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Effects of Neonatal Hippocampal Lesions on Contextual

Learning and Memory in Monkeys

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Effects of Neonatal Hippocampal Lesions on Contextual Learning and Memory in Monkeys

By

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M.A., Emory University, 2006

B.A., Yale University, 2004

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An abstract of a dissertation submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Psychology

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Abstract

Effects of Neonatal Hippocampal Lesions on Contextual Learning and Memory in Monkeys

By Courtney Glavis-Bloom

A large body of evidence stemming from electrophysiological recordings, neuroimaging, lesion, and developmental studies has provided strong support to the assertion that the hippocampus is critical for accurate contextual learning and memory. Developmental lesion studies in primates are inconclusive as regards to the role of the hippocampus in contextual memory given that, in all previous monkey studies, the hippocampal lesions included cortical areas adjacent to the hippocampus. Thus, it remains possible that the impairment in contextual memory may have resulted from residual damage to the adjacent cortex, especially given that selective damage to parahippocampal areas (TH/TF) impairs contextual memory. Therefore, this study examined whether selective neonatal hippocampal lesions in monkeys (*Macaca mulatta*), which left the surrounding cortical areas intact, affect contextual learning and memory compared to controls. Monkeys were tested with an automated touch-screen apparatus so that stimuli and contextual cues could be manipulated independently of one another. The data suggests that animals with neonatal hippocampal lesions have sparing of function in regards to contextual learning and memory when (1) contextual information is irrelevant or relevant for good discrimination performance, (2) transferring a contextual rule to new discriminations, (3) discriminating between stimuli presented in previously associated contexts, and (4) on an incidental recognition task with context manipulations. These

findings are at odds with studies examining contextual learning and memory in monkeys with selective adult hippocampal lesions, and those with non-selective neonatal hippocampal lesions, which have demonstrated impairment in contextual learning and memory. Therefore, the sparing of function seen in this study may be due to the early nature of the damage and the plastic nature of the infant brain, as well as the intact medial temporal lobe cortical areas as a result of the lesion methodology. Specifically, by removing the hippocampus early in life, before it has begun to function, the parahippocampal (TH/TF) and perirhinal cortices may be able to support context processing throughout life.

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Table of Contents

List of Tables

List of Figures

INTRODUCTION

Memory is a cognitive process fundamental in virtually every aspect of social, emotional, and cognitive functioning. Recent decades of memory research have led to significant progress in understanding mnemonic function and its neural substrates, and have led to the view that memory is not a unitary process but can be divided into separate systems supported by different neural circuits (for review, see Sherry & Schacter, 1987). For the purpose of this paper, we will focus on the declarative memory system, mediated by the medial temporal lobe.

The medial temporal lobe includes a set of cortical areas that receives highly processed multimodal information. These temporal cortical areas are involved in the storage and retrieval of stimulus representations, and are viewed as storing information or knowledge independently of the context in which they are learned (fact or semantic memory). This cortically processed information is sent to the hippocampus (defined as the CA fields, dentate gyrus, and subicular complex) that in turn acquires, stores and recollects inter-item relations and their context, and supports recollection of specific episodes or events (Brown & Aggleton, 2001; Eichenbaum, 2003; Lavenex & Amaral, 2000; Mishkin et al., 1997; O'Reilly & Rudy, 2001; Yonelinas, 2002). Thus, the hippocampus is critical when task demands require learning and retaining relationships among different items or among items and their spatial relationships, or among items and the context in which they occur. This later type of relation (i.e. that between objects and the context in which they are presented) will be further investigated in the present paper.

Before reviewing the literature on the critical role of the hippocampus in contextual memory, it is important to define what is meant by "context". The term

"context" or "contextual information", as defined by Smith and Mizumori (2006), refers to a particular situation or set of circumstances that must be differentiated from other situations or sets of circumstances in order for subjects to select the appropriate behavioral output. Context can be as complex as the physical environment in which an event occurred or as simple as the color of the background onto which a letter appeared. Studies in humans have manipulated contexts within this range of complexity and found that changing semantic (Light & Carter-Sobel, 1970; Tulving & Thompson, 1973; Reder et al., 1974; Stumpfel & Kirsner, 1986), cue specific (Dalton, 1993; Russo et al., 1999), olfactory (Cann and Ross, 1989), auditory (Geiselman and Bjork, 1980) or environmental (Smith, 1985; Smith, 1986; Emmerson, 1986; Canas and Nelson, 1986) contexts between study and test disrupt recognition memory. Similarly, a few studies in rodents (Dellu et al., 1997; Aggleton, 1999) and primates (Pascalis & Bachevalier, 1995; Pascalis et al., 2009) have demonstrated that, although animals could recognize an object when presented in an environment different from that in which it was first encountered, recognition was best when the familiar context was used. For example, Dellu and colleagues (1997) exposed rats to two identical objects in one context, and a different pair of identical objects in another context. During the test, the experimenter placed a single copy of each object in both contexts, and rats were allowed to explore. Rats spent more time investigating the object that was new to the context than the object that was previously experienced in the context. Therefore, the rats seem to have established a representation of the two contexts and what they had encountered in them, so that when they encountered something not in the correct context, they explored it further.

Although an extensive body of literature has provided evidence for the role of the hippocampus in contextual processing, the majority of this research has failed to make a distinction between contexts that include spatial information, and contexts that do not. This distinction is important in light of the large body of research implicating the hippocampus in spatial processing (for review see Burgess, 2008; Moser et al., 2008). Therefore, tasks that measure contextual memory but which also include the use of spatial information to be solved may not be useful to assess whether the hippocampus mediates or not contextual learning and memory in and of itself. Evidence from electrophysiological recordings, neuroimaging, lesion, and developmental studies will be reviewed below with the specific goal of discussing whether or not the memory tasks truly reflected contextual memory per se.

Contextual Tasks Including Spatial and Temporal Cues

Electrophysiological Studies

Electrophysiological recordings of hippocampal place cells (O'Keefe & Dostrovsky, 1971) first demonstrated the high sensitivity of these cells to context manipulations (Smith & Mizumori, 2006). For example, in a "plus" maze, rats learned to distinguish between two contexts that differed in their spatial and temporal cues to receive a food reward (Smith & Mizumori, 2006). Progressive learning was associated with the development of two highly differentiated spatial firing patterns of the hippocampal cells, each related to one of the contexts. When muscimol was infused into the hippocampus to temporarily deactivate the structure during training sessions, there was a loss of this differentiated spatial firing pattern and, at the same time, an emergence

of highly inflexible behavioral strategies during the test trials (Smith & Mizumori, 2006). Likewise, Moita and colleagues (2003) recorded from the hippocampus in freely moving rats during an auditory fear-conditioning task, and found that following the acquisition of an association between a conditioned stimulus (tone) and an unconditioned stimulus (foot shock), hippocampal neurons fired in response to the tone only when the rat was in the cell's place field. The authors suggested that this finding could elucidate how the hippocampus contributes to context-specific memory formation during associative learning. However, because recordings were done from hippocampal cells that fired depending on the location of the rat in its environment, the findings may be able to elucidate how the hippocampus contributes to memory formation when the nature of the task necessitates a spatial component, but can say very little in regards to contextual processing without spatial components.

Neuroimaging Studies

Results from neuroimaging studies further suggest that the hippocampus is involved in contextual learning and memory when spatial aspects are included in the task. For example, activation of the hippocampus has been observed during recognition of the contextual information associated with objects (Burgess et al., 2001). Subjects navigated through a virtual reality town and collected objects from different places and people in the town. Then, while undergoing functional magnetic resonance imaging (fMRI), subjects were asked a series of questions in the form of choice tests about the objects they had collected, ranging from "What object did you collect in this location?" to "What object did this person give you?" Because all information had been encoded within the spatial environment of the virtual reality town, and because questions were asked about

specific locations within the town, contextual cues are difficult to disambiguate from the spatial cues that were necessary to perform well on the task.

Hippocampal Damage in Patients

Patients with damage to the hippocampus can provide a unique view on cognitive processes mediated by the hippocampus. For example, Spiers and colleagues (2001a) tested patients with a unilateral temporal lobectomy on the same virtual reality task as discussed in the section above, and found that these patients could remember information about specific objects, but could not recognize contextual information that was associated with the objects. Similarly, amnesic patients with Korsakoff's syndrome or non-specific MTL damage did not benefit from the availability of contextual cues on a task that required them to remember different "target" images amongst "distracters", specifically when the "distracters" later became "targets" and vice versa (Parkin et al., 1990). Finally, amnesic patients were impaired on a task requiring visual search of targets, even when consistent, but subconscious, visual cues were presented, a manipulation that usually helped performance of control subjects (Chun & Phelps, 1999).

Although all of these lesion studies demonstrate the role of the hippocampus in contextual processing, each has used memory tasks than could be solved by the spatial cues provided in the task. For instance, in the Spiers and colleagues' study (2001a), similar to the Burgess and colleagues' study (2001) discussed in the "Neuroimaging Studies" section above, all contextual questions asked to the patients may be answered using spatial cues provided by the three-dimensional, virtual reality environment. Parkin and colleagues' (1990) study contained contextual cues that were temporal in nature, presenting an additional challenge to the interpretation of these results since memory for

temporal order represents an important component of episodic memory processes mediated by the hippocampus (Tulving, 2002; Kesner & Hunsaker, 2009; Tulving & Markowitsch, 1998). Additionally, Chun and Phelps (1999) assessed whether a subconscious visual cue, which consisted of a spatial arrangement of objects, would assist amnesics in their search for a target. This contextual cue, which is entirely spatial in nature, may preclude a clear conclusion regarding the role of the hippocampus in contextual processing per se. Finally, because the damage in all of these patients extended beyond the hippocampus proper and into the surrounding cortical areas, the inability to use contextual information, either with or without a spatial component, cannot be ascribed specifically to a dysfunction of the hippocampus per se.

Developmental Studies

The effects of early damage to the hippocampus in humans would serve as an excellent comparison to damage created neonatally in animals. One such patient, Jon, has selective bilateral hippocampal pathology caused by perinatal anoxia. When tested in the same virtual reality town as has been described above, Jon demonstrated poor recognition of contextual information (Spiers et al., 2001b). Specifically, Jon was able to remember information about objects encountered while navigating in the virtual town, but was unable to recollect contextual information that was associated with the objects. While these results are intriguing, interpretation of them is difficult given that the impairment could be associated with the use of spatial cues within the contextual memory task and that the integrity of the adjacent cortical areas is difficult to demonstrate using neuroimaging measures (Adlam et al., 2009), and could be associated with the contextual memory impairment observed.

Contextual Tasks Not Including Spatial Cues

As opposed to the above studies, several studies have examined the role of the hippocampus in contextual processing making certain that spatial cues cannot provide additional information for performance on the memory task. These studies provide crucial and more direct evidence for the role of the hippocampus in contextual learning and memory because any unique firing patterns from hippocampal neurons, or any deficits following damage to the hippocampus, cannot be attributed to its role in spatial processing.

Electrophysiological Studies

The hippocampus has been shown to have different neuronal responses to a variety of non-geometric changing task demands. For example, Anderson and Jeffery (2003) recorded from subfield CA1 in the rat hippocampus while rats explored several environments that differed in their color (black vs. white) and/or odor (lemon vs. vanilla). They found different firing patterns depending on which context the rats were in. That is, some neurons fired to changes in the color, others to changes in odor, and still others to the combination of colors and odors, which discriminated one context from another. Similarly, Hayman and colleagues (2003) and Bostock and colleagues (1991) found that the firing of hippocampal place cells changed in response to changes in color of the environment, when spatial location was held constant.

Neuroimaging Studies

The neural response to contextual cues in the absence of spatial components has been examined using fMRI. For example, Goh and colleagues (2004) assessed which brain structures adapted (i.e. showed lessened activation) to repeated exposure to object-

scene pairings in subjects who passively viewed the stimuli. They found bilateral adaptation in fusiform areas when the same object was repeatedly shown either on a novel or repeated scene, bilateral adaptation to parahippocampal cortical regions when background scenes were repeated, regardless of whether they were presented behind a novel or repeated object, and hippocampal adaptation when subjects were shown a novel object presented on a novel scene. These results suggest that fusiform areas are sensitive to object processing, parahippocampal cortical areas are sensitive to background scene processing, and the hippocampus is sensitive to the association between background scenes and objects.

Hippocampal Damage in Patients

Patients with damage to the hippocampus have provided additional evidence for its role in contextual learning and memory when the memory task controlled for spatial cues. For example, amnesic patients were impaired in using semantic contextual cues on a task requiring them to choose a "target" word, even when words that were meaningfully relevant to the target were presented along with it (Mayes et al., 1992). More direct evidence of the role of the hippocampus in contextual learning and memory comes from the study of a few patients with damage limited specifically to the hippocampus. For example, Patient YR, who sustained selective damage to the hippocampus from an ischemic event (as demonstrated via MR imaging), was able to recognize a familiar object when it was presented in the same context (background), but not when it was presented in a new context (Pascalis et al., 2009).

Hippocampal Damage in Adult Animals

Lesion studies in animals provide mounting evidence for the involvement of the hippocampus in contextual learning and memory without spatial components. For instance, hippocampal lesions in adult rats impaired conditioned fear responses to non-spatial contextual stimuli (Kim & Fanselow, 1992; Phillips & LeDoux, 1992). That is, whereas normal rats will display an innate defensive freezing response when placed into a conditioning context in which they were previously shocked (Rudy et al., 2002), rats with hippocampal lesions will not exhibit this type of behavior (Kim & Fanselow, 1992; Phillips & LeDoux, 1992). Additionally, hippocampal or entorhinal cortex lesions in adult rabbits rendered subjects insensitive to non-spatial changes in context such as visual, olfactory, and tactile cues (Penick & Solomon, 1991; Freeman et al., 1997). Kennedy and Shapiro (2004) trained adult rats to approach different goals depending on their internal motivational state (hunger or thirst). The goals at which food or water could be obtained were indicated only by non-spatial cues, such as differences in color and illumination. Following acquisition of the contextual cues that indicated where food and water could be obtained, rats underwent fornix transaction or neurotoxic lesions to the hippocampus. Following surgery, rats with fornix transaction or neurotoxic hippocampal lesions were unable to use the pre-surgically acquired contextual cues to locate food and water accurately. These results suggest that the hippocampus is necessary for using internal motivational state to approach goal locations indicated by non-spatial contextual cues.

There are a few studies, however, which have found no impairment on conditional discriminations following hippocampal lesions. For example, when rats were placed into

one of two chambers differing in their visual, tactile, auditory, and olfactory features, and learned to press one lever to obtain food in one chamber, and a different lever to obtain food in the other chamber, performance of rats with hippocampal lesions was indistinguishable from that of normal rats (McDonald et al., 1997; Good et al., 1998; Coutureau et al., 2002). Similarly, monkeys with fornix transections performed in adulthood were impaired on delayed match-to-sample and discrimination learning when stimuli were naturalistic scenes (Gaffan, 1993, 1994a), or when objects were embedded in complex scenes, but locations were held constant (Gaffan, 1994b, object-in-place task). More importantly, selective neurotoxic lesions of the hippocampus in adulthood, which spare the surrounding cortical areas, impaired performance on discrimination problems learned pre- and post-operatively when information about the background was required to indicate which object was rewarded (Ridley et al., 2001). In this study marmosets were trained on a task in which two objects covered two food wells (one baited, one unbaited) on the testing tray. The selection of the correct baited object was dependent on the patterned background that was used on each trial. Thus, on one background (A), one object (a) was "correct" and on the other background (B), the other object was "correct" (b). Following surgical removal of the CA fields, subiculum and presubiculum, monkeys were re-tested on the discriminations and were impaired as compared to unoperated monkeys. Ridley and colleagues (1995) found similar deficits following small lesions of the hippocampus restricted to the CA1 field. Additionally, Dore and colleagues (1998) showed that monkeys with selective damage to the hippocampus did not use background contextual cues to enhance performance on a discrimination task. Specifically, monkeys were trained on a discrimination paradigm in

which they were required to learn which of five objects presented in an array, would deliver a reward when touched. There were a total of eight such discriminations, and on every trial the location of the objects changed so that spatial cues could not be relied upon for good performance on the task. Dore and colleagues (1998) found that monkeys with excitotoxic lesions to the hippocampus were impaired relative to controls when learning these discrimination problems, indicating that the hippocampus is necessary for using non-spatial contextual cues provided by the existence of other objects in an array. Finally, using an incidental recognition task (visual paired-comparison) Bachevalier and Nemanic (personal communication) demonstrated a lack of novelty preference when a familiar object when presented over a new background in monkeys with selective hippocampal lesions given in adulthood.

Thus, investigations of patients and animals with damage to the hippocampus in adulthood demonstrate the importance of this brain structure in learning and remembering about objects and the non-spatial contextual information associated with them.

Developmental Studies

A role for the hippocampus in non-spatial contextual learning and memory is also provided by developmental memory studies. The reasoning behind the developmental studies is that hippocampal-dependent memory functions, such as contextual memory, should emerge at a time during development when the hippocampus reaches its functional maturity. Several studies have now shown that the hippocampus has a protracted postnatal development in rodents, monkeys, and humans (see Seress, 2001 for review) that correlates with the emergence of hippocampal-dependent functions. For

example, Rudy (1993) and Rudy and Morledge (1994) found that the ability of rats to condition to contextual cues coincided with the maturation of the hippocampus at around postnatal day 21. Furthermore, the monkey's hippocampus is not fully mature and functional until approximately 1-2 years of age (Payne et al., 2009), and in humans, the hippocampus does not reach full maturity before 4-5 years of age (Overman et al., 1996; Rudy et al., 1993). Kirasic and colleagues (1980) tested context recognition memory in kindergarteners, fourth graders, and adults. Subjects studied objects in a context, and then were given a choice test where the studied objects were presented both in the context they were studied, and out of the context in which they were studied. The speed and accuracy of recognizing objects in a different context increased with age. Similarly, recognition memory for complex scenes that have real-world contextual associations (eg. flowers and a watering can) improves across development (Hock et al., 1978). Currently, no developmental studies investigating the emergence of contextual learning and memory have been done in monkeys, although we predict that such a memory ability should emerge between 1-2 years of age.

Much less, however, is known about the effects of early damage to the hippocampus on contextual learning and memory. Studies in rodents have demonstrated that neonatal damage to the hippocampal formation before the structure fully matures (i.e. < 21 days) disrupted the emergence of hippocampal-dependent functions, some of which were related to context. For example, van Praag and colleagues (1998) gave one-day-old rats unilateral electrolytic hippocampal ablations and measured their exploratory behavior and spatial navigation in a Morris water maze eight and twenty weeks following surgery. Rats with neonatal hippocampal damage did not respond to novelty of the environment

during the test of exploratory behavior. That is, rats with neonatal hippocampal lesions spent an equivalent amount of time exploring a quadrant of an open field both when there was a new stimulus and when there was not. In contrast, rats with adult hippocampal lesions and control animals spent an increased amount of time in the quadrant when a new stimulus was presented in that quadrant. These results indicate that rats with neonatal hippocampal lesions may not have been processing contextual cues. These results also suggest that in some instances, early damage to the hippocampus can cause more impairment than damage in adulthood. Similar contextual memory impairment followed neonatal hippocampal lesions in monkeys. Thus, hippocampectomized infant monkeys were able to learn discrimination problems (Killiany et al, 2005; Rehbein et al., 2005, Kazama & Bachevalier, personal communication), but were unable to retrieve the contextual information in which these problems occurred (Killiany et al, 2005; Rehbein et al., 2005). In addition, neonatal aspiration lesions of the hippocampus in monkeys (Pascalis et al., 2009) altered recognition memory when the background onto which the objects were presented was changed from study to test.

Nevertheless, these developmental lesion studies in primates are inconclusive as regards to the role of the hippocampus in contextual memory given that in all developmental monkey studies so far, the hippocampal lesions included cortical areas adjacent to the hippocampus. Thus, it remains possible that the impairment in contextual memory reported may have resulted from residual damage to the adjacent cortex.

Specific Hypotheses

To more directly investigate whether selective neonatal hippocampal lesions affect contextual learning and memory in and of itself, we designed a series of experiments using an automated testing apparatus (touch screen computer) that allowed us to manipulate stimuli and the contextual cues onto which they are presented, and to test learning abilities when the contextual cues were made irrelevant or relevant for reliable performance on the task. For the purposes of this series of experiments, contextual cues were provided by a background presented behind objects on a touch screen computer monitor, and in some of the experiments, contextual memory was assessed when the use of spatial cues was controlled for. This type of contextual cue, that is, where an association can be made between an object and the background on which it was presented, has been specifically termed "contextual binding" (Chalfonte & Johnson, 1996; Mitchell et al., 2000).

Adult monkeys that had received selective neonatal damage to the hippocampus in the first weeks of life and their sham-operated controls were used for these experiments. Given that several studies in our laboratory had already demonstrated that these animals with neonatal hippocampal lesions, like those with the same lesions acquired in adulthood, showed impaired incidental object recognition memory processes (Zeamer and Bachevalier, 2010, under revision) and spatial relational memory (Glavis-Bloom MA Thesis, 2006; Glavis-Bloom et al., 2006; Blue et al., 2009), with little evidence of functional sparing, we predicted that animals with selective neonatal hippocampal lesions would likewise be impaired in learning discrimination problems when the context onto which these problems were presented was made relevant for good

performance on the task. Conversely, we predicted that the same animals would show normal discrimination learning when the context onto which the discrimination problems were presented was made irrelevant for good performance on the task.

METHOD

Subjects

Ten rhesus macaques (*Macaca mulatta*) of both sexes (6 males, 4 females), weighing five to eight kilograms, and ranging between seven and nine years of age at the beginning of testing, were divided into two groups: an experimental group (Neo-Hibo, n = 5) and a control group (Neo-C, n = 5). Between eight and twelve days of age, animals in Group Neo-Hibo received MRI-guided neurotoxic lesions of the hippocampus and animals in Group Neo-C received sham-operations.

All animals were acquired from the MD Anderson Cancer Center Science Park breeding facility (Bastrop, TX), and brought to the primate nursery at MD Anderson Cancer Center (Houston, TX) between one and four days of age. They were hand fed a diet of infant Similac formula, and reared according to procedures developed by Sackett and colleagues (2002). These procedures included daily social interactions with peers and humans, along with cognitive testing (for more detail, see Goursaud & Bachevalier, 2007). Between 1.5 and three years of age, animals were transferred to Emory where they were housed individually at the Yerkes National Primate Research Center Neuroscience Building, given water *ad libitum*, and fed fresh fruit, vegetables, and monkey biscuits (Lab Diet #5037, PMI Nutrition International Inc., Brentwood, MO) daily. Animal housing rooms were maintained on a 12:12 hour light-dark cycle.

The MRI-guided surgical procedures were carried out while the animals were at the University of Texas Health Science Center in Houston and were approved by the Internal Animal Care and Use Committee of the University of Texas-Houston (these procedures were completed by others, before the author of this dissertation had joined the laboratory). Behavioral testing occurred at the Yerkes National Primate Research Center where these animals were moved and was approved by the Internal Animal Care and Use Committee of Emory University.

During behavioral testing for Experiments 1 through 5, food intake was adjusted for each animal to ensure adequate motivation during the tasks, but the animals' weights were maintained at 85% or higher of their normal weight. For Experiment 6, food intake was not restricted. Also, to reduce potential effects of circadian rhythm on the subject's motivation to perform on the tasks, each animal was tested at the same time each day.

Neuroimaging and Surgical Procedures

Neuroimaging Procedures

Before surgery, each infant monkey in Group Neo-Hibo underwent an MRI of the brain in order to calculate the coordinates for neurotoxin injection sites during surgery. They were first sedated by placing the animal into an inducing box to inhale Isoflurane (1.0 – 3.0% to effect), and then intubated with an endotracheal canula to maintain and monitor anesthesia through the entire scanning procedure. The sedated animals were taken to the University of Texas M.D. Anderson Cancer Center MRI facility in a temperature and humidity controlled incubator. Once in the MRI facility, in preparation for the surgical procedure immediately following the neuroimaging procedures, the

animal's head was shaved and an intravenous catheter was placed in the saphenous vein. Before immobilizing the animal's head in a stereotaxic apparatus, EMLA cream (lidocaine 2.5% and prilocaine 2.5%) was applied to the ear canals and to the skin just below the eye orbits to reduce any pain caused by the ear bars and eye pieces of the apparatus, respectively. Ophthalmic ointment was applied to the eyes to prevent ocular dryness during the procedure.

The animal's head was then secured in a non-ferromagnetic stereotaxic apparatus (Crist Instruments Co., Inc., Damascus, MD) and centered in the GE Sigma 1.5 Tesla Echo Speed scanner (GE Medical Systems, Milwaukee, WI). Three types of images were taken using a 3-inch coil over the animal's head to increase the resolution of the MR images. The first type of images (T1-weighted spin-echo sequence, echo time (TE) = 11ms, repetition time (TR) = 450ms, contiguous 4mm sections, 12cm field of view (FOV), 256x256 matrix) was acquired in the sagittal plane and was used to align the other two types of images that were both taken in the coronal plane. The second set of images (3D T1-weighted fast spoiled gradient (FSPGR)-echo sequence, TE = 2.6 ms, TR = 10.2 ms, 25^{0} flip angle, contiguous 1 mm sections, 12 cm FOV, 256 x 256 matrix) provided high-resolution structural images that were used to identify the hippocampus, select the injection sites along the structure, and calculate three dimensional coordinates of each site. The third set of images (Fluid Attenuated Inversion Recovery (FLAIR) sequence, TE = 140 msec, TR = 10000 msec, inversion time (TI) = 2200, contiguous 3 mm sections, 12 cm FOV, 256 x 256 matrix) was repeated three times with an offset of 1mm in the posterior direction to obtain one image every millimeter. This last series of MR images was used for comparison with the post-surgical FLAIR images to identify

location of hypersignals. Throughout the entire 45 to 60 minute MRI scanning procedure, the animal's heart rate, body temperature, and SPO_2 were monitored. Five to eight days after surgery, the same three sets of MR images were taken and were used for assessment of lesion extent (see below).

Determination of Injection Coordinates

The FSPGR images were used to locate three reference points, which were used to calculate the stereotaxic coordinates for each injection site. First, the coronal image that showed the tips of the ear bars (filled with vitamin E) were selected and the anterior-posterior (A/P) and dorsal-ventral (D/V) MR coordinates for the left and right ear bars were recorded. Second, using the same image, the superior sagittal sinus and the ventral tip of the third ventricle at the midline were identified and their MR coordinates in the medial-lateral (M/L) plane were recorded. The MR reference points (A/P, D/V, and M/L) of each injection site were also recorded and then transposed into stereotaxic coordinates using the MR and stereotaxic reference points of the earbars. Seven to eight injection sites were selected per hippocampus. Posteriorly, five to six injection sites were located two millimeters apart and centered in the body of the hippocampus, and anteriorly, where the uncus was visible, two injection sites were selected two millimeters apart and positioned one medially within the uncus and one laterally within the head of the hippocampus.

Surgery

After completion of the pre-surgical scans, animals were maintained anesthetized and secured in the stereotaxic apparatus, and immediately transported to the surgical suite where the animals were prepared for the surgical procedures. The scalp was disinfected

with Nolvasan Solution and an intravenous drip solution (0.45% NaCl) was given to maintain hydration. A local anesthetic (Marcaine 25%, 1.5m., s.c.) was injected along the incision line at the midline (beginning at the supra-orbital ridge and ending at the occipital notch) to reduce pain, and after the incision, the skin and galea were gently retracted. A bone opening was made just above the injection sites in each hemisphere and the exposed dura was slit open to allow passage of the Hamilton syringes held onto the Kopf electrode manipulators (David Kopf Instruments, Tujunga, CA). Injections of the neurotoxin, ibotenic acid (Biosearch Technologies, Novato, CA) were made in each hemisphere simultaneously for each of the 7-8 sites selected. A total of 3.2-5.4 µl (10mg/ml in PBS, pH 4.0) was injected at a rate of 0.2 µl/30sec. After each injection, the needles were kept in place for an additional three minutes to maximize diffusion of the neurotoxin into the hippocampal tissue and minimize its spread along the needle path when the needle was retracted. The incision was closed in anatomical layers, the animal was removed from the Isoflurane gas anesthesia, and then recovered in the surgical facility until it regained consciousness.

Sham surgeries followed the same procedures outlined above, except that there were no needle penetrations and no injections done.

Pre- and Post-surgical Treatment

Beginning 12 hours before surgery, and maintained until post-surgical day seven, all animals received dexamethazone sodium phosphate (.4 mg/kg, s.c.) and oral doses of Cephazolin (25 mg/kg) to control swelling and minimize risk of infection, respectively. A topical antibiotic ointment was also applied to the incision daily. Additionally,

acetaminophen (10mg/kg, p.o.) was given four times a day for three days after surgery to reduce pain.

Lesion Verification

The extent of ibotenic acid lesions was assessed with the pre- and postsurgical MR images, both Fluid Attenuated Inversion Recovery (FLAIR) and 3D T1 FSPGR images, according to procedures already described by Nemanic et al. (2002). The FLAIR images were used to identify areas of hypersignal (indicative of brain edema caused by cell death) and were compared to the FSPGR images to accurately identify the borders of the brain structures showing hypersignal. The extent of hypersignal seen on each image (1mm interval) was then drawn onto matched 1mm-coronal sections through the brain template of a normal infant rhesus macaque (approximately 12 days of age). These drawings were then imported into a Java-based image analysis program (ImageJ; Rasband, 1997) to measure the surface area (in pixels square) of damage to intended and unintended brain areas. For each hemisphere, the total volume of damage for a given area was calculated by summing the surface damaged on each section and multiplying this sum by image thickness (1 mm). The volume of damage was then divided by the normal volume of this area estimated from the brain template to estimate a percentage of the total volume damaged in a given brain area.

General Behavioral Procedures

Experiments 1 through 5 took place within a sound-attenuated testing box equipped with a touch-screen computer and an automatic mini M&M dispenser (Med Associates, Inc., St. Albans, VT) mounted on a shelf secured to the outside of the testing

box (see Figure 1). Each day, the animal was brought to the testing room in a transport cage that was positioned approximately 15cm in front of the touch screen. The software "Presentation" (Neurobehavioral Systems Inc., Albany, CA) was used to present stimuli (digitized pictures of objects displayed over either a black background or a scene) to the monkey on the touch screen computer. The program controlled the number and order of the trials, locations of the stimuli on the screen, delivery of the food rewards (mini M&Ms), and length of the inter trial interval (ITI). The program also recorded several parameters about the animal's performance on each experiment, including test session and trial number, correct or incorrect choice, the location on the screen of the correct choice and the chosen location, and the latency from stimulus onset to choice. In all cases, trials remained displayed on the screen until the monkey made a choice. When a correct choice was made, a "ding" coincided with the dispensing of a mini M&M into a food cup located directly underneath and in the center of the touch screen, and the offset of the stimuli. When an incorrect choice was made, a "door closing" sound coincided with the offset of the stimuli, but no reward was dispensed. The details of the behavioral procedures used in each of the 5 experiments will be described below. After completing each daily session, the monkey was wheeled back to their home cage and fed their daily ration of food.

Experiment 6 took place within an enclosure comprising a computer screen positioned approximately 40 cm in front of a monkey seated in a primate chair (Crist Instruments, Damascus, MD). Visual stimuli were presented onto the screen via a computer that controlled the presentation of the stimuli. Above the screen, a video camera was positioned so that the monkey's eyes were visible and their movements could

be recorded. The video feed was also displayed on a television screen so that the experimenter could monitor the monkey during the task. The details of the behavioral procedures used in this experiment will be described below. After completing each daily session, the monkey was wheeled back to their home cage and fed their daily ration of food.

Statistical Procedures

All statistical analyses were performed using the SPSS 12.0 statistical analyses package. Data was analyzed using ANOVAs and MANOVAs. Group was always the between-subjects factor and repeated measures were used for the within-subjects factor when needed. A Huynh-Feldt correction for degrees of freedom was used for the repeated measures. Pairwise comparisons were made using univariate analysis of variance and/or Bonferoni corrected *t*-tests, as appropriate. Pearson product moment correlations were performed to examine whether the extent of damage (intended or unintended) to any brain region correlated with behavioral measures, and these, along with extent of lesion will be discussed following the description of the experiments.

EXPERIMENT 1: 24-HRS CONCURRENT DISCRIMINATION TASK

The main goal of this series of studies was to assess the effects of neonatal hippocampal lesions on contextual learning. For this purpose, we selected a behavioral task based on a 24-hrs object concurrent discrimination task, which was delivered via a computerized testing apparatus to permit the manipulation of both the stimuli and the background onto which they were presented. This task selection was based on earlier findings showing that animals with neonatal hippocampal lesions demonstrated normal

performance on a 60-pair 24-hrs object concurrent discrimination task administered within a Wisconsin General Testing Apparatus (WGTA) (Kazama et al., in prep). The purpose of this first experiment was to replicate these findings by demonstrating that animals with neonatal hippocampal lesions would perform normally when the concurrent discrimination task used pictures of objects presented onto a touch-screen computer instead of real three-dimensional objects presented on a test tray.

Behavioral Procedures

One hundred and twenty colored pictures of different objects were paired to form 60 discrimination problems. On each trial, the two stimuli of a pair were presented side-by-side on the left and right sides of the screen, 10 cm apart. For each pair, one of the objects was designated as positive (delivery of a reward followed if selected) and the other was designated as negative (no delivery of reward followed if selected). After the animal selected one of the stimuli, the screen went black for an inter trial interval of 30 sec, after which the second pair of objects was presented for choice and so on until the 60 pairs of stimuli were presented once each. The 60 discrimination problems were presented in the same order each day, but the left/right position of the positive object of the pair was counterbalanced each day. Daily testing was continued until the animal reached a criterion of 85% correct responses over three consecutive days of testing. Figure 2 displays an example of the trials given during this task. Parameters recorded and used to assess performance included sessions, trials, and errors to criterion. Additionally, some other behavioral measures were examined. Latency, defined as the amount of time between the onset of the stimuli and the animal's response, was examined

to assess whether this parameter varied according to the animals' responses (i.e. correct or incorrect). Finally, because animals' selection on a given trial could be influenced by the choice they made on the previous trial, we examined the presence of any response strategy used by the animals (i.e. win-stay/lose-shift) during the task.

Results

Sessions to criterion, trials to criterion, and errors to criterion for each animal of both groups are presented in Table 1. Monkeys with neonatal hippocampal lesions acquired the task at the same rate (9 sessions, 564 trials, and 205 errors) as sham-operated animals (11 sessions, 672 trials, and 236 errors). The two groups did not differ in any of the three measures (Sessions: $F(1,9) = .33$, NS; Trials: $F(1,9) = .33$, NS; Errors: $F(1,9) = .19$, NS; see Figure 3 for errors to criterion). In addition, both groups had similar latencies to select the correct or incorrect stimuli (Correct: $F(1,9) = .31$, NS; Incorrect: $F(1,9) = .11$, NS). Given that the neonatal hippocampal lesions did not affect the response latency to stimuli, this parameter was not analyzed in subsequent experiments. Animals in both groups were more likely to answer correctly if the correct choice was in a different location than in the previous trial, (i.e. used a win-shift strategy; effect of trial type: $F(1,8) = 8.72$, $p = .018$). This effect was especially pronounced in the last 25% of trials (Main effect of blocks of trials: $F(1,6) = 353.43$, $p < .001$; post-hoc paired samples T-tests: Group Neo-C: $t = 4.37$, $p = .01$; Group Neo-Hibo: $t = 3.54$, $p = .02$).

Comment

This experiment tested the effect of early damage to the hippocampus on a concurrent discrimination task presented on a touch screen computer. Both groups of animals learned the task at the same rate, and a win-shift strategy seemed to assist animals in making correct choices during the last 25% of testing. Additionally, animals in both groups made a similar number of errors to criterion when acquiring 60 discrimination problems with two-dimensional stimuli presented on the touch screen as compared with three-dimensional stimuli presented on the test tray of the WGTA.

EXPERIMENT 2: CONTEXT INDEPENDENT CONCURRENT DISCRIMINATION TASK

To assess whether the use of backgrounds onto which stimuli are presented will affect performance on the concurrent discrimination task, and more so for animals with neonatal hippocampal damage than for sham-operated controls, we modified the discrimination task and added a background to each of the discrimination problems of the concurrent discrimination task. However, in this experiment the information provided by the backgrounds was irrelevant for good performance on the task. Thus, on half of the problems, the background for each problem was kept the same from day to day, and for the other half of the problems the background changed for each day. Therefore, we predicted that the task could be solved using the same rule as the one learned in Experiment 1, i.e. one that is not dependent on an intact hippocampus, and that there would be no impairment after neonatal hippocampal lesions.

Behavioral Procedures

The basic concurrent discrimination task was used, but instead of a uniform black background, a colored and patterned background was introduced behind the pairs of stimuli, as shown in Figure 4. Sixty new pairs of stimuli were selected and presented on different patterned and multi-colored backgrounds. As shown in Figure 4, thirty of the pairs were presented on the same background each day ("same" trials), and the other thirty pairs were presented on a different background each day ("different" trials). These two types of discrimination problems were pseudo randomly intermixed within the session. As for Experiment 1, each pair of stimuli was presented one at a time with the objects in the pair presented on the left and right sides of the screen, counterbalanced across trials. Pairs were each presented once per day, in the same order, until a learning criterion (85% average over three consecutive days) was achieved for each type of problem separately as well as for both types of problems overall.

Results

Sessions to criterion, trials to criterion, and errors to criterion for each animal of both groups are presented in Table 2. Overall performance for the 60 discrimination problems was similar for both groups (Figure 5), with animals with neonatal hippocampal lesions averaging 18 sessions (1080 trials and 369 errors) to criterion as compared to 20 sessions (1176 trials and 370 errors) for the sham-operated controls (Sessions: $F(1,9) = .08$, NS; Trials: $F(1,9) = .08$, NS; Errors: $F(1,9) = .00$, NS). Analyses of the two types of discrimination problems separately (Figure 6) revealed that all animals, regardless of the group, acquired the discriminations presented over the same background ("same" trials)

faster than discriminations presented over different backgrounds ("different" trials), as revealed by a significant main effect of trial type ($F(1,8) = 9.11$, $p = .02$), but no effect of group ($F(1,8) = .02$, NS), and no interaction ($F(1,8) = .37$, NS). Thus, on the "same" trials, Group Neo-Hibo averaged 11 sessions (342 trials and 126 errors) as compared to 13 sessions (378 trials and 133 errors) for the sham-operated controls. By contrast, on the "different" trials, both Groups Neo-Hibo and Neo-C averaged 18 sessions to criterion (342 and 378 trials, and 126 and 133 errors, respectively).

To investigate whether the presence of contextual cues, even if irrelevant, impaired performance, we also compared performance for both groups in Experiment 1 with overall performance for the two types of trials of Experiment 2.

As displayed in Figure 7, all animals, regardless of group, made more errors for discrimination problems with a background (Experiment 2) than for discrimination problems with no background (Experiment 1). Thus, animals with neonatal hippocampal lesions made 205 errors to attain criterion in Experiment 1 but 369 errors to attain the same criterion in Experiment 2. Similarly, sham-operated controls made 236 errors in Experiment 1, but 370 errors in Experiment 2. This difference in performance for both groups reached significance [Experiment: ($F(1,8) = 13.38$, $p < .01$); Group ($F(1,8) = .03$, NS); interaction ($F(1,8) = .13$, NS].

Comment

This experiment tested the effect of early damage to the hippocampus on a concurrent discrimination task where context was present, but irrelevant for good performance on the task. Both groups of animals learned the task at the same rate,

although both groups made fewer errors to criterion on the "same" trials than on the "different" trials, indicating that although the context was irrelevant for good performance on this task, changes of backgrounds from the "different' trials slowed the speed of acquisition of the problems. Comparison of performance in Experiment 1 versus Experiment 2 suggests that contextual cues, even if irrelevant, slow down acquisition of the task. However, this effect was true for both animals with selective neonatal damage to the hippocampus, or for sham-operated controls.

EXPERIMENT 3: CONTEXT DEPENDENT CONCURRENT DISCRIMINATION TASK

As described in the introduction, previous research suggests that the hippocampus is necessary to process contextual information (Smith & Mizumori, 2006; Burgess et al., 2001; Spiers et al., 2001a; Pascalis et al., 2009; Kim & Fanselow, 1992; Phillips & LeDoux, 1992; Bachevalier & Nemanic, personal communication). Thus, we modified the concurrent discrimination task in this third experiment to assess whether neonatal hippocampal damage would affect learning of the discriminations when the background onto which stimuli were presented was made relevant for correct performance on the task. To this end, new pairs of stimuli were selected for the task but now one stimulus of the pair was correct when the pair was presented on background A, but the other stimulus of the pair was correct when the pair was presented on background B. In this case, to be correct the animals had to not only monitor the objects of the pair but also the backgrounds onto which the stimuli of the pair appeared. In addition, to ensure that spatial information of the stimuli on the screen could not be used to help the animals

solve the discrimination problems, their location within the background was modified with each stimuli-pair presentation.

Behavioral Procedures

Animals learned a total of four new pairs of stimuli over eight new backgrounds. Each pair of stimuli was presented over two different backgrounds, such that on one background, one stimulus was correct, and on the other background, the other stimulus was correct (see Figure 8).

Training began with presentation of the first pair of stimuli over two different backgrounds. Animals received 60 trials in which for half of the trials the pair of stimuli was presented over one background and for the other half the pair of stimuli was presented over the other background for that pair. These two types of trials were randomized across the 60-trial session. Animals were trained on this first discrimination problem until they demonstrated initial learning. (i.e. at least 70% correct on one daily session), after which, the second pair of discrimination problems was added and presented over two different backgrounds. Animals then received a total of 60 trials per session, where 30 trials consisted of Pair 1 with its two backgrounds and the other 30 trials consisted of Pair 2 with its two backgrounds. The order of pair presentation was pseudo randomized across the 60-trial session so that each pair was presented 15 times onto one of its backgrounds and 15 times onto the other background. Again, initial learning criterion was set for at least 70% correct on Pair 2 over two daily sessions of 60 trials. When Pairs 1 and 2 were intermixed, initial learning criterions were taken across two days of testing (i.e. 60 trials for each pair in a "block" of trials). Pair 3 and its

associated two backgrounds were then added to the training and intermixed with presentations of Pairs 1 and 2. Animals received again 60 trials per session comprised of 20 trials for Pairs 1, 2, and 3, and for each pair, 10 trials were presented over one background and 10 trials over the other background. Again, initial learning criterion was set for at least 70% correct on Pair 3 over three daily sessions, again in order to keep 60 trials of each pair in a "block" of trials across sessions. Then, the final pair (Pair 4) was added to the training sessions, using again 60 trials per daily session. At this point, animals received 15 trials for each Pair (1, 2, 3, and 4). Due to uneven number of trials for each pair in a daily session, trials were counterbalanced across daily sessions to maintain an equal number of presentations of each pair on each of its backgrounds within a four-session block of trials. Animals were tested in this way until they reached a learning criterion of 85% correct for each pair.

Results

Sessions to criterion, trials to criterion, and errors to criterion for each animal of both groups are presented in Table 3. Animals with neonatal hippocampal lesions acquired these contextual discrimination problems as rapidly as sham-operated controls, averaging 16 sessions (960 trials and 494 errors) as compared to 17 sessions (1032 trials and 567 errors). The group difference did not reach significance for any of the three learning parameters (Sessions: $F(1,9) = .06$, NS; Trials: $F(1,9) = .06$, NS; Errors: $F(1,9) = .20$, NS; see Figure 9 for errors). To investigate whether animals in the two groups learned each contextual discrimination problem similarly, data for each pair were analyzed separately and are illustrated in Figure 10 for the errors to criterion. Although

no reliable group differences emerged for any of the four pairs ($F(1,8) = .11$, NS), the main effect of pair was significant ($F(2,16) = 7.19$, $p < .01$) but the interaction was not ($F(2,16) = .54$, NS). Thus, both groups made significantly more errors to learn Pair 1 as compared to Pair 2 ($t = 5.08$, $p < .01$ and $t = 2.77$, $p = .05$ for Groups Neo-C and Neo-Hibo, respectively) and Pair 3 ($t = 3.53$, $p = .02$ and $t = 2.93$, $p = .04$ for Groups Neo-C and Neo-Hibo, respectively). Performance for both groups on Pair 4 did not significantly differ from performance on Pair 2 ($t = -2.20$, NS and $t = -2.08$, NS for Groups Neo-C and Neo-Hibo, respectively), or Pair 3 ($t = -1.84$, NS and $t = -1.70$, NS for Groups Neo-C and Neo-Hibo, respectively).

Comment

Animals with neonatal hippocampal damage were not impaired when contextual processing was necessary for acquisition of the pairs. Differences between errors made to criterion when acquiring the pairs is likely accounted for by the fact that during acquisition of Pair 1, animals were also learning the rule to apply to the stimuli, along with acquiring the stimuli and the backgrounds. After the rule had been learned, it was transferred to the subsequent problems and fewer errors were made in acquiring Pairs 2 and 3. However, unexpectedly, animals of both groups made more errors when learning the last problem, Pair 4 (168 for Group Neo-C, and 115 for Group Neo-Hibo). Because the stimuli and backgrounds on this pair were made as different as possible from each other and from the other pairs, the difficulty in learning Pair 4 might be attributed to memory load capacity, which may have been at its maximum when that last problem was introduced.

EXPERIMENT 4: CONTEXT DEPENDENT CONCURRENT DISCRIMINATION RULE TRANSFER

Although animals in both groups performed equally well on Experiment 3, this lack of impairment following neonatal hippocampal lesions could be associated with the nature of the task. Specifically, it is possible that presenting the pairs one at a time may have assisted animals with neonatal hippocampal damage to chunk information for each trial and to learn each of the 8 discriminations separately without using a contextual rule. Experiment 4 thus tested two of the issues raised in Experiment 3. First, to assess whether memory load capacity affected the acquisition, we added one additional discrimination problem, and animals had to learn 5 pairs. Second, to test whether animals of both groups were using a contextual learning rule to acquire the four contextual discriminations in Experiment 3, animals were required to transfer the rule to learning of a new set of stimuli and backgrounds. However, this time all pairs were presented simultaneously in a pseudo random order on their associated two backgrounds.

Behavioral Procedures

Five new pairs of stimuli and ten new backgrounds were selected. As before, each pair of stimuli was presented over two different backgrounds, such that in one background, one stimulus of the pair was correct, and in the other background, the other stimulus of the pair was correct (See Figure 11). Animals received 100 trials per daily session, consisting of 20 trials of each pair (10 trials presented over one background and 10 trials presented over the other background). The ITI was reduced from 30 seconds to 15 seconds to limit daily training to 35-45 minutes. Animals were tested until they

reached a learning criterion of 85% correct for each pair. As in previous experiments, the order of presentation of the pairs and the spatial location of the stimuli within the background were randomized.

Results

The mean number of sessions, trials, and errors to the 85% criterion for each pair as well as across the 5 pairs are presented for each animal of both groups in Table 4. As illustrated in Figure 12, sham-operated controls made twice as many errors overall (554 errors) than animals in Group Neo-Hibo (250 errors) to acquire the five contextual discrimination problems to criterion. This group difference reached significance for the three task parameters (Sessions: $F(1,9) = 5.26$, $p = .05$; Trials: $F(1,9) = 5.26$, $p = .05$; Errors: $F(1,9) = 5.25$, $p = .05$). When errors to criterion for both groups were analyzed for each pair separately, the two groups differed in the way they learned the five contextual discrimination problems. Performance for each animal on each pair was ranked, from the best to the worse, such that the pair on which they performed the best was designated 1, the pair on which they performed second best was designated 2, and so on, until the pair in which they performed worse, i.e. Pair 5. As illustrated in Figure 13, animals with neonatal hippocampal lesions performed better (made fewer errors to criterion) than sham-operated animals in all five pairs (Group effect: $F(1,8) = 5.53$, $p < .05$; Rank effect: $F(4,32) = 18.44$, $p < .001$; Rank x Group interaction: $F(4,32) = 4.48$, $p < .04$). The significant interaction indicated that the groups differed between the 5 pairs. Thus, post-hoc comparisons indicated that animals in Group Neo-C made more errors than Group Neo-Hibo only on rank 3 (80 vs. 39; $t = 2.52$, $p < .04$) and rank 4 (90 vs. 43; t

= 2.56, $p < .04$). However, a difference between groups approached significance for rank 2 (70 vs. 33; $t = 2.18$, $p = .06$) and rank 5 (144 vs. 57; $t = 2.34$, $p = .06$). Thus, only for the pair they acquired the fastest (Rank 1) did the two groups not differ. Within group performance was evaluated for each group separately using post-hoc paired samples t-tests. Animals in both groups made significantly more errors to criterion for each pair of ranks (all ps < .05), except between Ranks 2 vs. 1, 3 vs. 2, 4 vs. 3 and 5 vs. 4 for Group Neo-C and between Ranks 2 vs. 1 for Group Neo-Hibo

Comment

The data from this experiment demonstrated that neonatal damage to the hippocampus appeared to facilitate the learning of a new set of contextual discrimination problems when presented simultaneously. Thus, animals with neonatal hippocampal lesions showed a robust transfer of the contextual discrimination rule that they acquired in Experiment 3, making twice less errors to acquire the five problems of Experiment 4 (250 errors) than to acquire the four problems in Experiment 3 (494 errors). The same was not true for the sham-operated controls, however, that made as many errors to acquire the five problems of Experiment 4 (554 errors) than to acquire the four problems in Experiment 3 (567 errors). These findings were unexpected but could be explained in different ways. One possibility is that the group difference may have occurred from performance of the sham-operated controls. Thus, animals in Group Neo-C may have tried to use information provided by the background to solve the task, such that when faced with a new set of contextual discrimination problems they had to relearn the new stimulus/context associations to solve the task. On the other hand, animals in Group

Neo-Hibo may not have used information provided by the background at all and learned a different strategy (i.e. chunking information for each of the 8 discriminations) and continued to apply that strategy to solve the five new contextual discrimination problems of Experiment 4. A combination of these two possibilities is also likely to explain the results of Experiment 4.

Interestingly, not only were animals with neonatal hippocampal lesions not impaired in contextual discrimination learning (Experiment 3) but additionally, their persistence in using a previously successful strategy allowed them to acquire the second set of discrimination problems even faster than sham-operated controls. This facilitation in learning the five contextual discrimination problems in animals with neonatal hippocampal lesions parallels the facilitation the same animals demonstrated when learning a 60-pair concurrent discrimination task in a WGTA (Kazama et al., in prep) as well as an object discrimination reversal task (Kazama, personal communication). Similar facilitation was also previously reported in monkeys with fornix transections on a visual object discrimination reversal task in a WGTA (Mahut, 1972; Zola & Mahut, 1973), and following hippocampal or fornix lesions in squirrel monkeys on a visual pattern discrimination task (Schram, 1970). Other instances of facilitation have been reported in rodents. For instance, rats with bilateral fornix lesions (Eichenbaum et al., 1986), combined bilateral lesions of the fornix and amygdala (Eichenbaum et al., 1986), or lesions of the entorhinal cortex (Staubli et al., 1984) performed better than control animals on an odor discrimination reversal-learning task. Facilitation has also been observed in other memory tasks. For example, in rodents, fornix lesions facilitate acquisition of the delayed non-matching to sample task (Shaw & Aggleton, 1993) and

hippocampal lesions facilitate odor-pair associates learning (Eichenbaum & Bunsey, 1995).

Previously, facilitation of learning following hippocampal lesions has been explained in view of competitive interactions that could exist between the hippocampal-dependent and striatal-dependent memory systems (Kapur, 1996). Neuroanatomical interconnections between the two systems have been extensively described (Voorn et al., 2004; Sorensen & Witter, 1983; van Hoesen, 1985; Hyman et al., 1990; Christakou et al., 2004), and this connectivity may support the competitive interactions such that rendering one system dysfunctional may facilitate another (Mishkin & Petri, 1984).

EXPERIMENT 5: CONTEXT DEPENDENT AND REPEATING CONCURRENT DISCRIMINATION

Results from Experiments 3 and 4 demonstrate that animals with neonatal hippocampal damage can learn contextual discrimination problems as well as, or even faster than control animals. There are two possibilities that could support such findings. First, previous research has demonstrated that the role of the hippocampus in contextual processing is to encode the object and the context separately, so that they can be used independently of one another. Therefore, without a functioning hippocampus, objects and their contexts should be encoded as a single "snapshot", where the objects and the context cannot be used independently of one another. If this were the case, animals in Group Neo-Hibo may have learned 10 discrimination problems rather than 5 pairs in two different backgrounds. In doing so, they would have taken a separate "snapshot" of each pair of stimuli on each background. The other possibility for a lack of a deficit in

Experiments 3 and 4 is that monkeys in Group Neo-Hibo may have used an "infer strategy" whereby they could memorize the correct answer for Pair 1 when on background A, and then infer the correct answer for Pair 1 when on background B. To test this later possibility, in the fifth experiment the same backgrounds were used for different contextual discrimination problems so that animals could not simply memorize the correct answer to the pair when on one background, and then infer the other, as that same background was used over again with a brand new pair of stimuli. In this manner, we investigated whether monkeys with neonatal hippocampal damage would be impaired when it was necessary to use the same context with different stimuli pairs to discriminate the correct answer. We predicted that if animals in Group Neo-Hibo were using the "infer strategy" described above, they would show impairment on this experiment.

Behavioral Procedures

As for Experiment 4, animals were presented with five pairs of stimuli. Pairs 1, 2, and 3 were identical to those used in Experiment 4, whereas Pair 4 consisted of a new pair of stimuli presented over the same background as Pair 1in Experiment 4, and Pair 5 consisted of a new pair of stimuli presented over the same background as Pair 2 in Experiment 4 (See Figure 14). To state it differently, two pairs (1 and 4) were presented over the same backgrounds (A and B), two pairs (2 and 5) were presented over the same backgrounds (C and D), and pair 3 was presented over backgrounds E and F. Therefore, all backgrounds encountered in this Experiment were previously seen in Experiment 4, as were the stimuli comprising Pairs 1, 2, and 3. Thus, the only not previously encountered stimuli in this Experiment were the stimuli making up Pair 4 and Pair 5. Finally, because

Pair 3 was the only pair which was both identical to a pair from Experiment 4, and did not have any additional manipulations in Experiment 5, it served as a control, and thus comparisons between performance on Pair 3 versus Pairs 1 and 2 was examined for Experiment 5. The task was delivered in the same manner and with the same contingencies as Experiment 4.

Results

Sessions to criterion, trials to criterion, and errors to criterion for each animal of both groups are presented in Table 5. To investigate whether performance was impaired when learning new pairs of stimuli presented on backgrounds already learned in Experiment 4, we first compared performance (errors to criterion) on Pair 1 when learned for the first time in Experiment 4 to performance on Pair 4 from Experiment 5, which consisted of different stimuli presented over the same background as Pair 1. Similarly, comparisons were made between Pair 2 from Experiment 4 with that of Pair 5 from Experiment 5. As illustrated in Figure 15, no differences were found between initial learning on Pair 1 from Experiment 4 and Pair 4 for Experiment 5 as well as between Pair 2 and Pair 5. Although the effect of Group was significant for Pairs 1 and 4 ($F(1,8) = 11.38$, $p = .01$), it was not for Pairs 2 and 5 ($F(1,8) = 2.64$, NS). The group difference for Pairs 1 and 4 was mostly driven by the group difference already reported in Experiment 4 for Pair 1. The effect of Experiment and the interaction between Group and Experiment did not reach significance either for Pairs 1 and 4 or Pairs 2 and 5 [(Pairs 1 and 4: Experiment $F(1,8) = 1.05$, NS; Interaction $F(1,8) = 1.61$, NS) (Pairs 2 and 5: Experiment $F(1,8) = 3.50$, NS; Interaction $F(1,8) = 0.43$, NS)].

Additionally, it is also possible that learning new stimuli on old backgrounds (Pairs 4 and 5 of Experiment 5) altered performance on the pairs already learned in Experiment 4 (Pairs 1, 2 and 3). To test this possibility, we compared performance on Pairs 1, 2 and 3 at the end of acquisition in Experiment 4 to that on the same pairs in Experiment 5. As illustrated in Figure 16, for Pair 1, Group Neo-C made more errors than Group Neo-H in both experiments ($F(1,8) = 8.49$, $p < .02$) and both groups made more errors in Experiment 5 than at the end of Experiment 4 ($F(1,8) = 12.26$, $p = .008$). These differences were only marginally significant (Group Neo-C: $t = -2.59$, $p = .06$; Group Neo-Hibo: $t = -2.80$, $p = .05$) and were likely driven by large amounts of variability in Group Neo-C and small amounts of variability in Group Neo-Hibo. The interaction between Group and Experiment did not reach significance ($F(1,8) = 1.50$, NS). However, for both groups performance on previously acquired discrimination problems (Pairs 2, and 3) at the end of Experiment 4 did not differ from performance on the same discrimination problems in Experiment 5(Pair 2: Group $F(1,8) = 0.15$, NS, Experiment $F(1,8) = 0.62$, NS, Interaction $F(1,8) = .07$, NS; Pair 3: Group $F(1,8) = 1.05$, NS, Experiment $F(1,8) = 1.05$, NS, Interaction $F(1,8) = .29$, NS). As illustrated in Figure 17, performance by all animals on Pairs 1 and 2 was similar to performance on Pair 3, (Group: $F(1,8) = .60$, NS; Pair: $F(2,16) = 2.55$, NS), reinforcing the idea that using the background portion of a previously acquired discrimination problem does not cause impairment on the previously acquired problem itself. However, a significant interaction between Group and Pair ($F(2,16) = 3.98$, $p = .04$) suggests that the influence of a brain lesion on errors to criterion depends on the pair. That is, Group Neo-C made the most errors on Pair 1, and the fewest on Pair 2, whereas Group Neo-Hibo made the most errors

on Pair 2 and the fewest on Pair 3. Finally, as illustrated in Figure 18, when performance on each pair in Experiment 5 was evaluated individually, only differences within groups were found (Pair: $F(4,32) = 17.28$, $p < .001$; Group: $F(1,8) = 1.07$, NS; Pair by Group interaction $F(4,32) = 1.02$, NS). The effect of Pair likely arose because Pairs 1, 2, and 3 were already acquired in Experiment 4, whereas Pairs 4 and 5 consisted of new stimuli, which the animals had not yet seen and had to learn. Animals in Group Neo-C made more errors to criterion on Pair 4 vs. Pair 1 (81 vs. 15 errors; $t = -5.37$, $p = .006$), Pair 2 (2 errors; $t = -4.60$, $p = .01$), and Pair 3 (3 errors; $t = -4.79$, $p < .01$), and more errors to criterion on Pair 5 vs. Pair 1 (43 errors vs. 15 errors; $t = -2.57$, $p = .06$), Pair 2 (2 errors; $t = -3.78$, $p = .02$), and Pair 3 (3 errors; $t = -3.89$, $p < .02$). Animals in Group Neo-Hibo made more errors to criterion on Pair 5 vs. Pair 1 (31 vs. 2 errors; $t = -4.18$, $p < .02$), Pair 2 (7 errors; $t = -6.94$, $p = .002$), and Pair 3 (0 errors; $t = -4.08$, $p < .02$).

Comment

Animals with neonatal hippocampal damage were not impaired when it was necessary to use the same context with multiple pairs of stimuli, as results indicate no differences in the acquisition of discrimination problems when the same background is repeated. That is, it takes the same amount of time to learn a new discrimination presented over a previously acquired background, as it did for animals to learn to discriminate a stimuli pair over that same background originally. Thus, animals with neonatal hippocampal damage seem to treat the new stimuli pairs presented over previously acquired backgrounds as though they were completely new discrimination problems. Additionally, performance on previously acquired discriminations was not

negatively impacted by the association of portions of those problems (backgrounds) with new stimuli pairs. Performance for all animals was similar on the last session of Experiment 4 and the first session of Experiment 5 for Pairs 1, 2, and 3. However, there were significant differences between the different pairs of stimuli in a pattern which reflects the pre-learning of Pairs 1, 2, and 3 during Experiment 4, with the new learning of Pairs 4 and 5 in Experiment 5, even though acquisition of these pairs required the use of contextual cues that overlapped with previously learned pairs.

Using only the remaining medial temporal lobe cortical areas after selective neonatal hippocampal damage, we would expect that animals in Group Neo-Hibo would encode the stimuli and background as an inflexible "snapshot" where the background could not be used independently of the stimuli under which it is encoded. However, it may be that animals in Group Neo-Hibo are not actually using the repeated context separately from its originally encoded stimuli, but rather than they are taking a second snapshot, where the background is then encoded with the new overlaying stimuli. Thus, rather than being solved as a problem with two identical backgrounds, that necessitates using a background flexibly, animals with neonatal hippocampal damage may be using a more simple strategy to attain the correct answer, whereby they form 10 individual snapshots, regardless of whether some of the backgrounds are the same or not. This possibility was examined in Experiment 6.

EXPERIMENT 6: CONTEXT VISUAL PAIRED COMPARISON

Results from experiments presented thus far can be explained in a few ways. First, it is possible that these newly designed contextual tasks may be solved by strategies that are not mediated by the hippocampus. Second, it is possible that the lack of impairment in contextual learning and memory after the neonatal hippocampal lesions may be due to the time at which the hippocampal lesions were performed. The early lesions may have led to sparing of function due to reorganization after early insult to the hippocampus.

The purpose of Experiment 6 was to distinguish between these two possibilities. As indicated earlier, it is possible that without a functional hippocampus, animals may not be able to separately learn about the stimuli and their context, but rather form a "snapshot" of stimuli/background information for every pair they learn. Indeed, when the memory task does not allow the animal to use the binding stimuli/background strategy for good performance, animals with hippocampal lesions are impaired. For example, in a contextual paired-comparison task in which the animals are first familiarized with a stimulus presented over background A and after a short delay are required to recognize this stimulus when presented over background B, animals with adult hippocampal lesions show no novelty preference, likely because they cannot use the snapshot they have formed from stimulus/background A (Bachevalier & Nemanic, personal communication). Thus, to test whether animals with neonatal hippocampal lesions will likewise be impaired when unable to use a snapshot between stimulus/background, we tested them on the contextual paired-comparison task.

Behavioral Procedures

General Procedure

Procedures were modeled after Bachevalier and Nemanic (personal communication) so that results could be compared across studies. Therefore, each trial began with a familiarization phase where an image was presented on the screen until the monkey accumulated 30 seconds of looking time. Following a five second delay the first test phase ensued, where two images were presented side-by-side for a total of five seconds. Following another five-second delay, the second test phase ensued, where the same two images were presented side-by-side, with their left and right positions on the screen reversed, for a total of five seconds. A delay of 5 seconds was chosen in order to model this investigation as closely as possible to Bachevalier and Nemanic (personal communication). Additionally, previous research suggests that these monkeys with neonatal hippocampal damage have impaired recognition memory at long delays (Zeamer et al., 2010). Because we were specifically interested in the effects of selective and early damage to the hippocampus on non-spatial contextual memory, we chose a delay at which no deficits in recognition memory per se were found. Monkeys received a total of 20 trials, 10 of each type described below. This testing paradigm takes advantage of the monkey's innate preference for novelty. Therefore, the monkey's eye movements were analyzed frame-by-frame to acquire the percent of time the monkey looked at the novel image on each trial.

Control Trials

As seen in Figure 19, the familiarization phase image consisted of an object presented on a background. In the test phases, one image was identical to that seen in the

familiarization phase (familiar image), and the other image consisted of a new object, presented on the same background as that shown in the familiarization phase (novel image).

Context Trials

As seen in Figure 19, the familiarization phase consisted of an object presented on a background. In the test phases, one image consisted of the same object presented on a new background (familiar image), and the other image consisted of a new object, presented on the same new background (novel image).

Results

Percent of time looking at the novel image is displayed in Table 6 for each animal. As illustrated in Figure 20, animals in both groups had similar looking preferences on all trial types (Control Trials: $F(1,9) = .03$, NS; Context Trials: $F(1,9) = .44$, NS). Animals in Group Neo-C preferred to look at the novel image 69.8% of the time on the Control Trials, and 64% of the time on the Context Trials. Animals in Group Neo-Hibo also preferred to look at the novel image on both the Control trials (70.8%) and the Context Trials (66.2%). All animals' preference for the novel images, regardless of the type of trial, was statistically above what would be expected by chance (Group Neo-C: Control Trials: $t = 5.00$, $p = .007$, Context Trials: $t = 4.71$, $p = .009$; Group Neo-H: Control Trials: $t = 4.99$, $p = .008$, Context Trials: $t = 12.16$, $p < .01$).

Comment

Animals in both groups performed significantly above chance on both the control and context trials, indicating that monkeys with neonatal hippocampal damage are able to recognize a previously seen object, even if the object is presented in a new background context. Therefore, it is unlikely that monkeys with neonatal hippocampal damage are using a "snapshot" strategy to solve the discrimination problems in Experiments 3, 4, and 5, as that strategy would have resulted in impairment on context trials in Experiment 6 as well. These results differ from those obtained in animals receiving the same hippocampal lesions in adulthood (Bachevalier & Nemanic, personal communication) and suggest that the lack of impairment seen in the contextual paired-comparison task as well as in the contextual discrimination tasks of Experiments 3, 4, and 5 is likely due to sparing of function due either to the early nature of the damage to the hippocampus, and the plasticity of the brain during development, and/or the ability of the surrounding medial temporal lobe cortical areas to support contextual learning and memory in the absence of a functioning hippocampus. However, an additional factor that could be contributing to these results and may explain the lack of impairment in contextual learning and memory after neonatal hippocampal lesions relates to the extent of the lesions. It is possible that the neonatal hippocampal lesions were incomplete and allowed normal performance on all contextual tasks described above. To investigate this possibility, the extent of hippocampal damage in all cases is described below, followed by correlations between extent of lesions and performance of each of the contextual tasks.

LESION EXTENT AND CORRELATION WITH BEHAVIORAL MEASURES

Extent of Lesions

The percent damage estimated from the FLAIR MR images for the hippocampal formation (intended) and adjacent cortical regions (unintended damage) in both hemispheres are shown in Tables 7 and 8, respectively. Examples of intended, bilateral, and unilateral lesions with FLAIR MR images can be viewed in Figure 21, and lesion reconstructions for each of the cases below are illustrated in Figure 22. The weighted average (Hodos & Bobko, 1984) provides an excellent estimate of whether a lesion is mild to moderate and highly unilateral (W% < 25%) or extensive and symmetrical (W% > 50%). In all descriptions given below, "extensive" indicates greater than 60% damage, "moderate" indicates between 25% - 59.9% damage, "mild" indicates between 2% - 24.9% damage, and "negligible" indicates less than 2% damage.

Case Neo-Hibo-1: The hippocampal lesion in this case was mostly unilateral (see Table 7 and Figure 22) with 63.6% on the left and only 2.9% on the right. Sparing on the left was located medially along nearly the entire rostral/caudal extent. Unintended damage (see Table 8) included mild damage to the left amygdala (14%), TH/TF (3.1%), and ERh (2.6%). There was negligible damage to the right TH/TF (0.5%), but no damage to the amygdala or to areas TE and PRh.

Case Neo-Hibo-2: The hippocampal lesion was asymmetrical (see Table 7 and Figure 22) with more damage on the right (80.9%) than on the left (54.4%). Sparing on the left was located medially throughout the length of the hippocampus, and posteriorly, nearly all of the hippocampus was spared. Mild unintended damage (see Table 8) was inflicted bilaterally in TH/TF (21.4% left; 2.7% right) and unilaterally in PRh (5.4%).

There was negligible damage unilaterally in area TE (0.6%) and in the right PRh (0.5%). There was no damage to the amygdala or ERh.

Case Neo-Hibo-3: The hippocampal lesion was extensive and bilateral (see Table 7 and Figure 22) with slightly more damage on the right (96.3%) than on the left (78.5%). There was mild damage inflicted bilaterally in areas TH/TF (6.1% left; 5.5% right), and negligible damage unilaterally to the amygdala (1.7% right). There was no unintended damage to area TE, ERh, or PRh. (See Table 8).

Case Neo-Hibo-4: The hippocampal lesion was asymmetrical, with mild damage on the left (20.3%) and more extensive damage on the right (67.3%) (see Table 7 and Figure 22). However, the mild damage on the left in this case included the CA1 field of the hippocampus, disrupting the functioning of the trisynaptic circuit and the entorhinal-CA1 pathway. Sparing on the left was located throughout the rostral/caudal extent of the hippocampus. The anterior most and posterior most portions were entirely spared, but sparing in the middle portion of the hippocampus was located more medially. On the right, sparing was located medially in the posterior and anterior portions of the hippocampus, with no sparing along the middle extent of the hippocampus. There was mild unintended damage (see Table 8) to the right amygdala (4.7%) and left TH/TF (15.3%). There was negligible damage to area TE on the left (1%) and no damage to ERh or PRh.

Case Neo-Hibo-6: The hippocampal lesion was asymmetrical, with mild damage on the left (7.9%) and no damage on the right (see Table 7 and Figure 22). Sparing on the left was located throughout the hippocampus with the exception of the most anterior

portion. There was no unintended damage to the amygdala, TH/TF, TE, ERh, or PRh (see Table 8).

Lesion correlations

For Group Neo-Hibo, there were no correlations between extent and location of damage, whether intended or unintended, for any behavioral measures in any of the six experiments. This could be the case because of the relatively small sample size. Nonetheless, qualitatively, there are some interesting differences in performance by those animals with unilateral versus bilateral lesions. Thus, in Experiments 3, 4, and 5, animals with unilateral lesions performed worse than those with bilateral lesions. The animal with the smallest lesion performed better than all other animals in Group Neo-Hibo on Experiments 3, 5, and 6, and second best on Experiment 4. In contrast, the animal with the largest lesion performed second best on Experiments 3 and 4, and third best on Experiment 5. There was no noticeable difference between performance of the animal with the largest lesion and all other animals, with the exception of the animal with the smallest lesion, on Experiment 6. Subject Neo-Hibo-4, with a unilateral lesion, but one which included CA1, did worse than all other animals in Group Neo-Hibo on Experiments 3 and 4, and performed second worse on Experiment 5.

DISCUSSION

The primary goal of this project was to investigate the effects of neonatal hippocampal damage on non-spatial contextual processing in monkeys. The present series of experiments has demonstrated sparing of contextual learning and memory function, without a spatial component, following early damage to the hippocampus.

Experiment 1

Previous work comparing learning in a WGTA versus on a touch screen have reported conflicting results, with some studies suggesting that learning takes much longer when stimuli are presented on a touch screen, whereas others suggest that the length of time required for learning is similar in the two experimental paradigms (Mandell & Sackett, 2009). Ascertaining whether our monkeys required similar lengths of time to learn a task that was identical in all ways, except for the manner in which stimuli were presented, allowed us to be relatively certain that the same cognitive processes were measured across paradigms. Importantly, monkeys with neonatal hippocampal damage, as well as controls performed equally well when learning 60 pairs of three-dimensional objects presented in a WGTA (Glavis-Bloom et al., 2006; Kazama MA Thesis, 2006; Kazama et al., in prep), or 60 pairs of two-dimensional objects presented on a touch screen computer monitor. Thus, Experiment 1 established a touch screen computer task on which monkeys both with and without hippocampal damage performed well. This task offered a starting point to independently manipulate objects and the background context onto which they were presented to investigate the role of the hippocampus on contextual learning and memory.

Experiment 2

Experiment 2 introduced a control task in which background onto which objects were presented was manipulated but was made irrelevant for good performance on the task. The results showed that the existence of a consistent context ("same" trials) acted as an extra cue that assisted all animals in acquiring the pairs, compared to trials where the context was inconsistent ("different" trials). That is, even though the background context could have been ignored entirely, and good performance on the task could be reached in the same way as in Experiment 1, the consistency of the background on the "same" trials seemed to assist all animals in discriminating which object in the pair of stimuli was correct. By contrast, the inconsistency, and therefore the unreliability, of the background context in the "different" trials may have slowed acquisition of those discrimination problems. This increased difficulty in acquiring the 60 pairs when an irrelevant context (consistent or inconsistent) in Experiment 2 as opposed to trials where no context was present (Experiment 1) was present in both groups, indicating that the animals with hippocampal lesions were not more affected then the sham-operated controls by the introduction of an irrelevant background under the objects.

These data may be explained in a few different ways. First, it is possible that learning in Experiment 2 was more difficult than in Experiment 1 because the 60 discrimination problems learned in Experiment 1 interfered with the learning of the 60 discrimination problems in Experiment 2. Thus, either interference or a memory load capacity may be responsible for the delay in learning discriminations when the background was irrelevant. Second, the existence of a colorful and patterned background behind the stimuli pairs, despite its irrelevance for good performance on the task, may

have directed the animals' attention to it, thus reducing the speed of acquisition in Experiment 2.

Experiment 3

Experiment 3 introduced a relevant context behind pairs of stimuli, but as compared to Experiment 2, the use of the background contextual cues was critical for good performance on the task. Animals with neonatal hippocampal damage were again not impaired in this contextual discrimination task. These results were unexpected in light of previous findings demonstrating poor performance of monkeys with hippocampal lesions on a similar bi-conditional discrimination task given in a WGTA (Ridley et al., 2001). The different results between the two studies may be attributed to several factors. The first one relates to different species of monkeys, i.e. marmosets in Ridley and colleagues' study (2001) as compared to rhesus macaques (Old World monkeys) in the present study. Second, the timing of the hippocampal lesions varied between the two studies. Whereas in the Ridley and colleagues' study (2001) the hippocampal lesions were acquired in adulthood, in the present study the lesions were performed neonatally. Third, some of the procedures differed between the two studies. Ridley and colleagues (2001) presented all four discrimination problems intermixed within a daily session, whereas in the present study, contextual discrimination problems were introduced one at a time. That is, it was not before animals demonstrated early signs of learning on a given pair that the second pair was added. Additionally, whereas Ridley and colleagues (2001) presented three-dimensional objects in a WGTA, the current study presented two-dimensional objects on a touch screen. Among all of these differences that may account

for the disparity in results, two possibilities stand out as the most likely explanations for the differences: discrimination problem presentation (all four problems at once versus one at a time), and lesion timing (adulthood versus infancy). We began by exploring the former explanation in Experiment 4.

Experiment 4

As compared to Experiment 3, in Experiment 4 animals had to acquired 5 new contextual discrimination pairs when the pairs were intermixed within a testing session. All animals, regardless of group were again not impaired in transferring a contextual rule to a new set of discrimination problems, even when all pairs were presented at once, a manipulation that more closely mirrored that of Ridley and colleagues (2001). Interestingly, not only were monkeys with neonatal hippocampal lesions unimpaired on this task, but also they were facilitated. That is, hippocampal-operated animals made significantly fewer errors to criterion than sham-operated controls. Although this facilitation effect of hippocampal lesions was briefly discussed in the "Comment" section of Experiment 4, it will be further developed here.

Independent Memory Systems

Evidence gathered over the course of the last three decades has clearly established that independent neural systems mediate different types of memory. This multiple memory system theory has provided the framework for inquiring about the specific neural underpinnings of each type of memory (Cohen, 1984; Cohen & Eichenbaum, 1993; Cohen & Squire, 1980; Gabrieli, 1998; Squire, 1992). It has been suggested that the procedural memory system, subserved by a corticostriatal network,

uses stimulus feature - response relationships across different events (Packard et al., 1989), whereas the declarative memory system, reliant on the hippocampal formation (i.e. CA fields, subiculum, dentate gyrus) and adjacent cortical structures (i.e. entorhinal, perirhinal, and parahippocampal cortices), forms associations between specific elements of a situation or event (Sutherland & Rudy, 1989; Tulving, 1972; Sherry & Schacter, 1987).

Double-dissociation studies have been fundamental to demonstrate the existence of independent memory processes. More specifically, these studies have shown that, sparing of procedural memory can accompany severe declarative memory loss following damage to the hippocampal system, and vice-versa in the case of striatal lesions. For example, amnesic patients with damage to the hippocampal formation have impaired declarative memory, but intact procedural memory (Scoville & Milner, 1957), and thus perform well on tasks requiring motor skills, such as mirror tracing (Corkin, 1968), perceptual skills such as mirror reading (Cohen & Squire, 1980; Martone et al., 1984) and cognitive skills, such as the Tower of Hanoi (Cohen et al., 1985). Conversely, Knowlton and colleagues (1994; 1996) designed a classification task, "weather prediction task", which principally relies on the basal ganglia and requires subjects to look at cards presented two at a time and to determine whether the cards would predict sunshine or rain. Subjects were given feedback about the probability of their answer. Poldrack and colleagues (1999) demonstrated significant activation in the caudate nucleus using fMRI in normal subjects performing the task, a finding that was replicated by others (Aron et al., 2004; Moody et al., 2004; Poldrack et al., 2001). In addition, patients with Parkinson's disease (characterized by decreased dopamine activity in the basal ganglia)

or Huntington's disease (characterized by degeneration of neurons in the basal ganglia) were impaired at learning this classification task, although both types of patients had spared declarative memory (Knowlton et al., 1996).

In rodents, the double dissociation between hippocampal-dependent declarative memory and striatal-dependent procedural memory has been shown using a two-platform variation of the Morris Water Maze (Morris, 1982). In this task, a rat is placed into a water tank with two cues, each of which indicates a possible submerged escape platform, but only one is stable and large enough for the rat to escape the water (the correct choice). The other is too small for the rat to escape (the incorrect choice). In the spatial discrimination version of the task, the correct platform is always in the same spatial location, but the incorrect platform is moved among the other three quadrants of the tank from trial to trial. The visual cues for the two platforms are identical (e.g. unreliable), and so the rat is required to learn which platform to approach based solely on the spatial location of the platform in the tank. In the visual discrimination version of this task, the cues indicating the two platforms are distinctive from one another, and so the rat is required to learn which platform to approach based solely on the visual pattern of the cue. Packard and McGaugh (1992) found that rats with bilateral electrolytic lesions of the caudate nucleus were impaired on the visual discrimination version of the task, but performed similar to control animals on the spatial version. In contrast, rats with bilateral electrolytic lesions of the fimbria-fornix complex (afferent/efferent pathway of the hippocampal formation) were impaired on the spatial, but not on the visual, discrimination version of the task. A similar double dissociation has been described using two versions of the radial maze in rats with caudate nucleus or fornix lesions

(Packard, Hirsh & White, 1989). These data provide further evidence that the hippocampal formation and caudate nucleus are parts of neural circuits that differ in the type of memory processes they mediate (Packard & McGaugh, 1992; Packard, Hirsh & White, 1989).

Findings in non-human primates suggest a similar distinction between the neural underpinnings of the two different types of memory. For example, Teng and colleagues (2000) found that monkeys with damage to the hippocampal formation were not impaired on pattern discrimination or concurrent discrimination tasks, in which learning takes place slowly over a number of trials, but that monkeys with combined lesions of the hippocampal formation and the tail of the caudate nucleus were impaired on both of these tasks.

Taken together, evidence across species indicate the existence of parallel and independent memory processes, one of which is critically dependent on hippocampal functioning, and the other critically dependent on caudate nucleus functioning. This dissociation between memory processes led scientists to propose that, whereas the hippocampal formation is a component of the medial temporal lobe memory system important for rapid acquisition of information related to specific events, the caudate nucleus is a critical part of the corticostriatal system that subserves the gradual learning of habits and stimulus-reward associations.

In a normal subject for whom the two systems are available at any point in time, the declarative and procedural memory systems do not always work independently but may also interact, either in a cooperative or competitive way. In fact, there are several pathways that could support interactions between striatal- and MTL-based memory

systems. These include direct anatomical projections between the two systems, indirect modulatory influences of other brain structures, or influences at the level of response-selection processes (Poldrack & Packard, 2003).

Neuroanatomical interconnections between memory systems

Direct reciprocal anatomical connections have already been described between the MTL and striatum (Voorn et al., 2004). Tract-tracing methods have revealed direct projections from entorhinal cortex within the MTL circuit to dorsal striatum in rats (Sorensen & Witter, 1983). Furthermore, stimulation of entorhinal and hippocampal (subiculum/CA 1) neurons increases cell firing in both the caudate-putamen region and ventral striatum (Finch, 1996; Finch, Gigg, Tan & Kosoyan, 1995). The majority of the caudate-putamen responses to entorhinal cortex stimulation were inhibitory, consistent with the negative influence of the MTL structures onto the striatum as shown in the metabolic studies described above (Finch et al., 1995). There exist also connections between the striatum and the hippocampus via entorhinal and prefrontal cortex (Van Hoesen, 1985; Hyman et al., 1990; Christakou et al., 2004). Finally, in the cat, stimulation of the caudate nucleus reduces the occurrence of hippocampal spikes and induces theta rhythm in the hippocampus (La Grutta & Sebatino, 1988; Sabatino et al., 1985), a process associated with decreased hippocampal metabolic activity (Uecker et al., 1997).

Interactions between the MTL and striatum can also be modulated by activity within other brain structures. For instance, the basolateral nucleus of the amygdala exerts modulatory influence on the distinct memory processes mediated by the hippocampus and dorsal striatum, as seen by post-training intra-basolateral amygdala infusions of

amphetamine that enhances performance on both hippocampal-dependent and striatum-dependent learning tasks (Packard et al., 1994; Packard & Teather, 1998).

Finally, interactions between the two memory systems may be driven by feedback connections from structures supporting response selection or production. Such feedback connections may take the form of top-down attention modulation by the cognitive fronto-striatal circuit involving dorsolateral prefrontal cortex (PFC) and the head of the caudate nucleus (Alexander, DeLong & Strick, 1986). In addition, the PFC modulates processing in the lateral amygdala through projections to inhibitory interneurons, and so may have similar projections to other structures in the MTL (Rosenkranz, Moore & Grace, 2003). Because the PFC is involved in executive functions, such as optimization of lower-level functions implemented in subcortical regions (Miller & Cohen, 2001; Norman & Shallice, 1986), it is a likely candidate for mediating interactions between the two memory systems. Thus, although both the MTL and the striatum could be independently involved in task performance, the PFC could be responsible for driving the most efficient system to solve the task. Conversely, both the MTL and the striatum project back to the PFC via the pallidum and thalamus. Through these feedback projections the two memory systems could modulate the activity of the other. This scenario is exemplified by the recent findings of Floresco and Grace (2003). These authors showed that stimulating mediodorsal thalamic inputs to the PFC resulted in a subsequent inhibition of the hippocampal inputs to the PFC, and conversely stimulation of hippocampal inputs to the PFC resulted in a subsequent inhibition of the mediodorsal thalamic inputs to the PFC.

Reciprocal interactions between memory systems

Cooperation between the two memory systems has been highlighted by studies using behavioral tasks that can usually be solved by more than one strategy. For example, Willingham (1998) demonstrated that, although either system was sufficient for solving a motor sequence-learning task, cooperation between the two systems optimized learning. Further evidence of cooperation between memory systems comes from the reciprocal relationship between the two systems. For example, normal subjects performing the weather prediction task during an fMRI study showed a deactivation in the MTL that was associated with activation in the striatum (Poldrack et al., 1999), a finding that was replicated by Moody and colleagues (2004). Using a motor skill-learning task, Jenkins and colleagues (1994) found an increased activation in the putamen accompanied by deactivation of the MTL. A similar relationship between activation in the caudate nucleus and deactivation in the MTL was also reported by Poldrack and Gabrieli (2001) with a perceptual skill-learning task requiring subjects to complete mirror reading. Finally, Dagher and colleagues (2001) used PET imaging to compare brain activation in normal controls and Parkinson's disease patients following a planning task (Tower of Toronto). As task difficulty increased, activity in the striatum increased but activity in the MTL decreased for normal controls. These metabolic changes did not occur in Parkinson's disease patients, although their performance on the task was not different from controls. These data suggest that, when one memory system is deficient, the acquisition of a particular task may be successfully supported by the other system, but that normally, when both memory systems are available, they interact in an opposite way to support normal performance.

Reciprocal interactions between the two memory systems were also shown by Rauch and colleagues (1997). In this study, brain activation was measured using PET imaging during the completion of an implicit motor sequencing task in normal controls and patients with obsessive-compulsive disorder (OCD) who are also known to have dysfunction of the striatum (Kwon et al., 2003). Control subjects showed activation in the striatum, but no activation in the MTL, during learning, whereas OCD patients showed the reverse. Furthermore, other studies have demonstrated that reciprocal relationships between the two memory systems could occur at different times during learning. For instance, during the learning of the weather prediction task, the MTL was activated and the caudate was deactivated early in learning. By contrast, later in learning, activation in the MTL decreased, whereas that in the caudate nucleus increased (Poldrack et al., 2001). These data are supported by the earlier study of Poldrack and colleagues (1999) indicating that deactivation of the MTL dissipated late in the weather prediction task as well as the earlier studies of Knowlton and colleagues (1994; 1996) demonstrating that amnesic patients with MTL damage were impaired only in the later stage of learning.

All together, these studies provide substantive evidence that the neural circuits supporting declarative and procedural memory function interactively, and this conclusion is also supported by neuroanatomical data indicating that there exist numerous direct and indirect anatomical links between structures within these two neural circuits.

Competitive interactions between the two memory systems

Much less research has been conducted to characterize the competitive interactions that could exist between the hippocampal-dependent and striatal-dependent memory systems. The best example of such competition is when one memory system is

unexpectedly facilitated when the other system is dysfunctional. This phenomenon has been referred to as "paradoxical functional facilitation" (PFF). Kapur (1996) distinguishes between two types of PFF: restorative and enhancing. Restorative PFF refers to circumstances in which brain damage returns a subnormal level of functioning to normal or near normal levels. Enhancing PFF refers to circumstances in which brain damage coincides with above normal levels of functioning. This later type of PFF is the focus of the present study and will be illustrated in the studies reviewed below.

Enhancing PFF has been seen in a variety of contexts including sensory and perceptual functioning, and memory functioning across many species. The most widely known examples of enhancing PFF come from the sensory and perceptual functioning domains in which sensory loss in one modality enhances sensory functioning in another modality. For example, cats visually deprived from birth are able to localize a sound more accurately than cats with normal visual experience (Rauschecker & Kniepert, 1994). Similarly, blind humans perform better than normally sighted humans on three tasks, including auditory localization, temporal discrimination, and speech perception (Muchnik et al., 1991).

More interesting are the studies demonstrating PFF in the memory domain. Results of reversal learning discrimination tasks have indicated both deficits and functional facilitation depending on the site of the lesions in multiple species. In reversal learning, an animal first learns that one of two objects is associated with a reward. After reaching a learning criterion, the reward contingencies of the two objects are switched such that the previously rewarded object is now not rewarded, and the object previously not rewarded, is now associated with a reward. This "reversal" of reward contingencies

is repeated several times during an experiment. Hippocampal lesions impair reversal learning in rats (Winocur & Olds, 1978). By contrast, rats with bilateral fornix lesions (Eichenbaum et al., 1986), combined bilateral lesions of the fornix and amygdala (Eichenbaum et al., 1986), or lesions of the entorhinal cortex (Staubli et al., 1984) performed better than control animals on an odor discrimination reversal-learning task. Such paradoxical faciliation was also observed in other memory tasks. For example, in rodents, fornix lesions facilitate acquisition of the delayed nonmatching to sample task (Shaw & Aggleton, 1993) and hippocampal lesions facilitate odor-pair associates learning (Eichenbaum & Bunsey, 1995). Hippocampal lesions have also been found to facilitate a caudate-dependent win stay radial maze task (McDonald & White, 1993; Packard, Hirsh & White, 1989). In this task, rats were required to visit each of four illuminated maze arms twice in a daily training session. Because the hippocampus is responsible for providing information about which maze arms had already been visited, in the absence of the hippocampus, the interference stemming from the task requirement of entering each arm twice was significantly attenuated, allowing rats to show facilitation on this task. Similarly, pigeons with hippocampal lesions acquired a navigation task more quickly and more accurately than controls (Vargas et al., 2004; Strasser & Bingman, 1997). When probed, the pigeons with hippocampal lesions demonstrated they had only encoded feature information, whereas the controls had encoded feature as well as geometric information. Perhaps the inability of the pigeons with hippocampal lesions to encode geometric information allowed them to use the features more efficiently and thus to learn faster. In contrast, caudate-putamen lesions in rats facilitated acquisition of a spatial "Y" maze discrimination task (Mitchell & Hall, 1988), possibly by disrupting

the potentially interfering response strategy. Similarly, Irle (1985) found that cats with extensive lesions of the limbic system, including the septum, amygdala, hippocampus, anterior thalamus, mamillary bodies, cingulate cortex, and subicular cortex, were facilitated on spatial and delayed alternation tasks. Damaging a structure before training may eliminate competition between multiple memory systems by removing "online" processing during task performance. Similarly, post-training reversible inactivation of the hippocampus can enhance caudate-dependent response learning (Schroeder, Wingard & Packard, 2002).

The non-human primate literature also provides some examples of facilitation effects. For example, Mahut (1972) and Zola and Mahut (1973) found that monkeys with fornix transections performed significantly better than normal control animals on a visual object discrimination reversal task in a WGTA, and Schram (1970) described paradoxical facilitation of performance in squirrel monkeys on a visual pattern discrimination task after hippocampal or fornix lesions. Monkeys with neonatal (Kazama MA Thesis, 2006) or adult (Mahut, 1971) hippocampal lesions were also facilitated on this task. Hippocampal lesions impair transverse patterning performance when monkeys can manipulate stimuli on a tray (Alvarado & Bachevalier, 2005), but facilitate performance above normal levels when the stimuli were presented on a touch screen (Saksida et al., 2007), indicating that the two behavioral procedures may provide different strategies to solve the task. Furthermore, whereas monkeys with neurotoxic neostriatal lesions are impaired when learning 60 concurrent discrimination problems (Fernandez-Ruiz et al., 2001), monkeys with neonatal hippocampal lesions outperform sham-operated controls on this same task (Kazama MA Thesis, 2006).

PFF has also been shown in humans by examining task performance of clinical populations. For example, alcoholic Korsakoff patients were faster to complete word stems with words from a list they were previously exposed to than were non-Korsakoff alcoholic controls (Gardner et al., 1973; Cermak et al., 1988), and patients with global amnesia (Warrington & Weiskrantz, 1978). In addition, a patient with temporal lobe epilepsy (Kapur et al., 1986) and a patient with retrograde amnesia (De Renzi & Luchelli, 1993) both showed facilitation on a paired-associate task in which they were required to associate familiar famous names with novel occupations. Hinrichs and colleagues (1984) suggested that, because interference from prior associations affects performance of normal controls, "interference elimination" in patients with damage to the temporal lobe could be the mechanism by which the facilitation emerges.

These findings suggest that not only do different memory systems operate independently but also, in some instances, they may competitively interact, such that rendering one system dysfunctional may facilitate another (Mishkin & Petri, 1984), a theory also called competitive opponent-processing (Kapur, 1996). Taken together, these findings suggest that the facilitation seen in Experiment 4 of this project may in fact be due to the damage to the declarative memory system, which could leave the striatal-based habit system functioning in an even more efficient manner than in normally developing animals.

This experiment required the animals to process two kinds of information: concurrent discrimination of pairs of stimuli, and associations made between the stimulus pairs and the background context. Evidence presented above clearly demonstrates that an intact striatum, with or without the presence of a functional hippocampus, can support

concurrent discrimination learning, but not associations between the stimulus pairs and the background context. Therefore, the facilitation demonstrated by the animals with neonatal hippocampal lesions on this task cannot be explained by the possible mechanisms of facilitation described above. Further investigations of the facilitatory effects of hippocampal damage are clearly warranted to provide a better understanding on how the different memory systems may compete or interact in different task situations.

Experiment 5

Results from Experiments 1, 2, 3, and 4 showed that animals with neonatal hippocampal damage were unimpaired on contextual discrimination learning and memory even when a background context was necessary for good performance on a task. A likely explanation for such a sparing of function may relate to the use of strategies other than those intended to be measured by the contextual discrimination tasks. One alternative strategy animals with neonatal hippocampal lesions could have developed is that they could have memorized the correct object for a pair when presented on one of the backgrounds, and then infer the correct answer when that same pair is presented on a different background.

In order to investigate this later possibility, in Experiment 5 monkeys were presented with pairs of stimuli that were either overlaid on backgrounds that had been previously associated with the pair from Experiment 4, or new pairs of stimuli overlaid on backgrounds that had also been previously associated with a different pair in Experiment 4. Monkeys with neonatal hippocampal damage were not impaired in acquiring stimuli pairs, even when the background context was one they had previously

encountered and had associated with a different pair of stimuli. Thus, monkeys with neonatal hippocampal damage learned to discriminate new stimuli pairs presented on previously encountered backgrounds (Experiment 5) just as well as they learned new stimuli presented on a new background (Experiment 4). Additionally, acquiring new stimuli pairs presented on a previously encountered background (Experiment 5, Pairs 4 and 5) did not affect performance on previously learned stimuli pairs and backgrounds (Experiment 4 vs. Experiment 5, Pairs 1 and 2). As expected, in Experiment 5 all animals made more errors to criterion on Pairs 4 and 5 as compared to Pairs 1, 2, and 3, reflecting their previous learning of Pairs 1, 2, and 3 in Experiment 4. Thus, the data indicate that inferring a discrimination problem from a previous one using the same background may not be a strategy that would have allowed the animals with neonatal hippocampal lesions to solve the contextual discrimination task.

Summary of Touch Screen Result Implications

The results from the touch screen experiments, namely the lack of expected impairment after neonatal hippocampal lesions on Experiments 3, 4, and 5, might be explained in three different ways. First, it is possible that the lack of impairment reflects the incomplete nature of the lesions in Group Neo-Hibo. Second, the hippocampus may not be critical for contextual discrimination learning and memory, and more specifically, perhaps is not critical for contextual processing without a spatial component. Third, these newly designed non-spatial contextual learning and memory tasks may not require the hippocampus.

Incomplete Lesions

Since none of the neonatal hippocampal lesions in the Group Neo-Hibo animals was complete, the remaining hippocampus may have been able to support performance on the tasks. This idea, however, is unlikely given that amnesic patients with only between 24% and 50% damage to the hippocampus, still showed marked impairments on hippocampal-dependent tasks (e.g. Hassabis et al., 2007; Cipolotti et al., 2009; O'Kane et al., 2004; Stefanacci et al., 2000; Reed & Squire, 1998). Although the extent of damage alone may not account for the lack of impairment seen on this task, it is possible that the exact location of the lesion could play an important role. For example, case Neo-Hibo-4 had a unilateral lesion, with more damage on the right than on the left. However, the small amount of damage to the left hippocampus seems centered in CA1, thus interrupting the flow of information within the trisynaptic circuit and resulting in a bilateral lesion. This explanation for the lack of impairment is unlikely, however, since these same animals showed impaired performance on tasks requiring spatial processing.

For example, Blue and colleagues (2009) tested the same monkeys that were used in this series of experiments on a spatial re-arrangement version of the visual paired comparison task. Animals were first familiarized to an array of seven objects in the familiarization phase, and then presented with the same array and a novel array where three of the seven objects were in different locations. Unlike sham-operated controls, animals with neonatal hippocampal lesions did not show a preference for the novel arrangement of the objects, indicating they were insensitive to changes in spatial location of objects in an array. Additionally, these same neonatal hippocampal-operated animals were impaired on a spatial memory test that required navigation in an open maze to find

food (of varying palatability) in identical goal boxes (Glavis-Bloom MA Thesis, 2006; Glavis-Bloom et al., 2006). When tested to retrieve a particular food located in a particular goal box, the monkeys with neonatal hippocampal damage were impaired relative to controls. That is, although they were able to remember the locations of the most palatable foods as a whole, as opposed to locations of the less palatable foods, they were unable to make specific associations between which specific palatable food was in which specific goal location (Glavis-Bloom MA Thesis, 2006; Glavis-Bloom et al., 2006).

Hippocampus is Not Critical for Non-Spatial Contextual Processing

A second possible reason for a lack of impairment by animals with neonatal hippocampal lesions on Experiments 3, 4, and 5 is that the hippocampus is not necessary for contextual learning and memory processing, especially in the absence of a spatial component to the context portion of the task. Because the tasks developed for this project have not previously been used to test the role of the hippocampus in contextual processing, it is possible that they are in fact not sensitive to hippocampal lesions even in the adult. However, this explanation seems also unlikely given evidence from the literature indicating that the hippocampus is critical for contextual processing even when tasks do not have a spatial component. For example, electrophysiological recording studies in rats have revealed neurons that fire differentially in response to non-spatial contextual cues, such as odor and color (Anderson & Jeffery, 2003; Hayman et al, 2003; Bostock et al., 1991). Similarly, neuroimaging studies have demonstrated that the hippocampus is activated during non-spatial contextual processing (Goh et al., 2004), and hippocampal damage in patients and animals also implicates the hippocampus in non-

spatial contextual processing. That is, Patient YR, who sustained selective damage to the hippocampus, was unable to recognize a familiar object when it was presented in a new context (Pascalis et al., 2009). Likewise, hippocampal lesions in adult rats impaired conditioned fear responses to non-spatial contextual stimuli (Kim & Fanselow, 1992; Phillips & LeDoux, 1992), and similar lesions in adult rabbits caused subjects to become insensitive to non-spatial changes in context such as visual, olfactory, and tactile cues (Penick & Solomon, 1991; Freeman et al., 1997). Further, a few studies in monkeys have reported impaired non-spatial contextual processing following lesions to the hippocampus in adulthood. For example, monkeys with fornix transections were impaired on delayed match-to-sample and discrimination learning when stimuli were naturalistic scenes (Gaffan, 1993, 1994a), or when objects were embedded in complex scenes, but locations were held constant (Gaffan, 1994b, object-in-place task). Additionally, neurotoxic lesions of the hippocampus in monkeys in adulthood impaired performance on discrimination problems learned pre- and post-operatively when information about the background was required to indicate which object was rewarded (Ridley et al., 2001), did not use background contextual cues to enhance performance on a discrimination task (Dore et al., 1998), and were unable to recognize a familiar object when presented over a new background context. Finally, developmental studies in which animals were given hippocampal lesions early in life also demonstrate impairment in non-spatial contextual processing. For example, rats with selective neonatal hippocampal lesions did not respond to novelty of the environment in a test measuring exploratory behavior (van Praag et al., 1998), and monkeys with similar lesions were unable to

retrieve the non-spatial contextual information in which discrimination problems occurred (Killiany et al, 2005; Rehbein et al., 2005).

Taken together, these studies provide substantial evidence that the hippocampus is critical for processing contextual information, even in the absence of spatial components. Thus, an alternative explanation for the lack of impaired contextual learning and memory after neonatal hippocampal lesions is that these newly designed tasks may have favored the use of alternate strategies that could be supported by other brain regions.

Tasks Might be Solved by Strategies Not Mediated by the Hippocampus

As already alluded to above, one alternative strategy to solve the tasks could be to memorize the correct answer for a pair presented over a specific background, and then infer the correct answer for that pair when presented on any other background. The possible use of this strategy, however, was tested in Experiment 5 by requiring the animal to learn new pairs of objects on backgrounds that they had already encountered in Experiment 4 with different objects. If animals were using this strategy, they should have been impaired when acquiring new stimuli pairs (4 and 5) presented over previously memorized backgrounds, but they were not. However, another alternative strategy that monkeys could have used was to form "snapshots" of each stimuli pair and background. For example, in Experiment 5, the monkey would have formed and remembered 10 snapshots, rather than learning to discriminate the stimuli comprising the five pairs. This possible alternative strategy was further examined in Experiment 6.

Sparing of Function

We reasoned that if monkeys with selective neonatal hippocampal lesions, like those with the same lesions in adulthood, were impaired on a task known to measure non-

spatial contextual processing, it is likely that the lack of impairment seen in this series of touch screen experiments is due to the monkeys using strategies mediated by structures other than the hippocampus (i.e. "snapshot" strategy). If, however, monkeys with selective neonatal lesions of the hippocampus were not impaired on a task known to measure non-spatial contextual processing in monkeys with similar damage created in adulthood, it is likely that the lack of impairment seen in the series of touch screen experiments will be due to sparing of function in the animals with early lesions. Such a comparison was possible with the use of a contextual paired-comparison task because recent studies from our laboratory have revealed that monkeys with adult hippocampal damage were impaired on this task contextual memory task (the same task described in Experiment 6 - Bachevalier & Nemanic, personal communication)

Experiment 6

The results demonstrated that, contrary to those obtained by Bachevalier and Nemanic (personal communication), monkeys with neonatal hippocampectomies did show a preference for the novel image on both the control trials and the context trials. Thus, this additional sparing of contextual memory in animals with neonatal hippocampal lesions indicate that the animals could not have been using a "snapshot" strategy since such a strategy would have resulted in chance performance in Experiment 6 context trials. In other words, if monkeys with neonatal hippocampal damage were using a "snapshot" strategy, they would have taken a "snapshot" of the image to which they were familiarized. Then, in the test phase, neither side-by-side image would have matched the "snapshot", because both the familiar and the novel objects were presented on a novel

background, resulting in an equivalent amount of looking to each image. The results indicated otherwise and ruled out the use of this "snapshot" strategy to explain the normal performance of animals with neonatal hippocampal lesions in contextual discrimination learning. Thus, the data suggest that sparing of function may be the likely reason to explain the normal performance after hippocampal lesions. Before discussing how sparing of function could be mediated in the absence of a functional hippocampus early in life, it is worth investigating other possibilities that could account for the different outcomes of early versus late hippocampal lesions on the contextual visual paired comparison task.

The sparing of function on the contextual visual paired comparison task is in sharp contrast with previous work, which demonstrated impaired contextual processing after hippocampal lesions using the same task (Bachevalier & Nemanic, personal communication; Pascalis et al., 2009). There are, however, some important differences between these experiments and the present investigation. First, although in both Bachevalier and Nemanic (personal communication) and the current investigation, ibotenic acid was used to lesion the hippocampus, sparing the surrounding medial temporal lobe cortical areas, the timing of the lesions differed. Bachevalier and Nemanic lesioned the hippocampus in adulthood, whereas animals in the current study received hippocampectomies in infancy. It is likely that this difference in the timing of the lesion accounts for the contrasting results. The hippocampus has a protracted development and is not fully mature until 1-2 years of age (Payne et al., 2009). In the monkeys with neonatal hippocampal lesions, the surrounding cortical areas, which mature before the hippocampus (for review see Alvarado & Bachevalier, 2000), could support contextual

processing at the time the hippocampus was removed, and may have continued to support contextual processing when the hippocampus failed to functionally mature. In contrast, Bachevalier and Nemanic lesioned the hippocampus when it was fully developed and normally functioning. By this time, it is likely that contextual processing was primarily mediated by the hippocampus, and that after removal of the hippocampus in adulthood, the cortical areas could no longer support this functioning on their own.

Second, control animals in Bachevalier and Nemanic (personal communication) showed an overall reduced preference for novelty compared to the sham-operated animals in the present study, although both control groups had performance above chance level. This difference may be attributed to several factors. First, it is possible that the quality of the images differed between the studies. For logistical reasons beyond our control, it was impossible to use the exact same stimuli and backgrounds as Bachevalier and Nemanic, and therefore, the quality of the images may have differed. Specifically, whereas the current investigation attempted to use stimuli that had similar colors, and that stood out very distinctly from the backgrounds, the images were, in fact, different from those used previously. Second, the animals in the two studies had different cognitive testing histories. Whereas animals in the present study were tested on multiple occasions on different versions of the visual paired comparison task, animals in the Bachevalier and Nemanic (personal communication) study were not. Finally, different experimenters both administered the task to the monkeys and scored the data, in each study. Although the scorers were trained to be reliable compared to another lab member conducting the same research at the time, the scorers from the present study and Bachevalier and Nemanic could not be directly tested for reliability with each other.

The results in the present study are also at odds with the results obtained by Pascalis and colleagues (2009), but again, there is an important difference in the methodology. Although the lesions in both the Pascalis and colleagues (2009) study, and in the present investigation were performed in infancy, different lesion techniques were used. Specifically, Pascalis and colleagues (2009) used an aspiration technique that necessitates the removal of the medial temporal cortical areas to access the hippocampus, whereas the present study used ibotenic acid that spared these cortical areas. Therefore, animals in the present study maintained functionally intact cortical areas that could be used to support contextual processing

The results in the current investigation indicate that the lack of impairment seen on Experiments 3 through 6 is most likely due to a sparing of function, probably as a result of the early nature of the damage to the hippocampus and the selectivity of the damage. The sparing of function is related to specific mnemonic processes, those concerning context, but not those related to spatial processes, as described above (Glavis-Bloom MA Thesis, 2006; Glavis-Bloom et al., 2006; Blue et al., 2009). The impairment of performance on tasks requiring spatial processing, but the sparing of function on tasks requiring non-spatial contextual processing, warrants further discussion.

Investigating the Substrates of Sparing of Function

The sparing of function we have observed in the present experiments suggests that other neural structures could presumably support contextual discrimination memory in the absence of a functional hippocampus. In addition, it indicates that these remaining neural structures could mediate contextual memory but not spatial memory. Specifically,

by identifying which neural structures were not damaged by the lesion (because of the use of the neurotoxin, ibotenic acid, rather than an aspiration technique), and how these structures have been implicated in contextual and spatial memory, we may begin to find some candidate structures that are sufficient to support non-spatial contextual memory function, but not spatial memory. In order to identify these candidate structures, it is first necessary to review the functional connectivity of the medial temporal lobe, as well as to examine how and from where, information travels into the medial temporal lobe.

Overview of Medial Temporal Lobe Anatomy

Inputs leaving the primary visual cortex in the occipital lobe are processed in a hierarchical manner as the information is sent to extrastriate cortical areas. Specifically, information from the primary visual cortex is sent via two streams (dorsal stream and ventral stream) each specialized for the type of information it is responsible for (spatial and object, respectively), and the two streams converge in the medial temporal lobe cortical regions (Ungerleider and Mishkin, 1982; Desimone and Ungerleider, 1989; Boussaoud et al., 1990).

Inferior Temporal Cortical Anatomy

In the inferior temporal cortex, the perirhinal (PRh) and parahippocampal cortices (TH/TF) receive the majority of their inputs from the ventral and dorsal streams, respectively. PRh receives input mostly from visual cortical areas TE and TEO, as well as from the insular and orbital frontal (area 13) cortices, and is reciprocally connected to TH/TF (Jones & Powell, 1970; Van Hoesen & Pandya, 1975; Webster et al., 1991; Suzuki & Amaral, 1994a; 1994b). Information carried through these projections to PRh consists of primarily perceptual information about objects, including features such as

color, shape, and size. The parahippocampal cortices receive the majority of inputs from the cingulate gyrus, retrosplenial cortex, and parietal cortex. Additionally, TF receives small projections from visual areas including V4, TEO, and TE (Suzuki & Amaral, 1994b). Information carried through projections to TH/TF consists primarily of information about the spatial location of objects. Entorhinal cortex (ERh) receives two-thirds of its inputs from PRh and TH/TF, with PRh projecting to the rostral two-thirds of ERh, and TH/TF projecting to the caudal two-thirds of ERh (Insausti et al., 1987). The remaining one-third of inputs to the ERh are direct projections from retrosplenial and orbital frontal cortices, the dorsal bank of the superior temporal sulcus, and some auditory inputs from the superior temporal gyrus (Insausti et al., 1987).

Hippocampal Anatomy

Most sensory information reaches the hippocampus via the entorhinal cortex. Inputs from the entorhinal cortex into the hippocampus form the perforant path and synapse onto granule cells of the dentate gyrus (Suzuki & Amaral, 1994a; 1994b). The granule cell axons, called mossy fibers, synapse onto the pyramidal cells of CA3. The axons of these pyramidal cells, called Schaffer collaterals, diverge, with some projecting out of the hippocampus through the fimbria of the fornix to the septum, prefrontal cortex, and mamillary bodies, whereas others project to CA1 and synapse on the pyramidal cells there. CA1 also receives small projections directly from entorhinal cortex, perirhinal cortex, and TH/TF, as well as from the cingulate, parietal, and orbital frontal cortices, the dorsal bank of the superior temporal sulcus, and the insula (Suzuki & Amaral, 1994a; 1994b; Wellman & Rockland, 1997; Goldman-Rakic et al., 1984; Barbas and Blatt, 1995; Blatt and Rosene, 1998; Morris et al., 1999; Kobayashi and Amaral, 2000; Insausti and

Munoz, 2001). Information flows out of the hippocampus via the subiculum, which projects back to the entorhinal, perirhinal, and parahippocampal cortices (Lavanex & Amaral, 2000).

Candidate Structures

As discussed extensively above, the sparing of function seen in animals with selective early damage to the hippocampus is related to specific mnemonic processes. That is, the sparing of function relates only to the type of non-spatial contextual processing required by the tasks in the present series of experiments, but does not extend to tasks requiring spatial processing, on which these same animals were impaired (Glavis-Bloom et al., 2006; Blue et al., 2009). Possible explanations and candidate brain structures for this finding is reviewed below.

Candidate Structures Mediating Contextual Memory

Both the lesion technique (selectively damaging the hippocampus, while sparing the surrounding medial temporal lobe cortical areas), and the body of evidence concerning the anatomical organization of the medial temporal lobe reveal the same candidate structures, which, following selective neonatal hippocampal lesions, may be able to support functions normally mediated by the hippocampus. Thus, the contributions of the parahippocampal, retrosplenial, and perirhinal cortices to the types of processing required for successful performance on the tasks in this series of experiments, will be examined, in turn, below.

Parahippocampal Cortex (TH/TF)

Results from behavioral and neuroimaging studies support the idea that TH/TF may at least partially mediate the sparing of function seen in these animals. First, Pascalis and colleagues (2009) gave monkeys neonatal aspiration lesions of the hippocampus, which also included damage to areas TH/TF. When tested on the same context paired comparison task (see Experiment 6), monkeys with neonatal lesions of the hippocampus that included also areas TH/TF were impaired on the context trials relative to sham-operated controls. Similarly, Nemanic and colleagues (2004) directly damaged areas TH/TF in adult monkeys leaving the hippocampus intact. When tested on the same contextual paired comparison task, animals with selective lesions to TH/TF showed similar impairment to those animals with combined lesions of the hippocampus and TH/TF (Pascalis et al., 2009).

Evidence from neuroimaging studies also suggests that TH/TF is implicated in contextual processing. For example, there is activation of the parahippocampal cortices during: visual context processing (Gronau et al., 2008); retrieving contextual information associated with objects in a virtual reality town (Burgess et al., 2001; Rauchs et al., 2008); retrieving familiar faces encoded with contextual information (Hayes et al., 2009); recollecting context in a color-word association task (Diana et al., 2009); and differentiating between remembered and forgotten contexts (Preston & Gabrieli, 2008).

Taken together, these results suggest that areas TH/TF are necessary, and possibly sufficient, for contextual processing in monkeys especially if the contextual task does not require the processing of spatial information. That is, even when the hippocampus is functional, TH/TF seems to play an active role in processing contextual information associated with a task, and when the hippocampus is removed early in life via selective

lesion, TH/TF may still be able to support contextual memory function, at least to the extent that the tasks in this series of experiments require it.

Retrosplenial cortex (RSC)

Retrosplenial cortex has been shown to be involved in the processing of scenes. For example, Bar and Aminoff (2003) found that the RSC was more engaged when viewing objects that were strongly associated with a context, as opposed to objects that were weakly associated with a context. Specifically, Bar and Aminoff (2003) compiled two lists of objects: one list contained objects that are typically strongly associated with a particular unique context (e.g. a grocery cart is strongly associated with "supermarket" and a microscope is strongly associated with "lab"), and the other list contained objects not typically associated with a particular unique context (e.g. a rope, a camera, a basket). The objects on the former list were labeled strong context association, and the later weak contextual association. Subjects viewed pictures of the objects during fMRI scanning, and indicated through the press of a button when they recognized the object shown. Results suggested that when viewing pictures of objects on the strong context association list, there was increased activation in the RSC and TH/TF as compared to when subjects viewed objects on the weak context association list. This demonstration of activation in the RSC and TH/TF while identifying objects that are typically associated with a unique context suggests that these two cortical areas play a role in the mediation of contextual cues. This pattern of activation was also seen in relation to non-spatial contextual representations of context. Thus, Bar and Aminoff (2003) provided evidence that activation in the RSC and TH/TF may be related to non-spatial contextual processing, particularly when an object and context are associated with one another.

Perirhinal Cortex

Another structure that may support the types of processing required by contextual discrimination tasks in the absence of a functional hippocampus, is the perirhinal cortex, because of its role in both object and contextual memory.

The role of the perirhinal cortex in object identification is now well established. For instance, removal of the perirhinal cortex in rats (Mumby & Pinel, 1994) and monkeys (Meunier et al., 1993; Eacott et al., 1994; Baxter & Murray, 2001) yields impairment on a delayed match- or non-match-to-sample task and object identification when the objects were either embedded in complex scenes (Buckley & Gaffan, 1998) or presented in a view different from the view they were originally learned (Buckley & Gaffan, 1998), and in object discrimination learning (Buffalo et al., 1999). Furthermore, Wan and colleagues (1999) found that c-Fos activation in the perirhinal cortex, but not in the hippocampaus, when rats were viewing novel objects. Finally, the perirhinal cortex is necessary for linking sensory information with objects, such as tactile (Goulet & Murray, 2001), gustatory (Parker & Gaffan, 1998), and visual (Murray et al., 1993; Buckley & Gaffan, 1998; Higuchi & Miyashita, 1996; Tokuyama et al., 2000) information. Taken together, these data suggest that the perirhinal cortex associates the different visual (e.g. color, shape, and size) and nonvisual (e.g. smell and texture) attributes of objects in order to support object identification (Murray & Richmond, 2001).

Beside the role of the perirhinal cortex in object feature processing, other studies suggest that it also plays a role in contextual processing. For example, Gaffan (1994b) reported that monkeys with damage to the perirhinal cortex were impaired when learning complex scenes. Similarly, Bachevalier and Nemanic (personal communication) found

that monkeys with selective damage to the perirhinal cortex were impaired on the same contextual paired comparison task as presented in Experiment 6. Rodent studies have also shown that rats with perirhinal cortex lesions are slower to discriminate between two contexts, one in which saccharine was paired with lithium chloride, and the other with saline (Howse et al., 2003) and failed to show context aversion learning in a choice test (Howse et al., 2003).

Neuroimaging studies in humans further support the idea that the perirhinal cortex mediates both object and contextual processing in some way. Activation of the perirhinal cortex has been found during configural learning (Preston & Gabrieli, 2008), spatial and object memory encoding (Buffalo et al., 2006), encoding of non-associative item information and associative item binding (ex. item-color binding), but not during item-context binding (Staresina & Davachi, 2008). Similarly, the level of engagement of perirhinal cortex in configural learning predicts later memory for individual items (Davachi, 2006).

Candidate Structures Mediating Spatial Memory

The anatomical connectivity of structures projecting to the medial temporal lobe may also point to an explanation for why monkeys with selective neonatal hippocampal damage are impaired on tasks requiring spatial memory processing (e.g. Glavis-Bloom et al., 2006; Blue et al., 2009), but demonstrate sparing of function on the non-spatial contextual tasks in the present investigation. Drawing from what is known about the anatomical connections of structures projecting to the medial temporal lobe, there are, theoretically, a few candidate structures that could be implicated in spatial memory following early damage to the hippocampus, namely the retrosplenial cortex and parietal

cortex. Evidence for this assertion will be discussed below, followed by a discussion about why these structures may, in fact, be unable to support spatial processing on their own, in the absence of a functional hippocampus, but could in fact support non-spatial contextual memory.

Retrosplenial Cortex (RSC)

The retrosplenial cortex (RSC) has been implicated in memory disorders since the beginning of the 20th century (Ironside & Guttmacher, 1929; Valenstein et al., 1987; Rudge & Warrington, 1991; Gainotti et al., 1998; McDonald et al., 2001; Oka et al., 2003; Osawa et al., 20006). Specifically, the RSC has been implicated in spatial disorientation (Maguire, 2001; Ino et al., 2007; Aguirre & D'Esposito, 1999; Epstein, 2008; Takahashi et al., 1997; Alsaadi et al, 2000; Greene et al., 2006), where patients can recognize familiar landmarks, but fail to use the information that should be derived from the landmarks to navigate.

These findings are not surprising given that the RSC is uniquely situated and anatomically connected with structures critical for spatial processing. Specifically, axonal tracing studies in monkeys have revealed reciprocal connections with the hippocampal formation, the parahippocampal region including areas TH/TF and the entorhinal cortex, and the anterior thalamic nuclei (Kobayashi & Amaral, 2003; Kobayashi & Amaral, 2000; Kobayashi & Amaral, 2007; Morris et al., 1999). Thus, the RSC has prime anatomical connections to support spatial memory. In fact, lesions to the RSC in rodents impair spatial memory and navigation (Aggleton & Vann, 2004; Harker & Whishaw, 2004). Specifically, following RSC lesions, rats are impaired at learning the fixed (Vann & Aggleton, 2002; Sutherland et al., 1988; Harker & Whishaw, 2004;

Whishaw et al., 2001) and daily-changing (Sutherland et al., 1988; Harker & Whishaw, 2004; Vann et al., 2003) location of a platform in a water maze. Both of these tasks are allocentric in nature, meaning they require the use of distal visual cues for accurate navigation. Impairments have also been found on tasks requiring the use of egocentric, or response strategies following RSC lesions (Whishaw et al., 2001; Pothuizen et al., 2008). For example, inactivation of the RSC produces impairments in a radial-arm maze task requiring response strategies (Cooper & Mizumori, 1999; Cooper et al., 2001; Cooper & Mizumori, 2001). Finally, the RSC is required for the detection of novel spatial arrangements of objects, although does not seem to be necessary for detection of the novel objects themselves (Vann & Aggleton, 2002).

Additional evidence supporting the role of the RSC in spatial processing comes from electrophysiological recordings in rats. Thus, 10% of RSC neurons are head-direction cells (Chen et al., 1994), and other cells fire in response to specific combinations of location, direction, and movement (Cho et al., 2001). Finally, neuroimaging studies in humans have consistently reported activation of the RSC during passive viewing of navigation footage, mental navigation, navigation in virtual reality environments, learning of new environments, navigation of recently learned environments, and navigation in extremely familiar environments (Maguire, 2001; Epstein, 2008; Spiers & Maguire, 2007; Burgess et al., 2002; Bird & Burgess, 2008; Spiers & Maguire, 2006).

Taken together, these studies suggest that the role of the RSC is to transform allocentric representations into egocentric representations, and vice versa (Vann et al., 2009). In other words, the RSC may help switch between viewpoint-independent

(allocentric) frames of reference that are mediated by the medial temporal lobe, and viewpoint-dependent (egocentric) frames of reference that are mediated by the posterior parietal areas. As such, the parietal cortex is another candidate structure that may lend support to spatial processing in the absence of a functional hippocampus.

Parietal Cortex

The parietal cortex is the recipient of projections from the visual cortical areas that make up the dorsal stream (Mishkin & Ungerleider, 1982). In monkeys, the posterior parietal cortex is divided into several portions, each representing different parts of space, and contributing independently to spatial processing. For example, the lateral intraparietal (LIP) region contains a map of neurons that are retinotopically coded when the eyes are fixed (Kusunoki & Goldberg, 2003) and helps modulate the saliency of, and attention to, spatial locations (Goldberg et al., 2006). The ventral intraparietal (VIP) region receives multisensory information (Avillac et al., 2005) and its neurons fire with respect to head-direction and eye-direction (Zhang et al., 2004). Two regions of the posterior parietal cortex process information about objects that are being reached for. Specifically, neurons in the medial intraparietal (MIP) region encode the location of an object that is being reached for, whereas neurons in the anterior intraparietal (AIP) region respond to the shape, size, and orientation of the object (Pesaran et al., 2006; Murata et al., 2000). This holds true for both objects that are within the visual field (Pesaran et al., 2006) and those for which the location is remembered (Murata et al., 1996). Taken together, these data suggest that the primary function of the parietal cortex as it relates to spatial memory, is to represent spatial information in an egocentric manner.

What mediates sparing of non-spatial contextual memory function following selective neonatal hippocampal damage?

As discussed extensively above, behavioral data suggest various specific functions for the perirhinal, parahippocampal, and retrosplenial cortices. Specifically, substantial evidence implicates the perirhinal cortex in processing information about objects, TH/TF in processing contextual information, and retrosplenial cortex in processing object and context associations. Anatomical evidence indicates that these structures are connected in such a way that, in the absence of a functioning hippocampus, the type of non-spatial contextual processing required by the tasks in the current investigation, could be supported. Therefore, the sparing of function demonstrated by monkeys in the present investigation may be ascribed to the selectivity of the damage to the hippocampus, leaving the surrounding cortical areas intact, and/or to the early nature of the damage, thereby allowing the highly plastic infant brain to redistribute function permanently to the surrounding cortical areas. Nevertheless, recent investigations demonstrate that the retrosplenial cortex may not be entirely functional after neonatal hippocampal lesions in monkeys. Thus, Machado and colleagues (2008) found hypo metabolism in the retrosplenial cortex of adult monkeys who sustained selective early lesions to the hippocampus. Finally, investigation of the effects of the neonatal hippocampal lesions in monkeys in the present investigation revealed volumetric reduction in the splenium of the corpus callosum, an area that receives projections from the retrosplenial cortex (Cirrili et al., 2009). Therefore, the two most likely candidates for the sparing of contextual function remain the perirhinal and parahippocampal cortices.

Why don't the same candidate structures mediate spatial processing in the absence of a functional hippocampus?

As previously discussed, the sparing of function demonstrated by the animals with neonatal hippocampal damage in the present investigation is limited to the domain of non-spatial contextual processing. In fact, these same animals were previously impaired on two tests of spatial memory function (Glavis-Bloom et al., 2006; Blue et al., 2009). Possible explanations for why candidate structures did not, in fact, support spatial memory function in the absence of the hippocampus, will be explored below, by examining each of the two instances of impaired spatial memory in turn.

Glavis-Bloom et al., 2006

Glavis-Bloom and colleagues (2006) found that animals with selective neonatal hippocampal damage were impaired at making specific associations between food items and their locations in a task that required spatial navigation. Behavioral data suggests that the retrosplenial and parietal cortices could support the kind of processing thought to be necessary for this spatial navigation task. As discussed extensively above, the retrosplenial cortex has been implicated in navigation and spatial memory in a variety of independent investigations. It has also been suggested that a function of the RSC is to combine allocentric and egocentric spatial information such that both can be used to solve the same problem. Similarly, the parietal cortex has been implicated in numerous ways in spatial orientation.

Consideration of the anatomical data, however, suggests that these candidate structures are, in fact, unable to support spatial memory processing required by this task. Although it is clear that the retrosplenial cortex is capable of processing vast amounts of

spatial information required for accurate navigation, there is evidence to suggest that it cannot support spatial navigational processing without the hippocampus. For example, Warburton and colleagues (2001) demonstrated through disconnection studies that the interactions between the retrosplenial cortex and the hippocampus are necessary to support spatial learning. That is, rats were given unilateral lesions of the RSC, plus contralateral lesions of the hippocampus, and were impaired on the fixed platform version of the water maze. These results suggest that if either of these structures were not functional, spatial learning would be impaired. Additional anatomical evidence suggesting that RSC may not be able to mediate spatial processing following neonatal hippocampal lesions comes from examination of resting cerebral glucose metabolism through micro positron emission tomography (micro PET). Thus, Machado and colleagues (2008) found hypo metabolism in the retrosplenial cortex of adult monkeys who sustained selective early lesions to the hippocampus. Finally, investigation of the effects of the neonatal hippocampal lesions in monkeys in the present investigation revealed volumetric reduction in the splenium of the corpus callosum, an area that receives projections from the retrosplenial cortex (Cirrili et al., 2009

Blue et al., 2009

Blue and colleagues (2009) reported impaired performance on a spatial rearrangement visual paired comparison task by monkeys with selective neonatal hippocampal lesions. Specifically, monkeys were familiarized to an image that consisted of an array of seven objects. Following a short delay, the same array was presented side-by-side with an array that consisted of the exact same objects, but that had changed the locations of three of the seven objects. Monkeys with neonatal hippocampal lesions were

unable to recognize that they had previously seen one of the images. Behavioral data suggest that, in the absence of a functional hippocampus, perirhinal, retrosplenial, and parahippocampal cortices could support the types of processes thought to be important for this task. Specifically, Murray and colleagues (1993) found impairment on an object-object association task following perirhinal cortex damage in monkeys, suggesting that perirhinal cortex is able to support these associations. Similarly, the retrosplenial cortex, TH/TF, and the hippocampus have been shown to be required for detection of novel spatial arrangements, but not for detection of novel objects, themselves (Vann & Aggleton, 2002). Finally, rats performing spatial memory tasks using familiar spatial cues (Pothuizen et al, 2008) or novel configurations of spatial cues (Amin et al., 2006) show immediate early gene activation in both the RSC and the hippocampus. Although behavioral evidence suggests that any or all of these three candidate structures (perirhinal, retrosplenial, and parahippocampal cortices) may be able to support portions of the spatial processing required in this task, anatomical data suggests otherwise. For instance, Wan et al., (1999) investigated the independent contributions of the perirhinal cortex and the hippocampus to recognition memory. They measured c-fos as a sign of differential neural involvement in rats during a passive viewing of novel versus familiar single objects, and during passive viewing of novel versus familiar arrangements of arrays of objects. Perirhinal cortex and TE were differentially activated during viewing of novel relative to familiar objects, whereas the hippocampus was not. In contrast, the postrhinal cortex (the rodent homologue of primate TH/TF) and CA1 were activated during viewing of novel relative to familiar arrangements of arrays of objects, whereas perirhinal cortex and TE were not. Thus, the perirhinal cortex appears to be involved in

processing information about the familiarity of single objects, whereas the hippocampus appears to be involved in processing information about the particular arrangements of arrays of objects. These findings support those of Blue and colleagues (2009) who found impairment following neonatal hippocampal damage on a spatial rearrangement version of the visual paired comparison task. As discussed in the previous section, even though the behavioral evidence suggesting a role for the retrosplenial cortex in spatial processing suggests that it could support the functions required for successful performance on this task, without a hippocampus, it seems the information is unable to be utilized.

Conclusion

In summary, the current data show sparing of non-spatial contextual learning and memory function following early selective lesions to the hippocampus. The sparing of function is likely due to both the early nature of the damage and the selectivity of the lesion, which leaves the medial temporal lobe cortical areas intact. Therefore, by removing the hippocampus early in life, before it has begun to function, TH/TF, either alone, or in concert with the perirhinal cortex, may be sufficient to support context processing throughout life.

Taken all together, the evidence presented by the current investigation, as well as a vast amount of previous research, suggests that the role of the hippocampus is to associate bits of information received from numerous brain areas into complete representations of an event. These associations can take many forms, including object-object and object-context associations, both in the spatial and non-spatial domains. Although it is likely that the hippocampus evolved to support spatial navigation and

episodic memory, the mechanism that supports these functions seems to also be able to support a number of other more specific processes. Thus, by receiving bits of information from numerous other brain areas, the hippocampus relates all types of information to one another in order to form complete representations, which, once associated, can subsequently be used independently of one another.

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Table 1. Experiment 1: Sessions, trials, and errors to criterion.

Subject	Sessions	Trials	Errors
Neo-C-1	8	480	164
Neo-C-2	7	420	123
Neo-C-3	11	660	233
Neo-C-4	22	1320	481
Neo-C-6	8	480	180
Average	*11.2*	*672*	*236.2*
SEM	*2.78*	*166.93*	*63.69*
Neo-Hibo-1	8	480	195
Neo-Hibo-2	6	360	118
Neo-Hibo-3	11	660	211
Neo-Hibo-4	14	840	329
Neo-Hibo-6	8	480	172
Average	*9.4*	*564*	*205*
SEM	*1.4*	*84*	*34.76*

Table 2. Experiment 2: Sessions, trials, and errors to criterion.

Subject	Sessions			Trials			Errors		
	Total	Same Trials	Change Trials	Total	Same Trials	Change Trials	Total	Same Trials	Change Trials
Neo-C-1	24	10	21	1440	300	630	400	102	216
Neo-C-2	12	10	19	720	300	570	286	121	201
Neo-C-3	18	14	16	1080	420	480	321	129	163
Neo-C-4	31	20	16	1860	600	480	596	215	179
Neo-C-6	13	9	19	780	270	570	247	97	172
Average	*19.6*	*12.6*	*18.2*	*1176*	*378*	*546*	*370*	*132.8*	*186.2*
SEM	*3.56*	*2.04*	*0.97*	*213.5*	*61.2*	*29.1*	*61.9*	*21.4*	*9.7*
Neo-Hibo-1	18	13	20	1080	390	600	357	157	184
Neo-Hibo-2	16	7	16	960	210	480	325	81	190
Neo-Hibo-3	14	9	15	840	270	450	263	84	165
Neo-Hibo-4	34	23	34	2040	690	1020	748	249	446
Neo-Hibo-6	8	5	4	480	150	120	150	60	47
Average	*18*	*11.4*	*17.8*	*1080*	*342*	*534*	*368.6*	*126.2*	*206.4*
SEM	*4.3*	*3.2*	*4.8*	*260.2*	*95.6*	*145.2*	*101.2*	*34.8*	*65.3*

Table 3. Experiment 3: Sessions, trials, and errors to criterion.

Subject	Sessions					Trials					Errors				
	Pair 1	Pair 2	Pair 3	Pair 4	Tot.	Pair 1	Pair 2	Pair 3	Pair 4	Tot.	Pair 1	Pair 2	Pair 3	Pair 4	Tot.
Neo-C-1	10	1	5	4	11	600	60	300	240	660	183	18	94	80	455
Neo-C-2	3	1	3	9	17	180	60	180	540	1020	81	25	43	136	496
Neo-C-3	6	1	2	20	30	360	60	120	1200	1800	121	22	36	393	906
Neo-C-4	6	2	3	9	17	360	120	180	540	1020	109	34	55	179	615
Neo-C-6	9	2	1	2	11	540	120	60	120	660	203	47	18	50	363
Average	*6.8*	*1.4*	*2.8*	*8.8*	*17.2*	*408*	*84*	*168*	*528*	*1032*	*139.4*	*29.2*	*49.2*	*167.6*	*567*
SEM	*1.2*	*0.2*	*0.7*	*3.1*	*3.5*	*74.5*	*14.7*	*39.8*	*187.3*	*208.2*	*23.0*	*5.2*	*12.7*	*60.6*	*93.9*
Neo-Hibo-1	8	2	2	14	25	480	120	120	840	1500	180	46	43	240	728
Neo-Hibo-2	3	1	4	3	10	180	60	240	180	600	59	24	54	57	305
Neo-Hibo-3	4	2	1	3	11	240	120	60	180	660	79	43	21	47	287
Neo-Hibo-4	14	4	7	7	24	840	240	420	420	1440	279	86	140	178	903
Neo-Hibo-6	3	1	1	2	10	180	60	60	120	600	66	21	19	52	246
Average	*6.4*	*2*	*3*	*5.8*	*16*	*384*	*120*	*180*	*348*	*960*	*132.6*	*44*	*55.4*	*114.8*	*493.8*
SEM	*2.1*	*0.6*	*1.1*	*2.2*	*3.5*	*126.7*	*32.9*	*68.4*	*133.4*	*208.7*	*42.7*	*11.6*	*22.2*	*39.7*	*134.6*

Table 4. Experiment 4: Sessions, trials, and errors to criterion.

Subject	Sessions						Trials						Errors					
	Pair 1	Pair 2	Pair 3	Pair 4	Pair 5	Tot.	Pair 1	Pair 2	Pair 3	Pair 4	Pair 5	Tot.	Pair 1	Pair 2	Pair 3	Pair 4	Pair 5	Tot.
Neo-C-1	12	5	6	5	6	13	720	300	360	300	360	3900	250	105	122	126	147	929
Neo-C-2	5	4	1	3	3	6	300	240	60	180	180	1800	98	64	16	54	83	385
Neo-C-3	3	3	2	3	2	4	180	180	120	180	120	1200	58	48	36	62	48	303
Neo-C-4	11	5	5	5	5	12	660	300	300	300	300	3600	197	73	90	91	77	730
Neo-C-6	5	4	3	2	3	6	300	240	180	120	180	1800	113	72	49	48	72	425
Average	*7.2*	*4.2*	*3.4*	*3.6*	*3.8*	*8.2*	*432*	*252*	*204*	*216*	*228*	*2460*	*143.2*	*72.4*	*62.6*	*76.2*	*85.4*	*554.4*
SEM	*1.8*	*0.37*	*0.93*	*0.6*	*0.73*	*1.8*	*108*	*22.5*	*55.6*	*36*	*44.1*	*540*	*35.01*	*9.3*	*19.2*	*14.47*	*16.51*	*118.3*
Neo-Hibo-1	3	2	2	2	1	4	180	120	120	120	60	1200	61	26	43	38	29	286
Neo-Hibo-2	3	3	2	2	2	4	180	180	120	120	120	1200	46	51	37	54	38	259
Neo-Hibo-3	1	1	0	1	1	2	60	60	0	60	60	600	24	19	0	20	14	103
Neo-Hibo-4	3	4	3	4	4	6	180	240	180	300	240	1800	47	106	77	67	70	452
Neo-Hibo-6	2	1	1	1	1	3	120	60	60	60	60	900	39	24	14	26	18	148
Average	*2.4*	*2.2*	*1.6*	*2*	*1.8*	*3.8*	*144*	*132*	*96*	*132*	*108*	*1140*	*43.4*	*45.2*	*34.2*	*41*	*33.8*	*249.6*
SEM	*0.4*	*0.58*	*0.51*	*0.55*	*0.58*	*0.66*	*24*	*34.9*	*30.6*	*44.1*	*34.9*	*199*	*6.02*	*16.2*	*13.2*	*8.72*	*9.98*	*60.9*

Table 5. Experiment 5: Sessions, trials, and errors to criterion.

Subject	Sessions						Trials						Errors					
	Pair 1	Pair 2	Pair 3	Pair 4	Pair 5	Tot.	Pair 1	Pair 2	Pair 3	Pair 4	Pair 5	Tot.	Pair 1	Pair 2	Pair 3	Pair 4	Pair 5	Tot.
Neu-C-1	0	0	0	2	1	3	0	0	0	120	60	900	0	0	0	52	23	127
Neu-C-2	1	0	0	4	2	5	60	0	0	240	120	1500	15	0	0	89	36	221
Neu-C-3	3	1	1	7	5	8	180	60	60	420	300	800	47	11	16	152	78	495
Neu-C-4	0	0	0	3	4	5	0	0	0	180	240	500	0	0	0	67	66	257
Neu-C-6	1	0	0	2	1	3	60	0	0	120	60	300	15	0	0	46	14	127
Average	*1*	*.2*	*.2*	*3.6*	*2.6*	*4.8*	*60*	*12*	*12*	*216*	*156*	*800*	*15.4*	*2.2*	*3.2*	*81.2*	*43.4*	*245.4*
SEM	*.55*	*.2*	*.2*	*.93*	*.81*	*.92*	*32.9*	*12*	*12*	*55.6*	*48.7*	*204.9*	*8.58*	*2.2*	*3.2*	*19.2*	*12.3*	*67.5*
Neu-Hibo-1	1	1	0	8	2	9	60	60	0	480	120	900	10	11	0	146	45	411
Neu-Hibo-2	0	0	0	1	1	2	0	0	0	60	60	600	0	0	0	17	22	77
Neu-Hibo-3	0	0	0	1	1	2	0	0	0	60	60	600	0	0	0	28	17	100
Neu-Hibo-4	0	2	0	2	3	4	0	120	0	120	180	400	0	22	0	37	54	208
Neu-Hibo-6	0	0	0	1	1	2	0	0	0	60	60	600	0	0	0	22	18	71
Average	*0.20*	*0.60*	*0*	*2.6*	*1.6*	*3.8*	*12*	*36*	*0*	*156*	*96*	*620*	*2*	*6.6*	*0*	*50*	*31.2*	*173.4*
SEM	*0.20*	*0.40*	*0*	*1.36*	*0.40*	*1.36*	*12*	*24*	*0*	*81.8*	*24*	*80*	*2*	*4.4*	*0*	*24.2*	*7.65*	*64.35*

Table 6. Experiment 6: Percent looking to the novel image.

Subject	Control Trials	Context Trials
Neo-C-1	69.56	70.18
Neo-C-2	77.56	70.96
Neo-C-3	79.80	60.40
Neo-C-4	60.41	63.18
Neo-C-6	61.76	55.25
Average	*69.82*	*63.99*
SEM	*3.96*	*2.97*
Neo-Hibo-1	62.01	64.78
Neo-Hibo-2	61.4	66.28
Neo-Hibo-3	70.48	66.18
Neo-Hibo-4	77.39	62.75
Neo-Hibo-6	82.46	70.83
Average	*70.75*	*66.16*
SEM	*4.15*	*1.33*

Table 7. Intended damage in Group Neo-Hibo.

Percent damage to the hippocampal formation for the four animals in Group Neo-Hibo. Abbreviations: L% - percent damage to the left hemisphere; R% - percent damage to the right hemisphere; X% - average damage to both hemispheres; W% - weighted average damage to both hemispheres (W% = (L% x R%)/100).

Subjects	Hippocampal Formation			
	L%	*R%*	*X%*	*W%*
Neo-Hibo-1	63.6	2.9	33.2	1.8
Neo-Hibo-2	54.4	80.9	67.6	44.0
Neo-Hibo-3	78.5	96.3	87.4	75.6
Neo-Hibo-4	20.3	67.3	43.8	13.6
Neo-Hibo-6	7.9	0.0	3.9	0.0
Average	*44.9*	*49.5*	*47.2*	*27*

Table 8. Unintended damage in Group Neo-Hibo.

Percent unintended damage to areas surrounding the hippocampal formation for the four monkeys in Group Neo-Hibo. Abbreviations: ERh, entorhinal cortex, PRh, perirhinal cortex, TE, temporal cortical area and TH/TF: cytoarchitectonic fields of the parahippocampal gyrus as defined by von Bonin and Bailey (1947).

Subjects	Amygdala				TH/TF				TE			
	L%	*R%*	*X%*	*W%*	*L%*	*R%*	*X%*	*W%*	*L%*	*R%*	*X%*	*W%*
Neo-Hibo-1	14.0	0.0	7.0	0.0	3.1	0.5	1.8	0.0	0.0	0.0	0.0	0.0
Neo-Hibo-2	0.0	0.0	0.0	0.0	21.4	2.7	12.1	0.6	0.6	0.0	0.3	0.0
Neo-Hibo-3	1.7	0.0	0.8	0.0	6.1	5.5	5.8	0.3	0.0	0.0	0.0	0.0
Neo-Hibo-4	0.0	4.7	2.4	0.0	15.3	0.0	7.6	0.0	1.0	0.0	0.5	0.0
Neo-Hibo-6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean	*3.1*	*0.9*	*2.0*	*0.0*	*9.2*	*1.7*	*5.5*	*0.2*	*0.3*	*0.0*	*0.2*	*0.0*

Subjects	ERh				PRh			
	L%	*R%*	*X%*	*W%*	*L%*	*R%*	*X%*	*W%*
Neo-Hibo-1	2.6	0.0	1.3	0.0	0.0	0.0	0.0	0.0
Neo-Hibo-2	0.0	0.0	0.0	0.0	5.4	0.5	2.9	0.0
Neo-Hibo-3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Neo-Hibo-4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Neo-Hibo-6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean	*0.5*	*0.0*	*0.3*	*0.0*	*1.1*	*0.1*	*0.6*	*0.0*

Figure 1. Images of the testing setup.

(A.) Cage inside sound attenuated testing box. (B.) Touch screen mounted on the inside wall of the sound attenuated testing box. (C.) Computer that controls the touch screen and the automated mini-M&M dispenser.

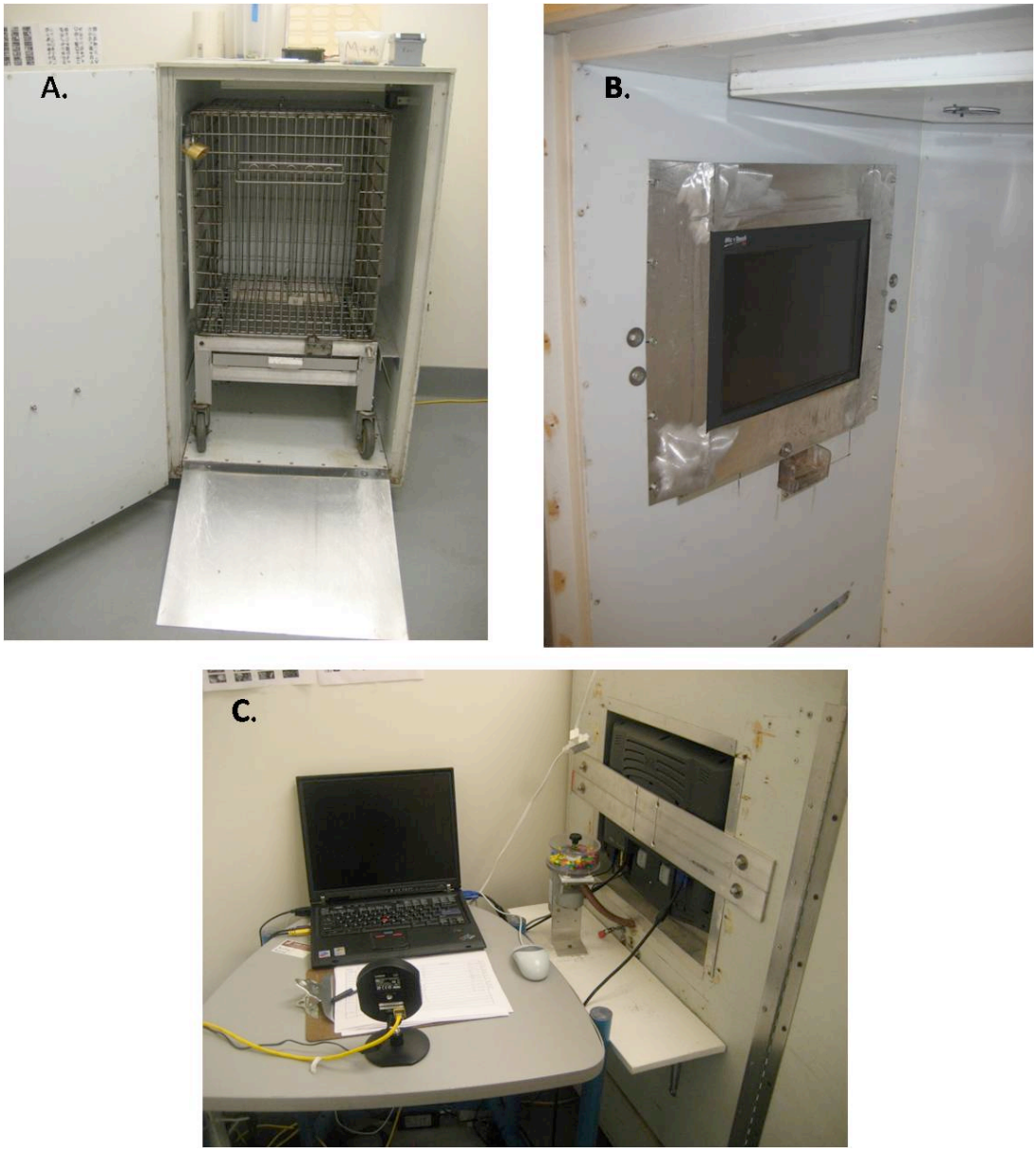

Figure 2. Experiment 1 stimuli.

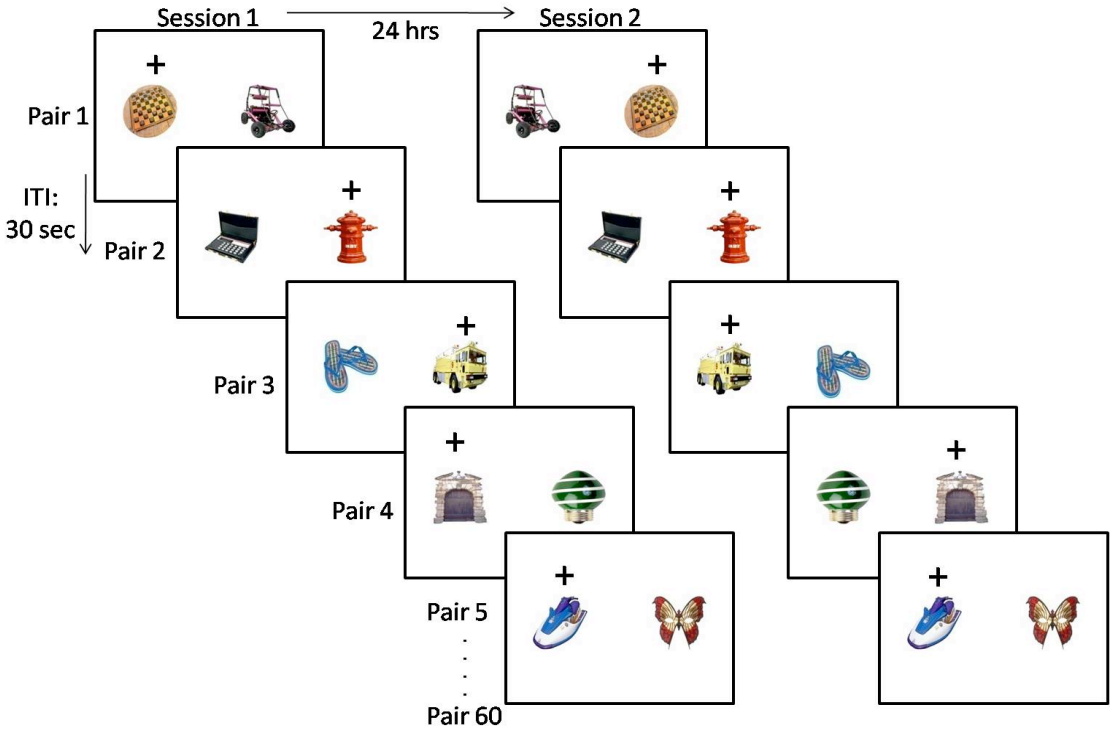

Figure 3. Experiment 1 errors to criterion.

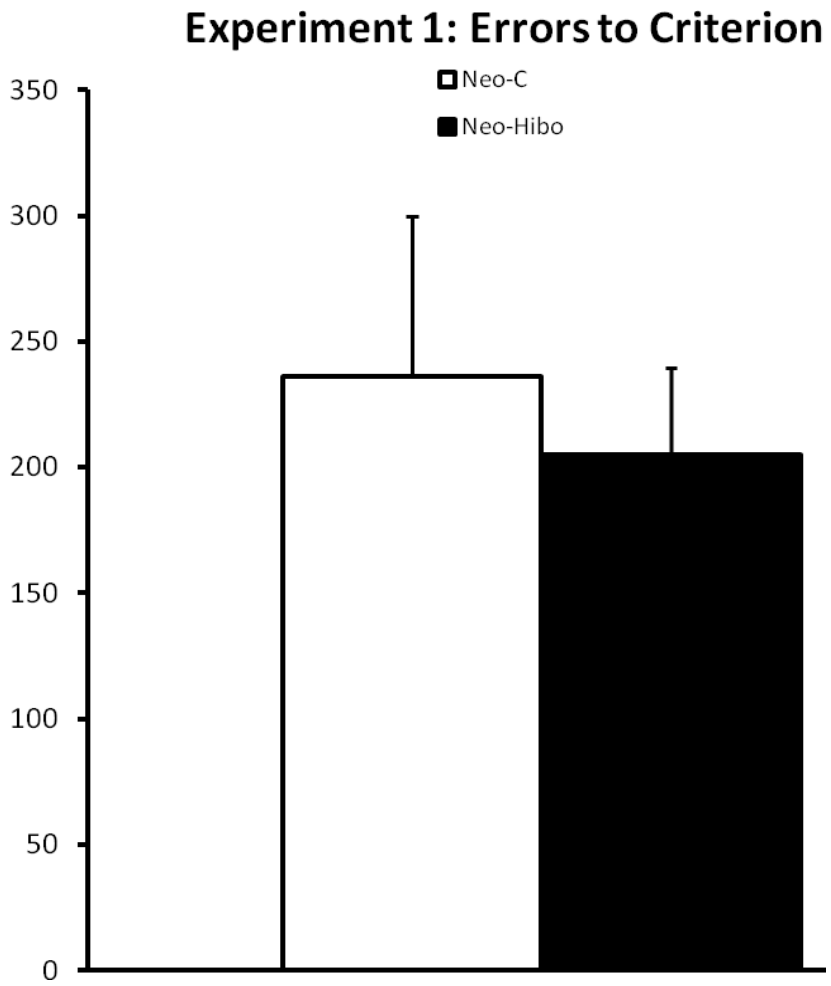

Figure 4. Experiment 2 stimuli.

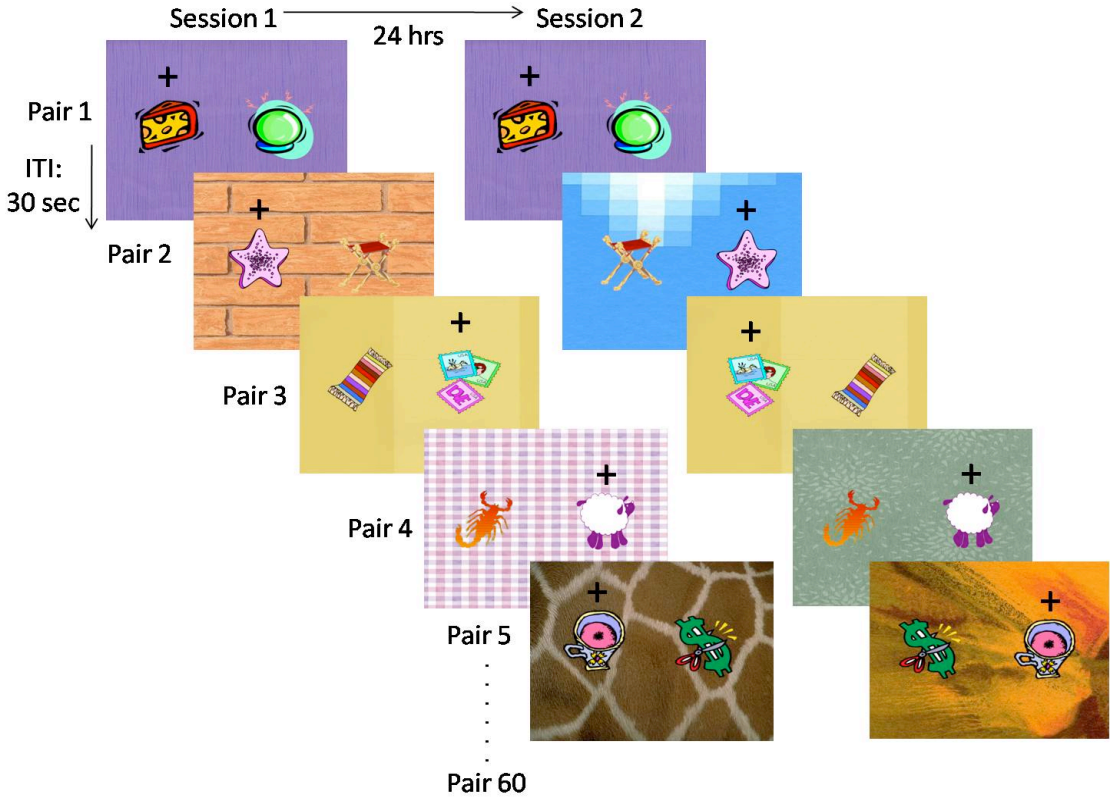

Figure 5. Experiment 2 errors to criterion.

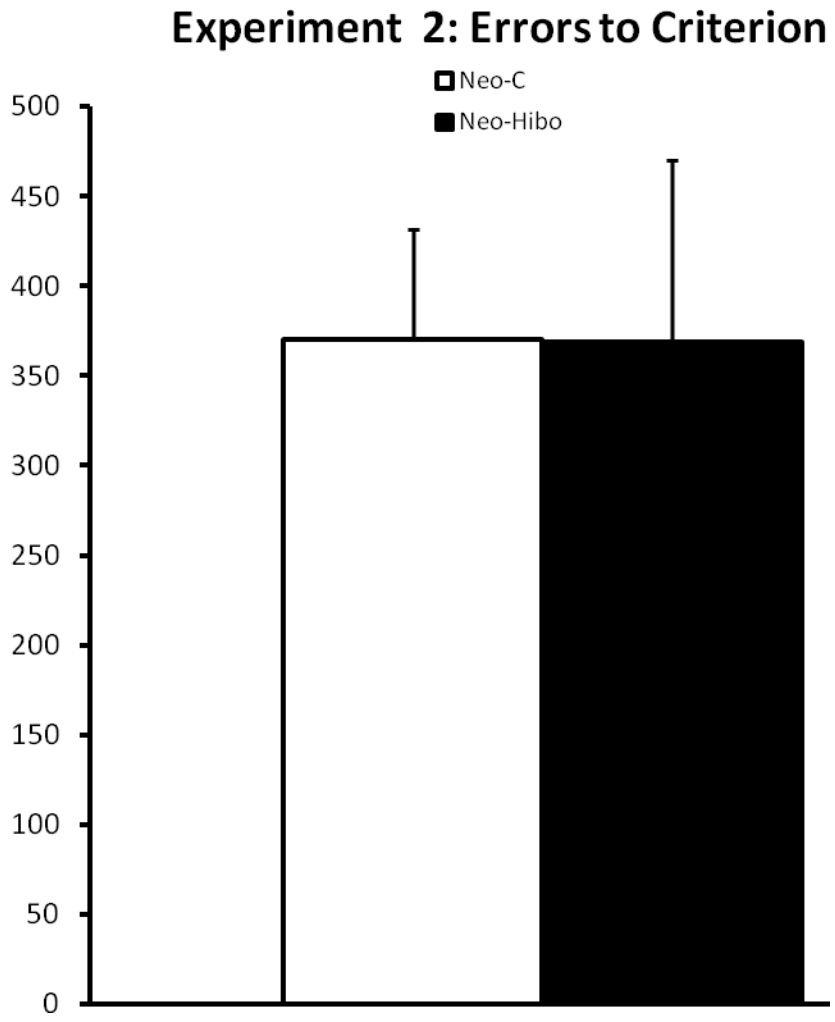

Figure 6: Experiment 2 errors to criterion by trial type.

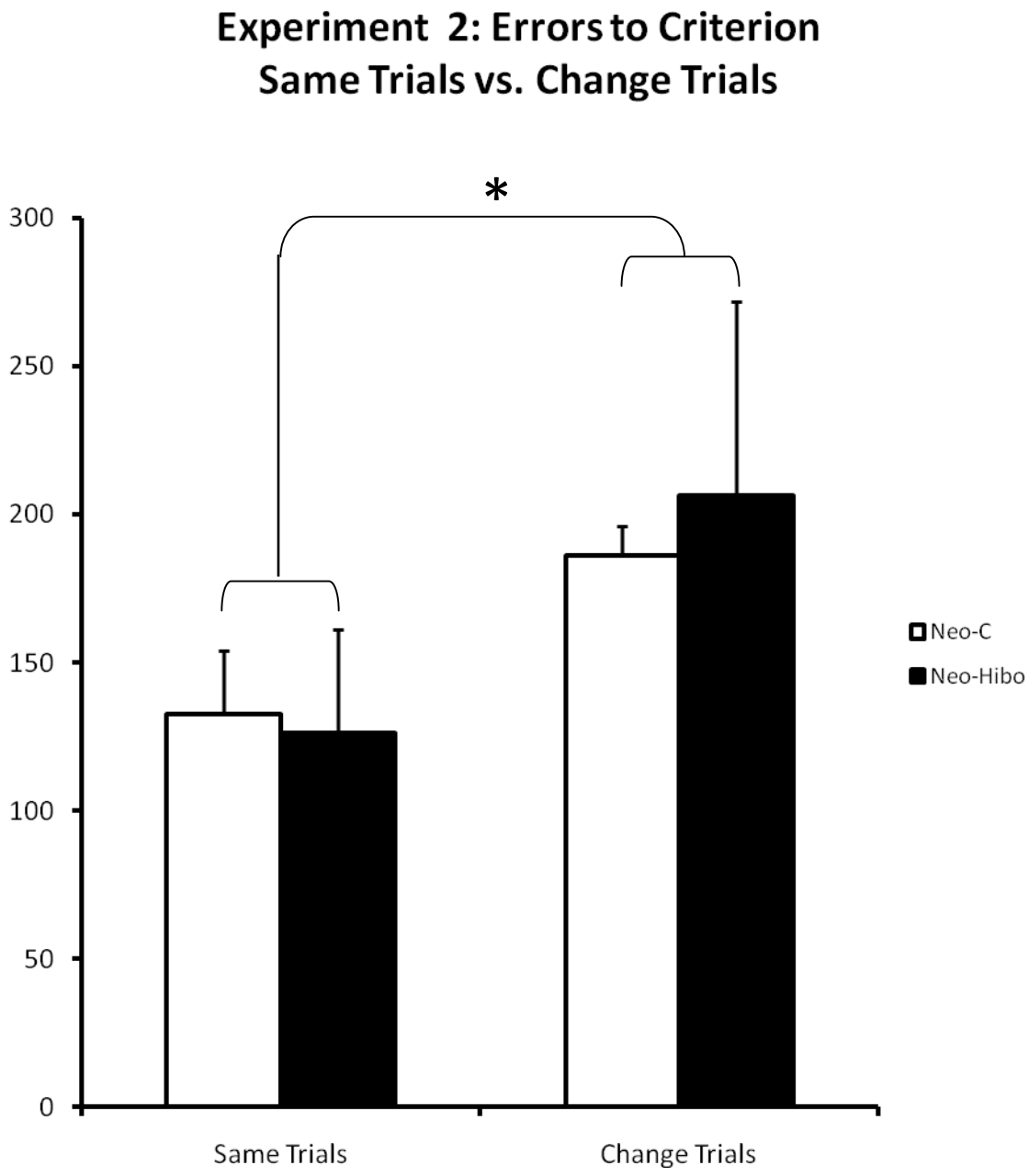

Figure 7. Experiment 1 vs. Experiment 2 errors to criterion

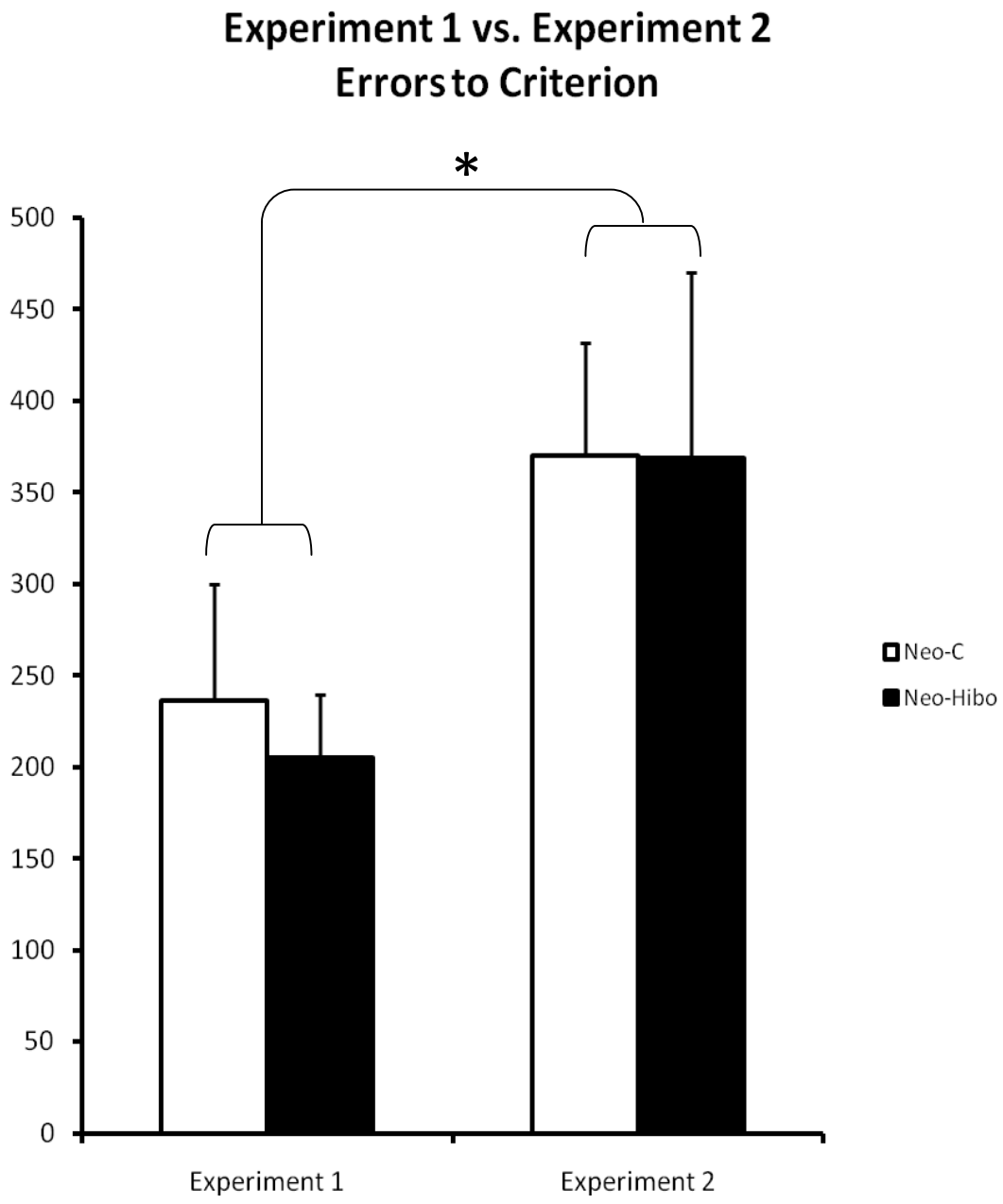

Figure 8. Experiment 3 stimuli.

Pair 1 was shown 60 times (30 over the orange background, and 30 over the purple background). When animals demonstrated initial learning (>70% correct), Pair 2 was added in. Sessions consisted of a total of 60 trials (30 of Pair 1 and 30 of Pair 2). When animals demonstrated initial learning of Pair 2, Pair 3 was added in. Sessions consisted of a total of 60 trials (20 each of Pair 1, 2, and 3). When animals demonstrated initial learning of Pair 3, Pair 4 was added in. Sessions consisted of a total of 60 trials (15 each of Pairs 1, 2, 3, and 4). Testing continued until animals reached a criterion of 85% on each pair individually and overall.

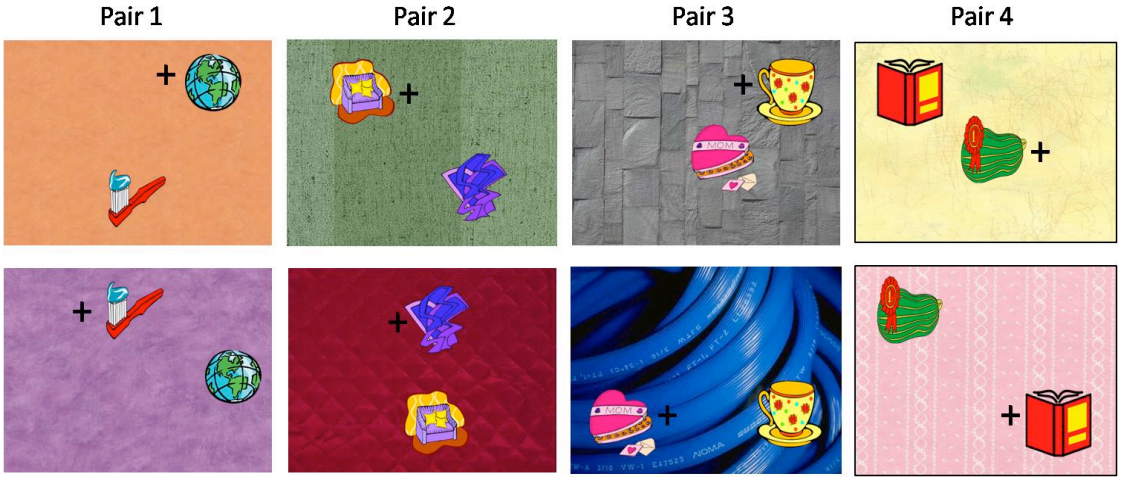

Figure 9. Experiment 3 errors to criterion.

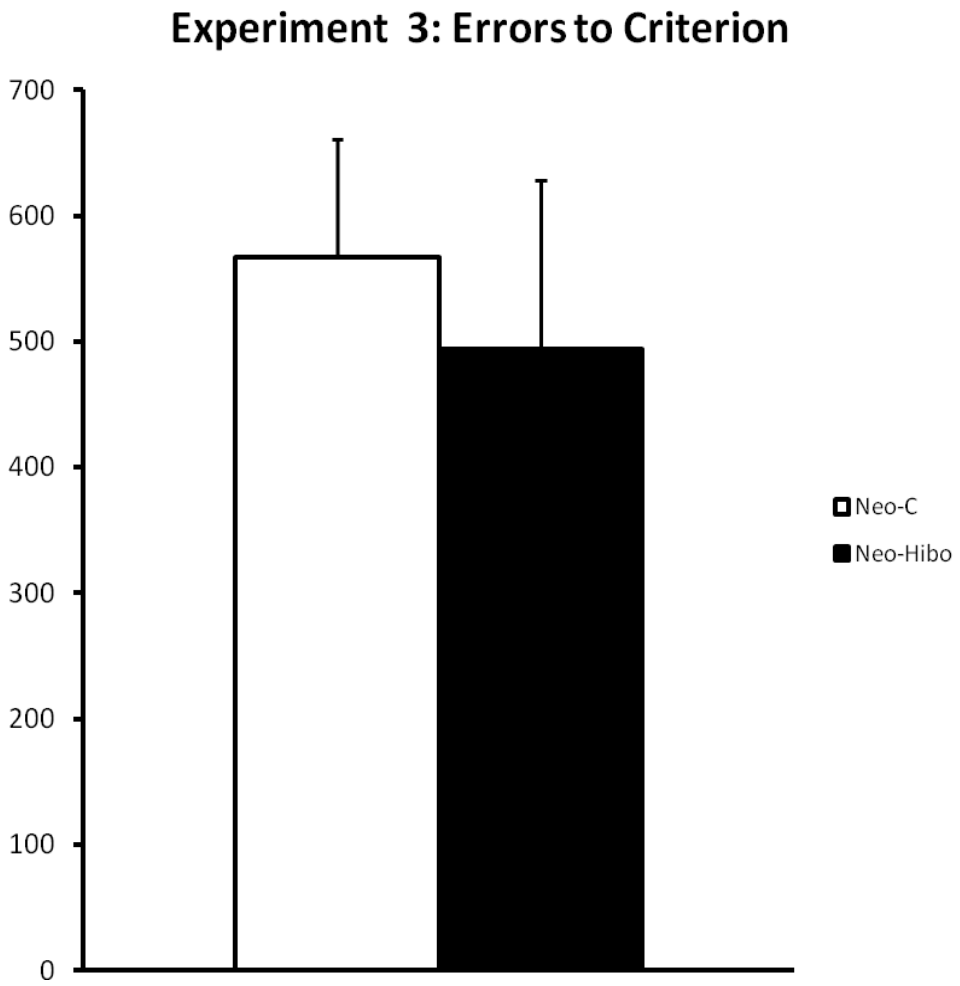

Figure 10. Experiment 3 errors to criterion by pair.

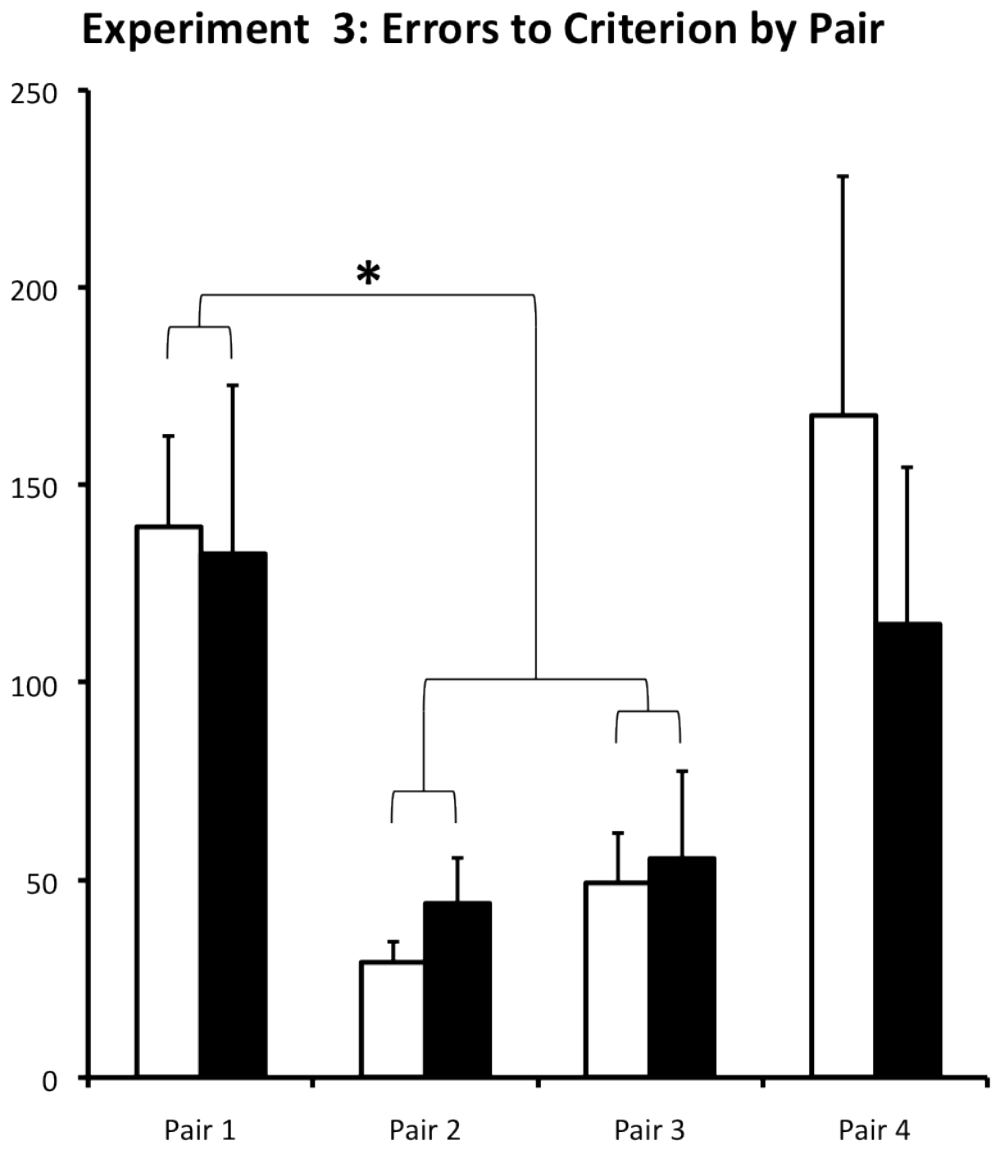

Figure 11. Experiment 4 stimuli.

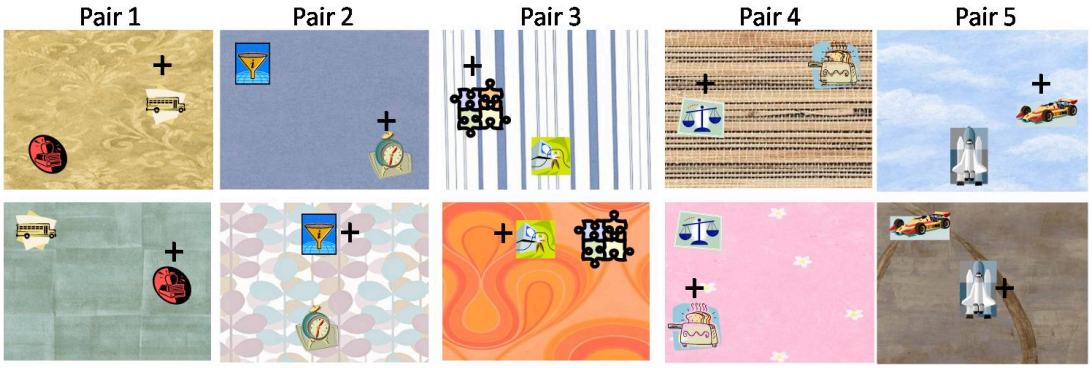

Figure 12. Experiment 4 errors to criterion.

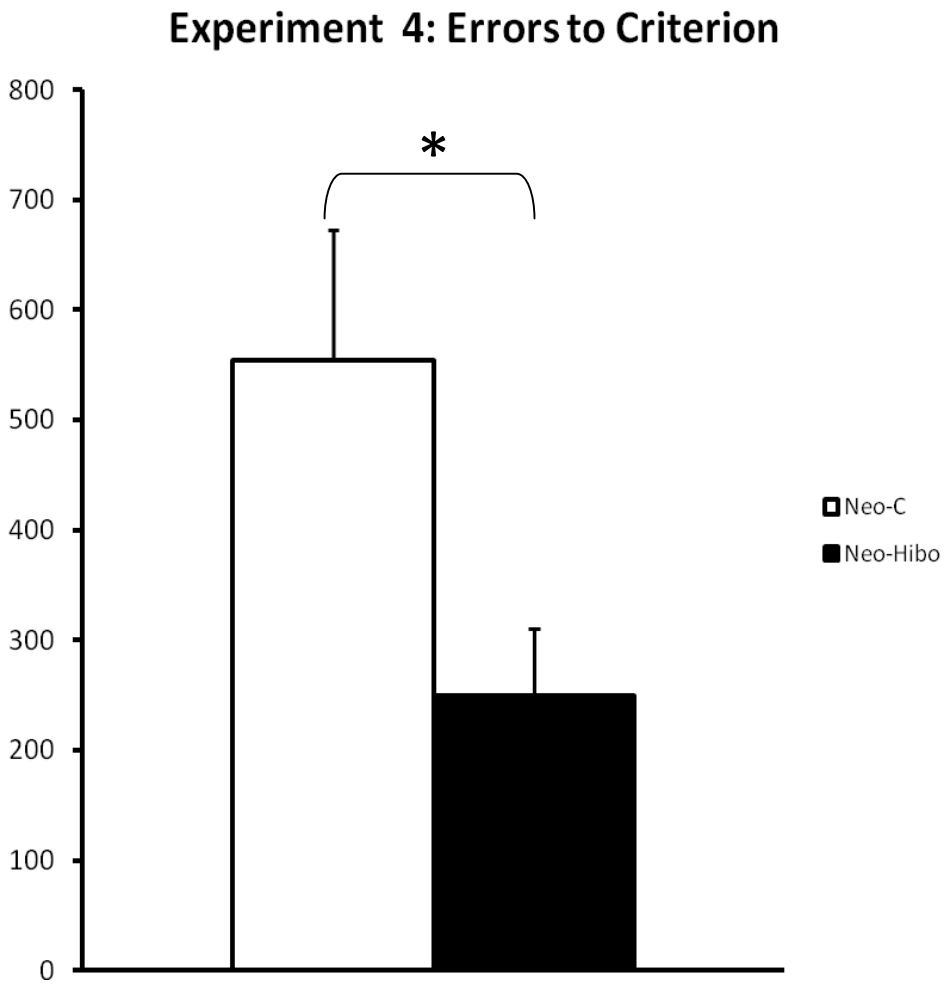

Figure 13. Experiment 4 errors to criterion by rank. (*): $p < .05$; (A): $p = .06$

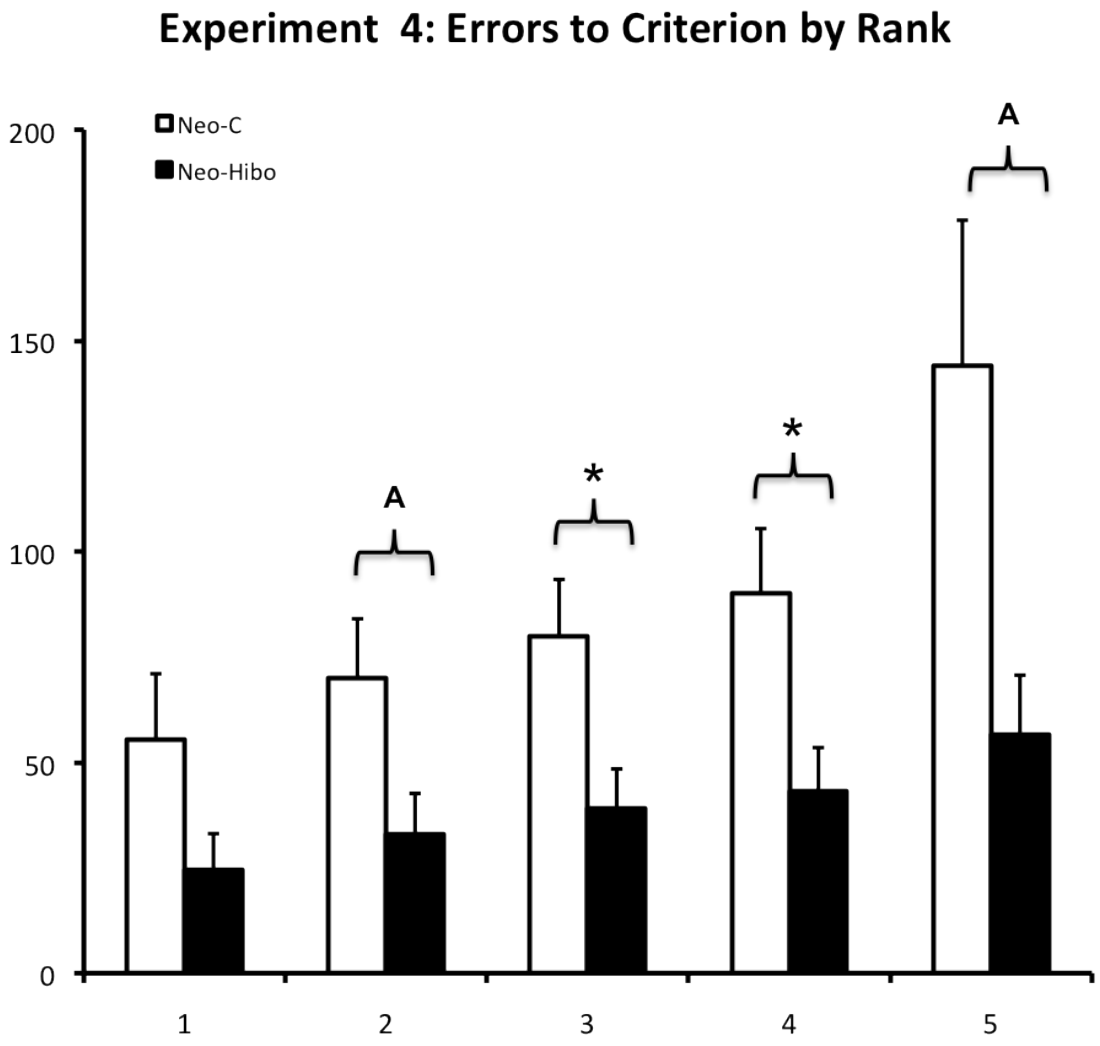

Figure 14. Experiment 5 stimuli.

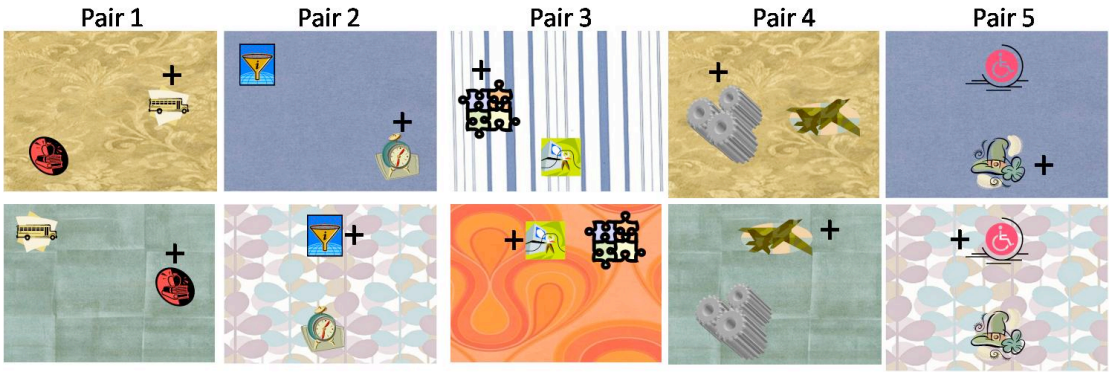

Figure 15. Experiment 4 vs. Experiment 5 errors across experiments

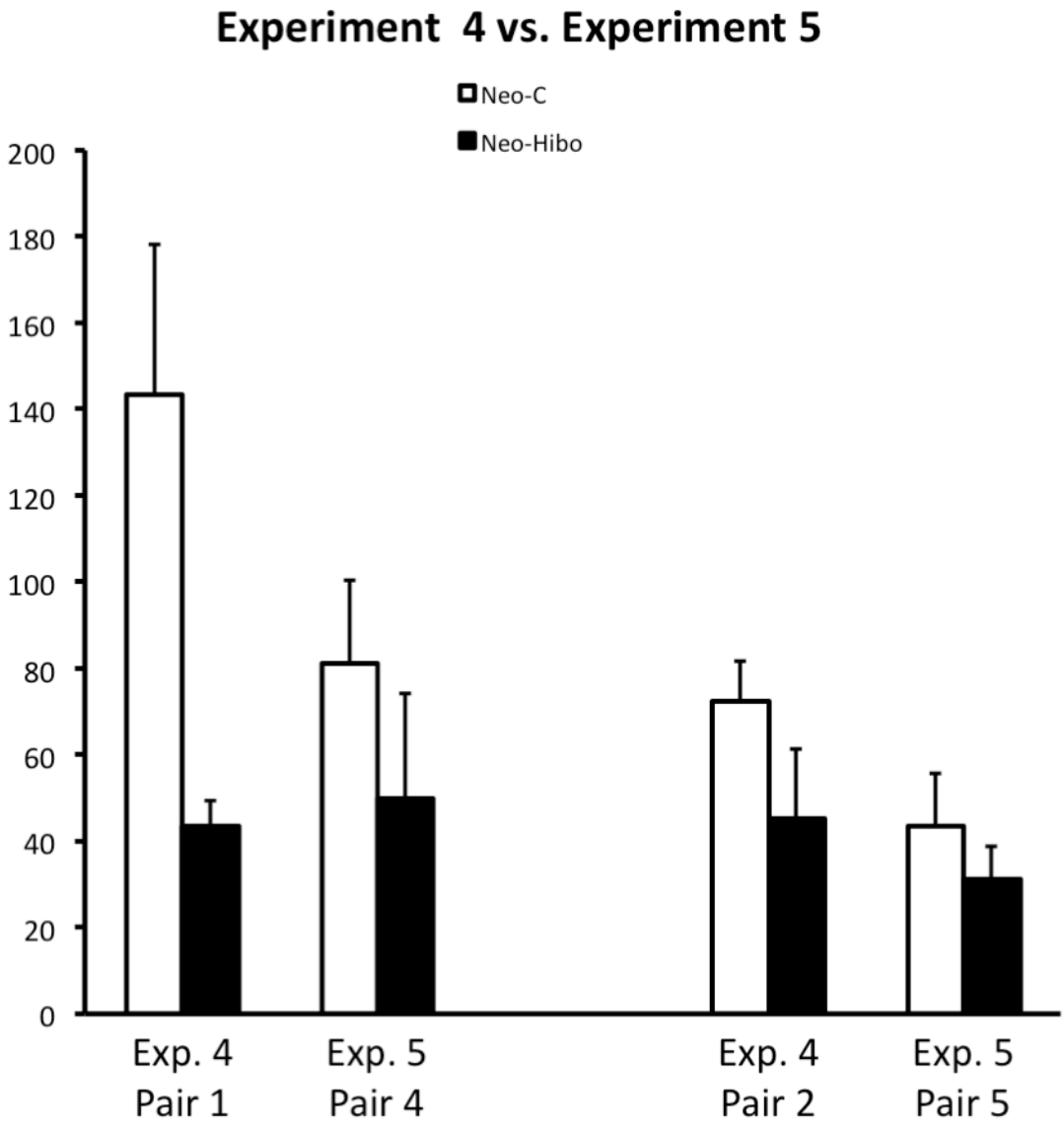

Figure 16. Experiment 4 vs. Experiment 5. Errors across pairs 1-3 - last session of Experiment 4, and the first session of Experiment 5.

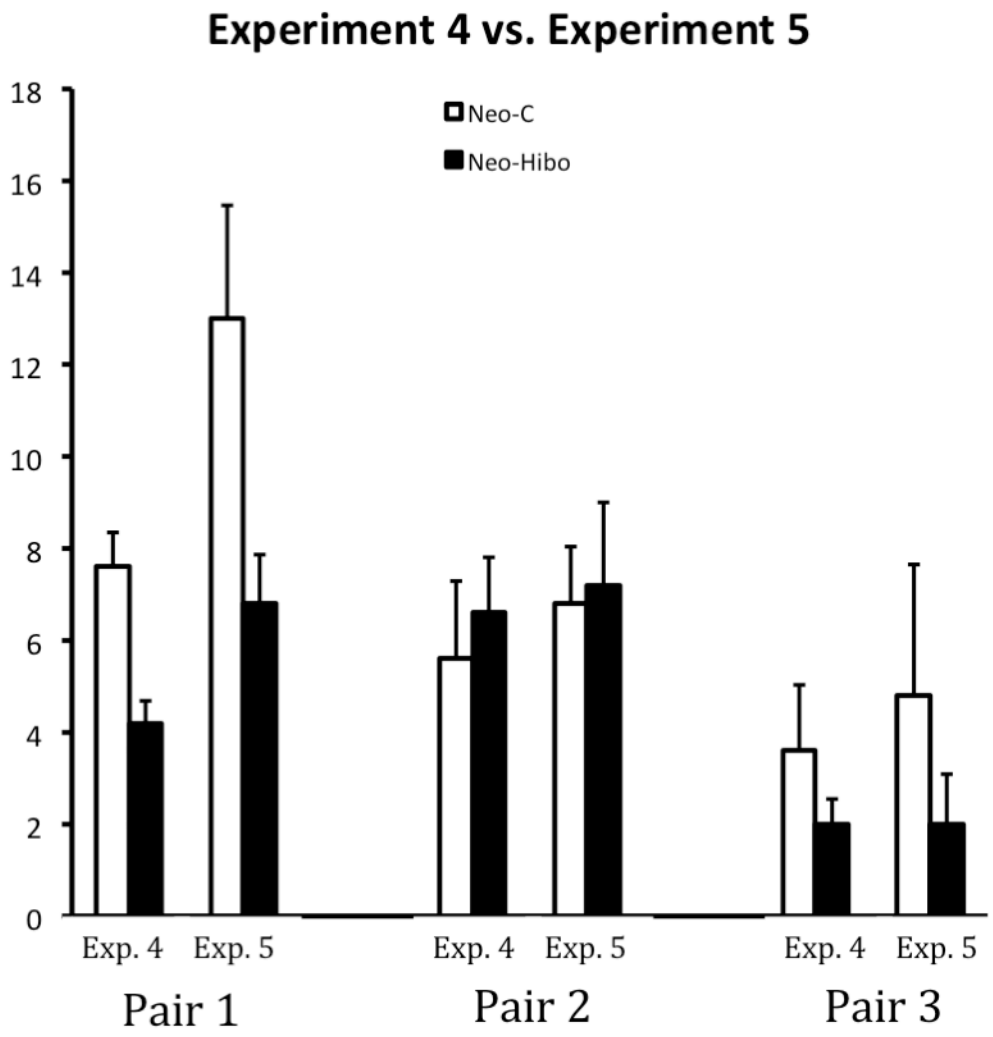

Figure 17. Experiment 5: Errors to criterion on Pairs 1, 2, and 3.

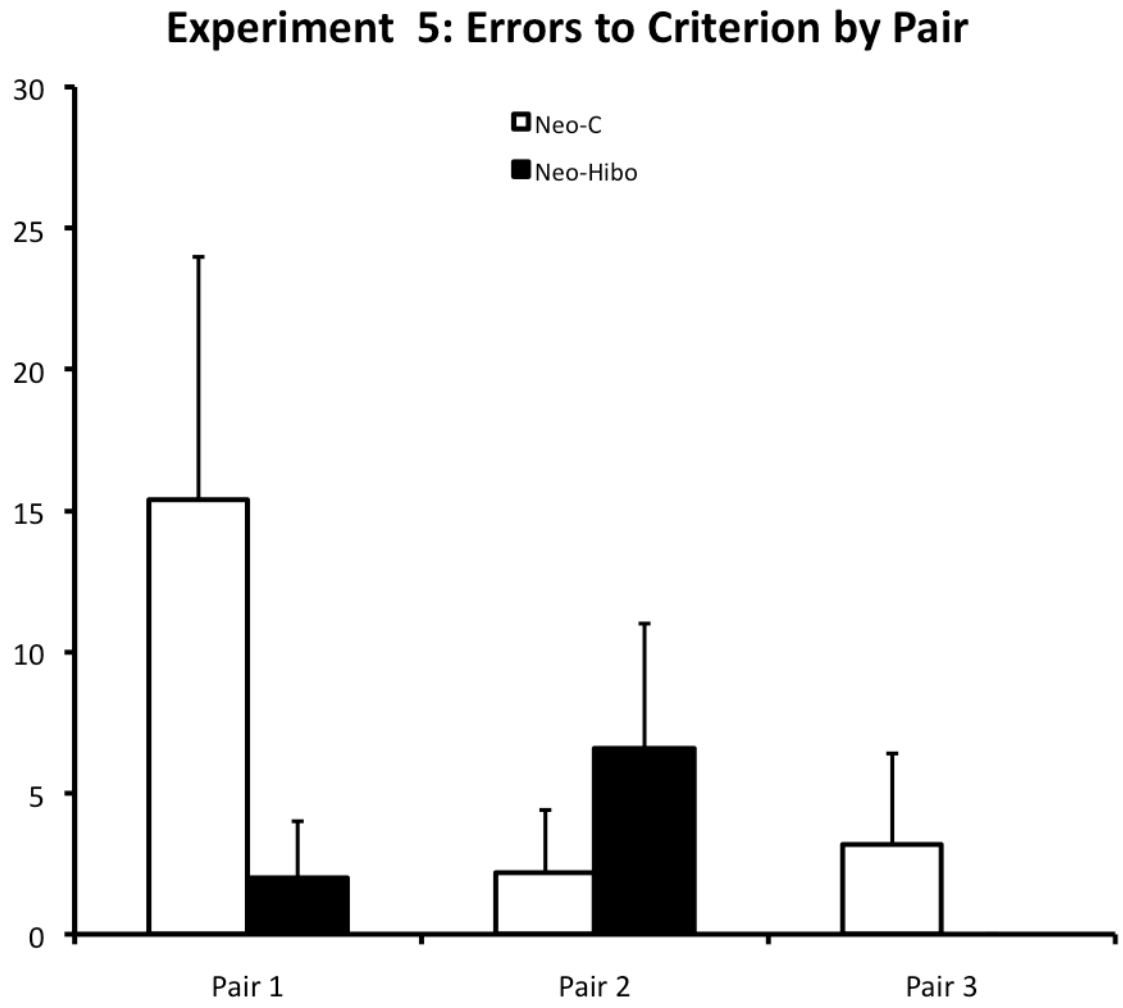

Figure 18. Experiment 5: Errors to criterion by pair.

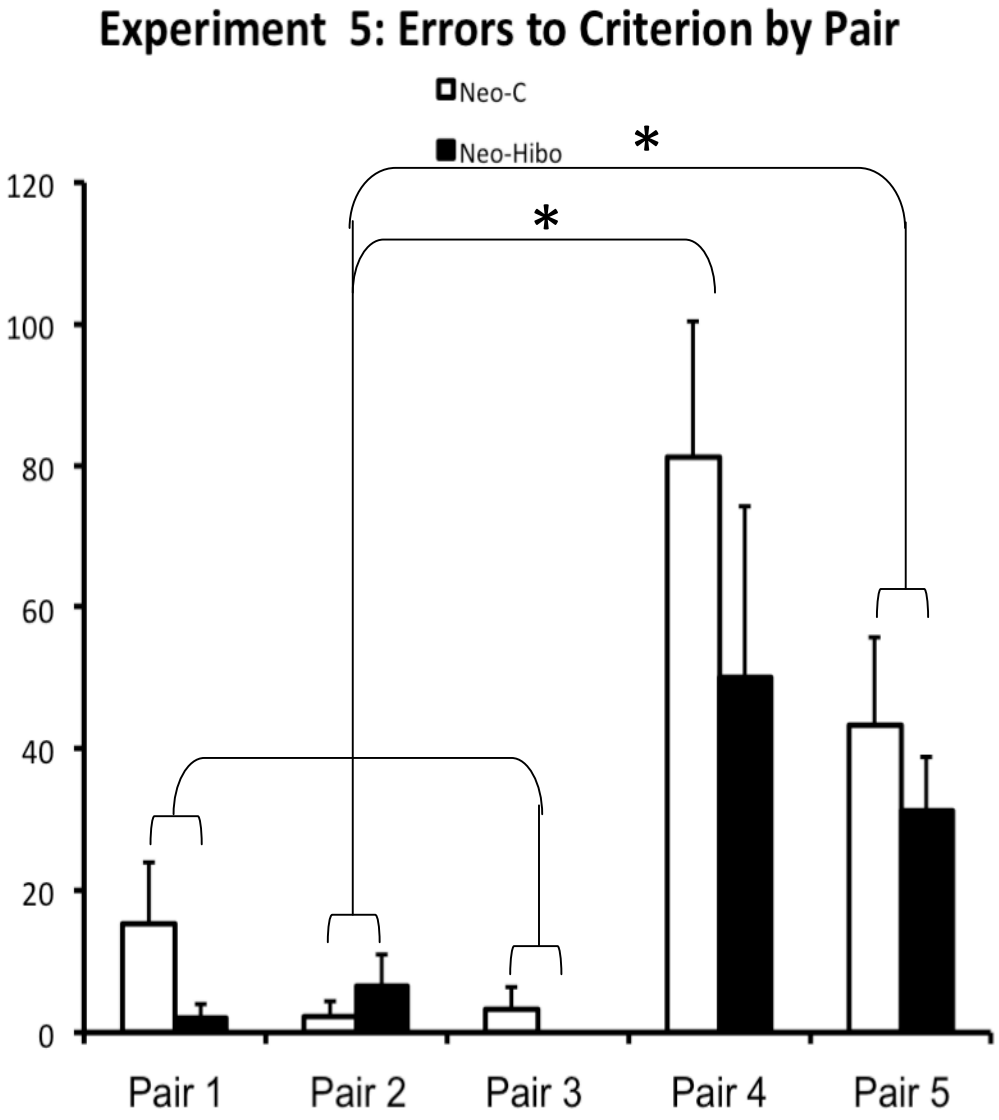

Figure 19. Experiment 6 Paired Comparison control and context trial examples.

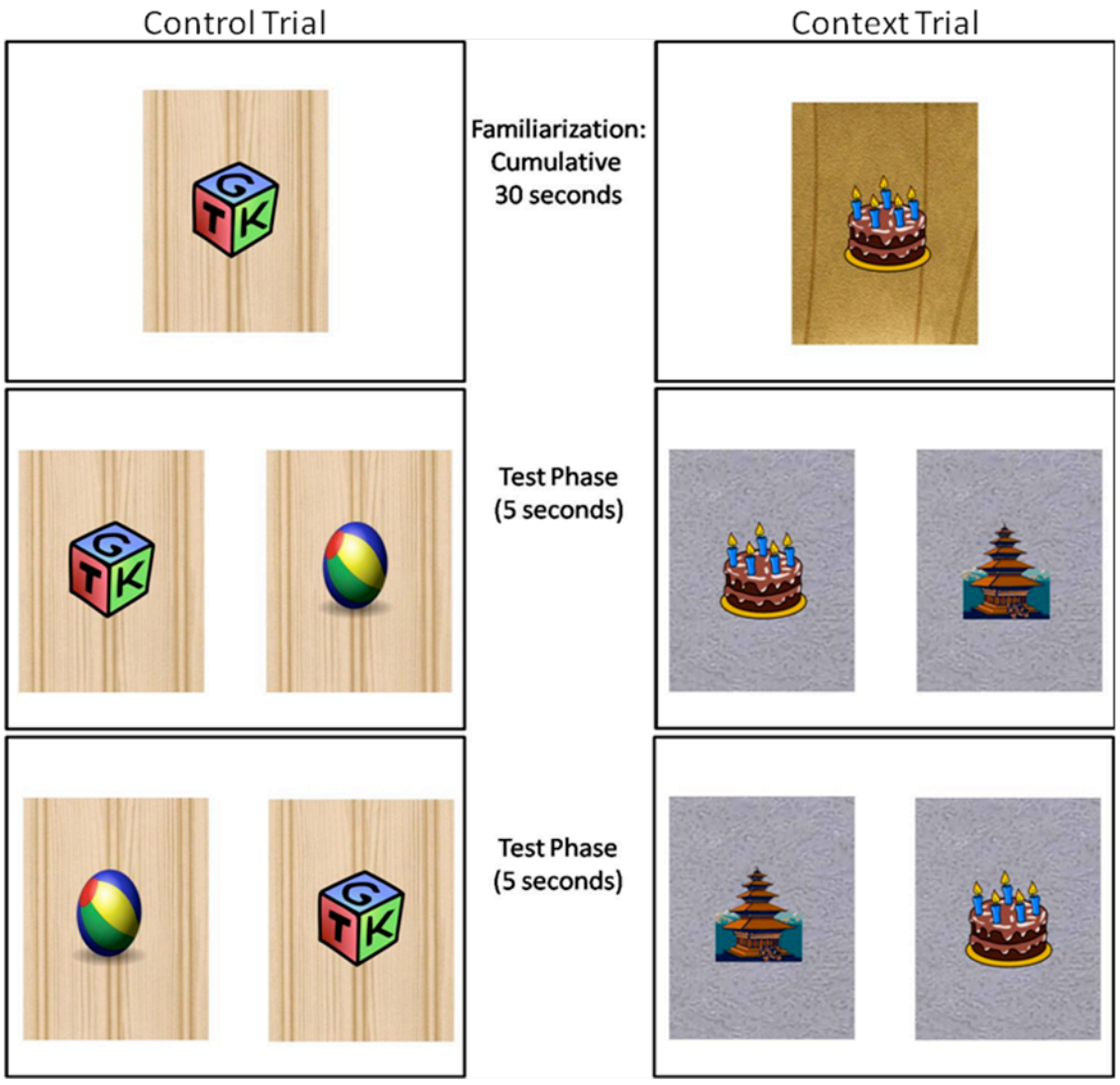

Figure 20. Experiment 6: Percent looking to the novel image.

Dashed line indicates chance performance.

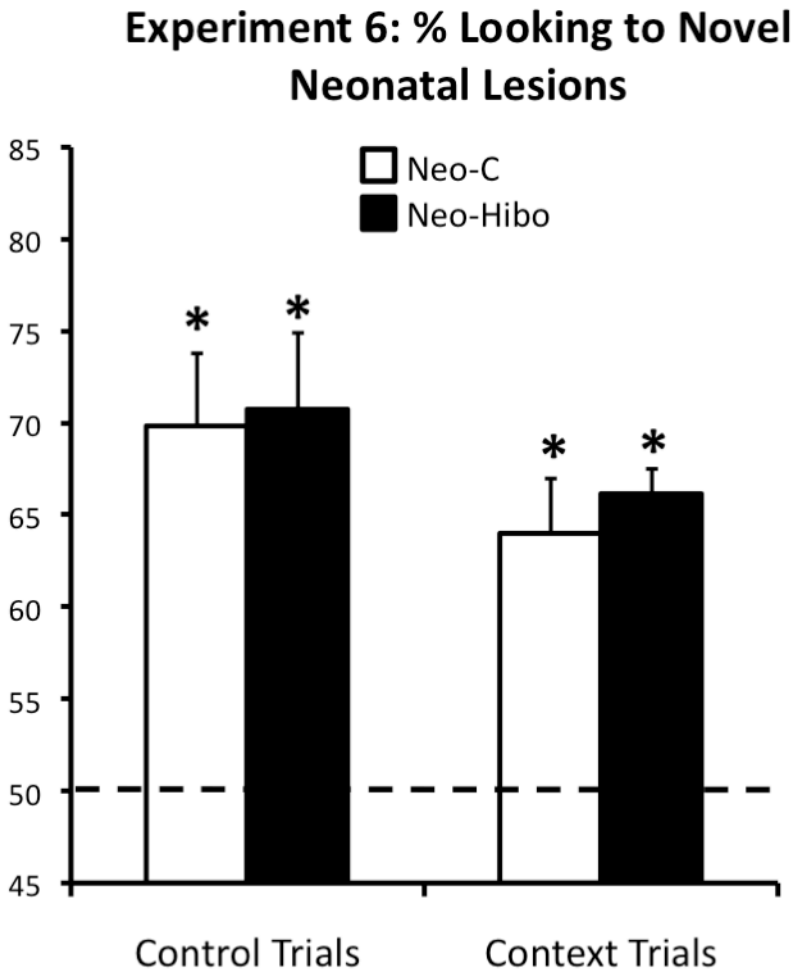

Figure 21. Examples of intended damage, a bilateral lesion, and a unilateral lesion.

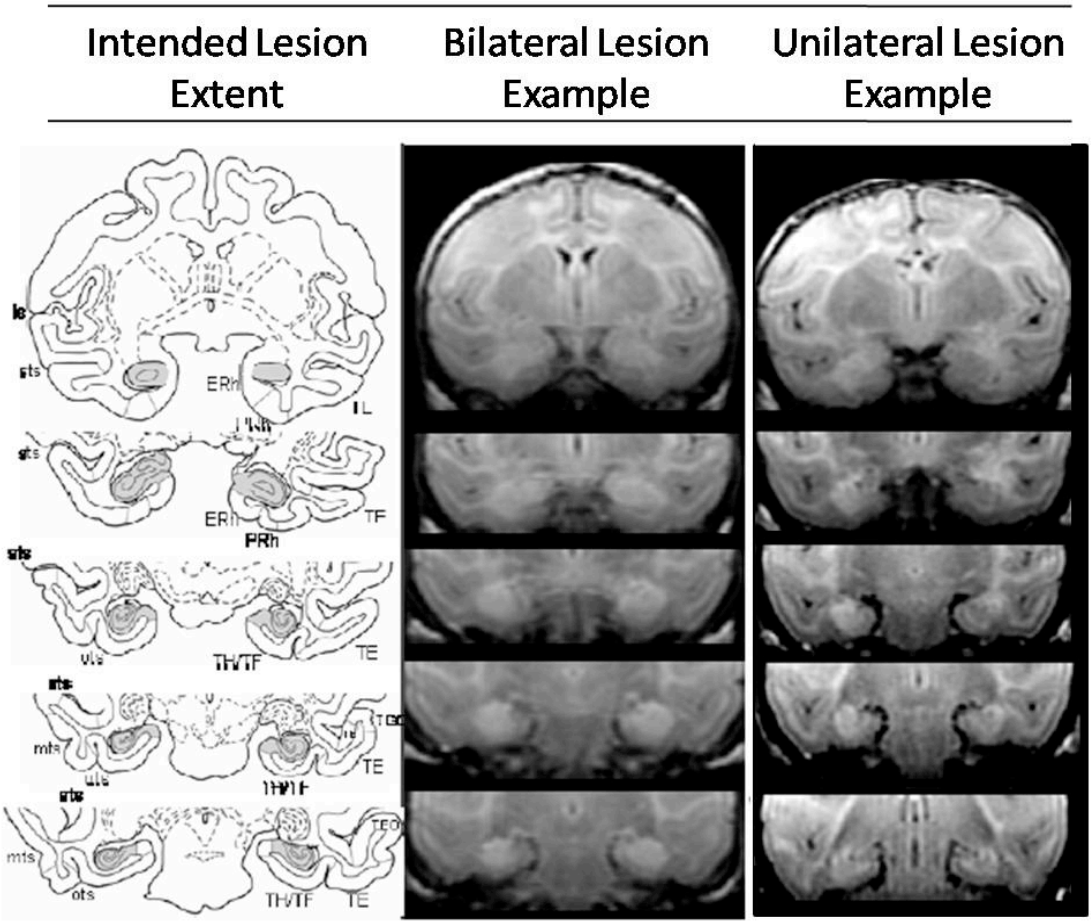

Figure 22. Lesion reconstructions for all animals in Group Neo-Hibo.