Deficits in Attentional Orienting Following Damage to the Perirhinal or Postrhinal Cortices

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The authors used an associative learning paradigm to assess the effects of perirhinal or postrhinal damage on attentional orienting. Control rats and rats with lesions of either the perirhinal or postrhinal cortex initially displayed high levels of orienting behavior (rearing) to presentations of a light cue. Continued nonreinforced presentations resulted in normal habituation of the response. In addition, orienting reemerged in control rats, indicating increased attentional processing of the cue. This conditioned orienting did not reemerge in rats with either perirhinal or postrhinal lesions, providing direct evidence that the rat perirhinal and postrhinal cortices each play a role in attention. These results are consistent with an emerging view that some structures within the medial temporal lobe have nonmnemonic functions.

A growing body of evidence indicates that medial temporal lobe structures, including the hippocampus and surrounding cortical regions, have distinct roles in learning and memory (reviewed in Aggleton & Brown, 1999; Eichenbaum, 2000; Squire & Zola-Morgan, 1991). A related issue is how relevant features of an object or scene are selected from all the available stimuli for further processing by the medial temporal lobe (e.g., for learning or memory). It is likely that associated brain structures are involved in the monitoring of available stimuli for possible relevance to ongoing behavior. Within the medial temporal lobe of the rat, the perirhinal and postrhinal cortices are reasonable candidates for supporting such a function.

The postrhinal cortex is closely connected with structures known to be involved in automatic, bottom-up orienting or visuospatial functions. These structures include components of the putative posterior attentional system (Posner & Dehaene, 1994), such as the lateral posterior nucleus of the thalamus (pulvinar in humans) and the posterior parietal cortex. The posterior parietal and retrosplenial cortices provide substantial cortical input to the postrhinal cortex (Burwell & Amaral, 1998a). Electrophysiological evidence suggests that the postrhinal cortex may indeed be involved in monitoring changes in the environment (Burwell & Haferman, 2003). As such, postrhinal function may be more consistent with higher level perceptual or attentional orienting processes than memory per se. In contrast, the perirhinal cortex receives cortical sensory input from all sensory modalities (Burwell & Amaral, 1998a), and behavioral studies implicate this region in mnemonic processing of individual stimuli (Bussey, Duck, Muir, & Aggleton, 2000; Eacott, 1998; Ennaceur & Aggleton, 1997; Kesner, Ravindranathan, Jackson, Giles, & Chiba, 2001; Mummy & Glenn, 2000; Myhrer & Wangen, 1996; Otto & Garruto, 1997; Wiig & Burwell, 1998). The perirhinal cortex, however, also receives a strong, weakly reciprocated, postrhinal afferent (Burwell & Amaral, 1998b). Thus, information processing in the postrhinal cortex might provide a background on which stimuli can be selected for more focused processing by other medial temporal lobe structures, such as the perirhinal cortex.

Associative learning paradigms have provided useful approaches for studying the brain mechanisms underlying attentional function (reviewed in Holland, 1997). For example, when a food-deprived rat is first presented with a visual cue, the attentional orienting response of rearing is observed (unconditioned orienting). If the cue is not followed by reinforcement, the orienting response habituates. Subsequent reinforcement of the visual stimulus results in reemergence of the response (conditioned orienting). This effect is thought to reflect increased attention to the conditioned stimulus (CS; Kaye & Pearce, 1984) and is sensitive to damage to the central nucleus of the amygdala and the posterior parietal cortex (Bucci & Chess, 2003; Gallagher, Graham, & Holland, 1990). Notably, the perirhinal and postrhinal cortices are interconnected with the central nucleus of the amygdala (Pikkarainen & Pitkanen, 2001), and the posterior parietal cortex provides input to the postrhinal cortex (Burwell & Amaral, 1998a). To assess the possible involvement of the perirhinal and postrhinal cortices in attentional orienting, we examined the effects of bilateral lesions of each region on unconditioned and conditioned orienting to a visual stimulus.

Method

The subjects were 65 male Long-Evans rats (Charles River Laboratories, Wilmington, MA) weighing 300–325 g at the start of the experiment. Rats
were maintained on a 12-h light–dark cycle with free access to food and water prior to surgery and during recovery. After surgery, rats were allowed to recover for 2 weeks. Following postoperative recovery, rats were placed on a restricted feeding regimen and gradually reduced to 85% of their ad libitum weights. Behavioral training was initiated when all rats had reached the target weight. Weights were maintained at 85% for the remainder of the experiment.

**Surgery**

Subjects were brought to a surgical level of anesthesia with halothane gas and secured in a Kopf stereotaxic apparatus (David Kopf Instruments, Tujunga, CA) in the flat skull position (bregma and lambda level in the horizontal plane). Under aseptic conditions, we made an incision to reveal the skull and retracted the skin laterally. A series of holes were then drilled through the skull above the intended lesion site. Bilateral neurotoxic lesions of the perirhinal or postrhinal cortex were made using ibotenic acid (10 mg/ml; Sigma Chemical, St Louis, MO) dissolved in 0.1 M sodium phosphate buffer. Ibotenic acid was pressure injected into the brain through a glass pipette (50-μm tip). For the postrhinal lesion group (POR, n = 19), we angled the pipette at 22° from vertical with the tip oriented rostrally and lowered through the skull at 2.0 mm posterior to lambda. An injection of 50–75 µl was made at each of three dorsal–ventral sites at 0.3 mm lateral from the lateral ridge (5.9, 5.5, and 5.2 mm below the skull surface). For the perirhinal lesion group (PER, n = 18), injections of 25–50 µl were made at 2.3, 3.3, 4.3, 5.2, 6.4, and 7.1 mm posterior to bregma; 6.3, 6.4, 6.5, 6.6, 6.7, and 6.1 mm lateral from the midline; and 8.0, 8.0, 8.0, 7.0, 6.1, and 5.2 mm below the skull surface, respectively. All injections were made at a rate of 33 µl/min, and the pipette was left in place for 30 s before and 2 min after each injection.

Neurotoxic lesions are known to cause damage to distal areas (Jarrard, 2002; Jarrard & Meldrum, 1993). A major concern in the present study was that adjacent regions might undergo damage that was not readily observable. Thus, the lesions were intentionally small in order to avoid neurotoxic damage to the amygdala, hippocampus, and visual cortex, which could have confounded the results of the study. Our experience is that distributed gross tissue damage effectively disrupts function of the target region while minimizing damage to nontarget areas. Indeed, our previous studies have shown that the extent, or distribution, of the lesion along the rostrocaudal axis is more predictive of efficacy of the lesion than the total area (Bucci, Phillips, & Burwell, 2000).

For the sham-lesioned control group (CON, n = 11), we anesthetized the rats and drilled holes as above, but we did not make any injections. Another set of control rats (n = 10) did not undergo surgery. The behavior of sham-lesioned and unoperated control rats did not differ on any measure during pretraining or conditioning. Therefore, data from the two control groups were combined.

**Apparatus**

Behavioral training was conducted in an operant testing environment interfaced with a Pentium 386 microcomputer and controlled by the MED-PC Version 2.1 software package. Custom software written in the Pascal-based, MED-PC notation controlled the behavioral tasks and recorded task events and responses. Experiments were conducted in four 24.0 × 30.5 × 29.0 cm operant test chambers with modular component aluminum panels in the front and back, Plexiglas side walls and top, and a grid floor. A partially shaded houselight mounted centrally at the top of the front wall provided background lighting. A dimly illuminated food cup was recessed in the center of one end wall. A photobeam mounted inside the recessed food cup permitted automated assessment of food-cup behavior. A 6-W panel light located 5 cm above the recessed food cup provided the visual CS. Each testing chamber was enclosed in a 62.0 × 56.0 × 56.0 cm sound-attenuating chamber fitted with an exhaust fan that provided air flow to the test chamber and background white noise. Cameras mounted on the back wall of the sound-attenuating chamber provided input to a video cassette recorder used to simultaneously record behavior in all four chambers.

**Behavioral Procedures**

Rats were first trained to eat from the food cups. Ten deliveries of two 45-mg food pellets, which served as the unconditioned stimulus throughout the experiment, were delivered at random times within a single 30-min session. All rats then received two daily sessions of pretraining, which consisted of six nonreinforced presentations of the visual stimulus over a 30-min session with an average intertrial interval of 5 min. On each of the six trials per session, the panel light was illuminated for 10 s. Following pretraining, rats received six daily sessions of conditioning during which six light cue presentations per session were immediately followed by delivery of two 45-mg food pellets.

**Behavioral Observation**

Two behavioral measures were used in the experiment: rearing (standing on the hind legs without grooming) and conditioned food-cup behavior (head inside recessed food cup) (Bucci, Holland, & Gallagher, 1998; Gallagher et al., 1990; Holland, 1984). For rearing behavior, we made observations prior to and during presentations of the visual CS during pretraining and conditioning. Pre-CS observations were made at 1.25-s intervals during the 5-s period immediately prior to onset of the visual cue. These observations of rearing prior to the presentation of the visual stimulus permitted assessment of spontaneous orienting behavior. CS observations were made at 1.25-s intervals throughout the 10-s CS presentations. The index of response frequency was the percentage of rearing, calculated as the number of times the subject was observed to be rearing divided by the total observations. The observer was unaware of lesion condition when scoring rearing behavior. Food-cup behavior was automatically monitored by the computer, which recorded the amount of time that the photobeam inside the recessed food cup was broken during the 10-s CS presentation.

**Histological Procedures**

At the end of behavioral training, subjects were deeply anesthetized with sodium pentobarbital (Nembutal, 100 mg/kg) and transcardially perfused with normal saline and 4% paraformaldehyde, as described previously. After fixation, each brain was removed, postfixed, cryoprotected, and then sectioned coronally at 40 µm. We used coronal sections at 240-µm intervals for postirhinal lesions and 480-µm intervals for perirhinal lesions to assess the amount of tissue damage. Using camera lucida techniques, we identified gross tissue damage as missing tissue, obvious necrosis, or marked thinning of the cortex. For each coronal section, areal measurements included the total area of the target region and the area of the target region that exhibited gross tissue damage. The primary measure of cortical damage, however, was the proportion of sections that exhibited gross tissue damage. Subjects were eliminated if the damage was not bilateral or was not distributed along the rostrocaudal axis.

**Data Analysis**

Rearing behavior during CS presentation (unconditioned orienting) was analyzed for each of the pretraining days using a repeated measures analysis of variance (ANOVA) with trial and session as the within-subjects variables and group as the between-subjects variable. Pre-CS rearing (spontaneous orienting) during pretraining was analyzed using the same approach. For the six daily conditioning sessions, we analyzed food-cup behavior, spontaneous rearing and conditioned rearing behavior (condi-
tioned orienting) with a repeated measures ANOVA using session as the within-subjects variable and group as the between-subjects variable. All analyses were conducted in SAS Version 8.0. An alpha level of .05 was used for all analyses.

Results

Histology

Five perirhinal-lesioned subjects were excluded because of unilateral sparing of tissue. Thirteen rats remained in the PER group. We excluded 5 postrhinal-lesioned rats from the study because no postrhinal damage was observed or because damage was unilateral, leaving 14 rats in the POR group.

In the remaining rats, damage produced by infusions of ibotenic acid into the perirhinal or postrhinal cortex was comparable with that observed in several previous studies (Bucci et al., 2000; Bucci, Saddoris, & Burwell, 2002; Burwell, Saddoris, Bucci, & Wiig, in press). Damage to the perirhinal cortex was apparent on 44% ± 5% of the sections, and the damage was distributed throughout the rostrocaudal extent of the region (see Figure 1A). Gross tissue damage was apparent in 17% ± 3% of the surface area of the perirhinal cortex. There was minor unilateral damage to the lateral entorhinal cortex or temporal association cortex on 22% ± 7% of the sections in 3 rats. Difficulties with the histology for 4 rats in the PER group resulted in missing sections such that fewer sections were available for analysis. These subjects were excluded from the lesion analysis, but the behavioral data were included because there were no behavioral differences between the PER subjects with complete histology and those with missing sections (p values ranged from p > .18 to p > .94). In postrhinal-lesioned rats, damage was apparent on 73% ± 5% of the sections along the rostrocaudal axis (see Figure 1B). Gross tissue damage was apparent in 18% ± 2% of the surface area of the postrhinal cortex. In four cases there was also slight unilateral damage to medial entorhinal cortex or temporal association cortex on 22% ± 6% of the sections analyzed in those rats.

Figure 1. Perirhinal and postrhinal lesions. Schematics of the largest (gray) and smallest (black) neurotoxic lesions are shown for (A) perirhinal and (B) postrhinal cortices. Arrows indicate cytoarchitectonic boundaries. LEA = lateral entorhinal cortex; MEA = medial entorhinal cortex; PER = perirhinal cortex; Pir = piriform cortex; POR = postrhinal cortex; Tev = temporal cortex; VISl = lateral visual association cortex.
The mean percentage of tissue sections damaged was substantial in each lesion group. The surface area of damage, however, was relatively small. Post hoc correlational analyses of the lesions of subjects with adequate histology showed marginally significant negative correlations between the percentage of sections damaged with mean conditioned orienting across all blocks (r = -0.29, p < .094) and with the mean of conditioned orienting in the first four blocks (r = -0.32, p < .067), suggesting that the more sections damaged along the rostrocaudal axis, the less conditioned orienting was observed. The same analyses for the percentage of surface area damaged yielded nonsignificant correlations (r = 0.10, p > .57 and r = 0.15, p > .39, respectively).

Behavior

Rearing. There were no group differences in spontaneous orienting during pretraining or conditioning. Moreover, there were no changes across trials during pretraining or across sessions during pretraining or conditioning. For pretraining, this was confirmed by the lack of a main effect of group, F(2, 41) = 1.23, p > .30, and the lack of significant interactions for Group × Session, F(2, 41) = 0.42, p > .65; Group × Trial, F(10, 205) = 0.99, p > .44; and Group × Session × Trial, F(10, 205) = 0.79, p > .62. Mean spontaneous orienting during pretraining was 3.57% ± 1.15%, 4.62% ± 2.57%, and 1.34% ± 0.81% for CON, PER, and POR groups respectively. There were also no group differences for conditioning, as confirmed by the lack of a main effect of group, F(2, 41) = 1.33, p > .27, and the lack of significant Group × Session interaction, F(10, 205) = 0.28, p > .98. Mean spontaneous orienting during conditioning was 4.44% ± 0.82%, 5.44% ± 1.49%, and 3.23% ± 0.69% for CON, PER, and POR groups, respectively.

Rats in all groups initially exhibited high levels of rearing (unconditioned orienting) in response to nonreinforced presentations of the visual stimulus (see Figure 2A). As pretraining continued, orienting behavior habituated as observed in previous studies (Holland, Hatfield, & Gallagher, 2001). An analysis of rearing in the first two trials of both sessions versus the last two trials of both sessions confirmed that all groups exhibited habituation over pretraining, F(1, 41) = 4.87, p < .033. There were no group differences in unconditioned orienting. A repeated measures ANOVA revealed no significant main effect of group, F(2, 45) = 1.33, p > .27; no Session × Group interaction, F(2, 45) = 1.37, p > .26; no Group × Trial interaction, F(10, 225) = 0.98, p > .46; and no Session × Trial × Group interaction, F(10, 225) = 0.60, p > .81.

When the visual stimulus was paired with food during the conditioning phase, the orienting response reemerged in control animals (see Figure 2B). Conditioned orienting was impaired, however, in both the POR and PER groups. A repeated measures ANOVA confirmed this observation, revealing a main effect of group, F(2, 45) = 4.70, p < .01, with a nonsignificant Group × Session interaction, F(12, 270) = 1.57, p > .12. Between-groups contrasts between the CON and PER groups revealed a significant effect of group, F(1, 32) = 8.88, p < .005, and a significant Group × Session interaction, F(6, 192) = 2.50, p < .03. Differences between the CON and POR revealed a significant effect of group, F(1, 33) = 3.86, p < .05, but no significant Group × Session interaction, F(6, 198) = 1.36, p > .24. There were no significant differences between the two lesion groups, F(1, 25) = 0.73, p > .39, nor was there a Group × Session interaction, F(6, 150) = 0.65, p > .64.

Food-cup behavior. Pairing the light with food resulted in increased food-cup behavior in all groups during presentation of
the visual cue, main effect of session, $F(5, 225) = 33.30, p < .0001$ (see Figure 2C). Despite the observed deficits in conditioned orienting behavior, food-cup behavior in the PER and POR groups did not differ significantly from controls as indicated by a nonsignificant effect of group, $F(2, 45) = 1.02, p > .36$. Likewise, there was no significant Group × Session interaction, $F(10, 225) = 0.81, p > .56$.

**Discussion**

This study was designed to examine the effect of damage to the perirhinal or postrhinal cortex on attentional orienting to a visual stimulus. Bilateral neurotoxic lesions of the perirhinal or postrhinal cortex did not affect either the initial orienting or subsequent habituation of orienting behavior in response to repeated presentations of a nonreinforced visual stimulus (unconditioned orienting). When the visual cue was subsequently paired with a food reward, lesioned rats failed to exhibit the reemergence of orienting behavior typically observed in normal animals (Holland, 1984). Despite this impairment in conditioned orienting, postrhinal-lesioned or perirhinal-lesioned rats displayed intact food-cup behavior. Thus, the observed deficits were not due to a general learning impairment or an inability to form associations.

Considerable behavioral evidence has shown that attentional processing of a stimulus can be affected by the relationship of that cue to subsequent events (Holland, 1997; Pearce & Hall, 1980). Attention is diminished when a CS provides no new information about subsequent events. Neither the perirhinal nor the postrhinal cortex appear to have a role in the decremental attentional processing of a highly salient and novel, but behaviorally irrelevant, stimulus, as suggested by normal habituation in the present study. In addition to these decremental processes, attention to a stimulus is normally enhanced when previously established expectations about its occurrence in relation to future events are violated. Here, we provide evidence that damage to either the perirhinal or postrhinal cortex impairs increases of attention to a stimulus when the relationship between that stimulus and subsequent events changes.

Evidence for postrhinal involvement in attentional orienting is interesting in view of a recent study of parahippocampal cortex function in humans (Strange, Otten, Josephs, Rugg, & Dolan, 2002). In that study, activity in the parahippocampal cortex was shown to be associated with increased attentional orienting during the encoding of verbal cues. These results are of interest because of the neuroanatomical evidence that the postrhinal cortex of rats may be homologous to the parahippocampal cortex of primates (Burwell, 2001; Burwell & Amaral, 1998a, 1998b; Suzuki & Amaral, 1994a, 1994b, 2003). The results of the present study together with those of Strange et al. (2002) provide important evidence that the postrhinal and parahippocampal cortices share similar behavioral functions as well as anatomical features.

Many studies have shown that both the perirhinal and postrhinal cortices make significant contributions to memory. For example, damage to either the perirhinal or postrhinal cortex disrupts learning and memory as assessed in contextual fear conditioning (Bucci et al., 2000), contextual fear discrimination (Bucci et al., 2002; Burwell et al., in press), working memory (Wiig & Burwell, 1998), and object recognition tasks (Aggleton, Keen, Warburton, & Bussey, 1997; Bussey, Muir, & Aggleton, 1999). The present findings provide the first direct evidence that the perirhinal and postrhinal cortices are involved in attention as well as memory. A recent study of the homologous regions in primates also provided evidence for dual functions (Buckley, Booth, Rolls, & Gaffan, 2001). In this study, monkeys with perirhinal ablations were impaired not only on a memory task, but also on a perceptual discrimination task clearly separable from memory function. The authors suggested that the perirhinal cortex does not contribute to memory exclusively, but is also involved in processing information at a perceptual level. Thus, studies in both monkeys and rats have indicated that these regions have more than just mnemonic functions.

A role for the perirhinal and postrhinal cortices in visuospatial attention is consistent with their cortical connectivity, and the subcortical connections lend further support to this view. The perirhinal and postrhinal cortices provide input to the central nucleus of the amygdala (Pikkarainen & Pitkanen, 2001). Damage to the central nucleus has been shown to produce deficits in conditioned orienting (Gallagher et al., 1990) that are similar to those following bilateral perirhinal or postrhinal damage. Notably, the perirhinal cortex also provides a heavy input to the lateral nucleus of the amygdala, which appears not to be involved in conditioned orienting (Holland et al., 2001). The present findings provide evidence that the perirhinal and postrhinal cortices are part of a circuit involved in regulating attention to behaviorally relevant stimuli.

In summary, the current findings provide direct evidence that both the perirhinal and postrhinal cortices are involved in attentional processing in rats. Further research is necessary to determine the extent to which the perirhinal and postrhinal cortices are involved in other aspects of attention and whether each region makes a unique contribution to attentional function. Such studies are particularly important in view of recent data suggesting that abnormal neural activity in the perirhinal cortex may have a role in attention-deficit hyperactivity disorder (Gallo, Gonzalez-Lima, & Sadile, 2002; Gonzalez-Lima & Sadile, 2000).

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Received December 23, 2003
Revision received April 21, 2004
Accepted April 22, 2004
