the number of approaches to the CS+ per 10 presentations, (b) the number of approaches to the CS− per 10 presentations, (c) the mean latency to approach the CS+ (to the nearest centisecond), and (d) the mean latency to approach the CS− (to the nearest centisecond).

Omission training. The day after the acquisition phase, all parameters of the task remained the same as during acquisition, except that contingencies were altered such that approaches to the CS+ prevented the delivery of a food pellet. Omission training consisted of 50 presentations of both the CS+ and CS− under this schedule.

Data Analysis

Data for each variable were subjected to an analysis of variance (ANOVA) using the CLR ANOVA Version 2 (Clear Lake Research, Houston, TX) statistical package. Further post hoc comparisons were made using the Newman–Keuls test. Skewed data, which violate the distribution requirement of the ANOVA, were subjected to appropriate transformations (Howell, 1987; Tabachnick & Fidell, 1989).

Results

Histology

Tracings of the outlines of the lesions in individual animals were made on the basis of the neuronal loss seen in the Cresyl-Violet-stained sections. Figure 2 shows the extent of the lesions, which were highly similar to those obtained in previous studies using identical lesion parameters (Bussey et al., 1996, 1997; Muir, Everitt, & Robbins, 1996). Histological analysis of the lesions revealed that in 1 animal in the ANT group the lesion was incomplete, with neuronal loss observable only in the most rostral portion of the target area. The data from this animal were therefore excluded from subsequent behavioral analyses. In no animal was there obvious or gross damage to the hippocampus or the cingulum bundle.

As shown in Figure 2, lesions of the medial frontal cortex were well placed and extended from approximately +4.2 mm from bregma to the genu of the corpus callosum, thus including areas Cg1 and Cg3 according to the nomenclature of Zilles (1985). In no animal was there damage to regions posterior to the genu. In the majority of cases, damage was greatest in the rostralmost areas of medial frontal cortex. Anterior cingulate cortex lesions extended from the genu of the corpus callosum to approximately −1.0 mm from bregma and removed areas Cg1 and Cg2. Posterior cingulate
Figure 2. Reconstructions of the medial frontal (left), anterior cingulate (middle), and posterior cingulate (right) cortex lesions at various anteroposterior levels (medial frontal cortex = +4.2 to +1.2 mm from bregma; anterior cingulate cortex = +2.2 to -1.8 mm from bregma; and posterior cingulate cortex = +2.2 to -1.8 mm from bregma; and posterior cingulate cortex = -1.8 to -5.6 mm from bregma). Black shading indicates the extent of the largest lesion within each group and cross-hatched shading the smallest lesion. Drawings of sections are from Swanson (1992).

cortex lesions extended from -1.8 mm from bregma to approximately -4.8 mm, with extensive cell loss in areas retrosplenial granular cortex and retrosplenial agranular cortex according to Zilles (1985).

Behavioral Results

During behavioral testing, 1 animal from the ANT group and 1 from the MF group became ill, and 3 animals from the MF group died after surgery. Thus, the final group numbers were as follows: SHAMant = 3, SHAMpos = 2, SHAMmf = 2, ANT = 7, POS = 9, and MF = 5. During pretraining, all animals reliably collected and consumed pellets from the magazine.

Discriminated Approach

Preliminary analyses: Sham-operated controls. Differences scores (approaches to the CS+ minus approaches to the CS− across the 10 blocks of 10 stimulus presentations) were analyzed for the three SHAM groups. Sham-operated controls demonstrated significant learning across trials, and there were no differences among the three SHAM groups in their ability to do so. Thus, there were no differences between the SHAMant, SHAMpos, and SHAMmf groups, $F(2, 4) = 0.14, p > .05$, nor was there a significant Group × Block interaction, $F(18, 36) = 1.02, p > .05$. There was, however, a significant main effect of block, $F(9, 36) = 2.25, p < .05$.

As training progressed, the number of approaches made to the CS+ by sham-operated controls remained constant but approaches to the CS− decreased. A separate analysis of the number of approaches to the CS+ revealed no differences among the three SHAM groups, $F(2, 4) = 0.02, p > .05$, no effect of block, $F(9, 36) = 0.72, p > .05$, and no Group × Block interaction, $F(18, 36) = 0.82, p > .05$. Analysis of the number of approaches to the CS− revealed no differences among the three SHAM groups, $F(2, 4) = 0.35, p > .05$, and no Group × Block interaction, $F(18, 36) = 0.72, p > .05$, but a significant effect of block, $F(9, 36) = 2.57, p < .05$. Because there were no differences among the SHAMant, SHAMpos, and SHAMmf groups, we treated these animals as a single SHAM group during subsequent analyses.

Effects of lesions. ANT animals failed to demonstrate discriminated approach. Specifically, they made significantly more approaches to the CS− than did sham-operated controls. Although there was a trend for POS and MF animals to make more approaches to the CS+ during the early and late stages of training, respectively, this did not reach statistical significance. Thus, analysis of difference scores (see Figure 3A) revealed a significant main effect of lesion, $F(3, 24) = 3.12, p < .05$, but no effect of block, $F(9,
Because the animals often made no approaches to the CS− within 10 presentations, we calculated the average approach latencies by taking the mean of the 100 presentations of the CS+ and the CS−. The results are shown in Figure 4. Although MF animals were slow to approach both stimuli, like the SHAM and POS animals, they demonstrated discrimination between the CS+ and CS−, approaching the CS+ more rapidly than the CS−. The ANT group, however, showed no evidence of an ability to discriminate these stimuli according to this measure. Furthermore, the ANT group showed longer latencies to approach the CS+ than did the SHAM group.

An ANOVA revealed a significant main effect of stimulus, indicating that animals were much faster to approach the CS+ than the CS−, $F(1, 24) = 25.18$, $p < .001$, and a significant main effect of lesion, $F(3, 24) = 3.58$, $p < .05$.
Newman–Keuls post hoc analysis of the lesion effect revealed that MF animals were significantly slower to approach the stimuli than were the SHAM or the ANT group ($p < .05$). No other groups differed from the SHAM group or from each other in this respect. There also was a significant Lesion × Stimulus interaction, $F(3, 24) = 3.16$, $p < .05$. Examination of simple interaction effects revealed a significant effect of stimulus for the SHAM, $F(1, 24) = 22.97$, $p < .001$, POS, $F(1, 24) = 9.15$, $p < .01$, and MF, $F(1, 24) = 4.29$, $p < .05$, groups, but not for the ANT group, $F(1, 24) = 0.12$, $p > .05$. To investigate the effect of anterior cingulate cortex lesions on the latency to approach both the CS+ and CS−, we performed a Newman–Keuls post hoc analysis of the Lesion × Stimulus interaction. This analysis revealed that the ANT animals approached the CS+ with longer latencies than did the SHAM animals ($p < .05$). However, there was no significant difference between these two groups in terms of latency to approach the CS− ($p > .05$).

**Omission Training**

Animals continued to discriminate between the CS+ and the CS− throughout omission training, although overall approaches decreased. The pattern of lesion effects observed during acquisition was maintained during omission training.

Analysis of difference scores (see Figure 5A) revealed a significant main effect of lesion, $F(3, 24) = 3.36$, $p < .05$, but no effect of block, $F(4, 96) = 2.02$, $p > .05$, and no Lesion × Block interaction, $F(12, 96) = 1.10$, $p > .05$. Newman–Keuls post hoc analysis of the main effect of lesion revealed that difference scores of the ANT animals were significantly lower than those of the SHAM, POS, and MF animals ($p < .05$). To determine whether SHAM animals maintained discriminated approach throughout training under this condition, we performed $t$ tests. These tests revealed that difference scores for the SHAM group were significantly greater than zero for each of the five blocks of omission training ($p < .001$).

Separate analysis of the number of approaches to the CS+ (see Figure 5B) revealed no effect of lesion, $F(3, 24) = 0.67$, $p > .05$, and no Lesion × Block interaction, $F(12, 96) = 1.51$, $p > .05$, but a significant effect of block, $F(4, 96) = 8.10$, $p < .05$.

Analysis of the number of approaches to the CS− (see Figure 5C) revealed a significant effect of lesion, $F(3, 24) = 3.85$, $p < .05$, and a significant effect of block, $F(4, 96) = 5.46$, $p < .05$, but no Lesion × Block interaction, $F(12, 96) = 0.70$, $p > .05$. Approach latencies during the omission schedule could not be analyzed because some rats made no approaches to the CS− during the 50 trials.

**Discussion**

We investigated the effects of lesions of three adjacent medial cortical regions in the rat—the anterior cingulate, posterior cingulate, and medial frontal cortices—on stimulus–reward learning using a differential Pavlovian conditioning procedure. Anterior cingulate cortex lesions disrupted dis-
discriminated approach in this paradigm; specifically, the lesioned animals made many more approaches to the CS− than did sham-operated controls. They also failed to discriminate between the CS+ and CS− in terms of latency to approach these stimuli. Animals in all other groups did discriminate according to this measure, approaching the CS+ with much shorter latencies than the CS−. Furthermore, ANT animals approached the CS+ with longer latencies than did the sham-lesioned animals. Medial frontal cortex lesions led to longer approach latencies overall; however, this lesion did not disrupt discriminated approach according to any measure. Posterior cingulate cortex lesions did not disrupt any aspect of the acquisition of this task, although there were trends for POS animals to make fewer responses to the stimuli in the first block of 10 presentations during task acquisition and to approach the stimuli with longer latencies.

Behavioral Considerations: Pavlovian Stimulus–Reinforcer Learning

As training progressed, sham-operated control animals came to approach the CS+, which predicted reward, more frequently than they approached the CS−, which was never followed by reward. Discriminated approach of this type has been observed many times (Mackintosh, 1974). In the current experiment, discriminated approach was characterized by animals making progressively fewer approaches to the CS− while maintaining the level of responding to the CS+.

An important consideration in developing this task was to ensure that it taxed stimulus–reward learning selectively. The procedure we used was essentially an autoshaping procedure (Brown & Jenkins, 1968), in which the CS+ comes to elicit responses that are normally elicited by the reinforcer. Although most authors agree that a Pavlovian stimulus–reinforcer association is learned during such a procedure, others have argued that the animal’s behavior may be maintained via implicit instrumental response–reward associations: Although responses are not necessary in order for reward to be delivered, they are “adventitiously reinforced” by virtue of reward reliably after a response. There are several reasons for believing that Pavlovian associations predominate during autoshaping procedures. For example, the instrumental account has great difficulty explaining why the topography of the autoshaped response is specific to the reinforcer. Pigeons, for example, will peck a key with their beak in “drinking” position if the reinforcer is fluid but in “eating” position if the reinforcer is food (Jenkins & Moore, 1973). Furthermore, if subjects are prevented from responding to the CS+ during pairings with the reinforcer, for example by installing a transparent barrier between the animal and the CS+, responding will commence immediately on removal of the barrier (Davey, 1981). Such responding could not have been learned by adventitious reinforcement. Finally, one of the most powerful early demonstrations was carried out by Williams and Williams (1969), who altered contingencies such that responding prevented the delivery of reward. Under this “omission schedule,” animals continued to respond to the CS+. Because no adventitious reinforcement for responding could have occurred, the persistent responding observed can be explained only by the Pavlovian stimulus–reward pairings that occurred on trials in which no response was made.

Under the omission schedule in our study, animals continued to display discriminated approach even after 50 presentations of each of the CS+ and the CS−. If behavior was governed by an adventitiously acquired instrumental response–reinforcer association, animals would alter their responses to accommodate the new instrumental contingency. Not only did our rats fail to do this, but by the end of the 50 CS+/CS− presentations, the difference scores of the sham-lesioned animals were increasing. In all animals the overall responding decreased across the 50 CS+/CS− presentations, probably reflecting a decrease in affective arousal or partial extinction after a decrease in the density of reinforcement. Thus, the data from the omission trials provide strong evidence that animals learned a stimulus–reward association during training in this procedure.

Effects of Anterior Cingulate Cortex Lesions

Lesions of the anterior cingulate cortex led to an impairment in discriminated approach: Approaches to the CS− were increased, but those to the CS+ were not significantly different from control levels. Because conditioning in control animals was characterized not by an increase in approaches to the CS+ but by a decrease in approaches to the CS−, one might expect a disruption of conditioning to be reflected in an alteration in the number of approaches to the CS−. However, the observation that CS− approaches are altered selectively may nevertheless provide insights into the particular contribution of the anterior cingulate cortex to this type of learning. Furthermore, Parkinson, Robbins, and Everitt (1996a) found that lesions of the nucleus accumbens decrease CS+ approaches as well as increase CS− approaches, showing that certain manipulations can result in a decrease in responding to the CS+ in this paradigm.

Perhaps the most parsimonious explanation for this pattern of results is that the ANT animals were unable to discriminate the CS+ and the CS− perceptually. Because these stimuli differed only in their spatial location, a failure to discriminate them could be attributable to an inability of these animals to discriminate egocentric spatial locations (ANT animals are able to discriminate complex nonspatial computer-graphic stimuli perfectly well on several different tasks; Bussey et al., 1997). Although some authors have reported deficits in spatial tasks after anterior cingulate cortex lesions (e.g., Meunier, Jaffard, & Destrade, 1991), there are many examples of spatial tasks in which animals must discriminate left from right where such lesions failed to produce deficits (e.g., Neave, Lloyd, Sahgal, & Aggleton, 1994). For example, a recent study showed that anterior cingulate cortex lesions made using the same protocol as those we used had no effect on the acquisition of a visuospatial conditional discrimination task in which animals learned a rule of the type, “If A go left, if B go right” (Bussey et al., 1997). Furthermore, in another study anterior
CINGULATE CORTEX AND AUTOSHAPING 915

cingulate cortex lesions facilitated the acquisition of this type of task (Bussey et al., 1996). If animals with lesions of the anterior cingulate cortex were unable to discriminate left from right, they would likely have been impaired on these tasks and certainly would not have demonstrated enhanced acquisition. (We return to the issue of perceptual discrimination later.)

A second possibility is that ANT animals failed to habituate normally to the stimuli, leading to the maintenance of high levels of responding to the CS−. This account seems plausible in light of the observation that humans with bilateral anterior cingulotomy are slow to habituate to stimuli, as measured by skin conductance responses (Cohen, Kaplan, Meadows, & Wilkinson, 1994). Furthermore, Kolb (1974) has shown that large lesions of prefrontal cortex in rats can produce an impairment in habituation; at least some subjects in that study had damage that included postgenual anterior cingulate cortex. Because habituation can be regarded as a decrease in attention to stimuli that provide no new information about subsequent events (Pearce & Hall, 1980), a deficit in habituation could provide support for a role for the anterior cingulate cortex in attention (Janer & Pardo, 1991). In the current study, animals were not habituated to the CS+ and CS− before conditioning to avoid the introduction of confounds related to stimulus preexposure such as latent inhibition effects. Thus, the two processes of habituation and conditioning would have occurred simultaneously during task acquisition (see Kaye & Pearce, 1984). These processes would have opposing effects: The process of habituation would lead to a decrease in the initial level of responding to the CS+, whereas the process of conditioning would lead to an increase. The observed level of responding would thus represent an equilibrium between these two effects. If anterior cingulate cortex lesions disrupted the habituation process, thus removing a process that drives down CS+ responding, then the predicted result would be an increase in approaches to the CS+ after such lesions. However, this was not observed (although the failure to observe such an increase could possibly be due to ceiling effects). Furthermore, Powell, Watson, and Maxwell (1994), using an aversive heart rate conditioning procedure, obtained a pattern of results strikingly similar to ours: Anterior cingulate cortex lesions enhanced the bradycardia observed in response to a CS− that signaled safety without affecting responses to a CS+ that predicted shock. In the Powell et al. study, animals were habituated to the stimuli before conditioning trials; therefore, impaired habituation cannot be the explanation for the pattern of results reported by them. Furthermore, Bussey et al. (1996) observed that animals with anterior cingulate cortex lesions habituated normally to novel activity cages. Finally, the approach latency data from the current study indicate that ANT animals were slower to approach the CS+ that signaled reward. This result cannot be accounted for in terms of an impairment in habituation and instead suggests that these animals had failed to acquire knowledge of the significance of the CS+. However, without data on the rate of habituation to the CS+ and CS− in the same apparatus used in our study, a potential contribution of an impairment in habituation cannot definitively be ruled out.

A third possibility is that ANT animals were unable to withhold responding to irrelevant stimuli, responding impulsively to the CS− when it was presented. This interpretation gains some support from the observation that in a continuous performance test of visual attention, in which animals must respond to a light when it is presented in one of five response apertures, lesions of the anterior cingulate cortex produce an increase in the number of “anticipatory responses” to the response apertures before the presentation of the stimulus (Muir, Everitt, & Robbins, 1996). However, the approach latency data in the current study again do not support the suggestion that these animals are simply impulsive. An impulsive animal would be expected to approach stimuli more rapidly than normal, particularly stimuli predictive of reward, and ANT animals were slower to approach the CS+. A possible resolution to this discrepancy between the effects of the lesion on the number of approaches to the CS+, compared with the latency to make these approaches, is that these measures may reflect qualitatively different conditioned responses (Konorski, 1967) that may have different neural substrates (Gallagher & Holland, 1992). Another is that a difference between the lesion and control groups according to the former measure may have been masked due to control animals performing at a behavioral ceiling.

In conclusion, it is clear that lesions of the anterior cingulate cortex markedly disrupt Pavlovian conditioning. Whereas other authors have reported such effects in aversive paradigms (e.g., Buchanan & Powell, 1982), we found that this result holds for the appetitive case. This suggests that the effects of lesions in these previous studies may not have been solely a consequence of an impairment in, for example, nociception. The precise nature of these impairments, however, remains unclear. Specifically, it is unclear whether these animals have an impairment in the ability to learn stimulus−reward associations or whether the impairment lies in the ability to express this learning in a discriminative conditioning setting. Although additional experiments will be required to address this issue, preliminary results from our laboratory are suggestive. Willoughby, Parkinson, Bussey, Robbins, and Everitt (1997) first trained ANT rats on the autoshaping task as described in this article. The pattern of results obtained here was replicated. Willoughby et al. then administered a probe test session consisting of 20 trials in which both the left and right stimuli were presented simultaneously. The test was run in extinction; no pellets were delivered after presentation of the stimuli. The stimulus that the animal first approached was recorded, and the number of approaches to the CS+ and CS− were compared. Because both of the stimuli, when presented simultaneously, compete for control of responding, this test provided a measure of discrimination unconfounded by any tendency of animals to approach impulsively a single stimulus presented alone. Sham-operated control animals consistently approached the CS+ more often than the CS−. ANT animals also demonstrated accurate discrimination according to this measure. Firstly, these data suggest that ANT animals are able to discriminate the left from the right stimulus perceptually.
(see the earlier discussion). Furthermore, it appears that these animals may be able to learn associations between stimuli and reinforcers but fail to express this learning under certain conditions, such as during the acquisition phase of this experiment. However, because the probe followed many acquisition trials, the apparently normal discrimination by the ANT animals may reflect their ability eventually to acquire the discrimination, although they clearly take many more trials than control animals to do so. Furthermore, the probe test may be a less sensitive method for detecting a discrimination impairment than the approach measure; indeed, it has been shown that simultaneous discrimination procedures can reveal conditioning that is not revealed by successive procedures (Mackintosh, 1974). Again, future research will attempt to address these issues.

The suggestion that the anterior cingulate cortex is involved in stimulus–reward learning, or the expression of that learning, is consistent with other behavioral and neurophysiological data. For example, anterior cingulate cortex lesions have been reported to impair an eight-pair concurrent discrimination task, in which animals were required to learn eight stimulus–reward associations concurrently (Bussey et al., 1997). Furthermore, Ono, Yamamoto, Nishijo, Uwano, and Yamashima (1995) observed neurons in the anterior cingulate cortex of the monkey that fire selectively to stimuli previously paired with reward. In addition, rats will learn to leverpress for rewarding electrical stimulation to the anterior cingulate cortex, sites caudal to the corpus callosum (the region examined in the current study) supporting the most rapid acquisition (Spence, Silverman, & Corbett, 1985). Anatomical evidence is consistent with these observations: Dopamine neurons in the ventral tegmental area, which have been implicated in reward-related processes (Phillips & Fibiger, 1989), innervate the anterior cingulate cortex (Beauregard, Ferron, & Descarries, 1989; Bjorkland & Lindvall, 1984), providing a mechanism by which reward signals could reach this region (see Porrino, 1993, for an alternative view). Finally, the anterior cingulate cortex is connected with other brain regions that have been implicated in stimulus–reward learning, most notably the amygdala (e.g., Aggleton & Mishkin, 1986; Everitt & Robbins, 1992; Gaffan, 1992), the mediiodorsal thalamus (Gaffan & Murray, 1990; McAlonan, Robbins, & Everitt, 1993), and ventral striatum (Everitt & Robbins, 1992; White, 1989), although the results of neuroanatomical studies investigating anterior cingulate–accumbens connections have been equivocal. These brain regions, along with the anterior cingulate cortex, may form a distributed neural system that mediates the acquisition or expression of stimulus–reward associations.

Finally, our data and those of others, as discussed earlier, provide evidence for both a deficit in Pavlovian conditioning and an overall increase in behavioral output and could indicate a dual role for this area of cingulate cortex. Dum and Strick (1993) provided strong evidence that in monkeys and humans, the anterior cingulate cortex can be divided on anatomical grounds into dorsal and ventral components. The dorsal component has strong connections with the spinal cord and motor output structures and can be regarded as “cingulate motor area,” whereas the ventral portion is connected preferentially with autonomic emotion and related processes (Porrino, 1993). Similar regions with similar connectivity have been delineated in the rat (Neafsey, Terreberry, Hurley, Ruit, & Frysztak, 1993; Zilles, 1985), and it has been suggested that these regions in rats and primates may be functionally homologous (Preuss, 1995). It is conceivable that the lesions we made, which included damage in both of these regions, produced both motoric changes due to damage to the dorsal region—anticipatory responding (Muir, Everitt, & Robbins, 1996), a trend toward an increase in locomotor activity (Bussey et al., 1996), and increased overall responding (the current study)—and a disruption of Pavlovian conditioning and emotional learning (discussed later) due to damage to the ventral region. Similar suggestions have been made by other authors (e.g., Neafsey et al., 1993).

**Effects of Posterior Cingulate Cortex Lesions**

Posterior cingulate cortex lesions did not affect the acquisition of discriminated approach; however, there was a tendency for POS animals to make fewer responses to the stimuli at the outset of training and for these animals to be slower in general to approach the stimuli. These trends are noteworthy because they are consistent with the suggestion that the posterior cingulate cortex may have a role in response generation (Bussey et al., 1997; Carlson & Goldman-Rakic, 1995).

**Effects of Medial Frontal Cortex Lesions**

MF animals were slower than sham-operated controls to approach the CS+ and CS− in our study, although they were able to discriminate these stimuli, as shown by differences in the number of approaches to these stimuli and by latency measures. Thus, we found no evidence to suggest that these animals were impaired in stimulus–reward learning. Other researchers have similarly failed to observe deficits in autoshaping after medial frontal cortex lesions; indeed, marked facilitations in learning have been observed (van Haaren et al., 1988). Instead, our data suggest that MF animals are slower to detect or respond to salient visual stimuli. This result supports the findings of Muir, Everitt, and Robbins (1996), who found that medial frontal lesions impaired the accuracy of performance in a serial reaction time task used to assess visual attention. Furthermore, Bussey et al. (1997) suggested that reversal learning deficits after medial frontal lesions in rats may be attributable to underlying attentional deficits. Indeed, prominent accounts of human prefrontal function emphasize a role for this region in attention (e.g., Shallice, 1988).

**Implications for the Neurobiology of Emotion**

A popular strategy in research on the neurobiology of emotion has been to use Pavlovian conditioning procedures as animal models of emotional learning (e.g., Davis, 1992; Everitt & Robbins, 1992; Gallagher & Holland, 1992;
This approach has led to considerable progress in the area, identifying structures such as the amygdala as essential components of the circuitry that mediates emotional learning. Although this approach has not been used to specifically investigate a possible role for the anterior cingulate cortex in emotion, results of several studies suggest that the anterior cingulate cortex is necessary for normal "fear conditioning." For example, Buchanan and Powell (1982) and Powell et al. (1994) reported that anterior cingulate cortex lesions attenuated an aversive Pavlovian conditioned response of bradycardia. Furthermore, Parkin-son, Robbins, and Everitt (1996b) found that anterior cingulate cortex lesions attenuated lick suppression during the presentation of a CS+ that had been paired previously with shock. Gabriel, Kubota, Sparenborg, Straube, and Vogt (1991) reported that anterior cingulate cortex lesions in rabbits impaired active avoidance learning, a component of which is likely the Pavlovian association of a stimulus (tone) with an aversive reinforcer (shock). These results from aversive conditioning studies, combined with the results of our study, suggest that the anterior cingulate cortex may be involved in learning about the significance of stimuli that predict both aversive and appetitive events, thus endowing these stimuli with both negative and positive affective value.

Indeed, several theorists have proposed a role for the anterior cingulate cortex in emotion (Brothers, 1995; Damasio, 1994; Devinsky, Morrell, & Vogt, 1995; Vogt, Finch, & Olson, 1992). The evidence in humans that the anterior cingulate cortex is involved in both positive and negative affective processes includes the observations that electrical stimulation of this region of cortex can result in fear or agitation or euphoria and well-being (Bancaud & Talairach, 1992; Laitinen & Livingston, 1973) and that damage to the cingulate cortex can produce apathy and depression (Devin-sky et al., 1995). More recently, positron emission tomographic studies have shown that the anterior cingulate region is activated during transient sadness or happiness (George et al., 1995), when observers view facial expressions with positive or negative emotional content (George et al., 1993), and when observers contract their facial muscles to induce a negative mood (Schiff, Bassel, & Houle, cited in Oatley & Jenkins, 1996; for a more thorough review see Devisky et al., 1995). A challenge for future research will be to investigate if and how the anterior cingulate cortex interacts with other brain regions such as the amygdala in both positive and negative emotional learning.

References


Sternberg Appointed Editor of Contemporary Psychology (APA Review of Books), 1999–2004

The Publications and Communications (P&C) Board of the American Psychological Association announces the appointment of Robert J. Sternberg, Yale University, as editor of Contemporary Psychology (APA Review of Books) for a 6-year term beginning in 1999.

Contemporary Psychology has been in existence for 42 years and, for most of the time, has been operating under the same coverage model. The model is a good one, as the current issues edited by John H. Harvey reflect, and the journal has long met the needs of individuals and libraries. The pace of change has increased during the past few years, however, and the P&C Board recently decided that it was time for a new model, one that would reflect the 21st century reader’s needs for information about books.

Sternberg, at the request of the P&C Board, will be embarking on a program to make the journal even more timely and interesting during his editor-elect year in 1998. Some of the changes envisioned include fewer but longer and more thoughtful reviews of books, reviews only of “new” books (with a few noteworthy exceptions), comparative textbook reviews at strategic times of the year, and changes in publication frequency and pricing. Sternberg welcomes suggestions for improving the journal and serving reader needs.

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Please note that all reviews are written by invitation. Publishers should note that books should not be sent to Sternberg. Publishers should continue to send two copies of books to be considered for review plus any notices of publication to

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As the editorial term of John H. Harvey comes to a close, the P&C Board wishes to express its appreciation for his hard work and dedication as well as that of his staff at the University of Iowa.