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# Effects of Excitotoxic and Immunotoxic Lesions of the Posterior Parietal Cortex on Attention

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# EFFECTS OF EXCITOTOXIC AND IMMUNOTOXIC LESIONS OF THE POSTERIOR PARIETAL CORTEX ON ATTENTION

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APPROVAL SHEET

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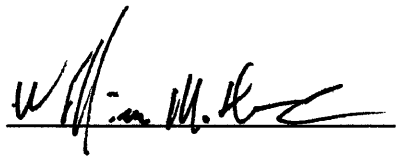

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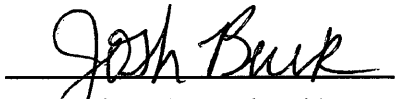

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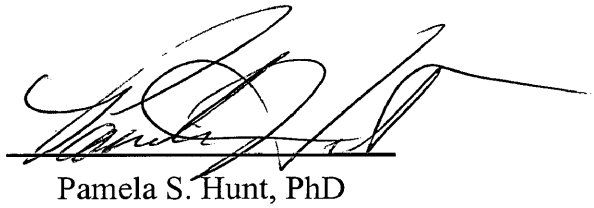

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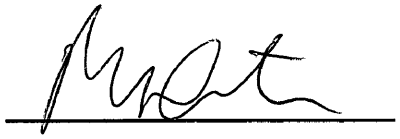

Peter M. Vishton, PhD

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# ABSTRACT

Basal forebrain corticopetal cholinergic neurons are necessary for normal attentional processing. However, the interactions of acetylcholine with processing mediated by particular cortical regions remain unclear. The posterior parietal cortex has been implicated in models of attention, including the ability to selectively attend to target stimuli when distracting stimuli are presented. In the present experiment, rats were trained to perform a two-lever attention task that required discrimination of visual signals and trials when no signal was presented. Animals then received infusions of the cholinotoxin, 192IgG-saporin, the excitotoxin, n-methyl-D-aspartate, or vehicle into the posterior parietal cortex (n=9/group). Postsurgically, rats were tested for 30 sessions in the same task trained before surgery followed by 30 sessions with the houselight flashed one sec prior to a signal or non-signal. Lesions did not differentially affect performance in the task tested immediately following surgery. However, when the houselight was flashed prior to the signal or non-signal, both lesion groups were differentially affected compared to sham-lesioned animals. Sham-lesioned animals showed a decrease in the latency to press a lever following lever extension when the houselight was flashed compared to sessions when it was not flashed. However, cholinotoxic lesioned animals did not show this effect. Furthermore, exploratory analyses revealed an elevated omission rate for excitotoxic lesioned animals compared to sham-lesioned animals during sessions when the houselight was flashed. The present data are discussed in regards to the posterior parietal cortex and its cholinergic afferents from the basal forebrain and the role they play in maintaining attentional performance when task irrelevant stimuli are presented.

# EFFECTS OF EXCITOTOXIC AND IMMUNOTOXIC LESIONS OF THE POSTERIOR PARIETAL CORTEX ON ATTENTION

# Introduction

## *Neuroanatomy of the Posterior Parietal Cortex*

In humans, the parietal lobe is located anterior to the occipital lobe and posterior to the central sulcus and frontal lobes. The caudal region of this lobe, the posterior parietal cortex, can be further divided into the inferior and superior parietal lobules (Zigmond, Bloom, Landis, Roberts, & Squire, 1999), which are separated by the intraparietal sulcus (Galletti, Battaglini, & Fattori, 1997). The primate parietal lobe is organized in a homologous fashion, and neuroanatomical investigations have revealed that the posterior parietal cortex (PPC) may be further characterized by its connections to thalamic and cortical structures. It shares reciprocal connections with several thalamic nuclei; namely the posterior lateral nucleus and pulvinar nuclei (Schmahmann & Pandya, 1990). Its distinctive cortico-cortical connections include inputs from the primary visual and somatosensory cortices, and reciprocal connections with the frontal cortex and the orbital cortex (Cavada & Goldman-Rakic, 1989; Bucci, Conley, & Gallagher, 1999).

Investigations utilizing anterograde and retrograde tracing methods (e.g. True Blue, WHP) have identified an area in the rat neocortex with similar connectivity to the primate PPC (e.g. Kolb & Walkey, 1987; Reep, Chandler & Corwin, 1994). This area receives inputs from the posterior lateral and dorsal lateral nuclei of the thalamus (Kolb & Walkey, 1987), which have been described as "homologues" to the posterior lateral nucleus and pulvinar nuclei in primates (Takahashi, 1985; Bucci, Conley, & Gallagher, 1999), as well as the basal ventral nuclei of the thalamus (Kolb & Walkey, 1987). Cortical connections within this region include inputs from the somatosensory, striate, and extrastriate cortices. Furthermore, reciprocal connections with the frontal cortex

(Kolb & Walkey, 1987), as well as the ventrolateral and medial regions of the orbital cortex (Reep et al., 1994) have also been identified. Thus the results of comparative neuroanatomical investigations have led to a consensus on the presence and location of the PPC in the rat. However, the extent to which this area is functionally similar across species is an issue that continues to spark debate.

*Behavioral Studies of the Posterior Parietal Cortex: Importance in spatial cognition*

An extensive literature describing the effects of organic and chemically induced lesions of the PPC in humans and primates has revealed that this region of the cortex is vital to normal spatial cognition. Of the many deficits that have been attributed to subjects with damage to the PPC, there are two broad categories of impairments that are consistent across both humans and primates.

The first of these categories is visual or "hemispheric" neglect. Hemispheric neglect refers to an inability to perceive or respond to objects in the area of the visual field that is monitored by a hemisphere of the brain that has been damaged, while retaining the ability to perceive and respond to stimuli ipsilateral to the site of the lesion (Galetti, Battglini, & Fattori, 1997). Human research has revealed that this neglect can have pervasive repercussions; when subjects with damage to the PPC are asked to recall a scene that has recently been presented to them, they fail to report details of the scene that fall on the side of the visual field contralateral to the lesion (Zigmond et al., 1999).

The second broad category of impairment associated with damage to the PPC in primates and humans deals with deficits in localizing an object's position in space. In humans and primates, damage to the PPC can lead to difficulties in many every day actions, such as attempting to insert a common house key into a lock or procure a morsel

of food, as well as in experimental tasks that require visually guided arm reach movements. The deficit is specific to the area in space contralateral to the hemisphere of the lesion, as well as to visually guided behaviors. This deficit differs from hemispheric neglect in that subjects are able to confirm the presence of a stimulus, however when they are required to reach for the same stimulus in a location contralateral to a lesioned hemisphere, they are inaccurate in their reach. (Galleti et al.,1997; Zigmond et al., 1999). Positron emission tomography studies have confirmed the role of the PPC in this ability. Kertzman, Schwarz, Zeffiro, & Hallet (1997) demonstrated that when subjects are asked to reach for a stimulus, significant increases in regional cerebral blood flow can be observed in the PPC in the hemisphere contralateral to the area of the visual field in which a target was located.

In the primate research, impairments associated with damage to the PPC often decrease in severity over time. This same trend has been reported in the human literature, although it tends to happen at a much slower rate (Galletti et al., 1997). The reason for the discrepancy between the effects of lesions in primates and humans may well lie in the lack of specificity in organically produced human brain lesions. Encephalitic trauma in humans often affects more than one region in the brain. However, there is a consistency in the nature of the impairments following damage to the PPC in humans and primates. Furthermore, investigations of the organization of the primate neocortex have demonstrated that the PPC projects to the presubiculum and parahippocampal gyrus, areas which themselves have long been considered the foundation of cognitive maps of space (Anderson, 1997). Thus, there has been a justifiable emphasis on the importance of

the PPC in spatial cognition, and studies of the functional organization of the rat neocortex have often sought to examine the PPC's role in spatial processes.

The majority of research with rats has implied a broader role for the PPC in navigating through space. One of the most comprehensive examinations of the role of the rat PPC in spatial cognition was conducted by Kolb & Walkey (1987), in which the PPC was removed bilaterally and animals were tested on a number of tasks requiring spatial cognitive skills. These tasks included beam walking, a radial arm maze, a place navigation task, and a landmark navigation task. Animals with lesions of the PPC exhibited impairments in the ability to locomote across a beam, taking longer and making more foot errors than control animals. Lesioned animals also made more "wrong arm" and "retracing" errors in the radial arm task that required them to explore the eight arms of the maze for food reward. In the place navigation and landmark navigation tasks, animals with lesions of the PPC were significantly less accurate in the routes they took towards a hidden platform when it remained in a constant location, and when its location was varied but indicated by a distal cue. These results led the authors to conclude that the PPC in rats plays an important role in spatial cognition as in humans and primates. This conclusion has been supported by studies like that of Spangler et al. (1994) which demonstrated that destruction of the PPC by thrombosis impairs the ability to learn the route to the goal arm of a 14-unit T-maze, and further from research demonstrating that the PPC may play a role in integrating kinesthetic and visual information and is thus important in utilizing both egocentric and allocentric information in spatial navigation (Save & Moghaddam, 1996; King & Corwin, 1992).

In humans, primates, and rats, damage to the PPC results in patterns of impairments that implicate a role for this region of the cortex in spatial processing and navigation. Research on hemispheric neglect points to a role of the PPC in the perception of cues in the visual field, however, it is reasonable to assume that it may also subserve a variety of cognitive abilities that rely upon the processing of visual information. Indeed, hemispheric neglect, an impairment classically used as evidence for the PPC in spatial cognition, has been described by some researchers in terms of an information processing impairment, one leading to dysfunction in spatial processing (e.g. Vecera & Flevaris, 2005). The PPC's extensive reciprocal connections with the frontal cortex, an area associated with a number of executive functions (Robbins, 2000), along with findings from positron emission tomography and functional imaging studies (e.g. Coull & Nobre, 1998; Hopfinger, Buonocore, & Mangun, 2000; Kastner & Ungerleider, 2000) have spurred a growing body of evidence which suggests that it may also play a role in modulating aspects of attention.

*The Posterior Parietal Cortex and Attention*

One of the most heavily cited models of the neural underpinnings of attention, developed by Posner and colleagues (1990; 1992), includes the PPC in its list of structures important to this cognitive process. This network consists of what can be regarded as two major systems, each of which plays an important contributory role in attention. The anterior system is comprised mainly of frontal cortical structures like the prefrontal and anterior cingulate cortices, and is most important for the detection of signals. The posterior system is made up of the superior colliculus, the pulvinar nuclei of

the thalamus, and the posterior parietal cortex. This system primarily functions to allow a human or animal to orient towards visual stimuli.

Studies utilizing functional magnetic resonance imaging and positron emission tomography have expanded the role of the PPC beyond Posner's initial conception. It has been identified as a region important in sustaining attention (Pardo, Fox, Raichle, 1991; Coull, Frackowiak, & Frith, 1998) as well as selective attention (Hopfinger, Buonocore, & Mangun, 2000). The implication of the PPC playing a role in various subtypes of attention has led some to hypothesize that it represents a site of interaction between these components of information processing (Coull & Nobre, 1998). Studies on clinical populations have further implicated a role for the PPC in focusing attention. Patients with damage to this region exhibit a higher susceptibility to irrelevant, distracting stimuli (Pavlova, Sokolov, Staudt, Marconato, Birbaumer, & Krageloh-Mann, 2005), and furthermore, the extent of the attentional impairment that is induced is proportional to the salience of the distracter (Friedman- Hill, Robertson, Desimone, Ungerleider, 2003).

Evidence for a role of the PPC in attentional processing is further derived from studies employing set shifting tasks. A set shift requires subjects to shift their attention from one perceptual domain to another, and studies on humans with an intact PPC have shown increases in the level of activity in PPC when performing such tasks (Rogers, Andrews, Grasby, Brooks, & Robbins, 2000). Comparative studies utilizing set shifting paradigms have also indicated a role for the PPC in attentional processing. Fox, Barnese, & Baxter (2003) employed a set shifting task to assess the effects of excitotoxic lesions of the PPC on performance in rats. Animals were trained to search cups for a food reward. In the initial stage of training, cups were filled with the same bedding medium,

and learned to discriminate between different scents in order to discern the location of the reward. After establishing scent as the modality indicative of the location of the reward, animals were presented with a dimensional shift in which the contents of a cup became the cue that indicated the presence or absence of a reward. Animals were tested on the speed with which they could adapt to this shift indicated by the number of trials it took to reach criterion (i.e. 6 consecutive correct responses). Rats that had bilateral lesions of the PPC required many more trials to reach criterion than non-lesioned animals, leading the authors' to conclude that damage to the PPC diminished the rats' ability to shift attention from one modality to another.

*Acetylcholine and Attention*

Identification of the macroscopic brain regions involved in cognitive processes like attention has proved to be an important source of information in regards to mapping the functional neuroanatomy of the brain. However, the understanding provided by this line of research is augmented by the supplementation of investigations aimed at pinpointing the neurochemical constituents of psychological processes. In Posner et al.'s original model a third system, dependent upon the activity of ascending noradrenergic projections from the locus coeruleus, is proposed for achieving and maintaining a state of alertness. Sufficient activation maintained by this system allows for the detection of sensory signals and is thus proposed to facilitate attentional function. The importance of noradrenergic activity in modulating attentional ability brings to the forefront the importance of the involvement of neurotransmitters in attention, and a growing body of research has implicated the cholinergic system as another mediator of this ability.

Pharmacological manipulations of cholinergic activity have supported the idea that the transmission of acetylcholine mediates attention. Administration of scopolamine, a muscarinic cholinergic receptor antagonist, impairs attentional processing of visual stimuli, while nicotinic receptor agonists enhance performance in humans (Wesnes & Warburton, 1984), as well as rats (McGaughy, Decker, Sarter, 1999).

Evidence for the importance of this neurotransmitter system has also been derived from studies implementing the five choice serial reaction time task. This task, designed for investigations of attentional processing in rats, requires subjects to monitor five locations for the presentation of a brief visual stimulus. The nucleus basalis of Meynert/substantia innominata of the basal forebrain provides cholinergic innervation to the neocortex (Dunnett, Everett, & Robbins, 1991; Chiba, Bucci, Holland, & Gallagher, 1995). Excitotoxic lesions of the basal forebrain, and thus, removal of cortical cholinergic input, impair animals' ability to detect signals in the 5 choice serial reaction time task (Robbins, Everitt, Marston,Wilkinson, Jones, & Page, 1989; Muir, Everitt, & Robbins, 1994).

The population of neurons in the basal forebrain is comprised largely of GABAergic and glutamatergic neurons (Zaborsky, Gaykema, Swanson, & Cullianan, 1997), and thus impairments that follow from a complete lesion of this area (as is created by infusions of chemicals that induce excitotoxic reactions) could reasonably be construed as the result of the disruption of neurotransmitters other than acetylcholine. The development of the immunotoxin 192 IgG-saporin, which selectively targets the p75 nerve growth factor expressed exclusively by basal forebrain cholinergic neurons and Purkinjie cells in the cerebellum (Waite, Chen, Wardlow, Wiley, Lappi, & Thal, 1995 )

coupled with the observation that infusions of this immunotoxin into the basal forebrain impairs performance on the five choice serial reaction time task (McGaughy et al., 2002; Risbrough , Bontempi, & Menzaghi, 2002) implies that the basal forebrain cholinergic system is particularly important in the preservation of normal attentional functioning.

The five-choice serial reaction time task requires animals to monitor five separate spatial locations, and thus necessarily involves aspects of spatial processing that may be independent of attentional function per se. Importantly, further evidence for the importance of the cholinergic system in attentional processes comes from investigations utilizing tests designed specifically to tax attentional resources that simultaneously minimize the demand placed upon spatial cognition. An operant task based upon the parameters identified by Parasuraman (1987) as sufficient for taxing attentional resources, has been designed and experimentally validated as a means of assessing attention in rats (McGaughy & Sarter, 1995). In the standard version of this task, rats are required to discriminate between brief, randomly and variably occurring visual signals and non-signals presented in rapid succession over prolonged periods of time. Unlike the five choice serial reaction time task, all stimulus presentations are localized in the same area. Similar to the five choice serial reaction time task, selective lesions of basal forebrain cholinergic neurons decrease signal detection. Furthermore, the overall performance of animals in this task correlates with cortical cholinergic fiber density (McGaughy, Kaiser, Sarter, 1996). This task has also led to the discovery of a positive linear relationship between levels of cortical acetylcholine and attentional demand (Himmelheber, Sarter, Bruno, 2000), placing further emphasis on the role of basal forebrain cortical cholinergic inputs in attentional function.

*Posterior Parietal Cholinergic Neurons and Attention*

Recent studies have revealed that the PPC receives its primary cholinergic input from the substantia innominata/ nucleus basalis region of the basal forebrain (Bucci, Conley, & Gallagher 1999), thus establishing a direct connection between the anatomical and neurochemical systems implicated in attentional processing. In spite of the overlap between the basal forebrain cholinergic system and the PPC, there are a sparse number of studies that have sought to examine the importance of the interaction of these two systems in modulating this aspect of cognitive processing. A study by Bucci, Holland, and Gallagher (1998) represents one of the few attempts at doing so. Basal forebrain cholinergic projections to the PPC were removed by infusing 192 IgG-saporin into the PPC. To assess the effect of the lesion on attentional processing, animals were tested in an associative learning paradigm. Briefly, the experimenters altered the predictive relationship between two conditioned stimuli such that the salience of one of the stimuli was increased in regards to the presentation of a reward. The alteration of this relationship led to an increase in the amount of attention paid to the newly salient stimulus in sham lesioned animals, an effect that was eliminated when PPC cholinergic inputs were removed.

Recall that research indicates a role of the PPC in optimizing attention in tasks that require subjects to discriminate the presentation of a test stimulus from irrelevant stimuli. The inclusion of irrelevant stimuli in an experimental paradigm has been hypothesized to "increase background noise" (McGaughy and Sarter, 1995), thus requiring the subject to filter irrelevant stimuli to correctly identify signal presentations. Filtering has been described as a top-down process, where in frontal cortical structures of

the anterior attention system "recruit" regions of the posterior attention system in order to augment overall signal detection and potentially counter-act the effects of irrelevant stimuli. The PPC has been proposed to represent one of the targets of top-down recruitment. Recent evidence detailing the function of the prefrontal cortex in attention has identified it as a critical component of the neuroanatomical network underlying this ability and implicated it as the initiator of top-down recruitment (i.e. McGaughy et al., 1998; Sarter et al. 2001; 2005). Further evidence has demonstrated the ability of the prefrontal cortex to modulate cholinergic activity in the PPC in rats (Nelson, Sarter, & Bruno, 2005). Thus converging lines of research implicate a particularly important role for cholinergic neurons within the PPC for optimizing performance in attention tasks that include irrelevant stimuli.

The present study was designed to further clarify the role of the PPC, and its cholinergic inputs, in attentional function. Attentional function was assessed using the attention task developed by McGaughy & Sarter (1995). In the standard version of this task, animals are required to discriminate between brief, randomly and variably occurring visual signals and non-signals presented in rapid succession over prolonged periods of time. Rats were trained to perform this task to a high level of accuracy before surgery. The work of Bucci et al (1998), showed that removal of cholinergic inputs to the PPC created impairments only when animals were required to increase attention. Because of the rats' extensive pre-surgical training we hypothesized that lesions of the PPC would have little to no effect on performance on the standard version of the task following surgery. The introduction of a continuously flashing houselight throughout a test session has been shown to increase task and performance demands (Gill, Sarter, & Givens, 2000;

Himmelheber et al., 2000). Thus, the introduction of an irrelevant visual stimulus that must be ignored to the standard task would place further demands on the animals in order to maintain a high level of performance. Therefore, we hypothesized that the addition of a continuously flashing houselight to the standard attention task would induce performance discrepancies between control and lesion groups.

In the present study, the effects of lesions that destroy all neurons in the PPC were compared to lesions made with a selective cholinergic toxin to isolate the role of the PPC's cholinergic inputs. The excitotoxin NMDA was used to completely lesion the area of the rat neocortex defined by previous studies as the homologue to the human and primate PPC (e.g. Reep et al., 1994; Bucci et al., 1998; 1999). In a second group of animals, cholinergic input to the PPC was selectively removed with 192 IgG-saporin. This manipulation allowed for several possible outcomes. First, removal of the PPC from the neocortex may result in patterns of performance identical to that of selective removal of its cholinergic inputs, thus implicating preservation of cholinergic neurons in this region as critical for maintaining task performance. Second, removal of the entire PPC via excitotoxic lesion may produce a different pattern of effects than removal of cholinergic inputs alone. The PPC shares connections with thalamic as well as frontal cortical structures (Kolb & Walkey, 1987) that have been implicated in models of attentional processing (Posner & Peterson, 1990). This system of connections would be largely spared by removal of cholinergic inputs from the basal forebrain alone, whereas removal of an entire component of the neural network of attention would compromise this connectivity and may create a different, or perhaps more drastic, pattern of effects on attentional processing. Third, selective removal of cholinergic inputs could more

profoundly affect attention than removal of the entire cortical region. Such a result could be explained in terms of a disruption of cortical homeostasis. Removal of the PPC would abolish all connectivity to other cortical and subcortical structures. Given time, other brain regions associated with attention and executive function (e.g. prefrontal cortex) may compensate for the loss. However removal of cholinergic inputs, while sparing other connections with areas like the frontal cortex could lead to an aberrant state of activation in the PPC and thus lead to greater disruption of the neural network that sub serves attention.

Along with the continuously flashing houselight that has been employed by other studies, the present experiment employed a second manipulation of the standard task. In the flashing houselight condition, the irrelevant stimulus is presented in a regular on/off pattern (1s on/ 1s off) that results in half of the signal stimuli being presented in a darkened chamber. The resulting pattern of the presentation of the flashing houselight may actually increase the salience of signals and decrease the demands placed on performance (Woolfrey, Hunt, &Burk, 2004). In the new version of the task, the additional stimulus was a single flash of the houselight presented immediately before the onset of either a signal or non-signal trial. This manipulation allowed for greater control of the presentation of the irrelevant stimulus, and overcomes the limitations of the flashing houselight condition by insuring that all trial events are presented in an illuminated chamber. Therefore, we hypothesized that this manipulation may further clarify the effects of lesions on performance in tasks that include irrelevant stimuli.

## Method

### *Subjects*

Subjects were 27 male Long-Evans rats (Charles River Laboratories, Wilmington, MA), approximately 60 days old (200-300g) at the onset of training. Animals were kept on a 14:10 light/dark cycle in a temperature and humidity controlled vivarium. Animals were housed in hanging wire mesh cages, and water was only available as a reward during testing and for 30 minutes upon the completion of the training/testing session. Food was available ad libitum. All training and testing took place during the light cycle between 0800-1700 hours. Animals were maintained in accordance with the NIH guide for the Care and Use of Animals and with the regulations set forth by the Animal Care and Use Committee at the College of William and Mary.

*Apparatus*

Rats were trained in one of twelve operant chambers (Med Associates, Georgia, VT) enclosed within a sound attenuating box and equipped with a fan to conceal any residual background noise. Each chamber contained a water port located between two retractable levers equipped with a pair of photocells to detect head entries. Three panel lights were located at the front of each chamber, one above each lever and one above the water port. A houselight was positioned at the back of the chamber. All training and testing programs were executed with a PC clone using Med-PC software (v. IV).

*Pre-surgical training procedures*

Animals were trained in the same chamber daily. In the first stage of training each lever press led to the dipper being raised and access to 0.1 mL of water (FR-1 schedule), with the rule that if there were more than five presses on one lever, then the other lever must be pressed to receive access to water. This rule was designed to discourage the

development of a lever or side bias. This phase of training continued until animals reached a criterion of 120 lever presses per session (approximately 45 mins.).

In the next stage of training, animals had to discriminate between signals (1 s illumination of central panel light) and non-signals (no illumination of central panel light). Each session included an equal number of signal and non-signal trials. After a signal or non-signal, the two levers were extended into the chamber. On non-signal trials, a press on the right lever was considered correct, and the trial was scored as a correct rejection. On these trials, a press of the left lever was considered incorrect, and was scored as a false alarm. On signal trials, a press on the left lever was considered correct, access to water was provided, and scored as a hit. An incorrect press on the right lever was scored as a miss. The levers were retracted after being depressed regardless of whether it was correct or incorrect. An omission was reported when animals failed to press either lever after 3 s. Both levers were retracted following an omission. Incorrect responses were followed by correction trials, which were identical to the previous trial. After three consecutive errors on correction trials, animals were given a forced choice trial where only the correct lever was extended. When the errors were on a signal trial, the lever was extended while the central panel light remained illuminated. The inter-trial interval was 12±3 s during this stage of training. Each session lasted approximately 35 minutes. Criterion performance for this stage of training was defined as >70% hits and correct rejections for three consecutive sessions.

The final stage of training manipulated the preceding task in three ways. First, the correction and forced trials were eliminated. Second, the inter-trial interval was decreased to 9±3 s. Finally, the duration of the visual signals was shortened and varied

(either 500, 100, or 25 ms). In this phase, sessions consisted of 162 trials, with a total of 81 signal (27 at each signal duration) and 81 non-signal trials. Sessions were further divided into three blocks of 54 trials. Within each block 27 signal (9 at each signal duration) and 27 non-signal trials were presented in a pseudo-randomized order. The houselight remained illuminated throughout the session. Criterion was set at >70 % hits at the 500 ms signal and correct rejections for three consecutive sessions. Animals trained for approximately 4-5 months before being assigned to a surgical group.

*Surgery*

Upon acquisition of criterion level-performance in the sustained attention task, animals were randomly assigned to one of three surgical conditions; excitotoxic lesion (n=9), cholinotoxic lesion (n=9), or sham lesion (n=9). Animals were anesthetized with intraperitoneal injections of ketamine (90.0 mg/kg) and xylazine (6.0 mg/kg). Once the pedal reflex could no longer be elicited, animals were placed in a stereotaxic apparatus (Kopf Instruments, Tujunga, CA). The incisor bar was set at 3.3 mm below the interaural line (IA). All surgeries were performed under aseptic conditions. Animals' heads were shaved and an incision was made down the midline of the scalp exposing the skull. Holes were drilled over the target sites. For all animals, infusions were made through a 26-gauge cannula attached to a 1.0 ul Hamilton syringe into eight sites (0.4ul/site; coordinates relative to bregma; AP -4.0, ML ± 2.5, DV 1.5; AP -4.0, ML ± 3.7, DV 1.7; AP -4.7, ML ± 2.5, DV 1.5; AP -4.7, ML ± 3.7, DV 1.7). Those assigned to the excitotoxic lesion group were infused with 0.4 uL of 150mM n-methyl-D-aspartate in phosphate buffered saline (pH = 7.4) per site. Animals in the cholinotoxic lesion group received 0.4 uL of 192 IgG-saporin dissolved in sterile 0.9% saline per site, while those

in the sham surgery group were infused with 0.4 uL of saline vehicle per site. Injections were made at a rate of 0.4 ul/min and the cannula remained in each site for 1 additional minute after the infusion was completed. Food and water were available ad lib for 7-10 days following surgery before animals were returned to the water deprivation schedule.

*Post-surgical testing*

*Standard task*

After reinstitution of the water deprivation schedule, animals were tested for 30 sessions (one per day) in the same version of the attention task as trained immediately prior to surgery.

*Increasing background "noise": Flashing houselight throughout the session*

Following 30 sessions of the standard attention task post-surgery, animals completed five sessions (one per day) of a version of the task where the houselight was flashed on and off throughout the session (1.0s on, 1.0s off). The flashing of the houselight occurred independent of any trial event throughout this session.

*Pre-trial Flashing Houselight*

Upon completion of the fifth day of the flashing houselight sessions, animals were transferred back to the standard version of the sustained attention task. A minimum of three consecutive days of criterion level performance (>70% hits at the 500 ms signal and correct rejections) was required before animals began the final phase of the experiment. This version of the task altered the standard task by including a 1 second flash (0.5s off/0.5s on) of the houselight immediately prior to the onset of the stimulus (signal/no signal). The houselight was off at no other point during the session. This task allowed for greater control of the onset/offset of the houselight with respect to the timing of signal

presentation. Data on performance during the pre-trial flash of the houselight manipulation was collected for 30 sessions (1 per day).

*Histology*

After completing behavioral testing, animals were transcardially perfused with a 10% sucrose solution followed by 4% paraformaldeyhyde at a pressure of 300mmHg with a Perfusion One apparatus (myneurolab.com, St. Louis, MO). Brains were removed and placed in 4% paraformaldehyde for two days and then transferred to 30% sucrose in phosphate buffered saline and allowed to sit until brains fell to the bottom of the container (approx. two days). Brains were then sectioned (40um) using a freezing microtome (Leica Microsystems Inc., Bannockburn, IL). Parallel sections were kept for histochemical analysis of AChE-positive fibers and for Cresyl Violet staining.

AChE staining was carried out using a modified version of the protocol outlined by Tago et al. (1986). Free-floating sections were rinsed in 0.1 M phosphate buffer (pH 7.3-7.4), and then incubated in 0.1% H2O2 for 30 minutes. Sections were then rinsed in 0.1M maleate buffer (pH 5.9) and immersed in a 0.1M sodium citrate, 5mM potassium ferricyanide, 30mM cupric sulfate, and 30.0 mg of acetylthiocholine iodide in 0.1 M maleate buffer (pH 5.9) solution. After removal from the solution, sections were again rinsed in a 30.0 mM Tris buffer (pH 7.6) and incubated in a 3,3' –diaminobenzidine tetrahydrochloride liquid substrate kit (DAB) (Sigma-Aldrich Co., St. Louis, MO) with 0.75 g of nickel ammonium sulfate per 250 ml of solution. Approximately 500 uL of 3% H2O2 per 80 ml of solution was added after 10 minutes and sections were allowed to incubate until cortical layering could be detected. Sections were then rinsed in 3mM Tris buffer and mounted onto gel-coated slides.

Verification of the presence/location of the lesions was accomplished using an Olympus BX-51 microscope (Olympus America Inc., Melville, NY). Photographs of the cortex were made with a camera connected to a Dell pc using ImagePro Discovery, v. 4.5 (Media Cybernetics, Silver Spring, MD).

*Behavioral Measures*

In each session, the total number of hits, misses, correct rejections, false alarms, and omissions were recorded. Using these values, the relative number of hits [h/(h+m)] and false alarms [fa/(fa+cr)] was determined. The relative hit rate represents a measure of response accuracy on signal trials. Conversely, a false alarm represents an incorrect "claim" for a signal on a non-signal trial. Therefore, the relative false alarm rate can similarly be used as a measure of accuracy; the higher the rate of false alarms, the less accurate an animal's responses are on non-signal trials. Lever press latencies, the time that elapsed between the extension of the levers into the chamber following a signal or non-signal event and the animal's response, were recorded in milliseconds for all trial outcomes (hit, miss, correct rejection, false alarm). No latency was recorded during trials scored as omissions as the animals failed to press either lever. The time it took for animals to break the photocells and enter the water port to retrieve a reward following a correct response was similarly recorded in milliseconds.

To examine the possibility that animals had developed a tendency to preferentially respond to the hit/false alarm lever ("side bias") following surgery, the proportion of responses to hit/false alarm lever to all responses was calculated [(h+fa)/total number of responses]. The complete absence of a side bias would be indicated by a proportion value equal to 0.50. However, given the increase in difficulty

due to the variability of signal duration, previous studies employing this measure have adopted the 0.30-0.40 range as indicative of normal performance (McGaughy et al., 1996, Himmelheber et al., 2000).

*Statistical Analyses*

For pre-surgical, post-surgical, and flashing houselight sessions, hits were analyzed with mixed-factor ANOVAs that included lesion (excitotoxic, immunotoxic, and sham), block (54 trials, 3 per session), and signal duration (500, 100, and 25 ms) as factors. The relative number of false alarms was similarly assessed with mixed analyses of variance, however without a within subjects factor of signal duration. ANOVAs for data on lever press latency and latency to retrieve reward included lesion, block, and trial outcome (hits, misses, correct rejections and false alarms for lever press latency; hits and correct rejections for latency to retrieve reward). Omissions were summed across each block of trials. Proportions of omissions (number of omissions/total number of trials) were analyzed with ANOVAs that included lesion and block as factors. One-way ANOVAs were used to compare groups on the side bias measure. All p-values are adjusted with the Huyhn-Feldt procedure.

For the pre-trial flashing houselight sessions, data was organized into groups of five days serving as a within subjects factor (session) for analyses of this condition. This additional factor was included to identify any potential interaction between lesion and performance over repeated exposure to the pre-trial houselight task.

To examine the effects of task manipulations, repeated-measures ANOVAs with a within subjects factor of task type (i.e. standard task, flashing houselight, pre-trial houselight) were constructed for each dependent measure (all animals are included in

these analyses). Simple contrasts were used to clarify the unique effects of each task manipulation on the dependent measure in question.

## Results

### *Pre-surgical Performance*

Data were compiled for the three days immediately prior to surgery for each animal. A 3(lesion) X 3(block) X 3(signal duration) mixed analysis of variance revealed no pre-surgical group differences on hits ($F$ (2,24) = 0.102, $p$ = 0.904), however a strong effect of signal duration on the relative hit rate was expected and observed ($F$ = 389.91, $p$ < 0.0001). Contrasts revealed that performance as measured by hits varied as a function of signal duration (hits at the 500ms signal > 100ms signal > 25ms signal; all $p$'s < 0.001). A significant effect of signal duration was present in all subsequent analyses.

A 3 (lesion) X 3 (block) mixed ANOVA revealed no differences between lesion groups on false alarms ($F$ (2,24) = 0.20, $p$ = 0.823), or omissions ($F$ (2, 24) = 0.06, $p$ = 0.944). A 3 (lesion) X 3 (block) X 4(outcome) similarly revealed no differences among lesion groups on lever press latency ($F$ (2,24) = 0.99, $p$ = 0.387), or photocell latency ($F$ (2,24) = 2.00, $p$ = 0.158). A significant effect of trial outcome was observed for lever press latencies. Observation of means revealed a tendency for animals to respond more rapidly to the signal lever than the non-signal lever (Signal: 425.37 ± 22.76ms; Non-signal: 469.45 ± 20.21ms), although this trend did not reach statistical significance.

A significant effect of block was observed for false alarms, lever press latency, photocell latency, and omissions, but not for latency to retrieve reward. Animals tended to exhibit a higher percentage of false alarms in the second and third blocks of trials than in the first (Block 1: 0.07 ± 0.007; Block 2: 0.14 ± 0.013; Block 3: 0.13 ± 0.012; $p$'s <

0.001). Animals were also faster to respond to the levers during first block than in the second, in the third block than in the second, however the first block did not differ from the third block (Block 1: 438.84 ± 14.76ms; Block 2: 497.79 ± 26.72ms; Block 3: 405.59 ± 20.46ms; $p = 0.004$, $p < 0.0001$, and 0.104 respectively). Further, animals had a higher proportion of errors of omission in the third block of trials than in first and second blocks ($p$'s $< 0.0001$), as well as in the second block compared to the first ($p = 0.01$; Block 1: 0.04 ± 0.009; Block 2: 0.09 ± 0.021; Block 3: 0.19 ± 0.035).

*Effects of Task Manipulations*

To examine the effect of post-surgical task manipulations across groups, repeated measures ANOVA's with the within subjects factor of task (i.e. standard task, flashing houselight, pre-trial flash of houselight) were conducted for each dependent measure. No significant effect of task was detected for response latency or latency to retrieve reward.

Analyses did indicate a significant effect of task on the proportion of hits [$F$ (2, 48) = 4.55, $p = 0.016$]. Simple contrasts revealed that animals had a lower proportion of hits in the flashing houselight trials and pre-trial flash of the houselight trials than on the standard task ($p$'s = 0.01 and 0.05 respectively) although the flashing houselight and pre-trial flash of the houselight trials did not differ from one another (Means: Standard task: 0.65 ± 0.01; Flashing Houselight: 0.58 ± 0.02; Pre-trial Flash: 0.61 ± 0.02). There was a main effect of task on the proportion of false alarms [$F$ (2, 48) = 22.97, $p < 0.001$], with animals committing more during the pre-trial flash of the houselight task than the standard task ($p < 0.0001$) or the flashing houselight task ($p = 0.010$), and more during the flashing houselight task than on the standard task ($p = 0.002$, Means: Standard task: 0.13 ± 0.01; Flashing Houselight: 0.22 ± 0.03; Pre-trial Flash: 0.33 ± 0.03). Analyses also

identified a main effect of task on the proportion of trials omitted [$F$ (2, 48) = 8.07, $p$ = 0.001]. Simple contrasts indicated that animals omitted more trials during the pre-trial flash of the houselight manipulation than during the standard task ($p < 0.0001$) or the flashing houselight task ($p = 0.016$), although the latter two tasks could not be differentiated from one another (Standard task: 0.07 ± 0.01; Flashing Houselight: 0.09 ± 0.01; Pre-trial flash: 0.12 ± 0.02). A main effect of task was also present for the side bias measure [$F$ (2, 48) = 8.96, $p$ = 0.002). Animals tended to push the hit/false alarm lever more during the pre-trial flash of the houselight task than the standard task ($p = 0.004$) and the flashing houselight task ($p = 0.003$) although the standard task and flashing houselight task could not be differentiated from one another (Standard task: 0.390 ± 0.01; Flashing houselight: 0.37 ± 0.02; Pre-trial flash: 0.49 ± 0.03).

*Effects of PPC lesions: Standard Task*

Data for performance on the standard attention task were averaged across the first 30 days following surgery. Mixed-model ANOVA's revealed no significant effect of lesion on relative numbers of hits [$F$ (2, 24) = 1.97, $p$=0.166], false alarms [$F$ (2, 24) = 0.79, $p$=0.467], latency to enter the water port [$F$ (2, 24) = 1.85, $p$ = 0.178], or number of omissions [$F$ (2, 24) = 0.09, $p$ = 0.910]. 192 IgG-saporin lesioned animals exhibited a trend towards increased lever response latencies following surgery this trend, however, the main effect of lesion was not statistically significant [$F$ (2, 24) = 2.87, $p$ = 0.076]. A one-way ANOVA indicated no difference in the side bias. For all groups the proportion of responses to the hit/false alarm lever was within the range established by Himmelheber et al. (2000) as indicative of typical performance (Sham: 0.38 ± 0.02; Excito: 0.41 ± 0.02;

Immuno: 0.39 ± 0.02). Means for hits, false alarms, and the side bias measure are presented in Figures 1 and 2.

*Flashing Houselight Sessions*

Data on performance during the flashing houselight manipulation were averaged across five experimental sessions. Analyses revealed no significant effect of lesion on the number of omissions [$F$ (2, 24) = 1.52, $p$ = 0.238] or latency to retrieve reward [$F$ (2, 24) = 1.90, $p$ = 0.171]. Animals lesioned with 192 IgG-saporin did exhibit a tendency toward more hits (Sham: 0.56 ± 0.02; Excitotoxic: 0.55± 0.03; Immunotoxic: 0.64 ± 0.04) and false alarms (Sham: 0.17 ± 0.02; Excitotoxic: 0.20 ± 0.03; Immunotoxic: 0.28 ± 0.07), however no significant effect of lesion was found for either measure [$F$ (2, 24) = 3.00, $p$ = 0.069; $F$ (2, 24) = 1.53, $p$ = 0.237, respectively].

A one-way ANOVA was conducted to examine the possibility that animals had developed a tendency to preferentially respond to the hit/false alarms lever ("side bias"). No significant differences were detected between lesion groups [$F$ (2, 24) = 2.54, $p$ = 0.100]. Mean values of this proportion are presented in Figure 3.

A mixed-model ANOVA revealed a significant effect of lesion on lever response latency [$F$ (2, 24) = 4.23, $p$ = 0.027]. Post-hoc Tukey's HSD multiple comparisons confirmed that animals lesioned with 192 IgG-saporin were significantly slower to respond across all trials when compared to sham-lesion animals (Sham: 500.87 ± 32.40 ms; Immunotoxic: 633.20 ± 35.51ms, $p$ = 0.020), but not animals lesioned with NMDA (Excitotoxic: 535.10 ± 32.20ms, $p$ = 0.116). Furthermore, there was no significant difference between excitotoxic lesion animals and sham lesion animals ($p$ = 0.751). The means for lever response latency are depicted in Figure 4.

*Pre-trial Flashing Houselight Sessions*

One animal from the excitotoxic lesion group developed a rapidly growing sebaceous cyst on its face and was euthanized before completing any sessions of the pre-trial houselight version of the task. One animal from the immunotoxic lesion group unexpectedly died, thus no data for these two animals was available for analyses of performance on the pre-trial houselight task.

Mixed-model ANOVAs did not indicate an effect of lesion on the relative number of hits ($F$ (2, 22) = 0.59, $p$ = 0.563) or false alarms [$F$ (2, 22) = 1.26, $p$ = 0.304]; nor did lesion interact with block, session, or signal duration. Similarly, there was no main effect of lesion on latency to retrieve reward [$F$ (2, 22) = 1.47, $p$ = 0.251]. A significant lesion by outcome interaction was identified [$F$ (2, 22) = 4.51, $p$ = 0.023]. Examination of means indicated that excitotoxic lesioned animals were slower to collect a reward following a correct response to a signal trial than immunotoxic or sham lesioned animals, however a one-way ANOVA for response latencies during trials scored as hits failed to confirm the nature of this interaction.

Subsequent analyses indicated the presence of a response bias to the signal lever in all experimental groups when first exposed to the pre-trial houselight manipulation. The aforementioned side bias measure was again calculated. A 3 (lesion) X 6 (session) mixed-model ANOVA was conducted to assess possible interactions between lesion and performance over repeated exposure to the pre-trial houselight task. For the side bias measure, analyses failed to reveal a session X lesion interaction ($F$ (10, 110) = 0.27, $p$ = 0.962), however a main effect of session was observed [$F$ (5, 110) = 46.42, $p < 0.0001$]. A side bias was present in all experimental groups during the first five days of the pre-

trial houselight manipulation (Sham: 0.62 ± 0.03; Excitotoxic: 0.67 ± 0.05; Immunotoxic: 0.63 ± 0.06). Simple contrasts revealed that the side bias was greater across all groups in the first five days of this version of the task than in any other block of five days (all $p$'s $\leq$ 0.001), however no other block of days could be differentiated from the rest. The means for the side bias measure across all sessions are presented in Figure 5.

A 3 (lesion) X 3 (block) X 4 (outcome) X 6 (session) mixed-model ANOVA exposed a main effect of lesion on lever response latency [$F$ (2, 22) = 3.85, $p$ = 0.037]. Post hoc Tukey's HSD multiple comparisons confirmed that animals in the immunotoxic lesion group were slower to respond across signal and non-signal trials when compared to sham lesioned animals ($p$ = 0.029), although not excitotoxic lesioned animals ($p$ = 0.309). Sham and excitotoxic lesioned animals did not differ from one another ($p$ = 0.451). Lesion did not interact with any other factor. The means for lever response latency are presented in Figure 6.

A 3 (lesion) X 3 (block) X 6 (session) mixed models ANOVA was conducted to examine the effect of lesion on the proportion of trials omitted throughout the pre-trial houselight sessions. A main effect of session was observed [$F$ (5, 110) = 5.24, $p$ = 0.001]. All animals exhibited a trend towards omitting a progressively smaller proportion of trials across sessions on the pre-trial houselight. Contrasts revealed that animals omitted fewer trials in the last session block than in the first or second session blocks ($p$'s < 0.05). Lesion did not interact with any factor.

The main effect of lesion on the proportion of trials omitted approached but did not reach statistical significance [$F$ (2, 22) = 3.39, $p$ = 0.052]. Upon further inspection it became apparent that animals in the sham lesion and excitotoxic lesion group had an

elevated proportion of trials omitted compared to controls (Sham: 0.08 ± 0.01; Excitotoxic 0.16 ± 0.03; Immunotoxic: 0.13 ± 0.03). An exploratory ANOVA that included only sham and excitotoxic lesion animals revealed a main effect of lesion [$F$ (1, 15) = 10.54, $p$ = 0.005], while a similar analysis with immunotoxic and sham lesion animals did not [$F$ (1, 15) = 2.92, $p$ = 0.108]. Lesion did not interact with any other factor. The means for proportion of trials omitted are depicted in Figure 7.

*Histological Analysis*

Examination of tissue confirmed that lesions selectively damaged the PPC while nearby cortical and subcortical structures where largely unaffected. In 4 of the 9 excitoxic lesion animals there was noticeable spared tissue. The target region was damaged in these animals, but was not completely destroyed. In the remaining animals from this group, infusions of NMDA resulted in a marked loss of tissue in the area of the PPC (Figure 8). Lesions made with the immunotoxin 192 IgG-saporin were characterized by a nearly complete absence of cholingergic neurons within the areas of the infusions (Figure 10). Microscopic analysis revealed an issue concerning the lesions that should be addressed. In animals from all groups there was evidence of mechanical damage in the area of the PPC, presumably the effect of contact with the drill used to make holes in the skull above the infusions sites. However, it should be emphasized that the extent of this damage was minor (ex. Figure 8), and examination of the drill damage in animals from the sham lesion group indicated that it did not adversely affect fiber density within the PPC.

The presence of a lesion could not be confirmed in one animal from the immunotoxic lesion group. The animal's unexpected death pre-empted transcardial

perfusion and the resulting tissue obtained from the animal could not be assessed due to poor quality. The analyses described include all available data from all animals; however, analyses excluding the data from the one animal whose lesion could not be confirmed were run and revealed no alterations in the significance of the previously described results.

## Discussion

The functional similarity between the area identified as the PPC in rats and the PPC in humans and primates remains unclear. Furthermore, to date, there have been few studies that have sought to illustrate the importance of basal forebrain cholinergic input in the PPC. Thus, the present study sought to compare the effects of lesions of the PPC created with infusions of excitotoxic chemicals to discrete lesions of cholinergic neurons on performance in the McGaughy and Sarter attention task in adult rats, as well as variants of the task that augmented its difficulty and the demands placed upon performing animals. To understand the nature of the deficits following PPC lesions, both the nature of the dependent measures and of the task manipulations when these dependent measures were differentially affected in lesioned animals must be considered.

### *Effects of the Task Manipulations*

Examination of the effects of the different post-surgical tasks indicated that all animals detected fewer signals (hits) and committed more false alarms in the flashing houselight sessions and pre-trial houselight sessions than during the standard version of the task. Animals also committed more omissions and had a higher proportion of responses to the hit/false alarm lever (side bias) during the pre-trial houselight sessions than any other task.

The decrease in correct responses to signal trials following the introduction of a continuously flashing houselight is consistent with previous investigations employing this manipulation (e.g. McGaughy et al., 1995), and the maintenance of this pattern in the pre-trial houselight sessions indicates that this version of the attention task similarly elevates the demands placed upon task-performing animals. Thus, these data provide preliminary support for its use as a means of increasing task difficulty.

The increase in false alarms following the introduction of the flashing houselight to the standard task has been previously reported (e.g. McGaughy et al., 1995) and was expected. The further increase in false alarms and subsequent bias towards the hit/false alarm lever in the pre-trial houselight task were unexpected results. Together, these findings speak to the strategies employed by animals in the context of performing these tasks. In training, animals are consistently rewarded for responses to the left lever following an increase in illumination in the operant chamber, imparting a rule of "increase in chamber illumination→press left lever". The flashing houselight and pre-trial houselight tasks required animals to discriminate irrelevant increases in chamber illumination from relevant ones. The increases in false alarms in both tasks are indicative of the fundamental nature of the aforementioned association, and imply that animals must learn to ignore the irrelevant chamber illuminations in order to continue receiving rewards.

The pre-trial houselight differs from the flashing houselight in the nature of its presentation (i.e. single flash vs. repetitive and continual flashes). Furthermore, it is presented immediately before the signal/non-signal event. Thus, it more closely mimics the single increase in chamber illumination that characterized signal trials in the standard

task, and its presentation would be relatively easy for animals to "mistake" the single flash of the houselight for the signal stimulus and further elevate responses to the left lever even during non-signal trials.

Because the irrelevant stimulus so closely mimics the relevant stimulus in the pre-trial houselight condition, preservation of a high frequency reward schedule requires the animal to learn to attend to the presence/absence of chamber illumination as well as the location the flash. Thus, the pre-trial flash of the houselight manipulation augments task difficulty by forcing animals to attend to the signal location (central panel light) in order to initiate the correct response.

Combined, the results described above (i.e. increase in false alarms, decrease in hits) indicate that the incorporation of a single flash of the houselight immediately before the onset of a trial serves as an effective means of increasing task difficulty and subsequent demands placed upon performance. Increases in acetylcholine efflux have been reported in animals performing the flashing houselight task employed by the present study (e.g. Himmelheber et al., 2000; 2001). Thus, future studies aimed at quantifying cortical acetylcholine release in animals performing the pre-trial houselight manipulation of the task could further support the hypothesis that this task augments demand by identifying increases in cortical acetylcholine release.

*Effects of PPC Lesions on Attentional Performance*

The most consistent finding from this study is that removal of cholinergic input to the PPC results in a general performance decrement that manifests itself as an elevated latency to press a lever relative to sham and excitotoxic lesion groups. This elevated

response time was statistically significant following task manipulations designed to require animals to ignore irrelevant stimuli.

Interpretations of response latency data from animal studies are often met with skepticism, particularly in cases where the animals have been subjected to some pharmacological or neural manipulation. The reason for this skepticism is because of difficulty discriminating the possible effect of the manipulation from that of unintended detriments to motivational, or sensory-motor functions (Sarter, et al., 2001). In the present study, there was no effect of immunotoxic lesion on the proportion of correct responses to the signal lever, nor could animals in this group be differentiated from others on proportions of false alarms or side bias, which seems to indicate that animals were continuing to respond based upon the basic rules of the task. Furthermore, animals in the immunotoxic lesion group did not exhibit a relatively greater latency to collect a reward, and such motivation-dependent performance disruptions are most often coupled with increases in this measure (Harrison, Everitt, & Robbins, 1997). Together these null effects of lesion detract from the possibility of an overall impairment in sensory-motor function or motivation.

Animals in the sham and excitotoxic lesion groups exhibited a general trend toward decreases in response time from standard task to the flashing houselight sessions, and from flashing houselight sessions to the pre-trial houselight sessions (Table 1). Unlike animals from the sham or excitotoxic lesion groups, immunotoxic lesion animals did not exhibit this decrease in response latency across tasks. Previous investigations of the effects of lesions of the PPC have reported that damage to this region in rats disrupts the ability of animals to initiate a response (Ward & Brown, 1997). The elevated reaction

time in the immunotoxic lesion group observed in the present study may be indicative of such impairment, however more explanation is necessary to illustrate how this may be indicative of a disruption in attentional function.

By attending to a location, animals may respond to events occurring at that location more rapidly (Posner & Peterson, 1990). Therefore, response times may be interpreted as descriptive of overall processing efficiency of the neural network of attention (Posner & Peterson, 1990; Fan, McCandliss, Sommer, Raz, & Posner, 2002). Thus, one possible interpretation of the elevated reaction times of the immunotoxic lesion group is that removal of PPC cholinergic inputs detracted from the animals' ability to focus attention on the central panel light. Animals in the immunotoxic lesion group exhibited elevated reaction times in the flashing houselight and pre-trial houselight tasks because of a diminished ability to focus attention on the central panel light, which in turn detracted from their ability to initiate a response in an efficient manner.

Excitotoxic lesions, and thus removal of the majority of PPC afferent and efferent connections resulted in an increase in the proportion of trials omitted in the pre-trial houselight sessions. Like response latency data, common interpretations of increased numbers of omitted trials include decreases in motivation and impairment of sensory-motor function. Excitotoxic lesions did not lead to increases in latency to retrieve reward. Thus animals showed no indication of a motivational decrement. It is also important to note that animals continually performed above chance levels, and further that it was required that baseline performance (i.e. >70% detections at the 500ms signal and >70% correct rejections) be re-established on the standard task before being transferred to the pre-trial houselight task. Therefore, animals retained the ability to perform the standard

task at a high level of proficiency, an observation that would not be expected in a group of animals with compromised sensory-motor functions.

Increases in the proportion of omissions could also be interpreted as impairment in the ability to initiate a response. However, such an interpretation would also imply elevated response latencies as observed in the immunotoxic lesion group. In the present study, the response latencies of excitotoxic lesioned animals could not be differentiated from sham lesioned animals in any task manipulation. Thus impairment in response initiation does not adequately account for the performance deficits exhibited by excitotoxic lesion animals.

For animals in the excitotoxic lesion group, damage to the entire PPC may have decreased animals' ability to ignore the irrelevant pre-trial flash of the houselight and attend to the central panel light. These effects lead to more instances in which rats failed to discriminate between signal and non-signal trials. Uncertainty about stimulus presentation may adversely impact response initiation, and thus lead to more omitted trials (Echevarria, Brewer, Burk, Brown, Manuzon, & Robinson, 2005).

*Learning to Ignore Irrelevant Stimuli*

The cholinergic system has been hypothesized to play a central role in learning (Gold, 2003), and furthermore the PPC has been implicated in aspects of learning (McDaniel et al., 1995). Thus the impairments following damage to the PPC or its cholinergic inputs could conceivably be interpreted as impairment of systems mediating learning processes.

In the present study, in order to maintain a frequent reward schedule, animals were forced to learn to ignore irrelevant stimuli and identify the location of the relevant

stimulus. The extent to which requiring rats to learn that the relevant visual stimulus occurs at the central panel light impacted lesioned animals performances is difficult to assess. The elevated lever-press latencies of the immunotoxic lesion group could be interpreted as indicative of a learning impairment such that unlike rats in the sham lesion and excitotoxic lesion groups, who in the process of learning to ignore the irrelevant stimulus and identify signals at the central panel took less time to initiate a response, removal of PPC cholinergic inputs blocked this decrease in response latency. However, the lack of group differences on proportions of false alarms and side bias during the flashing houselight manipulation, and the mean side bias proportions in Figure 5, indicate that immunotoxic lesion animals did not differ from sham lesion animals in their ability to learn to ignore the irrelevant stimuli or identify the location of the relevant stimulus. Thus, mean lever press latencies in Table 1 illustrate that response latency deficits appear independent of the learning curve. Therefore, it is difficult to tie the effects on lever press latency directly to learning. Rather, these results may indicate that PPC cholinergic neurons play a role in maintenance of processing efficiency within the rat attention system.

Similarly, the increased omissions in the excitotoxic lesion group could be interpreted as indicative of detriments to learning. This effect of lesion was evident only during the pre-trial houselight sessions. These animals appeared to have learned to ignore the irrelevant stimuli in the flashing condition, but had difficulty in a version of the task in which the irrelevant stimulus most closely resembles the relevant stimulus. Furthermore, the irrelevant stimulus in the flashing houselight condition occurs at regular intervals and more frequently, and therefore may have been easier to ignore. The

irrelevant stimulus in the pre-trial house light condition occurs only immediately before a signal or non-signal event, and thus irregularly due to the variable inter-trial-interval as well as less frequently. The introduction of the pre-trial houselight was accompanied by a greater increase in false alarms and side bias across all groups than in the flashing houselight condition. Thus data from the pre-trial houselight manipulation indicates animals may have more difficulty ignoring a single increase in chamber illumination in this task, which led to more left lever presses.

When animals in the excitotoxic lesion group initiated a response to the left lever following the pre-trial houselight they were not rewarded. Thus, an impairment in learning could explain this groups' increased numbers of omitted trials; because of a diminished ability to learn to ignore the irrelevant stimulus and identify the location of the relevant stimuli, animals were more likely to continue committing false alarms and subsequently were not rewarded for a response to the left lever following a single increase in chamber illumination. The lack of reward following a response could have led animals to omit more trials. However, impairment in learning in the excitotoxic lesion group would have been more strongly supported by consistently elevated proportions of false alarms or side bias. In the present study, no significant differences were detected between lesion groups on the extent of side bias or false alarms. Thus, the proportion of omitted trials occurred independently of the learning curve illustrated by the mean side bias proportions in Figure 5, and like lever press latency, is difficult to attribute to a learning impairment. A more parsimonious explanation of the results of the present study is that the PPC in the rat appears to play a role in ignoring irrelevant stimuli, focusing attention, and subsequently initiating a response.

It is worth noting that further examination of means in Table 2 indicates that animals in this group tended to commit more false alarms and have a higher proportion of bias to the left lever. The lesions in this group did not uniformly damage the entire PPC in all animals. It is therefore possible that a significant difference would have been detected in both of these measures, as well as the number of omissions had lesions been more complete in all animals.

*Summary*

Variants of the McGaughy and Sarter attention task were used to assess the effects of lesions on performance in the present study. Neither excitotoxic lesions nor selective lesions of cholinergic neurons disrupted performance in the standard attention task. Significant effects were observed only in the tasks that required animals to differentiate relevant stimuli from irrelevant stimuli. Damage to large portions of the PPC with infusions of excitotoxic chemicals increased the number of omitted trials and removal of cholinergic input alone elevated lever press latencies.

The effects of lesions do not appear to reflect impairments in sensory motor or motoric function, nor can they be attributed to a deficit of response initiation independent of attentional processes. Analyses of behavioral data imply that the PPC of the rat may, like the human and primate PPC, play a role in attention. The effects of removal of PPC cholinergic inputs alone imply that these neurons help mediate the processing efficiency of the attentional network. Damage to the entire PPC detracted from rats' ability to ignore irrelevant stimuli. Future studies seeking to clarify the role of the region of the rat neocortex in these cognitive processes are needed. Due to the lack of uniform damage to the entire PPC in the excitotoxic lesion group, a replication of the protocol described in

this study is necessary to determine if more complete lesions yield more substantial effects on attention and learning.

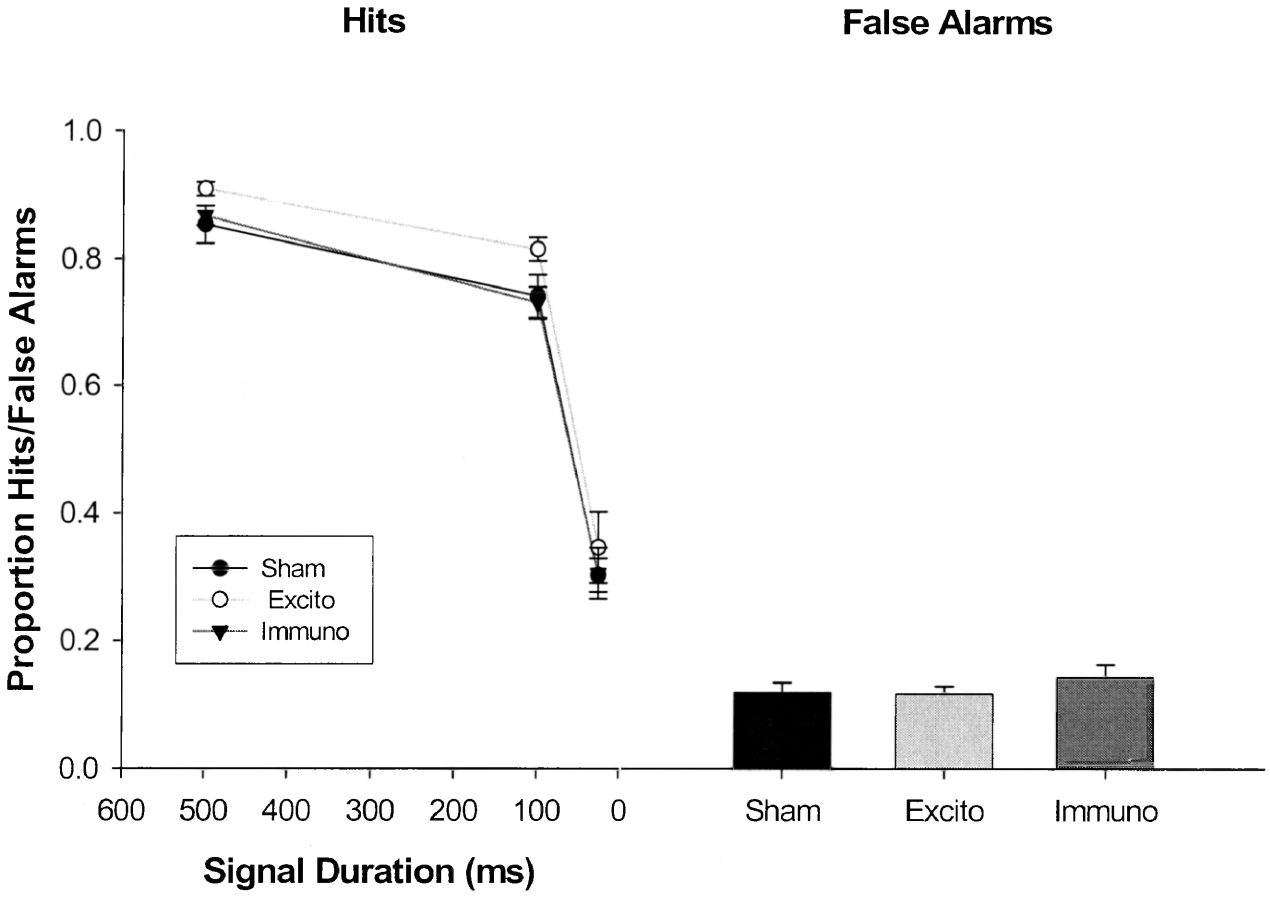
Table 1

| Group | Post-surg | Flashing H.L. | Pre-trial H.L. |
|---|---|---|---|
| Sham | 532.778 ± 27.5 | 500.872 ± 32.4 | 444.460 ±17.4 |
| Excito | 544.125 ± 28.1 | 535.102 ± 32.2 | 516.686 ± 44.3 |
| Immuno | 630.547 ± 38.0 | 633.205 ±35.5 | 613.246 ±61.3 |

Table 2

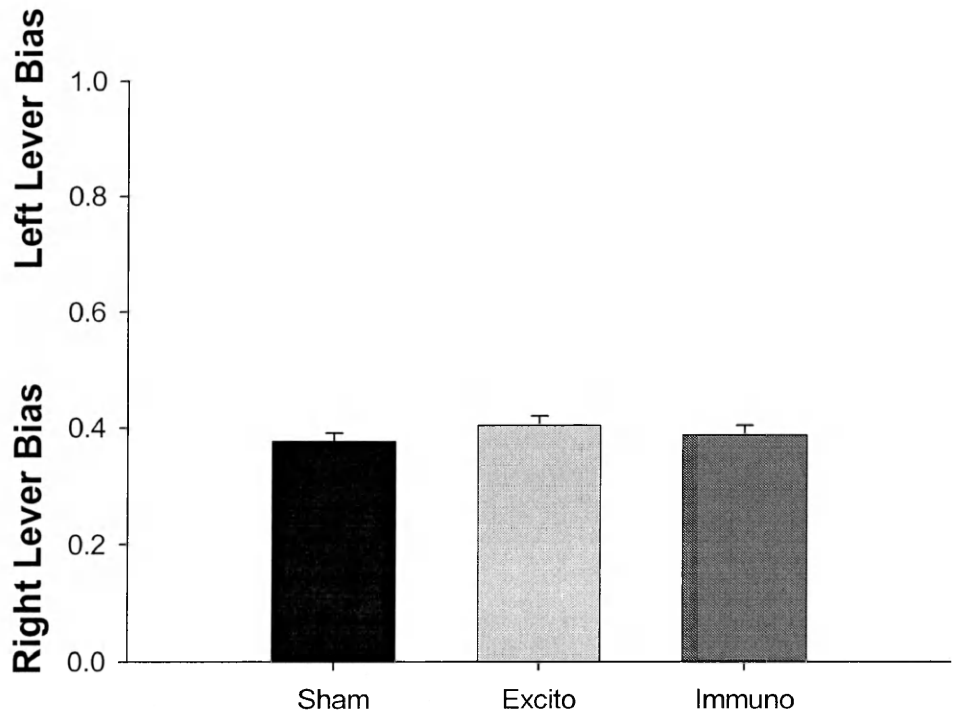
| | Post Surgery | | | | | Flashing Houselight | | | | | Pre-Trial Houselight | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Hits | FA | Side Bias | PC Lat | Omits | Hits | FA | Side Bias | PC Lat | Omits | Hits | FA | Side Bias | PC Lat | Omits |
| Sham | 0.63 ± 0.03 | 0.12 ± 0.02 | 0.38 ± 0.01 | 534 ± 40.3 (ms) | 6.2 ± 1.9 (%) | 0.56 ± 0.02 | 0.17 ± 0.02 | 0.34 ± 0.01 | 544 ± 49.0 (ms) | 6.0 ± 1.2 (%) | 0.59 ± 0.03 | 0.29 ± 0.03 | 0.44 ± 0.02 | 551 ± 39.6 (ms) | 7.7 ± 0.7 (%) |
| Excito | 0.69 ± 0.02 | 0.12 ± 0.01 | 0.41 ± 0.02 | 627 ± 36.4 (ms) | 7.3 ± 2.4 (%) | 0.55 ± 0.03 | 0.20 ± 0.03 | 0.35 ± 0.02 | 688 ± 94.3 (ms) | 9.2 ± 1.8 (%) | 0.64 ± 0.04 | 0.38 ± 0.06 | 0.59 ± 0.08 | 664 ± 52.0 (ms) | 16.2 ± 7.6 (%) |
| Immuno | 0.63 ± 0.02 | 0.14 ± 0.02 | 0.39 ± 0.02 | 541 ± 38.0 (ms) | 7.3 ± 2.0 (%) | 0.64 ± 0.03 | 0.28 ± 0.07 | 0.42 ± 0.04 | 515 ± 48.2 (ms) | 10.3 ± 2.3 (%) | 0.60 ± 0.04 | 0.31 ± 0.04 | 0.46 ± 0.37 | 590 ± 50.9 (ms) | 13.1 ± 3.3 (%) |

Figure 1



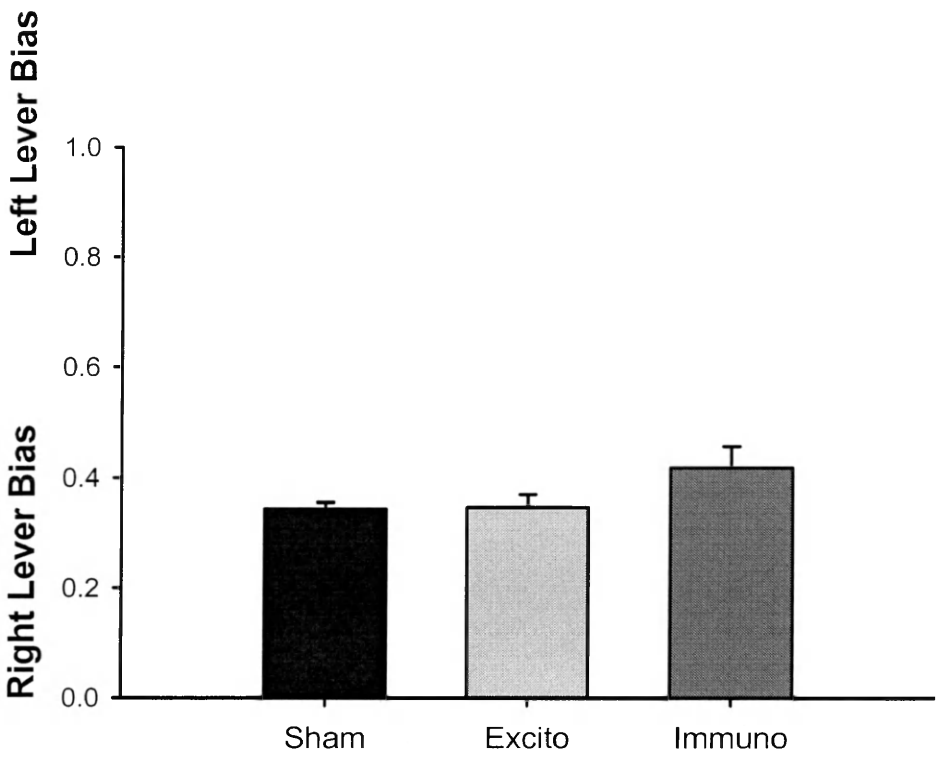

Mean proportions of hits and false alarms during the standard task over the thirty days immediately post-surgery. Neither excitotoxic nor immunotoxic lesions of the PPC lead to performance differences between groups.

Figure 2



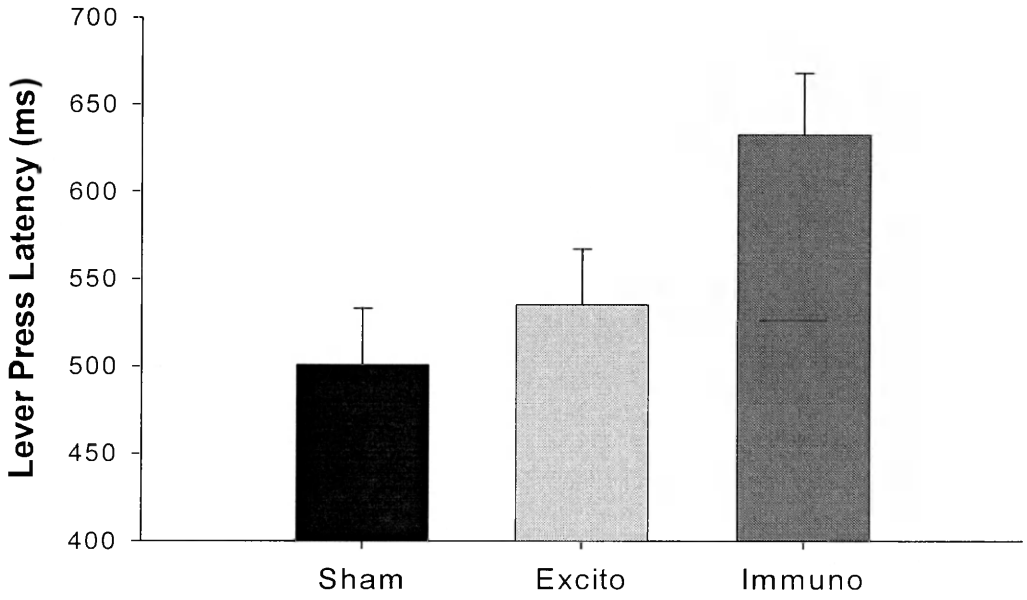

Proportions of responses to the hit/false alarm lever compared to the total number of responses for the thirty days immediately post-surgery. Lesions did not affect performance on the standard task.

Figure 3



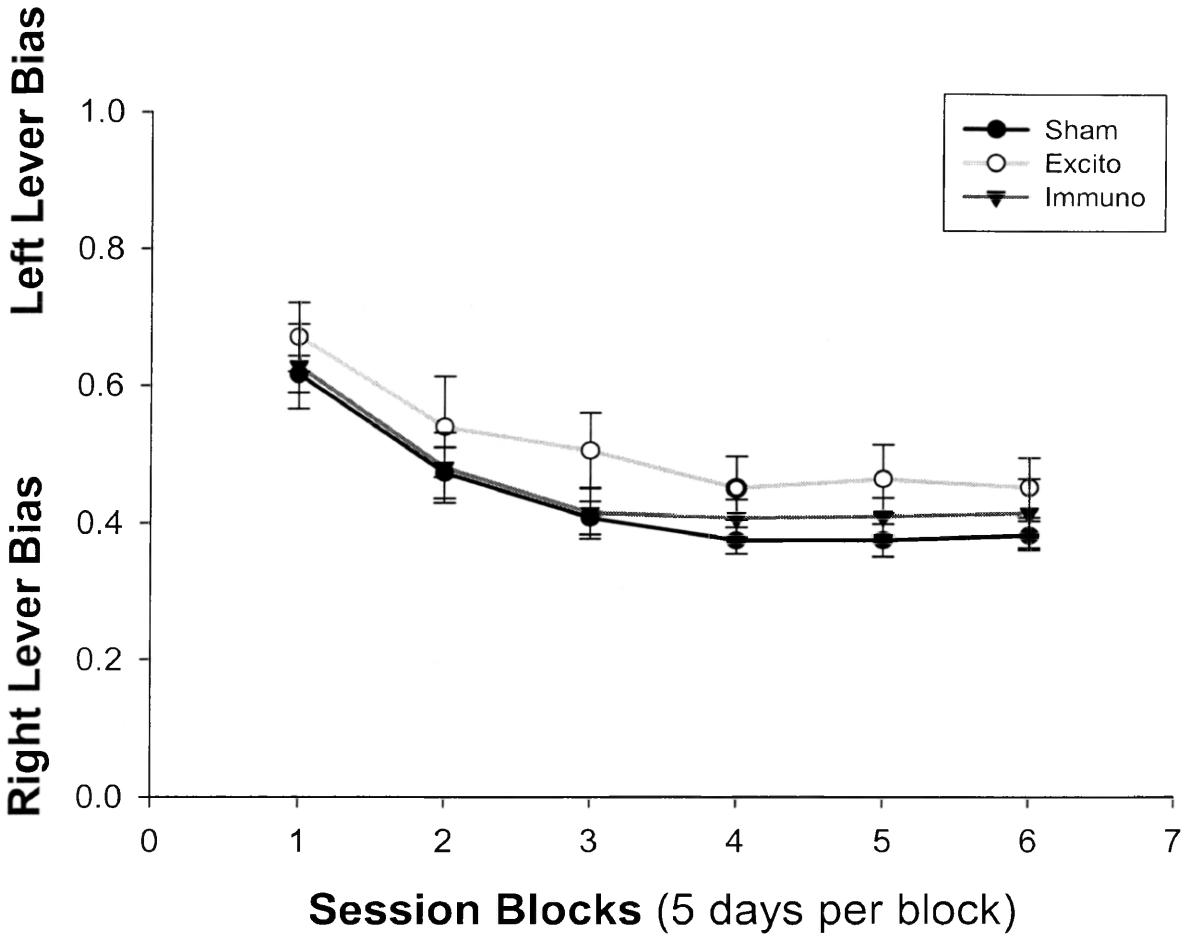

Mean proportions of responses to the hits/false alarm lever per responses to both levers. Animals in the immunotoxic lesion group exhibited a trend towards increased responses to the hit/false alarms lever relative to the sham and excitotoxic lesion groups during the flashing houselight manipulation, however trend did not reach statistical significance.

Figure 4



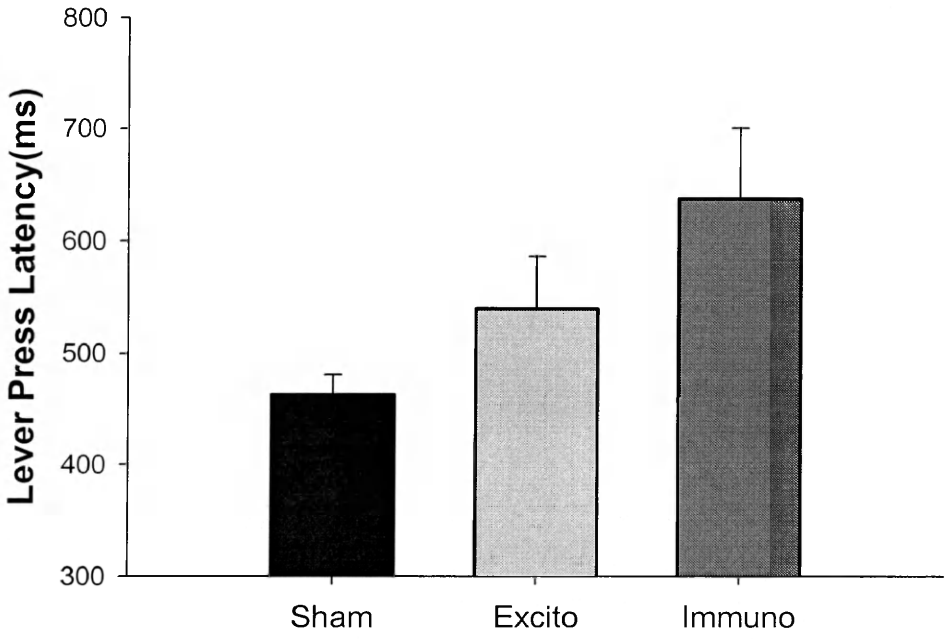

Average lever-press latency for flashing houselight manipulation sessions. Animals in the immunotoxic lesion group took significantly longer to respond to signal and non-signal events than animals in the sham lesion group.

Figure 5



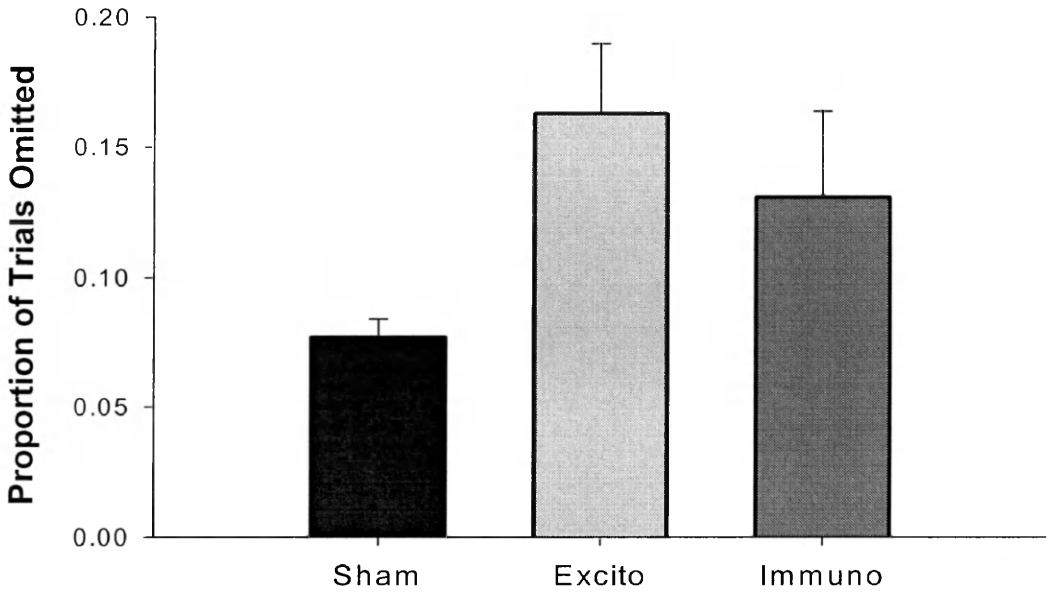

Mean proportion of responses to the hit/false alarm lever out of all responses during the pre-trial houselight manipulation. Animals in all groups exhibited an increase in this proportion during the first five days on the task, although this effect was attenuated with repeated exposure to the pre-trial houselight.

Figure 6



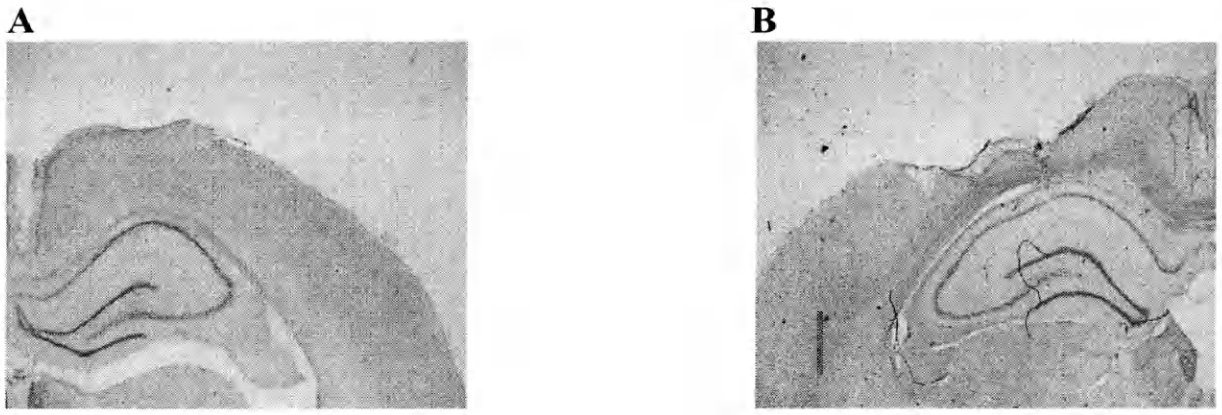

Average lever-press latency across thirty days on testing on the pre-trial houselight manipulation. As in the flashing houselight sessions, animals in the immunotoxic lesion group took significantly longer to respond to signal and non-signal events than animals in the sham lesion group.

Figure 7



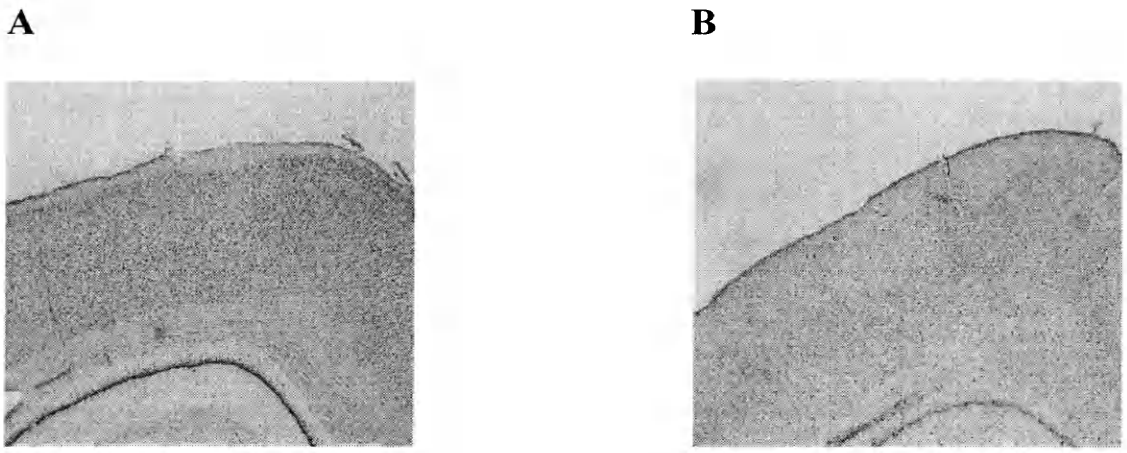

Mean proportion of trials omitted across all thirty days of testing on the pre-trial houselight task. Animals in the excitotoxic lesion group omitted significantly more trials than animals in the sham lesion group.

Figure 8



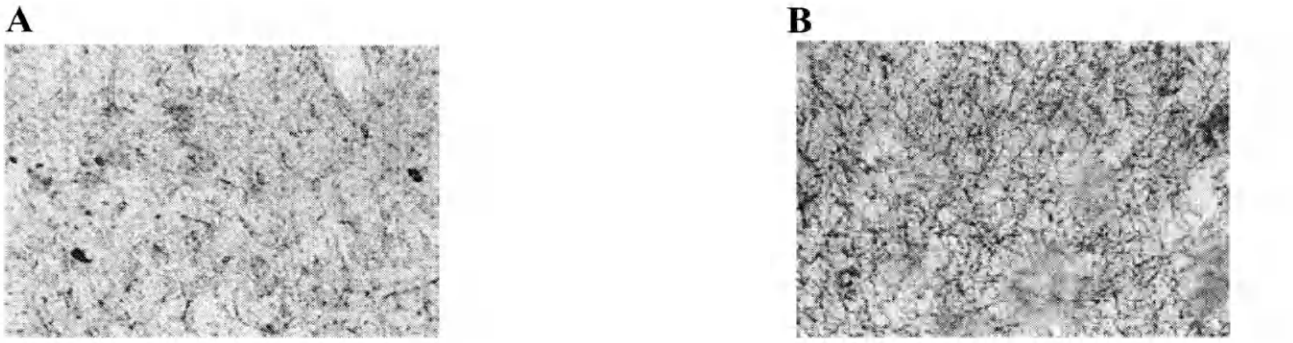

Photomicrographs of a representative cresyl violet stained sham lesion (A) and excitotoxic lesion (B) magnified 20X. Infusions of the excitotoxin NMDA resulted in a nearly complete loss of the posterior parietal cortex while sparing tissue medial, lateral, and ventral of the lesion site.

Figure 9




Photomicrographs of a representative cresyl violet stained (A) and acetylcholinesterase stained animal from the immunotoxic lesion group magnified 40X. Infusions of 192 IgG-saporin spared tissue in the posterior parietal cortex as revealed by cresyl violet staining (A), and yielded lighter acetylcholinesterase staining in the area of the posterior parietal cortex (B).

Figure 10




Photomicrographs of the posterior parietal cortex representative animal from the immunotoxic lesion group (A), as well as the posterior parietal cortex of a representative animal from the sham lesion group (B) magnified 400X. Acetylcholinesterase staining reveals a marked reduction in cholinergic fiber density in the area targeted by the immunotoxic lesion in comparison to other animals not infused with 192 IgG-saporin

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# VITA

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