Removal of Cholinergic Input to Rat Posterior Parietal Cortex Disrupts Incremental Processing of Conditioned Stimuli

David J. Bucci,¹ Peter C. Holland,² and Michela Gallagher³

¹Curriculum in Neurobiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, ²Department of Psychology: Experimental, Duke University, Durham, North Carolina 27706, and ³Department of Psychology, Johns Hopkins University, Baltimore, Maryland 21218

Recent research suggests that the basal forebrain cholinergic neurons innervating the cortex play a role in attentional functions in both primates and rodents. Among the cortical targets of these projections in primates is the posterior parietal cortex (PPC), a region shown to be critically involved in the regulation of attention. Recent anatomical studies have defined a cortical region in the rat that may be homologous to the PPC of primates. In the present study, cholinergic innervation of the PPC was depleted by intracortical infusion of the immunotoxin 192 IgG-saporin. Control and lesioned rats were then tested in two associative learning paradigms designed to increase attentional processing of conditioned stimuli (CSs). In one experiment, attention was manipulated by shifting a predictive relation between a light CS and another CS to a less predictive relation. Unlike control rats, lesioned rats failed to increase

attention when the predictive relation was modified. In a second experiment, attentional processing of a tone CS was increased when its introduction during training coincided with a change in the value of the unconditioned stimulus, a phenomenon referred to as unblocking. Unlike control rats, lesioned rats failed to exhibit unblocking. In both paradigms, lesioned rats conditioned normally when the training procedures did not encourage increased attentional processing. These findings, across different behavioral paradigms and stimulus modalities, provide converging evidence that intact cholinergic innervation of the PPC is important for changes in attention that can increase the processing of certain cues.

Key words: posterior parietal cortex; acetylcholine; attention; cholinergic basal forebrain; associative learning; 192 IgG-saporin; immunotoxin; rats

The posterior parietal cortex (PPC) plays an integral role in the regulation of attention in primates. Located between somatosensory and visual areas of cortex, this region is characterized by a distinct pattern of thalamic and cortical connectivity. The primate PPC has reciprocal connections with the pulvinar and lateral posterior nuclei of the thalamus, and connections with specific sensory, limbic, and frontal association cortices (Cavada and Goldman-Rakic, 1989a,b; Schmahmann and Pandya, 1990). Recent anatomical studies suggest that a homologous cortical region exists in the rat (Chandler et al., 1992; Reep et al., 1994). The rat PPC also has a distinct pattern of connectivity, differing from that of surrounding regions of cortex (Reep et al., 1994). Thalamic input to the rat PPC arises primarily from the lateral posterior and lateral dorsal nuclei, areas that may be homologous to the primate pulvinar nucleus (Takahashi, 1985; Price, 1995). As in the primate, the rat PPC receives multimodal sensory information through its connections with visual and somatosensory cortex. Furthermore, this region has reciprocal connections with medial agranular cortex (AGm) and ventrolateral and medial orbital areas, connections that also parallel those in the primate brain between frontal and orbital regions, and PPC (Reep et al., 1994).

Although few studies have examined the contribution of cortical systems, including PPC (King and Corwin, 1993; Muir et al., 1996; Ward and Brown, 1997), in attentional processing in rodents, a number of studies have now established a role in attention for the components of the basal forebrain cholinergic system that innervate cortex in the rat (Robbins et al., 1989; Muir et al., 1992, 1994; Chiba et al., 1995, 1998). In several studies, the cholinergic immunotoxin 192 IgG-saporin (Wiley et al., 1991) was infused into the substantia innominata/nucleus basalis (SI/nBM), selectively removing cholinergic innervation throughout the neocortex. Lesioned rats were impaired in a spatial cued reaction time task and in their ability to modulate attention in an associative learning paradigm (Chiba et al., 1995, 1998). This work, using a method to selectively remove cholinergic neurons, has provided information relevant to the basis of attention deficits observed both in humans with basal forebrain pathology [e.g., Alzheimer's disease (Parasuraman et al., 1992)] and in nonhuman primates with lesions of the basal forebrain nuclei (Voytko et al., 1994).

Recent studies have shown that 192 IgG-saporin can be infused directly into a limited region of cortex or hippocampus, where it binds to the low-affinity nerve growth factor receptor located on cholinergic terminals and is retrogradely transported to the basal forebrain (Holley et al., 1994; Ohtake et al., 1997). This method produces a selective removal of cholinergic input only to that region of cortex in which the immunotoxin was infused (Holley et al., 1994; Fadel et al., 1996), providing a means to examine the function of a subset of basal forebrain cholinergic neurons that project to a discrete area of cortex. In the present study, 192 IgG-saporin was used to selectively remove the cholinergic input to the rat PPC while leaving the projections to the rest of cortex

Received June 15, 1998; accepted July 17, 1998.

This research was supported by National Institutes of Health Grants F31-MH11247 to D.J.B., K05-MH01149 to M.G., and R01-MH53667 to P.C.H. We thank A. Chiba for valuable discussion of the data and assistance with the surgical procedures, and M. Conley for technical assistance.

Correspondence should be addressed to Dr. David J. Bucci, Walter S. Hunter Laboratory of Psychology, Brown University, 89 Waterman Street, Providence, RI 02912.

Copyright © 1998 Society for Neuroscience 0270-6474/98/188038-09\$05.00/0

Table 1. Outline of procedures for Experiment 1

Treatment condition (groups)	Phase 1: consistent L–T relation	Phase 2: experimental change in L–T relation	Phase 3: test of conditioning to L
Consistent (CTL-C, PPC-C)	L → T → food; L → T	L → T → food; L → T	L → food
Shift (CTL-S, PPC-S)	L → T → food; L → T	L → T → food; L	L → food

CTL, Control; PPC, lesion; L, light CS; T, tone CS; → signifies serial relation.

relatively intact. The effect of this lesion was examined in two behavioral tasks designed to modulate attention during conditioning.

EXPERIMENT 1

Considerable evidence shows that attentional processing of a conditioned stimulus (CS) is enhanced when previously established expectations about its occurrence in relation to future events are violated but is diminished when a CS provides no new information about subsequent events (Pearce and Hall, 1980; Holland, 1997). In Experiment 1, attentional processing of a CS was manipulated by varying the predictive relation between two CSs. In this task, designed by Wilson et al. (1992), attentional processing of a visual CS was decreased by maintaining a consistent predictive relation between that cue and another CS, and it was increased by shifting that invariable relation between the cues to a less consistent predictive relation. The description that follows explains the methods for the behavioral protocol shown in Table 1.

In the first phase of training, all subjects were exposed to serial conditioning trials in which a light-then-tone sequence was followed by a food unconditioned stimulus (US) half of the time (an equal mix of light → tone → food and light → tone → nothing trials). Because of its poor temporal relation with the food, the light was expected to acquire only minimal conditioned responding. In contrast, the tone was expected to acquire substantial conditioned responding directed toward the food cup. More important, although both the light and tone were followed by food on only half of the trials, the light consistently predicted the occurrence of the tone. Thus as training proceeds, attentional processing of the light should decrease (Pearce and Hall, 1980).

In the second phase of Experiment 1, one pair of control and lesioned groups (CTL-C and PPC-C) continued to receive the Phase 1 procedures in which the light was consistently followed by the tone, light → tone → food and light → tone → nothing. In a second pair of control and lesioned groups (CTL-S and PPC-S), the light → tone → nothing trials were replaced by light-alone trials. Thus, for groups CTL-S and PPC-S, the light–food relationship was maintained as in Phase 1, but the light no longer reliably predicted the tone. This shift in the light's predictive relation to the tone should increase attentional processing of the light.

Attention to the light was then assessed in all four groups by pairing the light directly with food in a final test phase. To the extent that the Phase 2 shift in predictive accuracy of the light in groups CTL-S and PPC-S increased attention to that cue, light–food conditioning in the test phase should proceed more rapidly in those groups than in the unshifted groups (CTL-C and PPC-C), as observed in previous studies using this paradigm (Wilson et al., 1992; Holland and Gallagher, 1993b; Chiba et al., 1995). However, if cholinergic projections to the PPC mediate the in-

creased attention to the light, then enhanced conditioning would be observed in the control group (CTL-S) but not in the lesioned group (PPC-S).

Materials and Methods

Subjects. The subjects were 48 male Long-Evans rats (Charles River Laboratories, Portage, MI) that weighed 325–375 gm at the start of the experiment. The rats were maintained on a 14/10 hr light/dark cycle, with free access to food and water before surgery and during recovery from surgery. After postoperative recovery, rats were placed on a restricted feeding regimen and gradually reduced to 85% of their *ad libitum* weights. The rats were maintained at those weights for the remainder of the experiment.

Surgical procedure. The cholinergic immunotoxin 192 IgG-saporin (batch C4M115; Chemicon International, Temecula, CA) was used to lesion the cholinergic input to the PPC. Rats were anesthetized with Nembutal (sodium pentobarbital, 50 mg/kg, i.p.) and placed in a Kopf stereotaxic apparatus. Under antiseptic conditions, an incision was made to reveal the skull, and the skin was retracted to the side. With the head level between bregma and lambda, eight holes were drilled through the skull, and the underlying dura was pierced at each location to facilitate needle penetration. Bilateral injections of 192 IgG-saporin (0.35 μ g/ μ l) or vehicle (Dulbecco's saline) were made in the PPC using a 28 gauge Hamilton syringe (model 701SN, 10 μ l). Injections were made at four sites on each side of the brain at the following stereotaxic coordinates: 4.0 and 4.7 mm posterior to bregma, 2.5 and 3.7 mm lateral from the midline at each AP coordinate, and 1.5 mm (medial sites) or 1.7 mm (lateral sites) below the skull surface, using an atlas of the rat brain (Paxinos and Watson, 1986). A total volume of 0.2 μ l was delivered at each site at a rate of 0.05 μ l/min. The needle was left in place for 30 sec before and 3 min after each injection. After the last injection, the drill-holes were filled with gel foam, the wound was sutured, and antibiotic ointment was applied to the wound. Rats were monitored during recovery from anesthesia and allowed 2 weeks of postoperative recovery in the home cage before they began behavioral training.

Apparatus. The behavioral apparatus consisted of eight individual chambers, each 22.9 × 20.3 × 20.3 cm, with aluminum front and back walls, clear acrylic sides and top, and a grid floor (0.48 cm stainless steel rods spaced 1.9 cm apart). A dimly illuminated food cup was recessed in the center of one end wall; a 6 W jeweled panel light, which was the source of the visual CS, was located 5 cm above the opening to that recess. Each chamber was enclosed in a sound-resistant shell with acrylic windows for viewing the rats. A speaker, used to present the auditory CS, was mounted on the inside wall of the shell so that it was 5 cm above, and 20 cm to the left of, the panel light. Ventilation fans provided masking noise (70 dB), and a 6 W lamp behind a red lens located opposite the speaker provided continuous dim background illumination. Two low-light television cameras were mounted 2.1 m from the chambers so that each could include four chambers in its field of view. Videocassette recorders were programmed to record behaviors that occurred during the 10 sec intervals before, during, and after CS presentation.

Training procedures. The rats were first trained to eat from the food cups. Sixteen deliveries of two 45 mg food pellets (which served as the US throughout the experiment) were provided at random times within a single 64 min session. The conditioning procedures used in Experiment 1 are outlined in Table 1. All rats received ten 64 min Phase 1 conditioning sessions. In each of those sessions, the rats received four reinforced and four nonreinforced presentations of a light–tone serial compound CS, randomly intermixed, with variable intertrial intervals that averaged 8 min. The serial compound comprised a 10 sec illumination of the panel light, followed immediately by a 10 sec presentation of a 78 dB,

1500 Hz tone. On reinforced trials, the tone was followed immediately by two 45 mg food pellets.

In Phase 2, the lesioned rats in group PPC-C and control rats in group CTL-C received 10 daily sessions identical to those given in Phase 1. For the lesioned rats in group PPC-S and the control rats in group CTL-S, the 10 daily 64 min Phase 2 sessions consisted of four light → tone → food trials like those given in Phase 1, intermixed with four 10 sec presentations of the panel light alone. As in Phase 1, the intertrial intervals were variable and averaged 8 min.

All rats then received five 64 min Phase 3 sessions. In each of those sessions, eight 10 sec illuminations of the panel light were followed by the two-pellet food US. Again, the intertrial intervals were variable and averaged 8 min.

Behavioral observation procedures. Observations were made from videotapes and paced by auditory signals recorded on the tapes. For each rat, observations were made at 1.25 sec intervals during the 5 sec period immediately before CS presentations and during CS presentations. At each observation, only one behavior was recorded.

Two categories of behavior were recorded: rear (standing on the hind legs, with both front legs off the floor, but not grooming) and food cup (standing motionless in front of the recessed food cup, with the head or nose within the recessed area, and head-jerk behavior, i.e., short, rapid, horizontal and/or vertical movements of the head oriented toward the food cup). Visual and auditory CSs paired with food typically evoke distinct patterns of conditioned behavior (Holland, 1977, 1984). With localizable visual CSs, rear behavior occurs immediately after CS onset, but is replaced by behavior directed toward the food cup as the time of food delivery nears. Typically, only low levels of rear behavior occur during the latter half of 10 sec visual cues like those used in these experiments (Holland, 1977). In contrast, auditory CSs typically generate a rapid jump or startle response, followed by food cup behaviors that are more evenly distributed across the CS-US interval. To provide more comparable measures of conditioned responding during auditory and visual CSs, in these experiments the primary measure of conditioning used was the level of food cup behaviors during the last 5 sec period of all CSs. Analyses of rear behavior observed during the first half of the visual CSs generally confirmed the results reported for second half food cup behavior; in the interest of economy, however, these data are not reported.

The index of conditioned response frequency used was percentage total behavior, obtained by dividing the frequency of the target behavior in any observation interval by the total number of observations made in that interval. Note that because the number of observations was constant within each observation interval, this measure is an absolute frequency measure, not a relative one. A single primary observer (D.J.B.) scored all of the behavioral data. To assess objectivity, a second observer also scored data from several conditioning sessions. The two observers agreed on 98% of 392 joint observations. Neither observer was aware of the rats' lesion condition when scoring the data.

Histological procedures. At the completion of behavioral testing, all rats were euthanized with a lethal dose of Nembutal (100 mg/kg) and then perfused transcardially with 0.9% saline, followed by 10% buffered formalin. Brains were removed and stored at 4°C for 48 hr in a 0.1 M phosphate buffer solution containing 20% sucrose and 1% dimethylsulfoxide. Brains were then sectioned (50 μ m) on a freezing microtome, and adjacent sections were processed for either acetylcholinesterase (AChE) histochemistry or parvalbumin immunocytochemistry or were Nissl-stained. Sections from a subset of rats were stained for myelin.

AChE histochemistry was used to reveal the presence or absence of cholinergic fibers in the PPC and to provide a measure of the degree of cholinergic denervation in lesioned rats. Sections were processed using a modification of the procedure designed by Karnovsky and Roots (1964). A butyrylcholinesterase inhibitor, tetraisopropyl pyrophosphoramidate (Sigma, St. Louis, MO), was added to the incubation solution (0.137%) to reduce nonspecific staining. Slide-mounted sections were histologically examined by an observer blind to both behavioral and lesion condition, using an Olympus BH-2 microscope. The stained sections were also digitized using an image analysis system (MCID, Imaging Research, St. Catherine's, Ontario). The degree of AChE staining within the PPC was determined by measuring relative optical density within the PPC on each side of the brain, on two consecutively stained sections, at $\sim$ 4.16 mm posterior to bregma.

For each control and lesioned rat, sections adjacent to those processed for AChE histochemistry were processed for parvalbumin immunocytochemistry, as described previously (Chiba et al., 1995), or Nissl-stained

Figure 1. Photomicrographs of AChE-stained coronal sections from a vehicle-injected control brain (*a*) and a PPC-immunolesioned brain (*b*). Note the decrease in AChE staining in the PPC (located between the arrows) of the immunolesioned brain. In contrast, staining in the cortex located medial to the PPC is comparable in the control and lesioned brains. Also note that the band of darker AChE staining in the intermediate layers of dorsal lateral cortex in the control brain is visible beyond the border of PPC in the lesioned brain.

with cresyl violet. Histological examination of parvalbumin-immunostained and Nissl-stained neurons was used to determine the specificity of damage produced by intracortical injection of the immunotoxin. In addition, sections from a subset of control and lesioned rats were myelin-stained according to the Quinn and Graybiel (1994) adaptation of the procedure developed by Schmued (1990). The integrity of noncholinergic association fibers located in the superficial layers of cortex was examined in control and lesioned rats.

Statistical analyses. Statistical analyses of all behavioral measures used two-tailed distribution-free statistics, using an α level of 0.05. Nonparametric inferential statistics were used because the limited range of discrete values generated by the behavioral measure that was used (on each trial, a rat could be judged as emitting only zero, one, two, three, or four responses) made it unlikely that standard assumptions of normality and homogeneity of error variance could be met. These same statistical analyses were used previously with comparable data (Chiba et al., 1995; Han et al., 1995).

Group differences in optical density measurements of AChE staining within the PPC were analyzed using a two-tailed independent-measures *t* test. An α level of 0.05 was adopted.

Results

Histological results

A bilateral reduction in AChE staining throughout the PPC was observed in 19 of the 22 rats that received infusions of the immunotoxin. The data from the remaining three rats were excluded from further analysis because these rats sustained only unilateral damage. Photomicrographs of AChE staining in lesioned and control rats are shown in Figure 1. In particular, note the decrease in staining in the intermediate layers of cortex within the PPC of the lesioned brain compared with the control brain. Optical density measurements of AChE staining in the PPC were reduced by $32 \pm 2\%$ ($t_{(40)} = 10.1$; $p < 0.0001$) in lesioned rats compared with controls, similar to the reduction in AChE-stained fiber density reported after infusion of the immunotoxin into other cortical regions (Holley et al., 1994). Moreover, the extent of depletion was highly similar in the lesion groups undergoing the two different behavioral treatments. Despite the loss of AChE-stained fibers in the PPC, parvalbumin immunostaining and Nissl staining within the PPC appeared comparable in lesioned and control rats. Injection of the immunotoxin into PPC also did not affect myelin staining of noncholinergic association fibers located in the marginal layer of the PPC. Photomicrographs of parvalbumin- and myelin-stained sections are shown in Figure 2.

Decreases in AChE staining were generally limited to the posterior parietal region of lesioned rats. Slight decreases in staining were occasionally observed in regions of cortex immediately adjacent to the PPC (e.g., occipital cortex), attributable to spread of the immunotoxin outside of the target region or possibly to damage to axon collaterals innervating immediately adjacent

Figure 2. Photomicrographs of stained sections within the PPC of a vehicle-injected control brain (*left*) and PPC-immunolesioned brain (*right*). Parvalbumin immunostaining (*a, b*) was comparable in control and immunolesioned brains (10 $\times$ magnification). Noncholinergic, myelin-stained fibers (*arrows* in *c, d*) in the superficial layers of PPC were intact in both control and immunolesioned brains (40 $\times$ magnification).

Table 2. Food cup behavior during phases 1 and 2 of Experiment 1

Group	<i>n</i>	Final two sessions of Phase 1		Final two sessions of Phase 2	
		Light	Tone	Light	Tone
PPC-S	8	18.0	54.4	7.1	69.9
PPC-C	9	18.2	55.2	18.4	71.2
CTL-S	12	22.5	61.9	22.5	77.1
CTL-C	13	17.2	49.6	9.6	57.9

Data are mean % of total behavior. There were no group differences in food cup behavior during Phases 1 and 2: Mann–Whitney $U_{(12,13)} \geq 55.5$; $U_{(12,8)} \geq 26.5$; $U_{(13,9)} \geq 38.5$; $U_{(8,9)} \geq 19$.

regions of cortex. The degree of depletion in these areas was much less pronounced compared with that observed in the PPC. Furthermore, the extent of sporadic damage to surrounding cortices was comparable in lesioned rats within the different behavioral conditions.

In five lesioned rats, there was a minor reduction in AChE staining in the hippocampus underlying PPC, limited to a relatively small segment of stratum radiatum layer of CA1 in dorsal hippocampus. In four of five cases, that damage was unilateral. The behavior of rats with this minor hippocampal damage did not differ from the rest of the lesioned rats in any phase of behavioral training: Mann–Whitney $U_{(6,2)} \geq 2.5$, $U_{(6,3)} \geq 3.5$.

Behavioral results

The data from three rats (one in each of groups PPC-S, PPC-C, and CTL-S) were excluded because these rats exhibited abnormally high levels of rear behavior during the entire 10 sec presentation of the visual CS. As a result, the frequency of food cup behavior was near zero, because the two behaviors were in competition during the second half of the CS interval. The histological analyses of these rats, however, did not differ from those of other rats in their respective groups.

Food cup behavior during the last two sessions of Phases 1 and 2 is reported in Table 2. Note that in both phases more conditioned responding occurred during presentation of the tone CS, compared with the visual CS (which was more temporally remote from the US). As expected in Phase 1, when all rats received the same partially reinforced conditioning trials, there were no differences among groups in the amount of food cup behavior during presentation of either the light or the tone. In addition, no significant differences among the groups occurred in Phase 2 for

responding to either the tone or the light. Although responding during the light appeared to be higher in group CTL-S than in group CTL-C, consistent with the prediction that the light's associability would be enhanced by the shift manipulation in control rats (but not lesioned rats), this difference was not confirmed statistically.

Figure 3 shows the primary data of Experiment 1, the acquisition of food cup behavior during presentation of the light in the light–food test sessions, in which temporal and predictive relations more favorable for conditioning were established between the light and food. Although conditioning occurred rapidly over the course of Phase 3 training, the amount of conditioned responding varied as a function of both Phase 2 treatment and lesion condition. The performance of the two groups of control rats, CTL-C and CTL-S, is shown on the left panel of Figure 3. As in previous studies (Wilson et al., 1992; Holland and Gallagher, 1993b; Chiba et al., 1995), control rats in group CTL-S, which received Phase 2 training designed to enhance attention to the light, showed more food cup responding than did rats in group CTL-C, which did not receive such training ($U_{(12,13)} = 39$). In lesioned rats, however, group PPC-S failed to show increased responding compared with group PPC-C ($U_{(8,9)} = 35$) (Fig. 3, *right panel*). In addition, the rats in group PPC-S exhibited reliably less responding than the rats in group CTL-S ($U_{(12,8)} = 23$). By contrast, responding was comparable in lesioned (PPC-C) and control (CTL-C) rats with consistent training ($U_{(9,13)} = 58$), suggesting that any decrease in attentional processing in those groups was unaffected by the lesion.

Discussion

Rats that received infusions of 192 IgG-saporin into the PPC failed to increase attention to a CS when it became an unreliable predictor of subsequent events. Lesioned rats exhibited a substantial reduction in AChE staining within the PPC, reflecting a loss of cholinergic input to that region. Although a slight decrease in AChE staining was occasionally observed in cortical regions immediately beyond the boundaries of PPC, staining in the rest of cortex remained intact. Because the loss of AChE-stained fibers in adjacent regions was minor, compared with that observed in the PPC, and comparable in the two behavioral groups, damage outside of the PPC is not thought to have contributed significantly to the observed behavioral deficit. For instance, minor damage to AChE-stained fibers in occipital cortex did not produce a general visual impairment: conditioning to the visual stimulus was com-

Figure 3. Acquisition of food cup behavior to the light CS during the test phase of Experiment 1 (mean $\pm$ SEM). The *left panel* shows the performance of control rats; the *right panel* shows the performance of PPC-immunolesioned rats. Groups for which the predictive validity of the light was shifted in Phase 2 (CTL-S and PPC-S) are indicated by $\circ$; groups for which the predictive validity of the light remained consistent with that in Phase 1 are indicated by $\bullet$.

parable in lesioned and control rats in the consistent condition (groups PPC-C and CTL-C).

An inability to increase attention, similar to that reported here, was observed after immunotoxic lesions of the SI/nBM (Chiba et al., 1995). In that study, 192 IgG-saporin was infused into the SI/nBM, resulting in selective denervation of the cholinergic input throughout the neocortex, including the PPC. Previous anatomical studies indicate that the cholinergic neurons innervating the PPC were among those removed by the larger, SI/nBM lesion (Bucci et al., 1997). Together with the results of the present study, these findings suggest that the cholinergic projections to the PPC play a significant role in the ability to increase attention to a CS. The generality of this interpretation was further tested in Experiment 2, using a different task designed to promote processing of a CS.

EXPERIMENT 2

An additional Pavlovian conditioning paradigm used in the analysis of attentional processes is the *blocking* procedure (Kamin, 1968), and a variant of that procedure referred to as *unblocking* (Dickinson et al., 1976). In blocking, learning about one element (e.g., a tone) of a compound CS (e.g., light and tone presented simultaneously) is reduced, or blocked, by previous training to the other element (e.g., the light alone). According to attentional accounts of blocking, initial training with one CS reduces attentional processing of the added element when the compound CS is introduced because the reinforcer is already well predicted by the original CS (Mackintosh, 1975; Pearce and Hall, 1980).

Support for this view is found in the phenomenon of *unblocking*, in which substantial conditioning occurs to the added element in a compound CS, despite previous conditioning to the other element, if the introduction of the compound CS coincides with a change in the US. The change in the US, similar to the shift in the predictive relation between two cues in Experiment 1, is thought to increase attentional processing of the CSs, thus permitting greater conditioning of the added cue. Experiment 2 was conducted to determine whether PPC cholinergic depletion would interfere with unblocking.

Table 3. Outline of procedures for Experiment 2

Treatment condition (groups)	Phase 1	Phase 2	Phase 3
Low (PPC-Lo, CTL-Lo)	L $\rightarrow$ US _L	LT $\rightarrow$ US _L	T
Down (PPC-Dn, CTL-Dn)	L $\rightarrow$ US _H	LT $\rightarrow$ US _L	T

CTL, Control; PPC, lesion; L, light CS; T, tone CS; LT, light-tone compound CS; US_L, low-value US; US_H, high-value US; $\rightarrow$ signifies serial relation.

In Experiment 2, the rats were first given pretraining using a light CS paired with either a low-value US (a single food pellet) or a high-value US (multiple pellets). Then, all rats received pairings of a light + tone compound CS with the low-value US. Little conditioning of the added tone would be anticipated in the rats that had previous training with the same low-value US (blocking). In contrast, the rats that had been trained with the high-value US should acquire substantial conditioning to the tone (unblocking), because the violation of their expectation about the US when the tone was introduced would enhance attention. Conditioned responding to the tone alone was assessed in a final test session. Note that altering the US by lowering its magnitude makes it unlikely that any unblocking could be the result of reinforcement mechanisms (Rescorla and Wagner, 1972) rather than modulation of attentional processes [for discussion, see Holland and Gallagher (1993a)].

Materials and Methods

Subjects. Forty male Long-Evans rats (Charles River Laboratories), weighing 300–350 gm, were used as subjects. Rats were maintained in the same manner as the rats in Experiment 1.

Surgical procedures. Twenty lesioned rats and 12 vehicle-injected rats were prepared as described in Experiment 1. In addition, eight unoperated control rats were included in Experiment 2.

Apparatus and histological procedures. The apparatus and histological procedures were identical to those described in Experiment 1.

Training procedures. Before training, the rats were shaped to eat from the food cups. Sixteen deliveries of the US that the rats were to receive in Phase 1 were given at random times within a single 64 min session. The conditioning procedures used in Experiment 2 are outlined in Table 3. In each of the 10 Phase 1 conditioning sessions, the rats received eight pairings of a 10 sec illumination of the panel light followed by either the

Table 4. Food cup behavior during Phases 1 and 2 of Experiment 2

Group	<i>n</i>	Final two sessions of Phase 1 (Light)	Final two sessions of Phase 2 (Light–Tone)
PPC-Dn	10	59.7	65.2
PPC-Lo	10	66.9	75.2
CTL-Dn	10	68.1	67.4
CTL-Lo	10	61.6	72.5

Data are mean % of total behavior.

low-value US (groups PPC-Lo and CTL-Lo) or high-value US (groups PPC-Dn and CTL-Dn). The low-value US was a single 45 mg food pellet, and the high-value US was the delivery of one pellet followed 5 sec later by two more pellets. Next, in each of the five sessions of Phase 2 conditioning, the rats in all groups received eight pairings of a 10 sec compound CS comprising the panel light and a 78 dB, 1500 Hz tone, followed immediately by the low-value US. Finally, in a single Phase 3 session, responding in the presence of the 10 sec tone alone was assessed. There were eight nonreinforced presentations of the tone in this session. The intertrial intervals in each of the three phases were variable and averaged 8 min.

Behavioral observation procedures. The behavioral observation procedures were identical to those described for Experiment 1. The same primary observer scored all of the behavioral data, and a second observer scored a subset of the conditioning sessions. The two observers agreed on 95% of 382 joint observations. Neither observer was aware of the rats' lesion condition when scoring the data.

Statistical analyses. The statistical methods were identical to those used in Experiment 1.

Results

Histological results

Injection of the immunotoxin into the PPC resulted in a bilateral reduction in AChE staining throughout the PPC of lesioned rats. The optical density of AChE staining was reduced by $29 \pm 3\%$ ($t_{(30)} = 7.8$; $p < 0.0001$) in the PPC of lesioned rats compared with vehicle-injected controls. Parvalbumin immunostaining and Nissl staining in PPC were comparable in lesioned and control rats. The degree of loss of AChE-stained fibers in adjacent regions of cortex was minimal and similar to that observed in Experiment 1. Six of 20 lesioned rats sustained minor hippocampal damage in the CA1 field, similar to that reported in Experiment 1. The damage was unilateral in five of the six cases. The behavior of these rats did not differ from that of the other lesioned rats: $U_{(6,4)} \geq 7$, $U_{(8,2)} \geq 5$.

Behavioral results

In each of the conditioning phases in Experiment 2, the behavior of unoperated control rats did not differ from that of vehicle-injected controls in either of the two treatment conditions ($U_{(6,4)} \geq 3.5$). Thus data from the unoperated and vehicle-treated control rats were combined for each of the behavioral training conditions, CTL-Lo and CTL-Dn.

Food cup behavior during the final two sessions of Phases 1 and 2 is shown in Table 4. In Phase 1, there were no differences among the groups in the amount of food cup behavior during presentation of the light ($U_{(10,10)} \geq 34.5$). Likewise, there were no group differences in food cup behavior during presentation of the light-tone CS in Phase 2 ($U_{(10,10)} \geq 31.5$).

The primary data of Experiment 2, food cup responding during presentation of the tone-alone, are shown in Figure 4. Unblocking was observed in control rats but not in lesioned rats. Control rats in group CTL-Dn, whose US was shifted from a high to low value when the tone was introduced, responded more to the tone alone than did control rats in group CTL-Lo, which received the same

Figure 4. Conditioned responding to the tone during the test phase of Experiment 2 (mean $\pm$ SEM). Groups for which the value of the US was downshifted from high to low in Phase 2 (CTL-Dn and PPC-Dn) are indicated by the empty bars; groups for which the value of the US remained low throughout Phases 1 and 2 are indicated by the filled bars.

low-value US in both Phase 1 and Phase 2 ($U_{(10,10)} = 23$). In contrast, responding during the tone-alone was not increased in lesioned rats in group PPC-Dn, compared with those in group PPC-Lo ($U_{(10,10)} = 37.5$). In addition, rats in group CTL-Dn responded more to the tone-alone than did rats in group PPC-Dn ($U_{(10,10)} = 19.5$). Finally, there was no reliable difference in responding between groups PPC-Lo and CTL-Lo ($U_{(10,10)} = 35$). This finding suggests that the lesion did not affect any blocking that might have occurred in those groups; however, the absence of any appropriate control comparison to evaluate blocking renders that claim tentative.

Discussion

Removal of the cholinergic input to the PPC disrupted the regulation of attention in two tasks designed to increase the processing of a CS. In Experiment 1, lesioned rats were unable to increase attention to a visual cue when it became an inconsistent predictor of subsequent events. In a different behavioral task, a change in the value of the US failed to increase attentional processing of a tone in lesioned rats (Experiment 2). These findings, across different behavioral paradigms and stimulus modalities, provide converging evidence that cholinergic input to the rat PPC plays an important role in the ability to increase attentional processing. Indeed, the behavioral deficit produced by cholinergic denervation of PPC was quite selective in both experiments. When the training procedures did not encourage increased attentional processing, rats with those lesions acquired conditioned responses normally to the cues in each task. Similarly, in both experiments, performance with procedures that lead to decreased attention (extensive exposure to consistent event relations in Experiment 1, and blocking procedures in Experiment 2) appeared to be unaffected by those lesions. Nevertheless, in both experiments, the lesioned rats, unlike control rats, failed to benefit from manipulations designed to increase attentional processing and enhance conditioning.

Although the effects of acetylcholine on neuronal processing in the PPC have not been studied, acetylcholine generally acts to facilitate the responsiveness of cortical neurons to sensory activation in various sensory cortices. For example, in rat somatosensory cortex, application of acetylcholine, or stimulation of the

basal forebrain, potentiates the discharge of cortical neurons in response to whisker stimulation (Donoghue and Carroll, 1987; Rasmusson and Dykes, 1988). Conversely, removal of cortical cholinergic input selectively reduced activation of neurons in barrel cortex in response to sensory stimulation (Jacobs et al., 1991; Jacobs and Juliano, 1995). Similar increases in neuronal excitability in response to acetylcholine have been noted in visual (Sillito and Kemp, 1983) and auditory cortex (Metherate and Weinberger, 1989; Metherate and Ashe, 1991). Basal forebrain cholinergic input has also been shown to modulate plasticity in various cortical regions (Bear and Singer, 1986; Juliano et al., 1991; Bakin and Weinberger, 1996). Conversely, selective removal of cholinergic input to cortex using 192 IgG-saporin reduced experience-dependent plasticity (Baskerville et al., 1997). Thus, a general function of the cholinergic input to cortex may include increasing signal-to-noise ratios (McCormick and Prince, 1986) and enhancing the processing of behaviorally relevant stimuli.

The removal of cholinergic innervation of the PPC was possible because subsets of basal forebrain cholinergic neurons project to limited regions of cortex in both primates and rodents (Price and Stern, 1983; Saper, 1984; Aston-Jones et al., 1985; Walker et al., 1985). Thus the specific function of a particular subset of cholinergic neurons may reflect the specialized information that is normally processed in the cortical region to which those neurons project. A role for the rat PPC in attention is consistent with the concept that this region may be homologous to the primate PPC.

Damage to the PPC of humans and nonhuman primates produces contralateral neglect and other deficits in visuospatial attention (Critchley, 1966; Heilman et al., 1970; Posner et al., 1984; Petersen and Robinson, 1986; Petersen et al., 1989). Complementary findings from neuroimaging studies indicate that the human PPC is active when subjects are required to attend to a specified stimulus (Corbetta et al., 1993, 1995; Gitelman et al., 1996). Neural recording studies in monkeys provide additional physiological evidence that the PPC is involved in attention. The activity of neurons in the PPC is often correlated with the allocation of attention, or processing resources, to behaviorally relevant stimuli (Robinson et al., 1978; Bushnell et al., 1981; Colby et al., 1996). In the context of the current research, it is particularly interesting to note that studies have shown an increase in the response of PPC neurons when a subject is presented with an unexpected stimulus or event (Robinson et al., 1995; Steinmetz and Constantinidis, 1995).

The present results support the idea that the PPC is likewise involved in attentional processing in the rat. Only a few other studies using rats have examined the role of this recently defined rat posterior parietal area in attention. Although a unilateral lesion of PPC in a recent study failed to impair performance in a spatial cueing task (Ward and Brown, 1997), other investigators found that lesions of the rat PPC resulted in neglect similar to that observed in primates (King and Corwin, 1993). A comparable deficit was also produced by a knife-cut of the axons connecting the rat PPC and AGm (Burcham et al., 1997). It has been suggested that the PPC and AGm may form part of a cortical attention network (Reep et al., 1994; Burcham et al., 1997), similar to that postulated to exist in the primate between PPC, the frontal eye fields, and cingulate cortex (Mesulam, 1981, 1990; Heilman et al., 1993).

In the primate, the function of this cortical circuitry involved in attention is subject to modulation via input from subcortical systems; disruption of these modulatory systems can also result in

attentional deficits. For instance, the frontal eye fields of primates and the AGm of rats both receive dopaminergic input from the ventral tegmental area and substantia nigra (Björklund and Lindvall, 1984). In rats, damage to these projections produces symptoms of neglect (Marshall, 1979; Marshall and Gotthelf, 1979), whereas treatment with dopaminergic compounds can attenuate neglect resulting from frontal cortex damage in both rats and humans (Corwin et al., 1986; Fleet et al., 1987). Likewise, the PPC of both primates and rats receives cholinergic afferents from the basal forebrain (Mesulam et al., 1983; Rye et al., 1984; Saper, 1984; Bucci et al., 1997). Lesions of the basal forebrain have also been shown to produce deficits in attention that resemble those produced by damage to parietal cortex in humans and nonhuman primates (Posner et al., 1984; Parasuraman et al., 1992; Voytko et al., 1994; Chiba et al., 1998). The current study provides more direct evidence that intact cholinergic innervation of the PPC is important for regulating the processing of conditioned stimuli. Further studies are needed to define the conditions under which this system participates in the regulation of attention in rodents.

REFERENCES

- Aston-Jones G, Shaver R, Dinan TG (1985) Nucleus basalis neurons exhibit axonal branching with decreased impulse conduction velocity in rat cerebrocortex. *Brain Res* 325:271–285.
- Bakin JS, Weinberger NM (1996) Induction of a physiological memory in the cerebral cortex by stimulation of the nucleus basalis. *Proc Natl Acad Sci USA* 93:11219–11224.
- Baskerville KA, Schweitzer JB, Herron P (1997) Effects of cholinergic depletion on experience-dependent plasticity in the cortex of the rat. *Neuroscience* 80:1159–1169.
- Bear MF, Singer W (1986) Modulation of visual cortical plasticity by acetylcholine and noradrenaline. *Nature* 320:172–176.
- Björklund A, Lindvall O (1984) Dopamine containing systems in the CNS. In: *Handbook of chemical neuroanatomy*, Vol 2, classical transmitters in the CNS, Part 1 (Björklund A, Hökfelt T, eds), pp 55–122. New York: Elsevier Science.
- Bucci DJ, Holland PC, Gallagher M (1997) Deficits in attention produced by selective removal of cholinergic projections to posterior parietal cortex. *Soc Neurosci Abstr* 23:1838.
- Burcham KJ, Corwin JV, Stoll ML, Reep RL (1997) Disconnection of medial agranular and posterior parietal cortex produces multimodal neglect in rats. *Behav Brain Res* 86:41–47.
- Bushnell MC, Goldberg ME, Robinson DL (1981) Behavioral enhancement of visual responses in monkey cerebral cortex: I. Modulation in posterior parietal cortex related to selective visual attention. *J Neurophysiol* 46:755–772.
- Cavada C, Goldman-Rakic PS (1989a) Posterior parietal cortex in Rhesus monkey: I. Parcellation of areas based on distinctive limbic and sensory corticocortical connections. *J Comp Neurol* 287:393–421.
- Cavada C, Goldman-Rakic PS (1989b) Posterior parietal cortex in Rhesus monkey: II. Evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. *J Comp Neurol* 287:422–445.
- Chandler HC, King V, Corwin JV, Reep RL (1992) Thalamocortical connections of rat posterior parietal cortex. *Neurosci Lett* 143:237–242.
- Chiba AA, Bucci DJ, Holland PC, Gallagher M (1995) Basal forebrain cholinergic lesions disrupt increments but not decrements in conditioned stimulus processing. *J Neurosci* 15:7315–7322.
- Chiba AA, Bushnell PJ, Oshiro WN, Gallagher M (1998) Selective removal of cholinergic neurons in the basal forebrain alters cued target detection in rats. *NeuroReport*, in press.
- Colby CL, Duhamel JR, Goldberg ME (1996) Visual, presaccadic, and cognitive activation of single neurons in monkey lateral intraparietal area. *J Neurophysiol* 76:2841–2852.
- Corbetta M, Miezin FM, Shulman GL, Petersen SE (1993) A PET study of visuospatial attention. *J Neurosci* 13:1202–1226.
- Corbetta M, Shulman GL, Miezin FM, Petersen SE (1995) Superior parietal cortex activation during spatial attention shifts and visual feature conjunction. *Science* 270:802–805.

- Corwin JV, Kanter S, Watson RT, Heilman KM, Valenstein E, Hashimoto A (1986) Apomorphine has a therapeutic effect on neglect produced by unilateral dorsomedial prefrontal cortex lesions in rats. *Exp Neurol* 94:683–698.
- Critchley M (1966) The parietal lobes. New York: Hafner.
- Dickinson A, Hall G, Mackintosh NJ (1976) Surprise and the attenuation of blocking. *J Exp Psychol Anim Behav Process* 2:313–322.
- Donoghue JP, Carroll KL (1987) Cholinergic modulation of sensory responses in rat primary somatic sensory cortex. *Brain Res* 408:367–371.
- Fadel J, Moore H, Sarter M, Bruno JP (1996) Trans-synaptic stimulation of cortical acetylcholine release after partial 192 IgG-saporin-induced loss of cortical cholinergic afferents. *J Neurosci* 16:6592–6600.
- Fleet WS, Valenstein E, Watson RT, Heilman KM (1987) Dopamine agonist therapy for neglect in humans. *Neurology* 37:1765–1770.
- Gitelman DR, Alpert NM, Kosslyn S, Daffner K, Scinto L, Thompson W, Mesulam M-M (1996) Functional imaging of human right hemispheric activation for exploratory movements. *Ann Neurol* 39:174–179.
- Han J-S, Gallagher M, Holland PC (1995) Hippocampal lesions disrupt decrements but not increments in conditioned stimulus processing. *J Neurosci* 15:7323–7329.
- Heilman KM, Pandya DN, Geschwind N (1970) Trimodal inattention following parietal lobe ablations. *Trans Am Neurol Assoc* 95:259–261.
- Heilman KM, Watson RT, Valenstein E (1993) Neglect and related disorders. In: *Clinical neuropsychology* (Heilman KM, Valenstein E, eds), pp 279–336. New York: Oxford UP.
- Holland PC (1977) Conditioned stimulus as a determinant of the form of the Pavlovian conditioned response. *J Exp Psychol Anim Behav Process* 3:77–104.
- Holland PC (1984) The origins of Pavlovian conditioned behavior. In: *The psychology of learning and motivation*, Vol 18 (Bower G, ed), pp 129–173. Englewood Cliffs, NJ: Prentice-Hall.
- Holland PC (1997) Brain mechanisms for changes in processing of conditioned stimuli in Pavlovian conditioning: implications for behavior theory. *Anim Learn Behav* 25:373–399.
- Holland PC, Gallagher M (1993a) The effects of amygdala central nucleus lesions of blocking and unblocking. *Behav Neurosci* 107:235–245.
- Holland PC, Gallagher M (1993b) Amygdala central nucleus lesions disrupt increments but not decrements in conditioned stimulus processing. *Behav Neurosci* 107:246–253.
- Holley LA, Wiley RG, Lappi DA, Sarter M (1994) Cortical cholinergic deafferentation following the intracortical infusion of 192 IgG-saporin: a quantitative histochemical study. *Brain Res* 663:277–286.
- Jacobs SE, Juliano SL (1995) The impact of basal forebrain lesions on the ability of rats to perform a sensory discrimination task involving barrel cortex. *J Neurosci* 15:1099–1109.
- Jacobs SE, Code RA, Juliano SL (1991) Basal forebrain lesions alter stimulus-evoked metabolic activity in rat somatosensory cortex. *Brain Res* 560:342–345.
- Juliano SL, Ma W, Eslin D (1991) Cholinergic depletion prevents expansion of topographic maps in somatosensory cortex. *Proc Natl Acad Sci USA* 88:780–784.
- Kamin LJ (1968) Attention-like processes in classical conditioning. In: *Miami symposium on the prediction of behavior: aversive stimulation* (Jones MR, ed), pp 9–32. Coral Gables, FL: University of Miami.
- Karnovsky MJ, Roots L (1964) A “direct-coloring” thiocholine method for cholinesterases. *J Histochem Cytochem* 12:219–221.
- King VR, Corwin JV (1993) Comparisons of hemi-attention produced by unilateral lesions of the posterior parietal cortex or medial agranular prefrontal cortex in rats: neglect, extinction, and the role of stimulus distance. *Behav Brain Res* 54:117–131.
- Mackintosh NJ (1975) A theory of attention: variations in the associability of stimuli with reinforcement. *Psychol Rev* 82:276–298.
- Marshall JF (1979) Somatosensory inattention after dopamine-depleting intracerebral 6-OHDA injections: spontaneous recovery and pharmacological control. *Brain Res* 177:311–324.
- Marshall JF, Gotthelf T (1979) Sensory inattention in rats with 6-hydroxydopamine-induced degeneration of ascending dopaminergic neurons: apomorphine-induced reversal of deficits. *Exp Neurol* 65:398–411.
- McCormick DA, Prince DA (1986) Mechanisms of action of acetylcholine in the guinea-pig cerebral cortex *in vitro*. *J Physiol (Lond)* 375:169–194.
- Mesulam M-M (1981) A cortical network for directed attention and unilateral neglect. *Ann Neurol* 10:309–325.
- Mesulam M-M (1990) Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann Neurol* 28:597–613.
- Mesulam M-M, Mufson EJ, Levey AI, Wainer BH (1983) Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. *J Comp Neurol* 214:170–197.
- Metherate R, Ashe JH (1991) Basal forebrain stimulation modifies auditory cortex responsiveness by an action at muscarinic receptors. *Brain Res* 559:163–167.
- Metherate R, Weinberger NM (1989) Acetylcholine produces stimulus-specific receptive field alterations in cat auditory cortex. *Brain Res* 480:372–377.
- Muir JL, Dunnett SB, Robbins TW, Everitt BJ (1992) Attentional functions of the forebrain cholinergic systems: effects of intraventricular hemicholinium, physostigmine, basal forebrain lesions and intracortical grafts on a multiple choice serial reaction time task. *Exp Brain Res* 89:611–622.
- Muir JL, Everitt BJ, Robbins TW (1994) AMPA-induced excitotoxic lesions of the basal forebrain: a significant role for the cortical cholinergic system in attentional function. *J Neurosci* 14:2313–2326.
- Muir JL, Everitt BJ, Robbins TW (1996) The cerebral cortex of the rat and visual attentional function: dissociable effects of mediofrontal, cingulate, anterior dorsolateral, and parietal cortex lesions on a five-choice serial reaction time task. *Cereb Cortex* 6:470–481.
- Ohtake T, Heckers S, Wiley RG, Lappi DA, Mesulam M-M, Geula C (1997) Retrograde degeneration and colchicine protection of basal forebrain cholinergic neurons following hippocampal injections of an immunotoxin against the p75 nerve growth factor receptor. *Neuroscience* 78:123–133.
- Parasuraman R, Greenwood PM, Haxby JV, Grady CL (1992) Visuospatial attention in dementia of the Alzheimer type. *Brain* 115:711–733.
- Paxinos G, Watson C (1986) The rat brain in stereotaxic coordinates. San Diego: Academic.
- Pearce JM, Hall G (1980) A model for Pavlovian learning: variations in the effectiveness of conditioned but not of unconditioned stimuli. *Psychol Rev* 106:532–552.
- Petersen SE, Robinson DL (1986) Damage to parietal cortex produces a similar deficit in man and monkey. *Invest Ophthalmol Vis Sci [Suppl]* 27:18.
- Petersen SE, Robinson DL, Currie JN (1989) Influences of lesions of parietal cortex on visual spatial attention in humans. *Exp Brain Res* 76:267–280.
- Posner MI, Walker JA, Friedrich FJ, Rafal RD (1984) Effects of parietal injury on covert orienting of attention. *J Neurosci* 4:1863–1874.
- Price JL (1995) Thalamus. In: *The rat nervous system* (Paxinos G, ed), pp 629–648. San Diego: Academic.
- Price JL, Stern R (1983) Individual cells in the nucleus basalis-diagonal band complex have restricted axonal projections to the cerebral cortex in the rat. *Brain Res* 269:352–356.
- Quinn B, Graybiel A (1994) Myeloarchitectonics of the primate caudate-putamen. In: *The basal ganglia IV: new ideas and data on structure and function* (Percheron G, McKenzie JS, Féger J, eds), pp 35–41. New York: Plenum.
- Rasmusson DD, Dykes RW (1988) Long-term enhancement of evoked potentials in cat somatosensory cortex produced by co-activation of the basal forebrain and cutaneous receptors. *Exp Brain Res* 70:276–286.
- Reep RL, Chandler HC, King V, Corwin JV (1994) Rat posterior parietal cortex: topography of corticocortical and thalamic connections. *Exp Brain Res* 100:67–84.
- Rescorla RA, Wagner AR (1972) A theory of Pavlovian conditioning: variations in the effectiveness of reinforcement and nonreinforcement. In: *Classical conditioning II* (Black AH, Prokasy WF, eds), pp 64–99. New York: Appleton-Century-Crofts.
- Robbins TW, Everitt BJ, Marston HM, Wilkinson J, Jones GH, Page KJ (1989) Comparative effects of ibotenic acid- and quisqualic acid-induced lesions of the substantia innominata on attentional function in the rat: further implications for the role of the cholinergic neurons of the nucleus basalis in cognitive processes. *Behav Brain Res* 35:221–240.
- Robinson DL, Goldberg ME, Stanton GB (1978) Parietal association cortex in the primate: sensory mechanisms and behavioral modulations. *J Neurophysiol* 41:910–932.
- Robinson DL, Bowman EM, Kertzman C (1995) Covert orienting of attention in macaques. II. Contributions of parietal cortex. *J Neurophysiol* 74:698–712.

- Rye DB, Wainer BH, Mesulam M-M, Mufson EJ, Saper CB (1984) Cortical projections arising from the basal forebrain: a study of cholinergic and noncholinergic components employing combined retrograde tracing and immunohistochemical localization of choline acetyltransferase. *Neuroscience* 13:627–643.
- Saper CB (1984) Organization of cerebral cortical afferent systems in the rat. I. Magnocellular basal nucleus. *J Comp Neurol* 222:313–342.
- Schmahmann JD, Pandya DN (1990) Anatomical investigation of projections from thalamus to posterior parietal cortex in the rhesus monkey: a WGA-HRP and fluorescent tracer study. *J Comp Neurol* 295:299–326.
- Schmued LC (1990) A rapid, sensitive histochemical stain for myelin in frozen brain sections. *J Histochem Cytochem* 38:717–720.
- Sillito AM, Kemp JA (1983) Cholinergic modulation of the functional organization of the cat visual cortex. *Brain Res* 289:143–155.
- Steinmetz MA, Constantinidis C (1995) Neurophysiological evidence for a role of posterior parietal cortex in redirecting visual attention. *Cereb Cortex* 5:448–456.
- Takahashi T (1985) The organization of the lateral thalamus of the hooded rat. *J Comp Neurol* 231:281–309.
- Voytko ML, Olton DS, Richardson RT, Gorman LK, Robin JR, Price DL (1994) Basal forebrain lesions in monkeys disrupt attention but not learning and memory. *J Neurosci* 14:167–186.
- Walker LC, Kitt CA, DeLong MR, Price DL (1985) Noncollateral projections of basal forebrain neurons to frontal and parietal neocortex in primates. *Brain Res Bull* 15:307–314.
- Ward NM, Brown VJ (1997) Deficits in response initiation, but not attention, following excitotoxic lesions of posterior parietal cortex in the rat. *Brain Res* 775:81–90.
- Wiley RG, Oeltmann TN, Lappi DA (1991) Immunolesioning: selective destruction of neurons using immunotoxin to rat NGF receptor. *Brain Res* 562:149–153.
- Wilson PN, Boumphrey P, Pearce JM (1992) Restoration of the orienting response to a light by a change in its predictive accuracy. *Q J Exp Psychol B* 44:17–36.