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Neural Basis and Development of Relational Memory in Primates

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## Abstract

### Neural Basis and Development of Relational Memory in Primates

By Shala N. Blue

The current literature on the development of relational memory (i.e., memory for object-location and object-context relations) suggest these abilities improve with age during early and middle childhood which may coincide with maturational changes in the medial temporal lobe. Furthermore, previous studies in human and non-human primates indicate impairments in memory for object-location and object-context relations following damage to or transient inactivation of structures within the medial temporal lobe (i.e., specifically to the hippocampus and perirhinal cortex) in adulthood. However, primate studies of the effects of early selective damage to medial temporal lobe areas are few and inconclusive. Due to the paucity of information regarding the development of relational memory abilities across primate species and the development of underlying neural substrates, two separate studies using modified versions of the preferential looking task were conducted to measure the development of object-location and object-context relations. In the first study, children and adults viewed visual stimuli using an eye tracker and their propensity to attend to changes in the stimuli was measured. Findings suggest differences in both object-location and object-context relations as a function of age. Four-year-olds had considerable difficulty detecting object-location changes but not object changes, whereas 8-year-olds exhibited less difficulty detecting these changes. In addition, we observed differences in performance between male and female adults in the object-location condition, which support the literature on gender differences in object-location memory. In a second study, subjects were monkeys with neonatal perirhinal cortex lesions and sham-operations that were tested longitudinally. All animals, irrespective of lesion, had difficulty detecting changes in object-location relations even at 36 months of age but could readily detect object changes at all ages tested. These findings suggest a delayed maturation of memory for object-location relations and an early emergence of object memory. However, this research could not provide clear evidence for the role of the perirhinal cortex in the development of relational memory. Overall, the findings in humans and non-human primates suggest a long developmental time course for relational memory abilities across species.

Keywords: relational memory, development, perirhinal cortex, lesion, monkeys (*Macaca mulatta*), humans

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## **Chapter 1: General Introduction**

Memory is an invaluable cognitive function, essential to many living things. Intact memory allows individuals to find familiar faces in a crowd, to learn about and attribute traits and qualities to others, to navigate different surroundings, to recognize what was previously seen or experienced in order to detect subtle changes in the environment, and to perform many other practical activities. Memory is inextricably intertwined with learning and seems to be at the foundation of cognition (Bauer & Pathman, 2008), social interactions, and social behavior (Spreng & Mar, 2010). Memory shapes development (and vice versa) and aids in identity formation; as individuals create life stories and goals based on personal and collective pasts (Bauer & Pathman, 2008; Conway, 1997, 2005; Conway & Pleydell-Pearce, 2000).

Memory is genuinely enthralling and for many reasons. Thus, it is not surprising that so many people have devoted their life's work to understanding it. In fact, the substantial body of literature on memory in recent years has contributed to our understanding not only of mnemonic functions and abilities, but also of the neural substrates underlying these functions. Many researchers have now reached the consensus that there are different types of memory and that they are mediated by multiple memory systems, rather than by a unitary one (for review see Sherry & Schacter, 1987). The prevailing view is that memory can be divided into general categories including declarative (e.g., episodic and semantic) and non-declarative (e.g., procedural, priming, and conditioning). The remainder of this paper will focus on a fundamental process within the declarative memory system, namely relational memory its development and the structures in the medial temporal lobe that support this function.

Declarative memories are ones that we can be explicitly aware of—for example, personal events or facts—either verbally or nonverbally. Memories of personal events experienced in a subjective time and place, are referred to as episodic memory (Tulving, 1983, 1993), and are dependent on context. For instance, remembering a visit to the nurse’s office in elementary school is memory of a personal event. The example includes the time in which the event occurred (i.e., a specific age in childhood) as well as where it occurred (i.e., nurses office/elementary school) that could be distinguished from a different memory occurring in childhood (e.g., a visit to the zoo). Therefore, one of the defining features of episodic memory is that a specific context is represented as a part of the memory trace. In contrast, memory for facts, also termed semantic memory, is independent of context. For instance, knowing that the Eiffel Tower is located in a European city is example of memory for a fact. You need not remember the specific event(s) in which you acquired the knowledge of the Eiffel Tower’s location in order to know it. Although, it is important to make the episodic/semantic distinction, relational processes support both forms of memory (albeit in different ways; see below). Thus, this paper will remain agnostic with regards to this distinction in declarative memory.

### **Defining Relational Memory**

It is especially difficult to pinpoint a precise definition of relational memory when researching the current literature. Relational memory has been described in myriad ways in the memory literature. It is commonly considered as a process which allows us to combine multiple, arbitrary components of scenes or events (Cohen & Eichenbaum, 1995; Cohen, Poldrack, & Eichenbaum, 1997; Cohen, Ryan, Hunt, Romine, Wszalek, & Nash, 1999; Eichenbaum, 2006; Eichenbaum & Cohen, 1988; Eichenbaum, et al, 1994;

Kumaran & Maguire, 2005). In addition, researchers have suggested a fundamental component of relational memory is *binding* of stimuli that co-occur, which may be disparate features and contexts (e.g., color, sound, emotion, etc), to form a coherent memory (Cohen & Eichenbaum, 1993; Sluzenski, Newcombe, & Kovacs, 2006).

In some other instances researchers described relational memory simply as “memory for relations among items” (Cohen, Poldrack, & Eichenbaum, 1997), “retention of relational information”(Hannula & Ranganath, 2008), or “memory for all manner of relations among the perceptually distinct elements of experience” (Konkel & Cohen, 2009). More commonly researchers suggested a more complex nature of relational memory, defining it as: (1) retrieval process which is measured by performance on tasks that require binding (Sluzenski, Newcombe et al, 2006); (2) a “flexible process of association” or the “flexible ability to generalized across existing stores of information, which allow us to make innovative memory decisions in novel situations” (Ellenbogen, Hu, Payne, Titone, and Walker, 2007); (3) a process by which the elements of a scene or event and the relationships among them are accessible and not combined in a rigid, inseparable manner (Cohen and Eichenbaum, 1991; Cohen et al., 1997); and (4) “formation and flexible use of representations of all manner of relation among items in scenes or events” (Hannula, Tranel, & Cohen, 2006).

Overall, what we may glean from these definitions is that memory researchers consider the combining of separate bits of information within a scene or event and the flexible use of that information as fundamental to relational memory (Cohen & Eichenbaum, 1991; Cohen, et al., 1997; Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999; Eichenbaum, 2004; Eichenbaum et al., 1994; Konkel & Cohen, 2009).

Therefore, they suggest that relational memory enables us to make within-context and across-context connections, by connecting the different elements of a particular event, or by linking previously unrelated material/events.

In the current paper, we will define relational memory as the ability to combine arbitrary component features into a coherent aggregate, which then can be used flexibly with other information (Cohen & Eichenbaum, 1991; Cohen, et al., 1997; Eichenbaum, et al, 1999; Eichenbaum et al., 1994).

### **Relational Processes in Declarative Memory**

Two fundamental features of declarative memory are that it is relational and flexible in nature (Eichenbaum, Otto, & Cohen, 1994; Konkel & Cohen, 2009). As previously stated, relations are present both within episodic and semantic memory. However, relational memory refers to different abilities within the two subsets of declarative memory. In the earlier example of a personal event, we would generally combine the different arbitrary elements of the occurrence, (e.g. the nurse's office) with other elements (e.g. the time of day, items/objects, people, physical and mental states, etc.), in order to formulate a cognitive representation of the experience, even in the absence of those particular elements at the time of retrieval. Therefore, the nurse's office event can be remembered, in whole or in part, even in a completely different setting. With regards to semantic memory example, the fact, "The Eiffel tower is located in a European city" contains arbitrary pieces of information (e.g. the Eiffel tower, it's location, a European city) that become linked into a comprehensive representation after repeated learning. Within semantic memory, relational memory also allow for learning novel facts. For instance, after learning two pieces of related information—Paris, France



is the home of the Eiffel tower, and, Paris is a European city—by conceptually linking (see Tulving, 1983) the two facts you could correctly assume that the Eiffel tower is located in a European city without ever acquiring that knowledge directly. These examples highlight the different ways in which relational processes contribute to declarative memory.

***What Constitute Relations?*** Whereas there are many possible arbitrary relations forming at any given time (e.g., linking a smell to an emotional state), much of the literature on relational memory has investigated very specific types of co-occurring relations (i.e., object-location/place and object-context; e.g., Bornstein, Mash, & Arterberry, 2011; Chalfonte & Johnson, 1996; Hannula, Tranel, & Cohen, 2006; Sluzenski, Newcombe, & Kovacs, 2006). Therefore, this paper will focus on object-location/place and object-context relations. Object-location (also called object-place) memory is a spatial relational process, which enables us to store and retrieve information regarding the associations among objects and their locations. Object-context memory is a process by which we are able to store and retrieve information regarding the connection of objects with the background in which they occur. Since a context, as described herein, refers to the general information associated with a stimulus at encoding (Nemanic & Bachevalier, 2002), it can be simple (e.g., a colored background in which a stimulus is presented) or complex (e.g., a learning environment).

***Relational memory across species.*** Another important feature of relational memory is that it is observed across species. A common view is that both humans and non-human animals exhibit relational memory—a view that has largely been supported by work in rodents (Cohen & Eichenbaum, 1995; Eichenbaum & Cohen, 1988;

Eichenbaum, et al, 1994). However, some argue that only humans have the capacity for declarative memory, which is thought to rely on language and self-awareness (Tulving, 1984). The purpose of this paper is not to address this controversy or to identify what would be regarded as declarative memory across species. Rather it is to comparatively investigate one of the fundamental processes in declarative memory which animals are not excluded from having, namely relational memory abilities.

In taking a comparative approach, we will be able to learn a great deal. The literature is laden with research studies in single species using very dissimilar tasks that measure different aspects of relational memory. With a comparative perspective we will be able to use a single paradigm to investigate relational memory across species, which will enable us to make qualitative comparisons between humans and non-humans. In non-human animals it is also possible to manipulate selective brain regions, functionally analogous or homologous to those in humans, which are thought to be important in relational memory.

### **Development of Co-Occurring Relations**

Whereas, the foundations of relational memory seem to emerge very early in development, there is evidence that it may require a long developmental course. For instance, it appears that infants can form word-object relations (e.g., Hollich, Golinkoff, & Hirsch-Pasek, 2007), face-voice relations (e.g., Brookes, Slater, Quinn, Lewkowicz, Hayes, & Brown, 2001), and word-action relations (e.g., Casasola & Cohen, 2000), which allow them to learn new words, distinguish familiar individuals from strangers, and learn appropriate actions from speech, respectively.

In addition, some researchers suggest an early emergence of memory for object-locations (e.g., Ahmed & Ruffman, 1998; Baillargeon & Graber, 1988; Káldy & Sigala, 2004) and for object-context relations (e.g. Jones, Pascalis, Eacott, & Herbert, 2011; Richmond & Nelson, 2009; Robinson & Pascalis, 2004). Although infants may exhibit rudimentary abilities, these abilities may need time to develop. Indeed, very young children have a limited capacity to remember multiple object-place relations (Ahmed & Ruffman, 1998; Baillargeon & Graber, 1998; Káldy & Sigala, 2004), and they demonstrate some difficulty in remembering object-context relations when contexts change (Haaf, Lundy, & Codren, 1996; Jones, et al., 2011; Robinson & Pascalis, 2004).

Within spatial relational memory, many studies find a developmental progression in the ability of children to use relational strategies (Balcomb, Newcombe, & Ferrara, 2011; Newcombe, Huttenlocher, Drummey, & Wiley, 1998; Haun, Call, Janzen, & Levinson, 2006a; Haun, Rapold, Call, Janzen, & Levinson, 2006b; Lehnung, Leplow, Friege, Herzog, Ferstl, and Mehdorn, 1998; Leplow, Lehnung, Pohl, Herzog, Ferstl, & Mehdorn, 2003; Overman, Pate, Moore, & Peuster, 1996; Pentland, Anderson, Dye & Wood, 2003; Sluzenski, Newcombe, & Satlow, 2004). Several of these studies suggest that spatial relational abilities remain relatively poor until around middle childhood (Lehnung and colleagues, 1998, 2003; Overman et al, 1996; Pentland et al, 2003).

Furthermore, developmental studies in place learning (in which baited objects are placed in different locations), repeatedly find that this ability greatly improves across early development (Aadland, Beatty, & Maki, 1985; Balcomb et al., 2011; Foreman, Arber, & Savage, 1984; Lehnung and others, 1998, 2003; Overman, et al., 1996). For instance, Balcomb et al. using a modified human analog of the Morris water maze

required 18- and 23-month-old children to search for a hidden puzzle in target locations. They found marked increases in spatial searches in the older toddlers. Similarly, Newcombe, et al. (1998) found that children younger than 22 months of age were not proficient in using external cues when searching for a target item. Studies of older children have found that children above the age of 7 years, are able to use a place strategy, that is, to use distal environmental cues to assist in finding baited target locations (Leplow et al., 2003; Overman et al., 1996).

This pattern of prolonged development is also observed in studies of object-location feature binding, which investigate memory for object, location, and object-location combinations (Cowan, Naveh-Benjamin, Kilb, & Sauls, 2006; Lorshbach & Reimer, 2005). The few studies assessing feature binding of object-context relations have demonstrated improvements in memory across early- to middle- childhood as well (Lloyd, Doydum & Newcombe, 2009; Sluzenski, Newcombe, and Kovacs, 2006; Picard, Cousin, Guillery-Girard, Eustache, Piolino, 2012). For instance, Lloyd and colleagues showed 4- and 6-year-old participants pictures of line drawing images, patterned backgrounds, and line drawings on top of patterned background. They assessed children's ability to correctly identify the drawings, backgrounds, and the combination of the drawings with their corresponding background. The performance of 6-year-old children was significantly better than 4-year-old children for identifying the object-background combinations. These authors concluded that younger children exhibited retrieval deficits when binding processes are required. In summary, these findings suggest that whereas rudimentary relational abilities may be present very early on (see

Oakes, Ross-Sheehy, & Luck, 2006), the developmental trajectory of relational memory might continue well into late childhood (Pentland et al., 2003), and possibly even later.

Although memory for object-location and object-context relations both appear to develop gradually, they may have markedly different developmental trajectories. However, studies have used such a diverse array of paradigms to investigate the development of these two relational abilities, that it is difficult to ascertain whether the tasks are tapping similar relational memory abilities. Furthermore, in many of the studies in young children, location or context was physically changed, some motor strategy was required, or children had to make some sort of verbal report. Therefore, the current paper aims to study development of both object-location and object-context memory using the same behavioral paradigm, one that does not require a motor strategy or use of language.

***Assessing relational memory in development: Preferential looking paradigm.***

Developed by Fantz (1956), the preferential looking (PL) paradigm or visual paired comparison (VPC) task has been used to study memory in infants for decades. The assumption of this task is that memory could be inferred by a propensity to look longer at a novel stimulus. This task has transitioned into the non-human primate literature because it is incidental in nature and does not require language abilities. Therefore, it makes an ideal paradigm to comparatively investigate memory across the lifespan in humans and non-human primates.

Memory for object-location relations and object-context memory have been measured using the VPC task (Bachevalier & Nemanic, 2008; Blue & Bachevalier, 2009; Glavis-Bloom & Bachevalier, 2010; Haaf et al, 1996; Jones et al., 2011; Nemanic & Bachevalier, 2002; Pascalis, Hunkin, Bachevalier, and Mayes, 2009; Robinson &

Pascalis, 2004). For instance, Bachevalier and Nemanic (2008) modified the traditional preferential looking paradigm to measure object-location relations. The modified version of this task clearly measured spatial relations because at test the familiar object array was presented with a novel object array in which no features of objects changed but their spatial locations did. In addition, intact performance on this task was dependent on the integrity of the neural system underlying relational memory (Bachevalier & Nemanic, 2008; Blue & Bachevalier, 2009).

Object-context has been measured using the preferential looking paradigm for quite a while. In an early study by Haaf et al. (1996), infants viewed objects background pairings and were tested on an object presented on either of two backgrounds- one that remained stable and one that changed. These researchers found difficulties in infants' memory for objects that appeared on a changed background. Since then other researchers have utilized variations of this task to measure object-context relations (Richmond & Nelson, 2009; Pascalis et al, 2009). Furthermore, recent evidence suggests that amnesic patients and monkeys with circumscribed brain lesions show impaired performance relative to controls on these procedures (Munoz, Chadwick, Perez-Hernandez, Vargha-Khadem, & Mishkin, 2011; Pascalis et al, 2009).

Developmental researchers have also used the preferential looking task to investigate different types of relations across various ages of children. A previous within-subjects investigation from our laboratory tested preschool and school-aged children (3-7 years of age) in an object-location visual paired comparison task and utilized eye tracking (Pathman, Bachevalier, & Bauer, personal communication). In this task, children saw an image consisting of a spatial array. After a brief delay, the

previously seen image was presented along with a novel image, in which some of the objects (2 or 4 objects) were either rearranged (object-location memory) or replaced (object memory). Children's performance was measured in terms of novelty preference (the amount of time a child attended to the novel stimulus as a function of their total looking time at both images) and the eye tracker allowed for fine grain online assessment of eye movement information. We were able to measure to where, to what, and when the children were attending during each trial.

We found that although 5-year-old children still exhibited some difficulty in memory for the rearranged objects within the spatial array, they were better than 3-year-olds. Specifically, 3-year-olds experienced difficulty detecting change in rearranged and replaced objects, and 5-year-olds, who did not have trouble detecting replaced objects, had difficulty only when two of the objects were rearranged. Seven-year-olds, on the other hand, did not exhibit any difficulties in detecting rearranged objects regardless of whether two or four of the objects had shifted. In addition, 5- and 7-year-olds demonstrated different viewing patterns during the trials.

Five-year-olds tended to notice the changed objects within the array much later than 7-year-olds; generally after 3-4 seconds of viewing the images. On the other hand, 7-year-olds were consistently able to detect changes within the first second of the trial. These findings could suggest retrieval-related processes (Richmond & Nelson, 2009) that may not be fully developed until after age 5 or a more accessible representation of the familiar array in 7-year-old children. These differences in patterns of looking coincides with findings in other non-VPC tasks in which older children exhibited different behavioral patterns than their younger counterparts (e.g. Overman et al., 1996). The

findings of Pathman, Bachevalier, and Bauer, suggest that memory for object-location relations as measured by the VPC paradigm gradually develops and can be accessed more quickly in older children (for a counter argument, see Richmond & Nelson, 2009). However, these findings also expound the importance of assessing pattern differences as a function of age.

With regards to object-context relations, an eye tracking study by Richmond and Nelson (2009) used a preferential looking paradigm to investigate object-context memory in young infants. They found that even at 9 months of age, infants could encode relations among objects and the contexts in which they are presented. In the match condition, these researchers showed infants face/scene pairs (the scene was presented first, then the face was presented on top of scene). Three study trials were presented in this manner followed by a probe test. During the probe trial, a familiar scene was presented first and then three equally familiar faces appeared on top of the scene. In one non-match condition, the study phase was similar to the match condition and a new scene was presented with equally familiar faces. In the other non-match condition, three novel faces appeared on a novel background during each study trial as well as during the probe test. The stimuli were presented either immediately or after a delay of 20-30 seconds. They hypothesized that if infants were able to encode relations, they would exhibit preferential looking during the matched condition.

These researchers found that whereas the amount of time the infants spent looking at the matching face did not differ from chance when the probe test was presented immediately following the study test, infants preferred the matching face significantly more when a delay was imposed. The pattern of fixations mimicked the looking time data



with respect to the delay imposed. In addition, these researchers also investigated preferential looking during an early period (1000ms) of the probe trial and found greater preference for the matching face on both the immediate and delayed trials. The pattern of looking was different for non-match trials. Infants looked equally at each non-match face as was expected. Some of these results were parallel to findings observed in adults (Hannula et al. 2007). Therefore, Richmond and Nelson (2009) concluded that 9-month-old infants could in fact encode relations. Whereas these researchers suggested that infants younger than 12 months of age could encode relations, other preferential looking studies have suggested that infants have difficulty flexibly representing object-context relations (Haaf et al, 1996; Jones et al, 2011; Robinson & Pascalis, 2004). Findings further suggest that toddlers may have less trouble (Jones et al., 2011; Robinson & Pascalis, 2004), which is consistent with studies that utilize other tasks (Jones & Herbert, 2006).

Overall the research suggests that a preferential looking paradigm would be an adequate measure of assessing memory for co-occurring relations across development. In fact, it is an important measure because it does not require language or strategy. The addition of eye-tracking technology will also enable assessment of memory as well as the assessment of differences in viewing patterns.

### **Medial Temporal Lobe Development and Relational Memory**

When discussing relational memory it is almost impossible to do so without mentioning the critical role of the medial temporal lobe (also called the hippocampal memory system) in supporting relational memory. Since the hallmark case study of patient H. M. (Scoville & Milner, 1957), the medial temporal lobe has received much

attention in supporting declarative memory. H.M., who became amnesic after surgical removal of large portions of his medial temporal lobe, had trouble remembering new locations, new people encountered, and new life events (Scoville & Milner). The hippocampal formation, located within this region has since become a candidate structure, seemingly responsible for the memory deficits observed in amnesic patients (see Spiers, Maguire, & Burgess, 2001).

*Importance of hippocampus in relational memory.* The hippocampal formation (further discussed as the hippocampus), which includes the hippocampus proper (Cornu Ammons fields [CA] 1-3), subiculum/parasubiculum, and the dentate gyrus, is thought to play a major role in relational memory by connecting the different elements of an event (for review see Eichenbaum, 2006; Alvarado, Wright, & Bachevalier, 2002; Alvarado & Bachevalier, 2000, 2005b; Cohen & Eichenbaum, 1995; Cohen et al., 1997; Cohen et al., 1999; Eichenbaum & Cohen, 1988; Eichenbaum et al., 1994; Kumaran & Maguire, 2005) and by flexibly representing specific elemental features across episodes (Konkel & Cohen, 2009). Konkel and Cohen (2009) highlighted a series of studies using a host of different methodologies that suggested a critical role for the hippocampus in relational memory. However, unlike studies of patients with large MTL lesions, fMRI studies in healthy adults and selective lesion studies in non-human animals are able to localize distinct regions of the MTL and measure their contributions to relational memory.

For instance, Davachi and Wagner (2002) tested adult humans on an fMRI task in which they viewed triplets of nouns on a screen. During the task participants either had to covertly repeat the words (item-based) or reorder them based on the desirability of the word in relation to the other words in the triplet (relational). Davachi and Wagner found

that relational processing was associated with greater bilateral activity of the hippocampus when compared to item-based processing. In addition, hippocampal activity during relational processing was correlated with subsequent memory. The findings of this study suggested that even abstract relations (i.e., subjective desirability of words) were processed by the hippocampus.

Another study by Hannula and Ranganath (2008) tested adult humans in an fMRI using 3D object renderings presented in unique 4-object arrays. At test the images were rotate 90 degrees. The participants were required to make a judgment about whether the objects were presented in the same location as in the sample array (match), whether one of the objects occupied a new location (mismatch position), or whether two objects switched positions (mismatch swap). They found that hippocampal activity was associated with accurate performance, specifically in the match trials, suggesting an important function of the hippocampus in retaining an intact representation of the sample relations. They concluded that the hippocampus was important for encoding and retrieval of object-location relationships.

***Extra-hippocampal areas and relational memory.*** The perirhinal cortex, parahippocampal cortex, and entorhinal cortex along with the hippocampus make up the hippocampal memory system (Eichenbaum, Yonelinas, & Ranganath, 2007) and support relational memory abilities, albeit in very different ways (see Aggleton, Kyd, & Bilkey, 2004; Alvarado & Bachevalier, 2005a; Aminoff, Gronau, & Bar, 2007; Bachevalier, & Nemanic, 2008; Buckmaster, Eichenbaum, Amaral, Suzuki, & Rapp, 2004; Bussey, Dias, Amin, Muir & Aggleton, 2001; Eichenbaum & Lipton, 2008; Gaffan & Parker, 1996; Haskins, Yonelinas, Quamme, & Ranganath, 2008; Jo & Lee, 2010; Liu & Bilkey, 2001;

Prince, Daselaar, & Cabeza, 2005). For instance, Haskins et al. (2008) tested human adults on a fMRI task in which they either had to silently combine two nouns, form conjunction words and rate how well a definition fit the new word, or to view noun pairs, fill in the blank with the appropriate word of the pair and rate how well the words fit the sentence. During the test phase participants provided confidence ratings for their recognition of the word pairs. Haskins and colleagues reported greatest activation in the perirhinal cortex during encoding of noun pair conjunctions, and that encoding word pairs as a new compound word increased memory for the word pair associations. They concluded that the perirhinal cortex was important for associations that could be processed as a single item.

Aminoff and colleagues (2007) found that the parahippocampal cortex mediated both spatial and non-spatial relations. In this study they utilized an fMRI paradigm in which participants viewed either triplets of objects always presented together in the same location (spatial condition) or in random locations (non-spatial condition), or a single object presented in random locations (no-context and novel conditions) during training. The participants had to make judgments about the category (spatial, non-spatial, or no-context) and features of the shapes (location, other shapes in triplet) and perform at >95% accuracy before entering the scanner. During the fMRI portion of the task, the participant viewed a single object (in its appropriate location for the spatial condition) and was required to report whether the object was part of a triplet and the number of single-colored shapes within the triplet. The authors reported a role for parahippocampal cortex in contextual relations (both spatial and non-spatial). They also described functional dissociations within this area, in which the anterior portion processed non-spatial

relations whereas the posterior portion processed spatial relations. Furthermore, they suggested that the posterior portion mediated spatial relations whereas the entire area mediated spatial locations, which combined location and identity information.

In another study, Buckmaster and colleagues (2004) tested monkeys with entorhinal lesions on the paired associates, transitive inference, and spatial delayed recognition span tasks, which measured different co-occurring relations. The training phase consisted of multiple conditional discriminations having overlapping elements. During test, animals had to make a memory judgment concerning novel configurations of familiar stimuli. These researchers found that whereas acquisition of the paired associates and transitive inference task occurred very slowly, monkeys were not able to use their knowledge of the task to help them make inferences and monkeys with entorhinal cortex damage were drastically impaired on these tasks. However, a limited number of studies have investigated the differential contributions of medial temporal lobe structures to relational memory (Bachevalier & Nemanic, 2008; Byun & Lee, 2010; Jo & Lee, 2010; Nemanic & Bachevalier, 2002).

***Importance of perirhinal cortex in object-location memory.*** The perirhinal cortex has emerged as a central structure in memory for objects (see Buckley, 2005; Winters & Bussey, 2005). The overwhelming view is that this area processes object/item information (Murray, Bussey, & Saksida, 2007), which contrasts it from the other medial temporal lobe structures (i.e., parahippocampal cortex, entorhinal cortex [medial entorhinal cortex], and hippocampus). However, several studies have suggested a specific role of the perirhinal cortex in object-location relations when object features are important (see Aggleton et al., 2004; Gaffan & Parker, 1996; Jo & Lee, 2010; for more

details on perirhinal cortex in representing object features see Murray et al, 2007; Eichenbaum, et al., 2007). The perirhinal cortex consists of Broadman's area 35 and 36, and is located ventral to the hippocampus in the medial temporal lobe. There are intimate reciprocal connections with the hippocampus mainly through the entorhinal cortex (Eichenbaum et al., 2007).

Several researchers (see for review, Rudy, 2009; Nadel, 2008) postulated two separate neural networks supporting declarative memory: one encompassing individual elemental features (e.g. object or background), dependent on neocortical areas surrounding the hippocampus, and the other system, supporting flexibly bound features, dependent on the hippocampus. Furthermore, it is possible that damage to any part of the system may impair function throughout that system. In fact, several studies in adult animals have found an important relationship between perirhinal cortex damage and object-location memory. For instance, Bachevalier and Nemanic (2008) tested monkeys with adult lesions of the perirhinal cortex in the modified visual paired comparison paradigm. They found that monkeys with perirhinal lesions were not able to detect changes in new images with rearranged or replaced objects. This study highlighted the importance of the perirhinal cortex in both memory for objects and memory for the combination of objects and their locations. Several other studies have found similar deficits in object-location relations following adult perirhinal cortex lesions (Gaffan & Parker, 1996; Jo & Lee, 2010).

*Amnesic patients and animal lesions.* Some evidence suggests that deficits observed in amnesic patients following medial temporal lobe/hippocampal damage may be related to fundamental deficits in relational memory (Chun, 2005; Chun & Phelps,

1999; Konkel, Warren, Duff, Tranel, & Cohen, 2008; Ryan Althoff, Whitlow, & Cohen, 2000). For instance, Chun and Phelps, using an implicit contextual cuing task (in which repeated visual context should aid in the visual search for target objects), found that patients with hippocampal damage could not learn to use contextual cues when searching.

Konkel and colleagues studied memory for items, and associative, spatial, and temporal relations. They utilized a task in which three novel objects were presented sequentially during the study phase. During the test phase, the subjects had to make yes/no judgments about whether the objects were previously seen (item memory), whether they appeared together (associative memory), whether they appeared in the same location on the screen during the study phase (spatial memory), and whether the same sequence as in the study phase was present (temporal memory). Konkel et al., found that as compared to control participants, patients with large medial temporal lobe damage were impaired on the item condition as well as all studied relations, whereas patients with hippocampal damage were unimpaired on the item condition but impaired on all of the studied relations. In addition, combined patient scores were significantly below non-amnesic adults in all relational conditions. Accordingly, Bachevalier and Nemanic (2008) found that adult lesions to the perirhinal cortex, parahippocampal cortex, and hippocampus in monkeys impaired memory for object-location relations.

A good amount of evidence suggests that the medial temporal lobe is important for object-context relations (Aminoff, et al., 2007; Doré, Thornton, White, & Murray, 1998; Hirsh, 1974; Luo, Tahsili-Fahadan, Wise, Lupica, & Astor-Jones, 2011; Pascalis, et al., 2009; Winocur & Gilbert, 1984). For instance, in one of the conditions in Nemanic and Bachevalier (2002), an object was presented on a patterned background, and after a

brief delay, the background changed. These researchers found that adult damage to the perirhinal cortex, parahippocampal cortex, and hippocampus resulted in impaired performance on this task. In addition, Pascalis and colleagues (2009), tested adult monkeys with hippocampal lesions and patient YR, an adult amnesic patient with hippocampal damage, in an object-in-context VPC paradigm. For both the adult amnesic patient and the monkeys with lesions, impairment was found when the background on which the familiar object was presented changed between the sample and test phases. These researchers suggested that the role of the hippocampus in particular was to support the flexible representation of objects across contexts. However, extra-hippocampal areas play important roles in supporting these relational functions.

### **Neuroanatomical Development in Humans and Non-Humans**

As mentioned, significant progress has been made in memory research over the years. Much of the early work investigated the neural substrates of memory abilities in adults. However, there are many cognitive and neural differences between adults and children. Therefore, there is still a need for the literature relating memory and the neural bases of memory to link the development of the neural substrates to functional development. Nelson (1995) stated almost two decades ago that the development of mnemonic functions and their underlying neural structures have been “relatively ignored” when compared to studies of memory in adults. This applies to both humans and non-humans.

The largest body of work directly linking the development of relational memory to neural structures has utilized rodent models (see for more information Alvarado & Bachevalier, 2000; Galea, Ossenkopp, & Kavaliers, 1994; Green & Stanton, 1989; Rudy



& Paylor, 1988; Rudy et al., 1987) for myriad reasons. Medial temporal lobe development in rodents occurs largely after birth (Alvarado & Bachevalier, 2000). This in turn, would make it easier to manipulate brain regions early in life and track the development of memory into adulthood in these animals. For instance, a number of studies using the Morris Water Maze to investigate spatial relational memory, found that functional development of the hippocampus occurred around three weeks of postnatal development and that early damage to the hippocampus would impair this development (Green & Stanton, 1989; Rudy & Paylor, 1988; Rudy, Stadler-Morris, & Albert, 1987).

In addition, some research in rodents also suggests rudimentary object-context relations could be supported by an immature hippocampus, but it appears as though a mature hippocampal circuitry is necessary to fully support this function (Foster, & Burman, 2010; Brasser & Spear, 2004; Esmorís-Arranz, Méndez, & Spear, 2008). Rodents have a very short period before puberty and sexual maturity occurs (several weeks), which coincides with hippocampal maturation and relational memory development in these animals (see Alvarado & Bachevalier, 2000; Green & Stanton, 1989; Rudy & Paylor, 1988; Rudy et al., 1987). In humans and monkeys this period spans years, which makes it difficult to pinpoint an exact time during which specific memory abilities mature (Bachevalier & Vargha-Khadem, 2005). Although the work in rodents has been fundamental to our understanding of the development of memory and the underlying neural mechanisms, there are stark differences in the time course of structural and functional development of neural structures between rodents and primates and differences between the modalities within which information is received that limits what these studies can infer about primates.

The close evolutionary relationship of non-human primates to humans, and the fact that unlike rodents, vision is the dominant mode of sensory experiences in both human and non-human primates (Murray, et al., 2007), makes non-human primates a more suitable model to study complex behaviors that also occur in humans, like relational memory for visual stimuli (Carlsson, Shapiro, Farrah, & Hau, 2004). In addition, one of the most frequently used species of monkeys, *Macaca mulatta*, possesses homologous brain structures to those in humans. These may be similar in location, shape, structure, and function as compared to brain areas in humans. The structures in the medial temporal lobe are examples of brain regions that fit this profile (see Murray et al., 2007).

Medial temporal lobe structures in primates mature rather slowly compared to rodents, and relational memory abilities relying on the integrity of the medial temporal lobe also develop slowly. For this reason, developing a primate model that can directly link the maturation of relational memory to specific neural substrates is essential. However, due to the paucity of information about the maturation of neural correlates underlying primate memory development, it is critical to conduct comparative investigations across primate species, if at all possible. Several attempts to link relational memory abilities to the integrity and development of neural structures supporting these functions have utilized early lesions to the medial temporal lobe, specifically the hippocampus, in a few cases of humans and non-human primates.

***Neuroanatomical development of MTL.*** Important developmental changes occurring in the hippocampus and surrounding structures may be related to functional development of memory abilities dependent on this area. As a result, damage to the

medial temporal lobe early in development may impact later performance on tasks that utilize relational abilities (Alvarado & Bachevalier, 2000; Alvarado et al., 2002).

According to neuroanatomical evidence, whereas the structures in the medial temporal lobe form early in prenatal development in primates (Rakic & Nowakowski, 1981; Seress & Ábrahám, 2008), refinements in dendritic growth and synapse formation continue into the fifth postnatal year in children (Seress, 2001; Seress & Ábrahám, 2008). Specifically, the formation of connections between the granule cells in the dentate gyrus and Ammons horn of the hippocampus, occur at this age. However, this period does not mark the end of development of the human hippocampus. Morphological changes continue well into adolescence (Giedd, et al., 1996; Lenroot & Giedd, 2006) and into adulthood in specific subregions of the hippocampus (Gogtay et al., 2006). Development of structures outside of the hippocampus has been studied less frequently. However, Grateron and colleagues (2002, 2003) demonstrated an increase in interneurons of the entorhinal cortex over the first year of postnatal development in humans. Structural development of the perirhinal cortex is unclear.

Non-human primates have a shorter period of postnatal neuroanatomical development than humans (Bachevalier & Vargha-Khadem, 2005). For instance, morphological and connectivity changes within the monkey medial temporal lobe continue to show maturational changes across the first 2 postnatal years (Bachevalier, & Vargha-Khadem, 2005; Lavenex, Lavenex, & Amaral, 2007a). Recent stereological studies of macaque monkeys found increases in hippocampal volume from birth to adulthood, as well as prolonged development and late maturation of the granule cells of the dentate gyrus extending past the first year of life (Jabès, Lavenex, Amaral, & Lavenex,

2010, 2011). These cellular and volumetric changes in the hippocampus may coincide with the emergence of relational memory abilities in monkeys. Accordingly, Blue and Bachevalier (2009) argued that relational abilities emerge some time after 18 months and before 5-6 years in the monkey. In fact, Alvarado and Bachevalier (2000) posited that relational memory abilities often postdate the functional maturation of the tri-synaptic circuits (which consist of connections between the dentate gyrus, CA1 and CA3 fields) of the hippocampus.

***Developmental amnesia.*** Damage or dysfunction of the medial temporal lobe early in life may impact the functional maturation of relational memory abilities later on. Several neurodevelopmental conditions occurring in childhood including developmental amnesia, medial temporal lobe epilepsy, Williams's syndrome, and traumatic brain injury (TBI) involve abnormalities in medial temporal lobe areas. Therefore, it is increasingly important to understand how changes in neuroanatomical development of the medial temporal lobe can affect the functions dependent on this area throughout life.

The condition of *developmental amnesia* (see Vargha-Khadem et al, 1997 for more information, description of 3 cases: Kate, Jon, and Beth, and definition of this disorder; for all cases see Gadian et al, 2000; Vargha-Khadem, Gadian, & Mishkin, 2001) occurs as result of early focal insult to the medial temporal lobe, mainly to the hippocampus. Patients with this disorder have profound anterograde amnesia and exhibit some deficits in declarative memory well into adulthood (Vargha-Khadem, Gadian, & Mishkin, 2001; Vargha-Khadem et al., 1997). In these patients, impairments are also observed in memory for spatial and temporal information (see Burgess, Maguire, &

O'Keefe, 2002; King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001; Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001).

Neuropsychological profiles provide a clearer picture of disrupted memory functions in this group. For instance, Vargha-Khadem, Salmond, Watkins, Friston, Gadian & Mishkin (2003) tested children from 8-19 years of age and found that immediate recall was better for individuals who experienced ischemic events related to medial temporal lobe damage before the age of 1 as compared to individuals who experienced ischemic events later in life (between ages 6 and 14). On the other hand, they found comparable impairments in delayed recall in individuals with developmental amnesia regardless of the age at insult. Furthermore, fMRI in one patient (Jon), who was missing ~50% of his hippocampus, revealed greater activation of the hippocampus in memory for autobiographical and public events that he clearly remembered compared to those he knew details for but could not remember (Maguire, Vargha-Khadem, & Mishkin, 2001). Likewise, hippocampal-cortical connectivity in this patient involved different areas from those of typical adults (Maguire et al., 2001). Vargha-Khadem further suggested a profile of memory inflexibility in these patients that continue throughout life (personal communications). In summary, studies of individuals with developmental amnesia suggest pervasive impairments in memory abilities dependent on medial temporal lobe structures.

Close correspondence between memory profiles in humans and non-human primates are observed following early lesions. In non-human primates models, early damage to the medial temporal lobe impairs relational memory abilities in adulthood (Bachevalier, Málkova, & Alvarado, 1999; Blue & Bachevalier, 2009; Blue, Kazama, &

Bachevalier, 2008; Alvarado, Wright, & Bachevalier, 2002). This evidence suggests that early damage to the medial temporal lobe have long-term effects on relational abilities with little sparing of function. However, other studies in non-human primates found little or no deficit in relational abilities following early damage to medial temporal lobe structures (Glavis-Bloom & Bachevalier, 2010; Lavenex, Lavenex, & Amaral, 2007b). Therefore, more research is needed to provide a clearer understanding of primate memory, which is an essential component in evaluating treatment options for impaired memory in humans.

Memory can be disrupted at any point in life. However, disruption in memory from ischemic events and brain trauma early in life may go unnoticed until some demand is place on memory to complete age appropriate tasks. When mature relational memory emerges, a clearer picture of memory deficits can be obtained.

### **Rationale for Current Study**

Defining the specific functions and neural processes supported by different components of the medial temporal lobe is vital to understanding how memory processes are distributed and organized in the brain and how they interact, work synergistically, or in some instances compete. This understanding is also needed to define the type of memory processes that are disrupted by malfunction of this system. There are many neurodevelopmental disorders, including developmental amnesia, that arise following abnormalities and dysfunction in the hippocampus and surrounding cortices. In addition, the result of these disorders could be deficits in declarative memory. Therefore, the current combination of studies will address 2 main aims: (1) To investigate the typical

development of multiple relational memory abilities, and (2) to investigate the development of relational abilities after early damage to the medial temporal lobe.

In order to test typical development, we utilized the preferential looking paradigm, in both human and non-human primate subject. In humans, we investigated multiple forms of relational memory abilities (i.e., object-location memory and object-context memory) in children and adults. Using a single paradigm will help us clarify developmental trajectories of object-location and object-context memory without relying on unrelated tasks that may or may not be placing very different cognitive demands on participants. In non-humans, we investigated the development of object-location memory using the preferential looking paradigm in monkeys with selective bilateral lesions to the medial temporal lobe. Two separate studies are included in this paper: one which assesses relational memory across different domains in human children and adults, and a longitudinal study in non-human primates investigating the role of the medial temporal lobe in supporting relational memory across development.

Relational memory seems to be dependent on the integrity and full maturation of medial temporal lobe structures. In adults, damage to the medial temporal lobe presents with clear deficits in relational memory (for review see Konkel & Cohen, 2009; Konkel et al, 2008). However, because many of these patients present with large lesions to the medial temporal lobe it is not completely clear how early damage to different medial temporal lobe areas impact memory throughout life. The problem faced by amnesic humans and animals with medial temporal lobe lesions is thought to be related to difficulty in binding different types of elemental information in order to create a cohesive event/episode/context and flexibly representing the associated information in the

presence of other information, which is specifically thought to be dependent on the integrity of the hippocampus (Cohen & Eichenbaum, 1995; Chun, 2005; Konkel, et al., 2008; Ryan, et al., 2000). Although the hippocampus is critical for relational memory, the surrounding parahippocampal areas (more specifically, the perirhinal cortex) may also have a significant part in supporting relational memory. However, compared to investigations of the hippocampus with regards to relational memory, studies assessing the specific involvement of the perirhinal cortex are few. Moreover, research on the impact of early perirhinal cortex damage on relational memory development is largely unexplored.

Studies focusing on the development of relational memory are largely limited to rodents and humans. Whereas, in some non-human animals it is possible to investigate direct brain-behavior relationships throughout development, this is not the case in humans. In humans, the mechanisms underlying the developmental of memory for object-location and object-context relations, though inferred as a result of converging evidence, are not clearly defined. Therefore, studies in humans are limited in that it is not possible to manipulate specific neural structures implicated in relational memory early in development. Furthermore, studies in rodents use very different tasks to measure relational memory than those in humans. Non-human primates serve as an ideal model for examining relational memory development since these primates can be tested on tasks similar to those applied to humans. In addition, we can manipulate specific neural structures associated with adult-like relational memory abilities and track the development of these abilities. Despite this, in monkeys, there is very little evidence for development of relational memory.



The current investigation is important because of the limited developmental studies in humans and non-human primates assessing relational memory abilities. From the pair of experimental studies discussed herein, we hoped to better understand the development of memory across closely related species using a task that can be translated across species. Since poor memory performance on the VPC task is observed following medial temporal lobe damage in adult humans and monkeys (Nemanic & Bachevalier, 2008; Pascalis et al., 2009), we can infer that the VPC task is sensitive to medial temporal lobe damage in both humans and monkeys. We can also infer the neural basis of relational memory by selectively targeting these areas early in development and by tracking memory performance throughout life.

### **Hypotheses**

In the first study we built on the research of Pathman, Bachevalier, & Bauer (personal communication) and tested preschool (4-year-old) and school age (8-year-old) children and adults. We expected memory for object-location and object-context relations would improve with age. In the second study, we also expected an improvement in relational memory as a function of age in monkeys. We hypothesized that memory for relations should be apparent by 3 years of age in typically developing animals. In addition, we used the work by Nemanic & Bachevalier (2008) to hypothesize an effect of perirhinal lesion on development of relational memory in non-human primates.

## **Chapter 2: Typical Development of Relational Memory Abilities in Humans**

The ability to recognize familiar objects, scenes, and people, is an essential cognitive function in humans. Even more important is the ability to recognize objects, people, and places over time, and in different contexts (backgrounds and environments). This flexibility in our recognition is thought to be dependent in part on the integrity of a neural network that encompasses the hippocampus and the surrounding cortices (Cohen & Eichenbaum, 1995; Eichenbaum, 2006). The hippocampus is thought to have a protracted development that coincides with functional maturation of relational abilities including memory for object-location and object-context relations (Overman et al., 1996, Sluzenski, et al., 2006).

### **Development of Relational Memory**

As in rodents and monkeys, relational abilities in humans seem to gradually develop. For instance, studies in young children suggest that memory for spatial relational and object-context relations might be protracted (Aslan, Samenieh, Staudigl, & Bäuml, 2010; Haun et al, 2006a, b; Newcombe et al, 1998; Sluzenski et al., 2004, 2006; Vaidya, Huger, Howard, & Howard, 2007). However, in some instances relational abilities are present in very young children when using certain paradigms (e.g. object-context relations using the preferential looking task; Jones et al, 2011; Robinson & Pascalis, 2004). Nevertheless, most findings in children suggest improvements in relational memory over the first 7-10 years of life.

For instance, Sluzenski, Newcombe, and Kovacs (2006) used an incidental picture recognition task consisting of single items (either animals or backgrounds) and combination of items (animals against arbitrary backgrounds) to test relational memory in

4-, 5-, and 6-year-old children. They found an improvement in recognition of animal-background combination, whereas they failed to observe age differences for recognition of either animals or backgrounds alone. These researchers also tested young children on their level of relations made in a free recall of a story they were told an hour prior. They observed that 4-year-old children were significantly worse at recalling the story and at mentioning relations within their free recalls. However, this occurred only when children were tested after a fairly short delay. The authors concluded that the poorer performance of younger children may be due to the inability of these children to adequately encode relations and/or to recognize/recall them at a later time. Sluzenski and colleagues therefore hypothesized that two mechanisms might likely be taking place in development. First, an early improvement in encoding relations may be occurring, and second, there may also be improvements in retrieval of relations as well.

In studies of preschool and school age children, improvements in relational memory were observed as a function of age. Vlach and Sandhofer (2011) investigated how changes in background context affected word learning and generalization in 2.5-, 3-, and 4-year-old children. Four-year-old preschool children were able to learn new words irrespective of context change whereas younger children (2.5 and 3 years old) could learn new words better when the training context matched the testing context. In another study, using list learning in the same and different contexts, Aslan et al. (2010) found differences in the ability of younger elementary school children (in kindergarten and first-grade) and older elementary school children (in fourth grade) to recall word lists across contexts. Furthermore, they found that older children showed similar memory effects as adults across contexts. Furthermore, a recent study found that young school-aged children

do not reliably demonstrate learning of spatial contexts as compared to adults (Vaidya et al., 2007). These findings suggest that relational abilities continue to mature into middle- to late-childhood. Whereas the full maturation of relational abilities may take a long developmental course, infants and pre-school children may still have some rudimentary abilities that allow them to remember relations. In fact, Townsend, Richmond, Vogel-Farley, and Thomas (2010) suggest that the development of memory for relations precedes the development of the ability to use relational knowledge flexibly in new situations.

***Spatial Relations: Object-location.*** In humans, very young children have difficulty using relational strategies to locate targets (Newcombe et al., 1998; Sluzenski, et al., 2004). In fact, in order to complete spatial tasks, pre-linguistic infants (age 1) preferred a strategy in which a reward remained in a static location but hidden under different objects, whereas older linguistic children (age 3) preferred a strategy in which the location of the reward changed with the object under which it was hidden (Haun et al., 2006a). Balcomb and colleagues (2011) investigated spatial place learning in very young children (16- to 24-month-old) using an adapted Morris water maze and found that there was a sharp increase in children's use of spatial relational strategies at 17 months of age as compared to 16 months of age, even though the strategy increase was not related to task success. Balcomb et al. suggested the developmental shift in spatial relational strategy use could possibly reflect changes in early hippocampal maturation, in addition to experience-dependent behavioral changes and cognitive development. Accordingly, preschool children (age 4) showed a preference for viewpoint-independent (allocentric) cues over viewpoint-dependent (egocentric) cues in solving spatial relational tasks (Haun

et al., 2006b). In general, however, when compared to adults, children demonstrate poorer spatial relational abilities until around 7 years of age (Lehning et al., 1998; Leplow et al., 2003; Overman et al., 1996; Pentland et al., 2003).

In our laboratory (Pathman, Bachevalier, and Bauer, personal communication), 3-, 5-, and 7-year-old children were tested on similar modified versions of the spatial VPC task used by Bachevalier and Nemanic (2008) and Blue and colleagues (Kazama et al., 2003; Blue & Bachevalier, 2009; Blue et al., 2009). In this task, some of the objects in a spatial array were rearranged at test. In addition, the eye movements of these children were recorded using an eye-tracking device.

Three-year-old children performed similar to chance on two versions of the spatial relational task (in which two and four objects were rearranged, respectively). On the other hand, whereas 5-year-old children had some difficulty in the two-object rearrangement condition, they exhibited less difficulty in the four-object rearrangement condition. In close examination of viewing behaviors during the test phases, Pathman and colleagues observed that 7-year-old children consistently looked longer at the novel stimulus in the first second of the phase, whereas 5 year old children tended to look longer at the novel stimulus in the final seconds of the phase (3-4 seconds after stimulus onset). These findings may indicate some important cognitive retrieval processes related to visual development and/or experience.

*Can Scenes Improve Memory for Object-Location Relations?* Organized scenes are remembered better than unorganized scenes (Mandler, Seegmiller, & Day, 1977). Whereas, this may be the case, it is unclear whether organized scenes are sufficient to support adequate memory for object-location relations early in development. Allen and

Ondracek (1995) tested children's knowledge of landmarks across development (from age 5 to age 9), and the relation of landmarks to their contexts using a scene recognition task. They found an effect of age in scene recognition, where older children were faster at recognizing familiar neighborhood scenes than younger children. They concluded that the reason older children were able to acquire landmark knowledge faster stemmed from their ability to more readily and efficiently encode and retrieve relevant information from complex visual arrays, especially information regarding an object in relation to other objects within a scene.

The study by Allen and Ondracek followed Kirasic, Siegel, and Allen (1980), who used a similar scene recognition task. Kirasic et al. found that 5-year-old children were slower and less accurate at recognizing the components of complex scenes than 9-10-year-old children and adults. However, adults were not different from older children in scene recognition for the same and different contexts. In addition, they observed that across all ages when the background and objects were completely different, recognition was greater than when one component of the scene (either the landmark or background context) remained unchanged.

In adults, studies investigating the role of semi-naturalistic scenes in visual memory found that scenes aided memory for object features and object locations (for review see Hollingworth, 2006b; Hollingworth, 2006a, 2007, 2009), and that previewing a scene facilitated the search of a target object in a subsequent presentation of that scene, even if the preview scene did not contain the target object (Hollingworth, 2009). For instance, Hollingworth (2006a) investigated whether objects were stored independently or bound as a part of a larger scene. He tested memory for the object replacement or

orientation and found that memory performance was more robust when the object was presented within a scene.

Hollingworth (2007) conducted several experiments to investigate the role of scenes in object-location binding. He found that memory was enhanced when objects remained in the same location between sample and test. However, changing the features of the background diminished facilitation of memory for the target object. Hollingworth concluded that binding of objects to their location within a scene allows for that ability to form episodic scene representations. Furthermore, Torralba, Oliva, Castelhana, and Henderson (2006) proposed a computational model demonstrating the important role of global scenes in facilitating performance on search tasks. Following a series of experiments, these authors concluded that the features within complex real-world scenes could direct attention to relevant information very early in visual processing. Unfortunately, none of the studies conducted by Hollingworth and others investigated development. Therefore, there is a large gap in the literature on the role of scenes in the facilitation of object feature and location information across development.

***Object-context relations.*** General findings suggest early in development memory performance is enhanced when context remains stable between learning and retrieval situations, but is compromised when the learning and retrieval contexts are different (Haaf et al., 1996). Many of the studies in humans assessing flexible memory of object-context relations have been conducted with very young infants and adults.

The mobile conjugate reinforcement task, in which an infant's foot is attached to a crib mobile and the infant learns that her/his kicking enables the movement of the mobile, has reliably demonstrated that infants respond differently if the context within which the

kicking was learned is changed (see for review Rovee-Collier, Hayne, & Colombo, 2001). However, it is still unclear whether this task is hippocampal-dependent or medial temporal lobe dependent. Context dependency, using other tasks, has also been observed in young children (Haaf et al., 1996; Bornstein et al., 2011), whereas flexible memory for object-context relations (after brief exposure to an object within a specific context) is apparent in adults (e.g. Pascalis and colleagues, 2009). However, performances of infants on other tasks do not demonstrate the clear context-dependency as previously described. For instance, in human infants, context change did not disrupt recall of event sequences measured by deferred imitation (Klein & Meltzoff, 1999) nor did it disrupt recognition of a previously studied face displayed on a new background (Richmond & Nelson, 2009).

Haaf, Lundy, and Codren (1996) using a preferential viewing paradigm tested object-context relations in 6-month-old infants. In a series of experiments, Haaf and colleagues found that infants attended to context. They observed that changing the background of an object after it was initially presented diminished recognition of that object in the subsequent changed background. However, when the context remained the same between the initial and subsequent presentations, recognition of that object was strong. They concluded that context was important for very young children. However, the results of their findings could either imply a clear dependence on context for object recognition in infancy or an inability to flexibly represent objects across different contexts (immature relational memory).

Hartshorn and colleagues (1998) found that altering the external context between sample and test impaired recognition in infants (i.e., 3, 9, and 12 months) after long



delays. These researchers concluded that infants encode the context but may not integrate the cue with the context. These findings corresponded with those observed in Haaf et al. (1996). Moreover, a recent study by Jones, Pascalis, Eacott, and Herbert (2011), using a preferential looking task, found that 6-, 9-, 12-, and 18-month-old infants show a novelty preference score (which is used to quantify memory performance) above chance when the context remain the same between familiarization and test. On the other hand, performance was at chance in the 6- and 9-month-old infants when the context changed between familiarization and test. These findings were similar to Robinson & Pascalis, 2004, who demonstrated that, when the background immediately changed between familiarization and test, 6- and 12-month-old infants showed no novelty preference, while older children (18 and 24 months) demonstrated novelty preference scores above chance.

Some authors proposed that, the hippocampus aids in memory by facilitating the relation between item and context information (Cohen & Eichenbaum, 1995; Pascalis et al, 2009). For instance, Pascalis and colleagues (2009) hypothesized a flexible representation of an item across different contexts. To test this, they conducted an experiment using a preferential looking paradigm in (a) an adult patient with focal hippocampal damage, YR, and 6 control adults, and (b) monkeys with adult lesions to the hippocampus and control monkeys. The experiment had two conditions. In general, an item was initially presented on a patterned/textured (e.g., orange speckled) background for a period of time during familiarization. Then after a short delay, the item was presented along with another item. The two items were either presented on the same background as during familiarization (same background condition) or were presented on

a completely new background (background change condition). Preferential looking to the novel item was measured as memory in this task.

Pascalis and colleagues (2009) found that the adult amnesic patient, YR, and monkeys with adult-onset hippocampal damage displayed equal looking behaviors at both the novel and familiar objects only when the background changed between familiarization and test, suggesting inflexibility in representing item information across a change in contexts (dysfunction of relational memory). These authors argued that previously experience elements of an event could be fused into a novel representation (e.g., when a familiar object is displayed on a new background), potentially influencing the response to the combination of familiar and novel elemental features of a stimulus as though it was a completely novel stimulus. Therefore, they stressed that the integrity of the hippocampus was to create item-context relations that could be flexibly represented when one of the components of that relation changed.

In the current chapter, we investigated the development of relational abilities. To reach this end, we employed the visual paired comparison paradigm (VPC) to account for three different types of relations: (1) memory for object-location relations, (2) memory for object-location in semi-naturalistic scenes (1) memory for object-context relations. We hypothesized an age related improvement in relational memory abilities in all tasks.

## **Methods**

### **Participants**

Fifty-nine individuals (29 females) participated in the current study. Two groups of children each containing 20 individuals—4 years old (9 females;  $M = 4.06$ ,  $SD = .11$ ) and 8 years old (9 females;  $M = 8.11$ ,  $SD = .12$ , respectively)—were recruited. Children

were drawn from a pool of families who expressed interest in participating in research. A single group of adults over 18 years of age (9 females;  $N = 17$ ,  $M = 20.05$ ,  $SD = .21$ ) also participated in the study. Adults were drawn from the undergraduate pool of Emory University students. Two additional female adult participants failed to follow study protocol throughout their sessions and were excluded from analyses. Participants were compensated with either incentives (for children- a small toy; for parents- a gift certificate) or course credit (for undergraduates). The Institutional Review Board (IRB) at Emory University approved all procedures for recruiting and testing participants. Verbal assent procedures for 8-year-old children and informed consent for parents and adults participating in the study followed APA guidelines and were obtained prior to initiating any study procedures.

## **Materials**

**Stimuli.** Individuals saw images of objects and object-background configurations presented on the eye tracker display using Tobii Studio presentation software. Objects included household items, toys, vehicles, animals, etc (see Figure 1A). Backgrounds were either fractal images or patterns. Images used for testing were trial unique (Figure 1B). Therefore, participants were only exposed to a given image for one trial across all conditions. Each participant viewed the same set of images.

**Apparatus.** Eye movements were recorded using a Tobii T120 eye tracker (Tobii Technology, Stockholm, Sweden). The eye-tracking device is integrated into a 1280 × 1024 pixel 17" thin film transistor (TFT) display monitor with built in speakers and a user camera, which uses infrared technology to track pupil movements at 120Hz (see Figure 2A). The infrared light generates corneal reflections, which are measured relative

to the position of the user's eyes. In addition, the device offers high precision with spatial resolution at  $\sim 0.3^\circ$ , drift at  $\sim 0.1^\circ$ , and accuracy at  $\sim 0.5^\circ$ , and a relatively naturalistic range of head motion (approximately 25cm/sec) within a space of  $30 \times 22 \times 30$  cm from a distance of  $\sim 70$  cm. Housed in a behavioral testing room, the eye tracker setup included the Tobii eye tracker device monitor and CPU, which was situated adjacent to a secondary monitor used by the experimenter to view real time gaze information from the participants. In order to avoid distracting the participant during the session, the secondary monitor was positioned at  $\sim 60^\circ$  angle out of the view of the participant (Figure 2B).

A local live viewer setup was integrated into the eye tracker system (Figure 2C). This allowed the experimenter to view the real time the gaze data overlay on a secondary computer monitor. The live viewer was used to ensure that the participants were actively attending to the images and that during each trial the eye tracker was reliably collecting eye movement data.

**Preferential looking tasks.** Each trial began with a familiarization period of 10 seconds, in which the participant viewed a target stimulus. Following familiarization, depending on the condition, a short delay period of 5 seconds was followed by either one 10-second or two 5-second test phases (Figures 3A-B, respectively). During the test phase(s), novel stimuli were presented together with the previously viewed stimuli. For the trials with two test phases, the left/right positions of the novel and familiar images were reversed during the second test phase to control for any side bias (Figure 3B). The presumption of this task is that memory for the familiar image can be measured by the tendency to devote greater attentional resources (i.e., viewing) to the novel image/objects.

Seven task types were used to measure three different relations (i.e., object-location relations, object-location relations within scenes, and object-context relations). Each task type was randomly intermixed within the experimental session. Each task was comprised of 6 trials. Forty-two trials, which were presented in a single session, are described herein.

## **Procedures**

All behavioral testing took place in a research laboratory. Sessions lasted roughly 45 minutes. Participants sat approximately 70 cm from a 1280 × 1024 pixel 17" thin film transistor (TFT) display and viewed visual stimuli, some of which had depth. At the outset of each session, participants' eye movements were calibrated using the eye-tracking system to ensure accuracy of looking data. Individuals were told to attend to the series of images presented on the screen as though they were watching television.

**Calibration.** Prior to commencing the recording session, each participant was taken through the calibration procedure. The calibration process ensured the machine was able to process the characteristics of the participants' eyes and use them along with a computerized eye model to accurately calculate her/his gaze information. The model included several different types of information including eye shape, and refraction and reflections properties of different parts of the eyes. A calibration screen appeared first (Figure 4A). After accepting the calibration, a single calibration dot appeared on a location on the screen then moved to four different subsequent locations (Figure 4B). Once calibrated, the participant was prompted to start the recording session (Figure 4C). Recalibration was performed between runs to ensure accuracy of eye movements.

**Stimulus presentations.** Participants were prompted to fixate on a blank screen with a crosshair in the center. Once the participant looked at the crosshair, the researcher clicked on the mouse to begin the session. Once the session had begun, the participant first viewed a to-be familiarized image, which stayed on the screen for 10 seconds. A blank screen appeared automatically and stayed on the screen for 5 seconds and was followed by the test phase(s) (Figure 3). After each trial, a crosshair was present on the screen and a mouse click was required to begin each subsequent trial. Trials were displayed in blocks of twelve. After each block, participants were given a distracter task to minimize fatigue (i.e., Woodcock Johnson Test of Cognitive Abilities subscales). Following the distracter task, the researcher initiated the upcoming block by mouse click. At the conclusion of the session, participants received their incentive.

### **Task Parameters and Statistical Analyses**

Fixation analyses measured eye movement patterns using Tobii Studio software. Valid trials were selected from the raw data based on the total time looking at the familiarization image and the total looking times at test. Because of variability in looking times for participants, trials with looking times lower than 1/4 of the familiarization phase (2.5 sec) and a total of 1/10 of the test phase(s) (1 sec) were excluded from the analyses. The valid trials criteria for the familiarization phase were taken from Richmond and Nelson (2009) and criteria for looking times during the test phase was taken from Zeamer, Heuer, and Bachevalier (2010). The average number of valid trials for each age group was greater than 90%.

Fixation duration and areas of interests were recorded. Fixation analyses assess how children and adults process visual information (i.e., via scanning and fixation

patterns) and whether they view the objects equally or preferentially focus on shifted or changed objects. We also defined specific areas of interest (AOIs) and analyzed the duration of fixation within each AOI.

Behavioral parameters regarding the amount of time looking at the stimuli during the familiarization phase (familiarization time), the total time looking at either the familiar or novel images on the screen during the test phase (total looking time), the average percentage of time looking at the objects within the novel image (mean novel image preference) and the average percentage of time fixating the novel objects within the novel image (mean novel object preference), were extracted from the Tobii Studio software and analyzed using Statistical Package for the Social Sciences (SPSS 19.0).

### **Experiment 1: Object-Location Relations (Importance of Background)**

We examined the development of spatial memory using an incidental preferential looking task derived from Bachevalier and Nemanic (2008). This task does not require a strategy; instead, it utilizes the subject's natural tendency to spend longer periods inspecting a novel spatial arrangement as a measure of memory for a previously experience arrangement. Trials in this task were used to investigate the development of memory for object-location relations. In addition, based on research suggesting the role of context in guiding visual behaviors (Torralba, Oliva, Castelhana, & Henderson, 2006; Hollingworth, 2006a, b), we also examined whether including a semi-naturalistic scene could change any age differences observed using the preferential viewing task.

**Object-Location (No Background).** A total of 12 trials were presented to each participant: six experimental (Object-in-Place) and six control (Object-Control) trials. During a 10-second familiarization, a single image consisting of an array of 5 objects on

a white background was presented in the center of black screen. During the test phase, the familiar image appeared on the screen with a novel image, in which some of the familiar objects shifted positions or changed. Each trial consisted of two 5-second test phases (Figure 5A-B).

***Object-in-Place.*** The *Object-in-Place* condition was used to measure recognition memory for spatial relations across development. During the test phase, the familiar image, which consisted of a five-object array, was presented along with a novel image, which consisted of the same array of objects but with the location of three of the objects rearranged (see Figure 5A). The rearrangement condition was relational in nature since nothing about the objects other than their locations changed.

***Object-Control.*** The *Object-Control* condition was used to check that any differences observed in the Object-in-Place task were not due to perceptual difficulties in viewing complex images. The only distinction between this control task and the Object-in-Place task was that during the test phase of this control task, three of the objects in the novel image were replaced (see Figure 5B). Therefore, the object features changed between familiarization and test.

**Object-Location (Scene).** Participants viewed a total of 12 trials of objects presented within semi-naturalistic scenes to investigate whether the addition of a complex scene would facilitate or impede memory of object-location relations. Six trials were presented for the spatial relation condition (*Object Rearrangement*) and six trials were presented for the object control condition (*Object Replacement*). Full screen pictures displaying an array of objects within an ecological scene (i.e., office, bathroom, bedroom,



etc.) were used (Figure 6A-B). The target objects had depth and were relevant to the environment within which they were displayed. For example, there were hand towels and accessories in bathrooms, and office equipment and supplies (e.g., computers and printers) in office scenes.

***Object Rearrangement.*** This task was an adaptation of the Object-In-Place task in which an array of 5 objects was displayed in the foreground (e.g. tables, chairs, plants, etc.), so as to be distinct from any part of the background (e.g. walls, curtains, windows, etc). Three randomly selected objects within the array were rearranged between familiarization and test whereas the background scene remained consistent (Figure 6A). Similar to the Object-in-Place task, all of the objects from the initial presentation remained the same during the test presentation and only their locations changed.

***Object Replacement.*** The Object-Replacement task was an adaptation of the Object-Control task. Three objects in an array of 5 objects were replaced between familiarization and test, whereas the scene remained consistent (Figure 6B).

### **Preliminary Analyses**

Familiarization time and total looking time were recorded to account for any viewing differences between age groups and conditions that may contribute to difference in novelty preference. Tables 1 and table 2 depict the average familiarization times and total looking times across age and tasks, respectively.

Preliminary analyses revealed that familiarization times and total looking times consistently differed across ages and tasks. For instance, in the object-location (no background) conditions familiarization times differed among children and adults ( $F_{2, 51} =$

6.344,  $p = .003$ ,  $\eta^2 = .199$ ) and total looking times differed between tasks and among ages (Task:  $F_{1, 51} = 10.419$ ,  $p = .002$ ,  $\eta^2 = .170$ ; Age:  $F_{2, 51} = 13.875$ ,  $p < .001$ ,  $\eta^2 = .352$ ).

Familiarization time and total looking time results in the object-location (scene) conditions were similar to those indicated for the no background condition (all  $ps < .05$ ). For the object-context conditions, familiarization times were different depending on age and task (all  $ps < .02$ ) and total looking times differed as a function of age ( $F_{2, 49} = 14.407$ ,  $p < .001$ ). Therefore, to control for pre-existing differences in familiarization and total looking times, we co-varied out familiarization and total looking times in subsequent analyses.

To investigate whether differences in viewing behaviors were present among the groups of children and adults we conducted repeated measures ANCOVAs on the AOI with a between subjects factor of Age (4 years, 8 years, and Adults) and Task (Experimental vs. Control condition[s]). In addition, for each age group across each task, mean percent of looking time at the novel was compared to chance performance using a one-sided t-test. Huynh-Feldt corrections were used when sphericity was not assumed. Post hoc-analyses were conducted using Bonferroni and paired t-tests.

## **Experiment 1: Results**

### **Object-Location (No Background)**

Memory for object-location relations was measured using the *VPC-Object-in-Place* task and *VPC-Object-Control* tasks. The *VPC-Object-Control* task measures memory for objects and was used to confirm that any impairment observed in the *VPC-Object-in-Place* task was not the result of poor memory for arrays across development.

The arrays were similar in the familiarization phase of the two tasks but during test three of the objects were either replaced or rearranged.

*Novelty preference.* Based on the findings of Pathman, Bachevalier, and Bauer (personal communication), we hypothesized that 4-year-olds would perform similar to chance on the object-location task in which three of the five objects in an array were rearranged. On the other hand, 8-year-old children and adults were expected have less difficulty recognizing a change in the rearrangement of the objects after a delay. No age differences were expected in the control condition. We first measured the preference for the objects within the novel image, which was compared to 50% (see Figure 7A; 5 objects within the novel image in each test phase, 10 total, as a function of the number of objects in both test phases, 20 total). In addition, to understand whether the novel objects were preferred more or less than familiar objects, we measured the preference for the only the novel objects (3 in each test phase, 6 total) as a function of the number of objects in the test phases (20 total). Consequently, preference for the novel objects was compared to 30% (see Figure 7B). Figure 8A and 9A depicts novel image and novel object preference scores, respectively, as a function of age for the Object-in-Place and Object-Control tasks.

*Object-in-Place.* Younger children (4-year-olds) looked equally at the objects within the novel and familiar images ( $M = 51.88$ ,  $SEM = 1.77$ ), whereas older children (8-year-olds) looked significantly more at the objects within the novel image during the test phase ( $M = 55.50$ ,  $SEM = 2.60$ ,  $t(19) = 2.114$ ,  $p = .048$ ). Contrary to expectations, adults showed only a slight preference for novelty in this task ( $M = 54.39$ ,  $SEM = 2.16$ ,  $t(19) = 2.034$ ,  $p = .059$ ). Neither age differences nor interactions were observed (Figure 8A).

With regards to average novel object preference, 4-year-olds did not look preferentially at the novel objects ( $M = 30.795$ ,  $SEM = .974$ ). Like 4-year-olds, 8-year-olds children also failed to exhibit a preference for the novel objects ( $M = 31.828$ ,  $SEM = 1.589$ ). On the other hand, adults looked preferentially at the novel objects ( $M = 33.06$ ,  $SEM = 1.45$ ,  $t(17) = 3.175$ ,  $p = .006$ ). No age differences or interactions were observed (Figure 9A).

The findings in adults are interesting because we expected to see clear preference for the objects in the novel image as well as a preference for the novel objects in particular, which we did not observe. Due to large within group differences and based on previous literature, we performed follow-up analyses to evaluate where these differences might lie. Voyer, Postma, Brake, and Imperato-McGinley (2007) argued that gender differences in object-location memory would be present in adults and would also favor women. In order to test this assumption, we separated the groups based on gender and measured novelty preference. In accordance with Voyer et al. (2007), we found that female adults exhibited clear preference for the objects within the novel image ( $M = 56.43$ ,  $SEM = 2.70$ ,  $t(8) = 2.377$ ,  $p = .045$ ) in the Object-In-Place task, whereas adult males did not (Figure 8B;  $M = 52.11$ ,  $SEM = 3.45$ ). We observed similar finding for the novel object preference (Figure 9B; Females:  $M = 34.219$ ,  $SEM = 1.60$ ,  $p = .030$ ; Males:  $M = 31.899$ ,  $SEM = 1.01$ ). Children, however, did not demonstrate the same pattern as adults. Four-year-old and 8-year-old females and males performed similarly on the Object-in-Place task, consistent with the findings of Voyer and colleagues that prior to adolescence, memory for object-locations would be similar in males and females.

*Object-Control.* All age groups preferred novel images more than expected by chance (Figure 8A). Four-year-olds looked more at objects within the novel images than at the objects within the familiar images during the two test phases ( $M = 55.10$ ,  $SEM = 2.08$ ,  $t(19) = 2.458$ ,  $p = .024$ ). Older children (8-year-olds) looked significantly more at the objects within the novel image during the test phase ( $M = 58.061$ ,  $SEM = 1.41$ ,  $t(19) = 5.726$ ,  $p < .001$ ). Adults exhibited similar preference for objects within the novel image ( $M = 58.41$ ,  $SEM = 2.262$ ,  $t(16) = 3.718$ ,  $p = .002$ ). No gender differences were observed for novel image preference in this task.

Novel object preference across the two test phases was greater than chance for 4-year-olds ( $M = 38.52$ ,  $SEM = 1.33$ ,  $t(19) = 6.397$ ,  $p < .001$ ), 8-year-olds ( $M = 41.10$ ,  $SEM = 1.49$ ,  $t(19) = 7.445$ ,  $p < .001$ ), and adults ( $M = 41.23$ ,  $SEM = 1.84$ ,  $t(16) = 6.116$ ,  $p < .001$ ). No age or gender differences, or interactions were found (Figure 9A).

*Object-in-Place/Object-Control Analyses.* No effect of task, age, gender, and no interactions were observed.

### **Object-Location (Scene)**

Memory for spatial relations across semi-naturalistic scenes was measured using the *Object Rearrangement* task, whereas object recognition memory in semi-naturalistic scenes was measured using the *Object Replacement* control task. Due to the findings in the Object-in-Place task, we also investigated whether there were any gender differences in memory for object-location relations within scenes.

*Novelty preference.* Several studies found that semi-naturalistic scenes aided memory for object features and object-locations (see Hollingworth, 2006a, 2007).

Therefore, we expect that if the background scene was able to aid in memory performance, novelty preference scores would be significantly greater than chance in both tasks at all ages. The familiar scenes were presented again during test, and three of the five objects were either replaced or rearranged within the scenes. As a result, we were only able to measure preference for the novel objects, which was set at 60% (see Figure 7C). Figure 10 depicts novel object preference scores across ages for the Object Rearrangement and Object Replacement tasks.

*Object Rearrangement.* No significant differences in age or gender were observed for novel object preference in the Object Rearrangement task (4-year-olds:  $M = 59.89$ ,  $SEM = 1.85$ ; 8-year-olds:  $M = 61.38$ ,  $SEM = 2.64$ ;  $M = 65.81$ ,  $SEM = 2.023$ ). Four year olds and eight year olds were not different from chance in this condition, whereas only adults displayed clear preference for novelty on this task ( $t(16) = 2.875$ ,  $p = .011$ ).

*Object Replacement.* We did not observe significant differences in novelty preference among the three age groups or between males and females in the Object Replacement task. However, younger children (4-year-olds) were not different from chance on the Object Replacement condition ( $M = 63.41$ ,  $SEM = 2.69$ ) whereas, older children, exhibited novelty preference scores well above chance ( $M = 66.10$ ,  $SEM = 2.11$ ,  $t(19) = 2.889$ ,  $p = .009$ ). Adults also had robust novelty preference scores ( $M = 70.37$ ,  $SEM = 1.93$ ,  $t(16) = 5.371$ ,  $p < .001$ ).

*Object Rearrangement/Object Replacement Analyses.* Age differences were observed between the Object Rearrangement and Object Replacement conditions (Age:

$F_{2, 50} = 4.495$ ,  $p = .016$ ,  $\eta^2 = .152$ ). Adults preferred novel objects significantly more compared to 4-year-olds ( $p = .017$ ), but only slightly more compared to 8-year-olds ( $p = .054$ ). No task differences were observed.

### **Experiment 1: Summary**

Some unexpected findings on object-location relational memory were observed. First, in the no background condition, 8-year-olds exhibited novelty preference for objects within the novel image but did not exhibit preference specifically for the novel objects. On the other hand, adults were only slightly greater than chance at preferring the objects within the novel images, but significantly greater than chance at preferring the novel objects. Second, very clear differences in performance on the Object-Location (No Background) condition were observed between male and female adults. In light of the meta-analysis suggesting better object-location memory in women (Voyer et al., 2007), the current results that women had greater memory for object-place relations in the No Background condition are not so unexpected. However, it is unclear why these gender differences were not observed in the Object-Location (Scene) condition. One possibility is that these scenes were able to facilitate object-location memory in males since both males and females were equally efficient at detecting changes in these conditions. Therefore, as a group, adults were significantly different from chance.

Whereas, 4- and 8-year-olds did not differ significantly from one another on the No Background or Semi-Naturalistic Scene conditions, they did exhibit different patterns of performance on each. Four-year-olds were at chance on the object-location version of the No Background task but were above chance on the other task (i.e., Object-Control). In addition, adding a scene increased the difficulty of detecting object replacements and

object rearrangements for 4-year-olds, whose group performance was at chance on both versions of the Scene task. Conversely, 8-year-olds were able to detect a novel object rearrangement within an image (albeit, not the individual rearranged objects) when there was no background but were unable to detect these changes when a scene was added. However, adding a scene did not diminish the ability of 8-year-old children to detect object replacements. These patterns of results are very different from the facilitation effects of contextual scenes in change detection studies of adults (Torralba et al., 2006; Hollingworth, 2006a, b; 2007; 2009). Therefore, there may be some development still occurring with respect to memory for complex visual information.

We initially expected that placing the array of objects within a semi-naturalistic environmental setting would increase the ability of even the youngest children tested to detect visual changes. Furthermore, more objects within the scenes were changed in the current study as compared to the Torralba and colleagues and Hollingworth studies. However, changing more parts of the scene did not facilitate children's ability detect object-location relations. Since complex scenes seemingly diminished object-location relation abilities in older children, it is important to understand the role of context with regards to relational memory. Therefore we conducted a follow up analysis of object-context relations.

### **Experiment 2: Object-Context Relations**

The object-context relational trials were modeled from Pascalis and colleagues (2009). These trials were used to test the flexibility of memory for object-background combinations. Participant viewed a total of 18 trials. Six trials were presented in each of three object-context conditions (see below). A set of pictures containing objects on



textured/patterned backgrounds was used. During the familiarization phase, a single object was presented on a background. During the test phases, the familiar object and a novel one were presented either on the same background as before or on a new background (see Figure 11A-C). Two test phases were included in each object-context trial.

***Experimental condition.*** During the test phase (Fig. 11A), the familiar object and the novel object appeared on a completely new background (*Background Change* experimental condition). This experimental condition investigated whether a previously familiar object would be viewed similarly or differently than a novel object when the background on which the objects appeared was novel. Adults exhibited robust memory performance on previous versions of this task (see Pascalis and colleagues, 2009). However, the findings are equivocal in young children but suggest that performance may increase with age (for instance see Haaf, Lundy, & Codren, 1996; Robinson & Pascalis, 2004 for data on infants). Therefore, we expect an increase in performance in this task based on age.

***Control conditions.*** In the two controls conditions, either the background or the object was kept constant from familiarization to test. These trials were included to ascertain whether any differences in viewing behaviors in the experimental condition could be due to the change in the background or to the presence of a new object regardless of a background change. Thus, the importance of these trials is that they attempt to separate the roles of objects and backgrounds across development. In the *Novel Object* control condition (Figure 11B), the background remained constant between familiarization and test, such that both the familiar and novel objects were presented on

the familiar background. Conversely, in the *Novel Background* control condition (Figure 11C), the object was constant from familiarization to test but the background changed, such that in the test phase the familiar object was presented both over the familiar background and over a novel background.

## Experiment 2: Results

### Object- Context Relations

Memory for and flexibility of object-context pairings was measured using the *Background Change Experimental Condition*, the *Novel Object Control Condition*, and the *Novel Background Control Condition* (see Figure 11A-C). We hypothesized that if memory for object-context relations follows the same trajectory as memory for object-location relations, we should see better performance in older children and adults than in younger children in the experimental condition. There should be no age differences in the control conditions.

***Novelty Preference.*** The percentage of time looking at the novel image as a function of the total looking time at test (mean novel image preference) represents memory performance on the VPC tasks. Chance performance, defined as equal looking times between the two images during test, was set at 50% and was calculated by dividing the novel image by the total number of images in each test phase (see Figure 12). See Figure 13 for depiction of mean novel image preference across all ages and tasks.

Pairwise comparisons revealed novel image preference scores were significantly higher in both the Background Change Experimental condition and the Novel Object Control condition than in the Novel Background Control condition ( $p_s < .001$ ). No age differences or gender differences were observed among the tasks.

Adults preferred the novel image in all of the three conditions (Background Change Experimental:  $t(16) = 5.848, p < .001$ ; Novel Object Control:  $t(16) = 5.064, p < .001$ ; Novel Background Control:  $t(16) = 4.553, p < .001$ ). Eight-year-olds exhibited a novel image preference for the Background Change condition:  $t(19) = 5.817, p < .001$  and Novel Object condition:  $t(18) = 5.137, p < .001$ , and a marginal preference for the Novel Background Control condition:  $t(18) = 2.005, p < .061$ . Four-year-olds performed similarly compared to 8-year-olds and preferred the novel image significantly more than chance in the Background Change condition:  $t(18) = 4.520, p < .001$  and Novel Object condition:  $t(19) = 6.797, p < .001$ , but was not different from chance on the Novel Background Control condition. Whereas, all groups showed robust memory for the novel image in the Novel Object Control and the Background Change conditions, only adults exhibited a clear novelty preference in the Novel Background Control condition (see Figure 4; 4 year olds:  $M = 52.215, SD = 9.129$ , 8 year olds:  $M = 53.843, SD = 8.354$ , and Adults:  $M = 57.870$ ).

### **Experiment 2: Summary**

Three important findings emerged from investigating simple memory for object-context relations. First, children can detect a change in the object when a change in the background also occurs, as highlighted by the findings that novelty preference was robust for both groups of children in the Background Change condition. However, the other finding suggests that children are not actually using the same strategies as adults to get to the same outcome. Namely, children may not necessarily be binding the background to the scene and then using relational flexibility to be able to detect changes across contexts until about age 8. Preference for the novel image was clearly observed in the conditions

in which a novel object was presented on a background that was either similar or different to familiarized one. However, when a familiar object was presented on both a familiar and novel background at test, a marginal preference for the novel background was observed. This pattern may suggest that the ability to flexibly use context information might be emerging at age 8.

Interestingly, good performance in the Background Change condition can be accomplished if children completely ignore the object-context combination and focus solely on the object. This, in fact, may be what they are doing. Therefore, the Background Change condition would be similar to the Novel Object control condition if, to the child, the most salient feature in the image was the object. In that instance, any background information becomes irrelevant to noticing changes in object identity. Findings from previous research suggest that 4-year-olds exhibit deficits in feature binding; the ability to identify previously viewed object-background combinations (Lloyd et al., 2009). The current results in children seemingly contradict this assumption; however, the observed looking patterns across the different tasks could possibly explain these anomalous findings. On the other hand, unlike children, adults were able to show a robust preference for the novel image even when the background was the salient feature and the objects remained the same (Novel Background) condition.

## **Chapter Discussion**

### **Object-location relations (No background)**

Two of the three modified spatial VPC versions proposed in Bachevalier and Nemanic (2008) were used in the current investigation. We found memory for objects improved across development (from preschool to adulthood). However, with respect to

object-location relations in the No Background task, some of our results are somewhat surprising. We expected to see improvement of memory for object-location relations between 4 and 8 years of age. In support of this hypothesis, we found that preschool children were unable to distinguish the novel from the familiar spatial array, whereas older children had were able to do so. Surprisingly, adults were only slightly above chance at distinguishing the novel from familiar array, despite having longer periods of familiarization than young children. A preference for the novel objects was also observed in adults, suggesting that during the trials they generally concentrate their looking to the novel objects more than would be expected by chance. However, older children did not exhibit this pattern; instead, they preferred the objects within the novel image but not the individual novel objects.

One could argue that the lack of novelty preference for young children is a result of needing more time to fixate the familiar image when a complex array is presented. This explanation cannot account for the results obtained in the current study, since we controlled for possible age differences in familiarization times and because preschool children were well above chance for the control task in the object-location condition. If younger children needed more time to view the image during familiarization, we would not have observed novelty preference during the control task in 4-year-olds. Our findings in young children are consistent with the previous study in non-human primates that utilized the same modified VPC task. Blue and colleagues (2009a, b) observed differential memory performance when the objects were rearranged as compared to the when the objects were replace across all ages tested in typically developing monkeys.

Monkeys also demonstrated memory for object-location relations as, suggesting that memory object-location relation occurs rather late in monkey development.

Similarly, Pathman and colleagues (personal communication), using the modified VPC from Bachevalier and Nemanic (2008), investigated memory for spatial relational memory. They found that young children had trouble distinguishing the novel from the familiar images. In addition, 5-year-olds were better than 3-year-olds, but still had trouble when fewer items were rearranged, whereas 7-year-olds did not. Here we see that 4-year-olds did not prefer the novel image and novel objects more than expected by chance when three of the objects were rearranged. On the other hand, 8-year-old children looked preferentially at the objects in novel image, however, they did not look preferentially at the individual novel objects. Therefore, we think that even at 8 years of age, memory for object-location relations may still be developing.

Spatial abilities may continue to develop into adulthood (see Luna, Garver, Urban, Lazar, & Sweeney, 2004). We tested university students with a mean age of 20 years, who only slightly preferred the novel images from the familiar ones. Even at 20 year of age, memory for object-location relations may still be developing. However it is unclear whether development might be continuing in adulthood since adults were able to detect the novel objects within the images. In addition, there may be another explanation for their performance on the object-location task in which the objects were rearranged (e.g., gender differences in object-location memory). In a meta-analysis investigating the effects of gender on object location memory, Voyer and colleagues (2007) contended that gender differences in this type of memory would be present in adults and would also favor women. When we looked at the performance of males and females separately, we

found a different pattern of preferential looking in adults. Specifically, adult females preferred the novel image whereas adult males did not. These patterns were not observed at any of the other ages tested.

The task difficulty could also contribute to the performance of adults on the task in which the objects were rearranged. Within each test phase, two images, each containing 5 objects were presented on the screen, all of the objects within the images were familiar with the only difference apparent in their locations. If the images were too difficult to distinguish, the novel object locations would be as well. However, relative to chance adults preferred the novel object locations within the images, despite only showing a marginal preference for the novel images. Finally, it is possible that novelty preference for relational stimuli in adults is a rapid process (see Hannula & Ranganath, 2008) and this may even be the case for children (Richmond & Nelson, 2009). Therefore, having two 5-second retention phases may create a situation where the novel image may become less novel over time.

### **Do Scenes Facilitate Object-Location Memory?**

One of the central questions we hoped to address with the tasks utilizing semi-naturalistic scenes to assess memory for object-location relations was whether scenes would help to facilitate memory for object-location relations. Instead what we found is that for younger children, scenes impacted memory for object-locations as well as memory of individual objects, whereas in older children scenes impacted object-location memory without impacting object memory. In adults, scenes helped to facilitate object-location relations in both males and females.

**Scenes and object memory.** Object recognition memory is thought to develop early and remain stable across development (see Bachevalier, 2008). This idea is consistent with the recent findings by Zeamer, Heuer, and Bachevalier (2010). Control monkeys were tested in a visual paired comparison task that measured recognition memory for objects. They found that across the first 18 months of life, typically developing monkeys exhibited robust novelty preference at delays lasting up to 120 seconds. Recognition memory is exhibited in humans and non-human animals at relatively long delays across development (see Bachevalier, 2008; Pascalis, de Haan, Nelson, & de Schonen, 1998).

In the current investigation, we found object memory in young children, when three objects were replaced within an array that lacked a scene, but not when the objects were replaced within a semi-naturalistic scene. These findings are interesting because it appears as though placing objects within a scene might have in some way encumbered the attentional resources young children were able to devote to recognizing object change. Another explanation is that the saliency of the replacement objects may not have been adequate enough to greatly influence recognition in young children. In fact, Zheng, Zhang, and Yan (2012) argued “saliency detection turns into a search for novel items within a scene.” In addition, they contend that while novelty guides visual attention, it is also influenced by dissimilarities from the global scene. The scenes in the current study contained information relevant to the space even at test (e.g., a kitchen scene contained items usually appearing in a kitchen). Therefore, the test objects may not have been dissimilar enough from the global scene to produce strong preferences for novel objects in children. The older children did not show the same pattern of results as the younger



ones, suggesting that there may be some age related differences in object recognition that can be tapped by tasks measuring object recognition within complex environmental scenes.

**Scenes in object-location memory.** Age-related changes in environmental scene recognition have been found previously in children (Doherty & Pellegrino, 1986).

Doherty and Pellegrino presented a series of neighborhood pictures to children 7-15 years of age. They found that younger children were less accurate in distinguishing familiar neighborhood scenes than older children. The findings of the current study suggest that changes in spatial relations within a semi-naturalistic scene may be difficult for children age 8 and younger. However, this was unexpected since studies investigating spatial relational memory within the backdrop of semi-naturalistic environments have shown marked increase in spatial relational memory in older vs. younger children (Overman et al., 1996; Lehnung and colleagues, 1998; 2003). Furthermore, the findings that in the absence of a scene, 8-year-olds could distinguish a novel arrangement of previously familiar objects (even without being able to distinguish the individual novel objects), suggest that at this age children do possess some spatial relational abilities.

### **Object-Context Relations**

The object-context relational memory task was used to investigate the flexibility of memory in children and adults across context. In the experimental condition, the background changed between familiarization and test. This manipulation is assumed to be relational in nature since the participant should use the information obtained initially to flexibly represent the object in a different context. In that case, the familiar object should still be recognized as familiar even when on a new background, and looking

should be directed to the novel item. This condition has been tested in a few studies in infants. For instance, Haaf, Lundy, and Codren (1996) using a preferential viewing paradigm suggested that 6-month-old infants were attending to context. They found that a change in the background context of a cue between familiarization and test decrease recognition as compared to a condition in which the context remains stable between familiarization and test. Thus, infants did not exhibit a novelty preference when the background changed but did show a novelty preference when the background remained unchanged. They concluded that context was important for very young children.

In another study with infants, Robinson and Pascalis (2004), using a similar preferential looking paradigm, tested 6-, 12-, 18-, and 24-month-old infants and found that only the 18- and 24-month old infants exhibited novelty preference for the condition in which the context changed between familiarization and test. They concluded that novelty preference as exhibited by the older infants represented flexible representation of the object across contexts. However, Robinson and Pascalis did not implement a delay between familiarization and test, they didn't use as many manipulations as Haaf and colleagues (1996), and they only measured the memory for the object in a same or different context.

In the current investigation, we tested older children (4 and 8 years of age), implemented a 5-sec delay period, tested them on the same or different context, and added a condition that assessed recognition performance when a familiar object was presented on either a familiar or novel background at test (adapted from Nemanic & Bachevalier, 2002). Our study did not find any differences in novelty preference between the conditions in which the background changed or remained the same between

familiarization and test. Novelty preference on these tasks was observed in both groups of children as well as in adults. At first glance, this would suggest flexible representation of objects across context. However, we also found that presenting a familiar image on two different test backgrounds (familiar vs. novel) did not produce the same pattern of results in children.

Instead, we found that both 4- and 8-year-old children had difficulty distinguishing the familiar from the novel image. This may suggest that the background fails to provide pertinent information when the object presented on the familiar and novel background is the same. Therefore, children may be using a different strategy to recognize the object as novel in the condition that assumes that changing the background would measure object-context relational flexibility. Presumably, children could do equally well in this condition if the initial background was not salient enough to be relevant to memory performance in children. In fact, children could be ignoring the background altogether, making this condition similar to the condition in which the background remained the same. As a result, the background might become irrelevant to support memory for the object. Adults, on the other hand exhibited a clear preference for novelty in all three conditions, suggesting that they may be able to use context in a different manner than children or that they possess the ability to not only flexibly represent an object across different contexts, but the ability to distinguish the elemental features of relational stimuli.

The aforementioned findings could also be related to some other feature of the background change condition. During the test phase of the background change condition, the novel image consisted of an entirely new background as well as a completely new

object. This manipulation creates a condition in which the novel image is completely novel (in both item and background) from what was seen before, which is not the case for either of the control conditions (in each either the object or background remained the same in the novel image). In the control conditions, however, the familiar image was presented with the same item-context configuration as in the familiarization phase.

Kirasic et al. (1980), albeit using a completely different paradigm, found that recognition memory was greater when the background and objects were completely different than when one of component of the scene (either the landmark or background context) remained unchanged. Therefore the complete novelty of the image in the background change condition could account for the current results. However, Kirasic and colleagues did not observe an age difference between the conditions in which the landmark or the context changed, whereas, in the current study we demonstrated marked differences in performance when only the context changed in the novel image. The results of Kirasic et al. could be attributed to their task, which unlike the object-context task in the current study was a scene recognition task, and which also provided several spatial cues. In addition, the differences observed in their study could be ascribed to the ages of the children tested. They tested children slightly older than both groups of children tested in the current investigation (5-year-olds and 9-10 year olds).

Our results suggest that for children, the background may not be important enough to support recognition. Haaf et al., (1996) found that habituating infants on an image resulted in context independence when subsequently tested on the background change condition. In addition, Haaf et al., (1996) and Jones, Pascalis, Eacott, and Herbert (2011) found that experiencing objects across multiple contexts resulted in robust

preference for novelty when the object was tested within a new context (a visual display or a testing room, respectively). Although, the current study did not show the objects across multiple presentations, the 10-sec familiarization period provided for children may have been enough for them to exploit only the salient features of the object and to subsequently ignore any background changes that occurred as irrelevant to the experimental task. Therefore, children could view the ‘relational’ Background Change condition, as an object memory task with no relations being formed between the object and the background during encoding.

Another explanation proposed by Jones and colleagues suggest that with age, contexts are “less likely to be bound or fused with a target item and more likely to be encoded in flexible relational associations, reducing the impact of a context shift on retention.” This reasoning can possibly explain the current findings, and extend it past infancy. However, although the youngest children tested at 4 years of age were able to exhibit recognition memory across contexts, there may still be differences in the underlying processes. Both groups of children were unable to distinguish the novel image when the object was the only component that remained stable across presentations. The results suggest however, that adults possibly form these relations at the outset and are able to distinguish the components flexibly in different situations.

Several studies concluded that early object-context relational memory abilities as measured by preferential looking could be present even in infancy (Jones et al., 2011; Richmond & Nelson, 2009; Robinson & Pascalis, 2004). For instance, Jones et al., (2011) tested infants using a VPC task in which the familiar item was paired with a novel item and tested either in the same room or in a different room. Novelty preference was

observed in 12- and 18-month-old children in both the same and new testing rooms suggesting object-context relations were apparent within the first two years of life. However, evidence in adults suggest that the flexible representation of objects across contexts is dependent on a fully functional medial temporal lobe, including the hippocampus (Pascalis et al., 2009) and damage to this area results in context-dependence, such that recognition of objects only occur when presented within the same context as was initially experienced.

### **Conclusion**

The current study aimed to investigate the development of relational memory. We tested preschool and school aged children as well as adults. We found that young children and school-aged children may still be developing relational abilities. Moreover, we observed that although rudimentary abilities to flexibly represent object-context relations may be present even in young children, they do not appear to be similar to that of adults. We also observed that spatial relational memory has a developmental trajectory that favors females in adulthood, which is in line with previous findings. Finally we found that scenes cannot enhance memory for spatial relations if those abilities are not currently fully developed. In summary, this study is essential as it allows the measurement of multiple forms of relational abilities using the same paradigm, which has previously not been explored in a visual memory task across young and older children, and adults.

### **Chapter 3: Does Damage to the Perirhinal Cortex Impact the Development of Relational Memory Abilities in Monkey?**

It has become increasingly important to study the development of the cognitive abilities typically studied in adults. The previous chapter discussed the time course of development of relational memory abilities in humans. Furthermore, relational memory can be disrupted following early trauma to the brain (i.e., developmental amnesia). Thus, it is also essential to examine the atypical development of this function. The current chapter will attempt to investigate both typical and atypical development of relational memory abilities.

The previous chapter compared relational memory in human children and adults using a purely behavioral paradigm. However, one limitation of these types of studies in humans is that we cannot manipulate underlying neural structures and can only infer the neural correlates of specific cognitive functions from a convergence of evidence from imaging, behavioral, and lesion studies. Based on some evidence for developmental amnesics and from animals with early damage to the MTL (Alvarado & Bachevalier, 2000; Alvarado et al., 2002; Blue et al., 2009; Green & Stanton, 1989; Rudy & Paylor, 1988; Vargha-Khadem et al., 1997, 2001), structures in this area likely underlie relational memory abilities throughout development. To date this notion has only been directly investigated in limited cases. In addition, these structures may mature gradually over the time course of early life, and this maturation may coincide with the emergence of early relational memory abilities (see Blue and Bachevalier, 2009; Bachevalier, 2008; Seress, 2001). In the current chapter, I will first briefly highlight the importance of MTL structures mediating relational memory abilities, specifically discuss the possible impact

of early damage to the perirhinal cortex in relational memory, and discuss the longitudinal study that attempted to elucidate its role in relational memory across development.

### **Importance of MTL in Relational Memory Abilities**

Relational memory seems to be dependent on the integrity of the medial temporal lobe (Crane & Milner, 2004; Hannula & Ranganath, 2008; Hannula, Ryan, Tranel, & Cohen, 2007; Hannula et al., 2006; Kohler, Danckert, Gati, Menon, 2005; Ryan & Cohen, 2004). However, there continues to be this ongoing debate regarding the contribution of the different MTL structures to relational memory. Specifically, the hippocampus is thought to be important for relational memory, whereas the perirhinal cortex is thought to be important for memory for object features (Eichenbaum et al., 2007). However, recent evidence suggests a greater role for the perirhinal cortex in different types of relational memory abilities.

**Perirhinal cortex and relational memory.** Recent findings have suggested that certain relational memory abilities within the spatial domain, such as object-location relations, may depend not only on the integrity of the hippocampus but also on an intact perirhinal cortex (see Aggleton et al., 2004). The perirhinal cortex (PRh) is a band of cortex situated along the ventromedial surface of the medial temporal lobe. PRh is located lateral to the rhinal sulcus and follows the extent of the sulcus from its anterior fronto-temporal border and continues a few millimeters beyond the posterior end of the rhinal sulcus. It consists of Brodmann's area 35, which sits medially, and area 36, which is larger, and sits just lateral to area 35 (Suzuki and Amaral, 2003). This structure is thought to process information regarding object features (Eichenbaum, et al., 2007) but



may also play a specific role in spatial relational memory (Aggleton et al., 2004).

Inconsistency in the participation of the PRh to spatial memory is striking. In a recent review of the literature, Aggleton and colleagues (2004) described several studies in which damage to the PRh spared spatial memory abilities (Bussey, Dias, Amin, Muir, & Aggleton, 2001; Bussey, Muir, & Aggleton, 1999; Ennaceur & Aggleton, 1997; Ennaceur, Neave, & Aggleton, 1996; Glenn & Mumby, 1998) whereas other studies reported varying degrees of impaired spatial memory following PRh damage (Gaffan & Parker, 1996; Bilkey & Liu, 2000; Liu & Bilkey, 1998a, 1998b, 1998c, 1999, 2001; Ramos & Vaquero, 2005; Wiig & Bilkey, 1994a, 1994b). For instance, Liu and Bilkey (2001) reported that PRh was critical when the position of an object was switched, and Bussey and colleagues (2001) found that the integrity of PRh was vital for learning conditional object discrimination on a task that integrated object and place information.

As previously stated, relational memory can be investigated using tasks that require *binding* and flexible representation of simultaneously presented information. Tasks that utilize object-location relations measure the ability to bind item and spatial information and have been used as meaningful measures of spatial relational memory. These types of tasks highlight the importance of the perirhinal cortex in memory for object-location relations since damage to the perirhinal cortex seem to disrupt performance (Bachevalier & Nemanic, 2008; Gaffan & Parker, 1996; Jo & Lee, 2010a). For instance, Gaffan and Parker (1996) found in a touch screen task, measuring object-in-place concurrent visual discriminations in monkeys, that performance was sensitive to both damage to the PRh as well as to the hippocampus. Bachevalier and Nemanic (2008) tested monkeys on memory for object-locations using a visual paired comparison (VPC)

paradigm (also referred to as preferential looking task) in which the subjects viewed objects in a spatial array that were either rearranged (object-location relation) or replaced (object recognition) during the test phase. In a third condition, an image was presented in a familiar and then in a novel location (spatial location) during the test phase. Monkeys with removal the hippocampus or perirhinal cortex were impaired on the object-location relation condition, but not on the spatial location condition. However, only monkeys with PRh lesions were impaired in the object recognition condition of the task.

In addition, a recent study by Jo and Lee (2010a) used an inactivation technique to investigate the involvement of PRh on an object-place relational memory paradigm in a radial arm maze. Rats that received injections of muscimol, a GABAA receptor agonist used to temporarily inactivate either the PRh or the hippocampus showed significant impairments. The deficits observed following PRh inactivation was equivalent to the deficits observed with the hippocampal inactivation in the object-place paired-associate task. Jo and Lee asserted that any disruption in the hippocampal hierarchy would equally impact tasks measuring object-location relations, since both representations of objects and place need to be sent to the hippocampus to represent a unitary event. Taken together, these results demonstrate that the perirhinal cortex might contribute in part to tasks that measure memory for spatial object-location relations.

### **Relational Memory and Development**

The aforementioned findings in humans and non-human primates highlight the importance of medial temporal lobe structures in relational memory tasks that measure object-location relations. However, very little is known about the development of memory for object-location relations across different ages. Findings largely in adult

rodent and primates have contributed to our understanding of relational memory.

However, understanding the developmental trajectory of relational memory is necessary to ascertain which underlying mechanisms could support this function throughout life.

Blue and colleagues (Kazama et al., 2003; Blue & Bachevalier, 2009; Blue et al., 2009), using the spatial VPC tasks developed for the adult monkeys (Bachevalier & Nemanic, 2008) demonstrated a protracted development of spatial memory abilities in typically developing monkeys. Memory for spatial locations seemed to emerge during adolescence (at 18 months), whereas memory for object-location relations seemed to emerge much later (after 18-24 months) and was apparent in adulthood. In addition, memory for spatial locations was only transiently disrupted by early hippocampal damage and recovered by adulthood, but memory for object-location was more permanently disrupted following early hippocampal lesions well into adulthood.

The current investigation serves two main purposes. First, we wanted to track typical development using smaller developmental time windows than was done in studies by Blue and colleagues (Kazama et al, 2003; Blue & Bachevalier, 2009; Blue, Kazama, & Bachevalier, 2009). Here, we tested monkeys at four different ages (beginning at 8 months), which were situated 6 months-12 months apart. The purpose for the smaller windows was to pinpoint a time course within which object-location relation memory emerges. We hypothesized that at the latest age tested (36 months of age), we would see an emergence of spatial relational memory abilities. The second focus of the investigation was an attempt to expand the effects observed in monkeys with adult perirhinal cortex lesions to determine whether there is a developmental role of the perirhinal cortex in memory for objects in their locations. We expected that lesions to the perirhinal cortex

would disrupt recognition of object-location relations at 36 months of age, the age at which it was expected to emerge.

## **Method**

### **Subjects**

Ten rhesus macaque monkeys (*Macaca mulatta*) of both sexes (5 females) were used in this investigation. Six monkeys received neonatal neurotoxic lesions of the perirhinal cortex (PRh) at 9-12 days of age, two monkeys received sham operations at 9-12 days of age, and two monkeys served as behavioral controls and received no surgical procedures. All groups contained equal numbers of females and males.

All animals were full-term and born at the Yerkes Primate Research Center Field Station (Lawrenceville, GA), and were brought to the Yerkes Primate Research Center Main Station (Atlanta, GA) within the first week of life. They were hand fed a diet of infant Similac formula (Abbott Laboratories, Abbott Park, IL). Monkeys were nursery reared in accordance with the procedures developed by Sackett, Ruppenthal, and Davis (2002), which included intensive human contact, behavioral testing with peers and humans, along with cognitive testing (see Goursaud & Bachevalier, 2007, for similar rearing conditions). Animals were pair housed and maintained in a 12:12 hour light-dark cycle. They were not food deprived during testing, received a diet of monkey biscuits (Lab Diet #5045, PMI Nutrition International Inc., Brentwood, MO), fresh fruit and vegetable enrichment, and water was given ad libitum. Behavioral testing began at 1.5 months of age. Each animal had been tested on several behavioral paradigms and had a history of chair training that included viewing images in a darkened room. For this study, monkeys were tested at 8 months, 18 months, 24 months, and 36 months of age. All

surgeries and experimental testing of animals in this study have been approved by the Animal Care and Use Committee of Emory University and conformed to the NIH Guide for the Care and Use of Laboratory Animals (HHS publication 85-23, 1985).

### **MRI-Guided Surgical Procedure and Lesion Verification**

All surgeries were performed under deep anesthesia using aseptic conditions at the Yerkes National Primate Research Center Main Station. Immediately preceding the surgery, Magnetic Resonance Images (MRIs) were obtained using a 3T/90cm whole-body MAGNETOM Siemens Trio scanner (Siemens Medical Solutions, Malvern, PA). Before being placed in the scanner animals were sedated, intubated with an endotracheal tube, and maintained under Isoflurane (~1%, v/v, to effect), which persisted throughout the scanning procedure. Each animal's head was shaved and an intravenous catheter was placed in the saphenous vein of the leg.

Each animal was positioned in a stereotaxic apparatus in order to maintain a fixed head position throughout the scanning and surgical procedures. Before being secured in the stereotaxic device, the animals received an application of EMLA cream (lidocaine 2.5% and prilocaine 2.5%) on the skin just under the orbits of the eyes and on the ear canals in order to reduce discomfort from the eyepieces and ear bars of the apparatus, respectively. In order to prevent ocular dryness, ophthalmic ointment was applied to the eyes. Each animal's head was then secured in a stereotaxic device (Crist Instruments Co., Inc., Damascus, MD) and centered in the MR scanner. Two sequences were performed for each subject: T1-weighted high resolutions scan on the coronal plane and a Fluid Attenuated Inversion Recovery (FLAIR) scan on the coronal plane. The high-resolution images were used to select and calculate the coordinates (anterior-posterior, medial-

lateral, and dorsal-ventral) of each injection site. Immediately following pre-surgical scanning, the MRI coordinates were transformed into stereotaxic coordinates and the stereotaxic surgeries were performed.

**Calculating injection site coordinates.** The stereotaxic coordinates were calculated using the T1-weighted high-resolution images. First, the MR image that clearly depicted the ear bars was identified, and the anterior-posterior (A/P) and dorsal-ventral (D/V) MR coordinates were recorded for the left and right ear bars. Second, the medial-lateral (M/L) coordinates were identified from the image depicting the superior sagittal sinus and the ventral tip of the third ventricle at the midline. Third, the A/P, D/V, and M/L coordinates for each injection site was recorded and then transposed into stereotaxic coordinates using the reference points of the ear bars. Three injection sites were selected two millimeters apart along the length of the perirhinal cortex.

**Lesion surgery.** Animals remained anesthetized and secured in the stereotaxic apparatus following MR scans and were immediately taken to the surgery suite to prepare for the surgical procedures. In the surgical suite, the animals' scalp was disinfected with a pre-saturated povidone-iodine sponge. In order to reduce pain, a local anesthetic (Bupivacaine 0.5%, 1mL, s.c.) was injected along the midline of the scalp (from the supra-orbital ridge to the occipital notch). For neurotoxin injection into the perirhinal cortex, consisting of Brodmann's areas 35 and 36, the skin was cut at the midline, the skin and galea were gently retracted, and the skull was exposed. Two small craniotomies were performed on each side of the midline, just anterior to Bregma and above the targeted regions. The dura was then cut to allow the 30-gauge needle of a 10 $\mu$ l Hamilton syringe held in Kopf manipulators (David Kopf Instrument, Tujunga, CA) to be lowered

at each site. Neurotoxic ibotenic acid (Biosearch Technologies, Novato, CA, 10 mg/ml in PBS, pH = 7.2) was infused bilaterally in 3 sites along each perirhinal cortex and 0.4  $\mu$ l was injected at each site at a rate of 0.2 $\mu$ l/30 sec for a total of 2.4 $\mu$ l. After each injection, the needles were left in place for three minutes to avoid retraction of the ibotenic acid along the needle track. Following all injections, the incision on the dura, galea, and skin were closed; the animal was removed from the anesthesia, and allowed recover in the nursery.

**Sham surgery.** Sham-operations consisted of bilaterally opening the skin, skull, and dura at approximately the same location as for the perirhinal cortex lesions, but no injections were performed. The dura, galea, and skin were sutured and the animal returned to the nursery to recover. Heart rate, respiration rate, blood pressure, expired CO<sub>2</sub>, and body temperature were monitored throughout each surgical procedure.

**Post-surgical treatment.** Animals were monitored and allowed to recover for approximately 10 days after surgery. All animals were maintained on the anti-inflammatory, dexamethasone sodium phosphate (.4 mg/kg, s.c.) to control swelling, starting the day before surgery until one-week post-surgery. Acetaminophen was administered four times a day for three days to reduce pain and a topical antibiotic ointment was applied to the incision daily until sutures healed.

**Post- surgical scans and lesion verification.** One week after surgery and one year after surgery, post-surgical scans were performed using T1-weighted high-resolution scans and Fluid Attenuated Inversion Recovery (FLAIR) scans. The extent of damage created by bilateral ibotenic acid injections was measured using the pre- and post-surgical

Magnetic Resonance scans. Each image slice used to estimate the lesion extent was 1mm thick. Using hypersignals seen on FLAIR images (see Figure 14, center image), the surface area (in pixels) of damage to the perirhinal cortex, as well as any unintended damage to adjacent areas (hippocampus, amygdala, entorhinal and parahippocampal areas TH/TF, areas TE, TEO and V2), were estimated with ImageJ software (Rasband, 1997). The total volume of damage in both hemispheres was calculated by summing the damage on each image and then by multiplying the sum by the image thickness. The percentage reduction of each area was calculated by dividing the total volume of observed damage in both hemispheres by the normal volume of the intended (perirhinal cortex) and unintended (other MTL) areas (obtained from the brain templates). The extent of the hypersignals identified on each 1mm slice of the MR image was then plotted onto a matching 1mm template of a normal infant rhesus macaque monkey. Figure 14 illustrates the extent of the intended lesions as well as the actual PRh lesions in a representative case.

## **Materials**

**Stimuli.** Subjects saw clipart images (Nova Development, Calabasas, CA and Microsoft, Redmond, WA) of objects (e.g. cars, hats, foods, etc.) presented on a computer using Microsoft PowerPoint presentation. All object stimuli were of similar size and color within each trial. Stimuli were trial and age unique so that no animal saw a specific stimulus in more than one trial across all ages tested.

**Apparatus.** On each day of testing, monkeys were seated in a primate chair 30cm from a video monitor in a darkened room. A computer controlled by the



experimenter displayed and sent images to the monitor. A video camera (Sony Digital8 TRV-140) was mounted above the monitor. The camera was positioned in such a way that the eyes of the monkey could be seen clearly and the monkey's eye movements could be recorded. A time/date generator, which received the camera output and provided time information during the trial, was attached to a VCR (JVC HR-S4800U). The VCR was connected to a 19" television display, which to allow the experimenter to monitor the animal's looking behavior during the task. A white noise generator was used to reduce external noise.

### **Conditions**

**Basic VPC Task.** The basic VPC task consisted of a familiarization period, which was followed by a delay period, and two test phases. During familiarization, the animal was required to look at the target stimulus for a total of 30 cumulative seconds. Subsequently, a 5-second delay period in which a black screen was present was followed by two 5-second test phases separated by a 5-second interval. In these test phases, a novel stimulus was presented together with the previously familiarized stimulus. During the first test phase, the two stimuli stayed on the screen for 5 seconds once the animal initiated looking at one of the stimuli. Following a 5-sec delay, a second 5-second test phase was presented with the left/right location of the two stimuli on the screen reversed to control for any side bias. A period of 30 seconds served as the inter-trial interval (see Figures 15-16 for basic VPC setup). A modification of the basic setup includes a single test phase in which the stimuli appear on the screen for 8 seconds (Figure 16). The general assumption of VPC task is that memory for a familiar object can be assessed by the subjects' propensity to look longer at the novel stimulus. In the experiment

described below, the stimuli were modified for each condition and 10 trials were presented for each condition.

To investigate whether early perirhinal cortex damage would affect spatial and non-spatial memory, we modified the basic VPC task to measure memory for spatial locations [VPC-Spatial-Location], memory for object-location relations [VPC-Object-in-Place]) and object recognition memory task (VPC-Object-Control; for details see Bachevalier & Nemanic, 2008).

***VPC-Spatial-Location.*** During familiarization in the *VPC-Spatial-Location* condition, one object was presented in a random location on the screen. During the test period, the same image was presented in the familiar location and also in a novel location on the screen (see Figure 17A). A single test phase of 8-seconds was used.

***VPC-Object-in-Place.*** During familiarization in the *VPC-Object-in-Place* condition, an image consisting of array of five objects on a white background appeared alone in the center of a black screen. During test, the image was presented along with a novel image, which consisted of the same array of objects but with the location of three of the objects rearranged (see Figure 17B).

***VPC-Object-Control.*** A *VPC-Object-Control* condition was used to confirm that any impairment in the Object-in-Place could not be explained by perceptual difficulties in viewing the images. Thus the familiarization phase of the control condition was similar to the familiarization phase of the VPC-Object-in-Place condition. However, during the test phase of the control task, the familiar image consisted of an array of five objects and the novel image consisted of the replacement of three of the five objects (see Figure

17C).

### **VPC Coding**

Animals were videotaped during each session and the information obtained through these videos was coded. A frame-by-frame examination of the corneal reflection of the stimuli (see for details Pascalis and Bachevalier, 1999) was used to obtain gaze information. During the familiarization phase, a single image was presented in the center of the screen and reflected on the pupils of each animal. In order for an animal to be coded as looking at the image, the image needed to fall in the center of the animal's pupil. This measure was obtained manually and in real time by the experimenter. The experimenter used a television display to view the eye movements of the animal. Whenever the image was viewed in the center of the animal's pupil, the animal was considered looking at the image in the center. Likewise, when the image fell outside the center of the animal's pupil, the monkey was not coded as looking at the image. The amount of each looking instance was obtained using a stopwatch. The experimenter measured 30 cumulative seconds of looking at the image presented during the familiarization phase.

During the test phases, the two images presented on the screen were reflected on the pupils of each animal. When the image on the animal's left was viewed in the center of its pupil, the animal was coded as looking at the image on the left side of the screen, when the image on the animal's right was viewed in the center of its pupil, the animal was coded as looking at the image on the right side of the screen. However, the animal was not considered looking at either the image on the left or the right, for instance, if both images fell in the center of the pupil (suggesting that the animal was looking in between

the pictures) or if a single image was viewed at the edge of the animal's pupil (suggesting that it was looking off the screen). A single experimenter coded all of the gaze information. The experimenter was trained on both real time and post-testing video coding procedures. The experimenter was more than 93% accurate (N = 45 trials) in coding the animals in real time and was more than 95% reliable (N = 75 trials) with other experienced observers in coding the frame-by-frame analysis of gaze direction of animals obtained from the videotapes ( $r = .99$ ,  $p < .001$ ).

### **Task parameters and statistical analyses**

Microsoft Excel 2010 (Redmond, WA) and IBM SPSS 19.0 (Armonk, NY) statistical software package were used for data reduction and to conduct all statistical analyses. An alpha level of  $\leq 0.05$  was used for all analyses.

**Behavioral Parameters.** The frame-by-frame analyses were used to quantify three behavioral parameters: 1) the time necessary to reach the 30 seconds cumulative looking at the stimulus during familiarization (referred to henceforth as *familiarization time*), 2) the total looking time, defined as the actual amount of time spent fixating the stimuli during the two test phases (hereafter referred to as *total looking time*), and 3) the percent looking time at the novel stimulus as a function of the total looking time (discussed hereafter as *novelty preference*). The two control groups (sham-operated controls and no-surgery behavioral controls) looked similarly at all stimuli as revealed by no effects of Task, no effects of Age, no Group effects and no interactions for any of the three behavioral parameters described earlier. Therefore, these groups were combined to form a single control group for all subsequent analyses.

**Familiarization and Looking Time Analyses.** Preliminary analyses investigated differences in familiarization times and total looking times between lesion groups (Neo-C and Neo-PRh) across the four ages tested (8, 18, 24, and 36 months) and across the different tasks ((VPC-Spatial-Location, VPC-Object-in-Place, and VPC-Object Control) using a  $2 \times 3 \times 4$  mixed effects ANOVA with Group as the between subjects factor and Age and Task as within subjects factors. When necessary, post hoc Bonferroni tests and paired t-tests were performed. These analyses were conducted to assess whether differences in looking behaviors between groups across the ages tested could contribute to any differences in novelty preference scores observed at any given age.

**Novelty Preference Analyses.** To investigate typical development of spatial memory and the effects of neonatal perirhinal lesions in VPC performance for each VPC version over development, comparisons were made between novelty preference scores of the monkeys with neonatal PRh lesions and that of control monkeys in each task and at each age. The lesion groups were compared using a mixed effects  $2 \times 3 \times 4$  ANOVA with Group (Neo-C and Neo-PRh) as a between subjects factor and with repeated measures for the factors Task (VPC-Spatial-Location, VPC-Object-in-Place, and VPC-Object Control) and Age (8, 18, 24, and 36 months).

When group differences and interactions were observed, the novelty preference scores of control monkeys at 8, 18, 24, and 36 months of age were analyzed separately from the PRh lesion group using a one-way ANOVA with repeated measures for Age or Task. To investigate group differences at each age, independent samples *T*-tests were performed for each task. Significant main effects of Age and Task were subjected to *post-hoc* Bonferroni tests and paired-sample t-tests. Huynh-Feldt corrections were used when

sphericity could not be assumed. For each group, mean percent of looking time at the novel were compared to chance performance (50%) using one-sample t-tests. Chance performance indicated equal looking at the novel and familiar objects and suggests no preference for either. Above chance performance indicated novelty preference whereas scores below chance indicated a familiarity preference. Finally, the novelty preference scores described above were correlated with the percent damage (intended or unintended) to each brain region using Pearson correlations.

## Results

### Preliminary Analyses

We first assessed whether there would be differences in the familiarization and total looking times between the groups.

**Viewing parameters.** Viewing parameters included the overall time required to accumulate 30 seconds of looking in the familiarization phase (familiarization time), and the total time spent looking at the two images during the test phase(s) (total looking time). Familiarization time and total looking time were recorded to account for any viewing differences between ages, comparison groups, and tasks, which may contribute to difference in novelty preference.

**Familiarization time.** No differences were observed between the control monkeys and lesion monkeys across the three tasks at any age as revealed by no Group  $\times$  Task  $\times$  Age interaction. Consequently, no main effect of Group, no effects of Task or Age, and no interactions were found. Animals in the control and PRh lesion groups took a relatively equal amount of time to familiarize on the single image during the

familiarization phase in the Spatial-Location, Object-in-Place, and Object-Control task (see Table 3).

**Total looking time.** A Group  $\times$  Task  $\times$  Age interaction was observed for total looking time ( $F_{6, 48} = 9.649, p < .001, \eta^2 = .547$ ). Total looking time decreased with age in both controls and lesion monkeys for the VPC-Object-in-Place and VPC-Object-Control tasks but not for the Spatial-Location task. An effect of age was observed for the VPC-Object-in-Place task ( $F_{\text{Huynh-Feldt}} = 19.953, p < .001, \eta^2 = .714$ ) and pairwise Bonferroni comparisons revealed monkeys looked longer at the two images during test at 8 months of age than at 18, 24, and 36 months of age (all  $p$ s  $< .05$ ). No group differences and no interactions were observed for the VPC-Object-in-Place task. A Group  $\times$  Age interaction was observed for the VPC-Object-Control task ( $F_{3, 24} = 3.134, p = .044, \eta^2 = .281$ ). In this task, both control and lesion monkeys looked significantly longer at the two images in the test phase at 8 months of age than at 36 months of age ( $p = .032$ , and  $p = .024$ , for control and lesion monkeys, respectively). However, control monkeys also spent more time fixating the images in the test phase at 8 months as compared to 18 months ( $p = .032$ ), and at 18 months compared to 36 months ( $p = .039$ ). No between group differences were observed for the Object-Control task. See Table 4 for total looking times.

**Percent looking at novel.** The percentage of time looking at the novel image as a function of the total looking time at test (percent looking at novel) represents memory performance on the VPC tasks. Chance performance, which is defined as equal looking times between the two images during test, was set at 50%.

## **Development of Spatial Memory**

The preference for novelty was expected to change based on the lesion, the age tested, and the type of task used. Briefly, we predicted a delayed emergence of spatial memory as measured by the VPC-Spatial Location and VPC-Object-In-Place tasks. Therefore, animals should not show robust novelty preference very early in development but as they develop, their performance on spatial memory tasks should improve. Based on evidence from our previous studies (Blue and Colleagues, 2009a, b; Kazama et al, 2003), we also predict that memory for spatial locations should emerge prior to memory for spatial relations. Furthermore, we hypothesized that damage to the perirhinal cortex early in development would have a lasting detrimental effect on spatial relational memory (as measured by the Object-In-Place task) and that this effect would be apparent relational memory abilities mature.

**VPC-Spatial-Location.** The VPC-Spatial-Location task was used to measure memory for the location of an object after it shifted its position. Overall, as the monkeys matured between infancy and adolescence, memory performance increased ( $F_{3, 24} = 5.493$ ,  $p = .005$ ,  $\eta^2 = .407$ ). At 8 months of age, monkeys looked significantly less at the novel image than at 36 months ( $p = .036$ ). Also at 8 months of age, control monkeys and those with neonatal lesions to the perirhinal cortex looked equally at the novel and familiar images during the test phases, therefore their performance scores did not differ from chance. However, as they matured performance scores differed significantly from chance for both group Neo-C (18 months:  $t(3) = 15.195$ ,  $p = .001$ ; 24 month:  $t(3) = 6.458$ ,  $p = .008$ ; and 36 months:  $t(3) = 3.544$ ,  $p = .038$ ) and group Neo-PRh (18 months:  $t(5) = 3.820$ ,  $p = .012$ ; 24 month:  $t(5) = 6.671$ ,  $p = .001$ ; and 36 months:  $t(5) = 4.489$ ,  $p <$



.006). The performance scores of control monkeys did not differ from those of monkeys with neonatal lesions at any age. Therefore, no main effects of Group and Group  $\times$  Age interaction were observed. See Figure 18 novelty preference scores for the VPC-Spatial-Location task.

**VPC-Object-in-Place.** The VPC-Object-in-Place was used to measure memory for object-location relations or spatial relational memory. During the test phases of this task some of the objects within a spatial array were rearranged. Similar looking patterns were observed during the two retention phases in the VPC-Object-in-Place task between group Neo-C and group Neo- PRh at all ages. No main effects of Age, Group, and no Group  $\times$ Age interaction were observed. The novelty preference scores for control monkeys did not differ from chance at any of the ages tested (see Figure 19). Animals with perirhinal cortex lesions were above chance only at 8 months,  $t(5) = 5.731$ ,  $p = .002$  but their performance scores did not differ from chance at any of the other ages (all  $p$ s  $> .05$ ). While both groups exhibited similar looking patterns across each age, only those with early perirhinal lesions exhibited above chance memory performance scores, and interestingly, only at 8 months of age.

### **Development of Object Recognition Memory**

Based on evidence from a number of developmental studies (Blue and colleagues, 2009a, b), we hypothesized that monkeys should show robust performance on the non-spatial object recognition task (VPC-Object-Control) even at the earliest ages and that performance should remain stable throughout development.

**VPC-Object-Control.** The VPC-Object-Control task measures object recognition memory and was used to ensure that any impairment observed in the VPC-Object-in-Place task could not be attributed to the complexity of the spatial arrays. The arrays were similar in these two tasks; however, during the test phases of the VPC-Object-Control task some of the objects were replaced instead of rearranged. Generally, monkeys looked longer at the novel image during the two test phases in the VPC-Object-Control task (see Figure 20). For both the control and lesion groups, performance scores differed from chance at all of the four ages tested (all  $p$ s < .05). Although, monkeys with perirhinal cortex lesions exhibited robust novelty preference scores, at 36 months of age their scores were significantly different from control monkeys,  $t(8) = 3.294$ ,  $p = .011$ .

#### **VPC-Object-in-Place/ VPC-Object-Control comparison**

A significant main effect of Task was observed for control monkeys ( $F_{1,3} = 121.692$ ,  $p = .002$ ,  $\eta^2 = .976$ ) and lesion monkeys ( $F_{1,5} = 23.091$ ,  $p = .005$ ,  $\eta^2 = .822$ ). Novelty preference scores were lower for the VPC-Object-in-Place task than for the VPC-Object-Control task in control animals as well as lesion animals (see Figure 21). Paired t-tests revealed significant differences between novelty preference scores for control monkeys [at 8 months:  $t(3) = -9.165$ ,  $p = .003$ ; 24 months:  $t(3) = -8.708$ ,  $p = .003$ ; and 36 months:  $t(3) = -3.913$ ,  $p = .030$ ] and for perirhinal lesion monkeys [at 18 months:  $t(5) = -3.231$ ,  $p = .023$ ; 24 months:  $t(5) = -5.442$ ,  $p = .003$ ; and 36 months:  $t(5) = -3.839$ ,  $p = .012$ ]. Lesion animals and control animals at 8 months and 18 months of age, respectively, showed a slightly lower novelty preference scores in the VPC-Object-in-Place task as compared to the VPC-Object-Control task [Neo-PRh: 8 months,  $t(5) = -$

2.362,  $p = .065$ ; Neo-C: 18 months,  $t(3) = -3.135$ ,  $p = .052$ ], however these differences did not reach significance.

### **Extent of Lesion Analysis**

There were very few relations between the extent of perirhinal cortex lesions and novelty preference scores. We found some unexpected results with regards to lesion extent. For instance, the extent damage to the perirhinal cortex was positively correlated to performance on the VPC-Object-Control task at 8 months of age (bilateral damage:  $r = .833$ ,  $p = .040$ ) and 18 months of age (left perirhinal cortex:  $r = .88$ ,  $p = .021$ ). Therefore, unexpectedly, greater perirhinal cortex damage was related to higher novelty scores on this task. On the other hand, the percentage of damage to the right perirhinal cortex was negatively correlated with novelty preference scores at 36 months of age ( $r = -.822$ ,  $p = .045$ ) in the VPC-Object-in-Place task. Therefore, more damage at 36 months corresponded with lower performance scores. Interestingly, unintended damage to the entorhinal cortex corresponded to higher novelty preference score on the VPC-Spatial-Location task at 18 months of age (left ERC:  $r = .824$ ,  $p = .044$ ) and lower novelty preference scores on the VPC-Object-Control task at 8 months of age (bilateral ERhs:  $r = -.812$ ,  $p = .0497$ )

### **Chapter Discussion**

The goal of the current chapter was to investigate the typical development of memory for spatial relations and to assess the effects of early damage to the perirhinal cortex on supporting this type of memory throughout life. The modified versions of the VPC tested recognition memory for spatial locations, spatial relations, and objects. The findings from the current study suggests that the ontogeny of object recognition memory

may occur first, followed by the emergence of recognition memory for spatial location, then the protracted development of object-location relations.

### **Relational Memory Development**

Spatial memory shows a protracted developmental trajectory as measured by the two spatial tasks used in the current investigation. In the spatial location task, above chance performance was observed at 18 months of age. This coincided with previous findings, which postulated the occurrence of neural development between 8 and 18 months of age to support later emergence of recognition of spatial locations (Blue, Kazama, & Bachevalier, 2009). In addition, Blue and colleagues (2009a, b) found that recognition of object-location relations also improved with age, where significant increases in memory were only observed in 5-6 year old monkeys. In that investigation, we argued that the ontogeny of object-location relations was protracted in nature and that clear emergence of memory for object-location relations occurred some time between 18 months and 5 years of age. In the current investigation, we failed to demonstrate a significant improvement in recognition memory for object-location relations even at 3 years of age in control monkeys. However, since the monkeys tested in the previous study were older, we would expect to see improvements occurring some time between 3 and 5 years of age. Subsequent testing of control monkeys on these versions of the VPC will help find a smaller time window within which to examine the emergence of object-location relations in monkeys.

### **Medial Temporal Lobe and Development of Relational Memory**

Interestingly, the different developmental trajectory of memory for spatial location and object-location relations may point to differences in the mechanisms

underlying performance in these tasks. Whereas some spatial abilities could be supported by early development of the medial temporal lobe, refinements in the neural connections in this area are likely to support spatial abilities requiring the relation of object and location information, for example. In fact, studies have suggested an improvement of relational abilities across development (Townsend et al., 2010; Blue & Bachevalier, 2009).

Alvarado and Bachevalier (2000) suggested that whereas some hippocampal-dependent memory functions can emerge before full maturation of the hippocampus, other functions require it to be fully developed. The maturation of the tri-synaptic pathway of the hippocampus or quite possibly the development of other related structures (i.e. perirhinal cortex, entorhinal cortex, parahippocampal cortex, or prefrontal cortex) could play a role in supporting the different types of spatial memory abilities (Alvarado & Bachevalier, 2000). With regards to the latter view, performance on the spatial location task may rely in large part on another structure in the medial temporal lobe, namely the parahippocampal cortex. Indeed, there is evidence for the critical role of parahippocampal cortex in spatial memory via the dorsal or “where” visual stream (see Eichenbaum et al, 2007; Buffalo et al, 2006; Ploner et al, 2000). Bachevalier and Nemanic (2008) found that damage to parahippocampal cortex resulted in impairment on both spatial tasks (Spatial-Location and Object-in-Place).

Maybe full development of the pathway between the hippocampus and cortical areas is necessary to support object-location relations, whereas a less mature pathway can support memory for spatial locations. An alternative structure that may play a role in the emergence of object-location relations is the prefrontal cortex. Structures in the medial

temporal lobe are intimately connected with different regions of the prefrontal cortex and information is fed both forward and backwards through the pathway connecting these areas (Gaffan & Parker, 1998; Schott et al., 2011).

In addition, it is well known that the prefrontal cortex has a long developmental course (Fuster, 2008). Therefore, it is quite possible that the maturation of the connections between the medial temporal lobe and maturation in specific regions of the prefrontal could impact the development object-place spatial relations. While this relation has not been directly studied in monkeys, in a recent electrophysiology study by Kim, Delcasso, and Lee (2011), rats were trained on an object-in-place task in a radial arm maze. Within the behavioral task, animals were required to connect an object to a particular arm to correctly displace the object and retrieve a food reward. The researchers recorded from the hippocampus and prefrontal cortex and found differential processing of object-in-place information between these regions. They observed a change in firing patterns in both the hippocampus and prefrontal cortex when the animals transitioned from a position based strategy to one that related the objects to the correct location. One interesting finding was that whereas the hippocampus increase firing in preferred fields in a single arm of the maze, the activity in the prefrontal cortex was modulated by similar events occurring in different arms of the maze. This study was conducted in adult rodents. It would clarify much in terms of neural processing if these types of studies could be performed with younger rodents.

We observed changes in visual behaviors across development (i.e. increase in total looking time) in control monkeys, which may have influenced their memory performance throughout development. One might argue that the youngest monkeys have

poorer memory performance not because of poorer spatial abilities, but rather because of poorer visual abilities. Thus, during infancy, monkeys may not only require more time to inspect objects and extract visual information from them, but they also may be unable to distinguish minute changes between the familiarized and manipulated images regardless of whether the change be in location or in the physical attributes of the image. This is an unlikely explanation when considering the comparisons of memory performance between the Object-in-Place and Object Control tasks. For both tasks each trial displayed an array of five objects, hence used a similar level of visual complexity, however, a propensity to attend to the novel image was clearly present in infants for the Object Control task but not for the Object-in-Place task.

These findings suggest that the differences in the infants' performance on the two tasks could be related to differences in cognitive processes rather than differences in visual abilities. For instance, the Object-Control task replaces three objects and may be based on a familiarity/novelty judgment (e.g., object recognition memory) since the majority of the objects was replaced. By contrast, in the new display of the Object-in-Place task, all five objects are familiar, so judgments cannot solely be based on memory for the familiar objects but rather on memory of the spatial relationships between the familiar objects (e.g., memory for place relations). Thus, the data suggest that memory based on familiarity/novelty judgment appear to be present in early infancy, whereas spatial memory has a more protracted development in monkeys, with memory for spatial location emerging earlier than memory for spatial relations. The data also suggests that the delayed emergence of recognition memory in spatial tasks cannot be attributed to poor visual abilities, because other forms of recognition memory are present very early in

development. In the current study, we observed robust recognition memory for objects very early in development (i.e., in infancy). This is consistent with previous literature (see Bachevalier, 2008; Bachevalier & Vargha-Khadem, 2005).

### **Perirhinal Cortex and object-location relations**

There is a wealth of evidence regarding the role of the perirhinal cortex in object recognition memory (for review see Eacott & Gaffan, 2005; see also Aggleton & Brown, 2005; Buckley, 2005; Holdstock, 2005), however, very little is known about the contribution of the perirhinal cortex to spatial memory in primates. Only a few studies have found deficits in spatial memory following perirhinal cortex damage in adult monkeys (Bachevalier & Nemanic, 2008; Murray et al, 1998). One study by Jo and Lee (2010a), which used an inactivation procedure to temporarily lesion the perirhinal cortex and hippocampus in rodents, suggested a critical role for encoding but not retrieving object-location relations. Briefly, the rats were trained to link an object to a location in a radial arm maze and following perirhinal cortex lesions, they were able to perform well on the object-location relation that they learned prior to their surgeries (intact retrieval). Contrarily they found that inactivation of the perirhinal cortex prior to training disrupted new learning of object-location relations (disrupted acquisition).

Furthermore, in Bachevalier and Nemanic (2008) only performance on the spatial relational task, but not on the other spatial (i.e., spatial location) task was disrupted following perirhinal cortex damage that occurred in adulthood. In another, Buffalo, Bellgowan, and Martin (2006) investigated the role of medial temporal lobe structures in object and spatial recognition memory. In their study, 11 participants viewed a series of six colored stimuli and were asked to memorize the object or the location of the object.



During the recognition test, the participants were shown either three new objects or the same object in three new locations and were required to make judgments as to whether the object or location was old or new. fMRI analyses revealed that the perirhinal cortex was equally involved in the encoding of objects and their location. These authors concluded that the perirhinal cortex played a distinct role in both object and spatial recognition memory.

These results do not clarify to what degree perirhinal cortex contributes to the ontogeny and functioning of spatial memory. Contrarily, it suggests that the perirhinal cortex may support spatial memory when an object is to be associated with its location. Since the prevailing assumption is that the perirhinal cortex is important in object-object relations or object recognition memory, the field has failed to address what functions other than object recognition may be disrupted as a result of early damage to the perirhinal cortex.

In the current investigation, we assessed the effects of neonatal lesions of the perirhinal cortex on the development of spatial abilities and whether these early lesions resulted in pervasive spatial memory loss. We could not elucidate the role of the perirhinal cortex in this current investigation. Therefore, future studies should investigate the effects of early damage to the perirhinal cortex on object-location relations, and whether any observed effects could be related to the age/time of lesion.

### **Object Recognition Memory**

One interesting finding observed in this study was the difference between the group with perirhinal cortex lesions and the control monkeys in the object recognition memory control task at 36 months of age. In the same instance, the monkeys with perirhinal cortex

exhibited scores above chance. These findings suggest that although object recognition memory is available early development there could be a time when the perirhinal cortex matures to take over this function. This could be driving the differences observed in the task measuring object recognition memory. However, it is with caution, that I make this assumption since the current study did not find pervasive differences in object memory abilities over the developmental ages in monkeys with perirhinal cortex lesions.

One study found that high levels of stress from early maternal and social deprivation resulted in an increase of acetylcholine activity in the hippocampus and perirhinal cortex, which was accompanied by deficits in memory performance in the novel object recognition task (Novel Object Recognition task; described by Ennaceur and Delacour, 1988) and in a social recognition task later in life (Benetti, Mello, Bonini, Monteiro, Cammarato, and Izquierdo, 2009). This study and others suggest the long-term deleterious effects of early insult to the medial temporal lobe structures.

Ontogeny of novel object recognition was demonstrated very early in postnatal development in rodents and primates. For instance, Reger, Hovda, and Giza (2009) using the novel object recognition task, found that object recognition was present in typically developing rodents. Even weanlings, at postnatal days 20-23 were able to exhibit object recognition at 0.25 and 1 hour, whereas older animals (juveniles: P29- 40, and young adults: P50+) were able to demonstrate more long-term object recognition memory. In monkeys, robust object recognition memory was observed as early as 1.5 months for up to 120 seconds as measured by a visual preferential looking paradigm, but was impaired at 18 months of age following with early lesions to the hippocampus (Zeamer, Heuer, & Bachevalier, 2010).

## **Importance of Postnatal Brain Development**

It is now understood that in primates, much of the structural development of the medial temporal lobe occurs prenatally (Seress, 2001; Alvarado & Bachevalier, 2000). However, this knowledge does nothing to detract the importance of postnatal development of this area. Experiences occurring after birth largely impacts brain organization and connectivity (Stiles, 2008). In fact, Stiles contend the role of experience in postnatal development is highlighted in studies examining the effects of early brain damage (Bachevalier & Mishkin, 1994; Goldman, 1974; Goldman and Galkin, 1978; Goldman & Rosvold, 1972; Goldman, Rosvold, & Mishkin, 1970a, b; Kolb, 1987; Kolb & Elliot, 1987; Kolb, Holmes, & Whishaw, 1987; Kolb & Tomie, 1988; as cited in Stiles, 2008). These studies, she argues, provide evidence for the pliable nature of the developing brain. In addition, she explained that the early abilities examined after perinatal damage were preserved in adulthood. In accordance with the evidence provided by Stiles, the current investigation of early, circumscribed injury to the perirhinal cortex seemed to produced very little pervasive deficits in memory, which could support the notion of plasticity in the developing brain (see de Haan et al, 2006; Lavenex et al, 2007b).

Namely, the only difference in performance between typically developing monkeys and those with brain lesions occurred at three years of age and only in recognition memory for objects. However, memory for spatial relations as well as for objects was compromised in adults with circumscribed perirhinal cortex lesions (Bachevalier & Nemanic, 2008). Furthermore, Stiles (2008) suggested that the immature brain is different from the mature brain in its ability to reorganize in order to support the

functions that would typically be subserved by the damaged areas. Other researchers have also forwarded this idea

### **Conclusion**

In summary, the findings show that there is a very clear delay in emergence of spatial memory in non-human primates. In addition, it also suggests that spatial abilities follow different time course of development when relying on different mechanisms and tapping different cognitive processes. In addition, we cannot discount perirhinal cortex in object recognition memory, since this area is where the most striking impairments are found, whereas there has been equivocal findings suggesting a role for the perirhinal cortex in object-place relational memory.

## **Chapter 4: General Discussion**

In this set of experiments, we assessed the development of relational memory across domains. The current study had two main aims: (1) to track the developmental trajectory of different types of relational memory in two different primate species and (2) to evaluate the long term effects of early damage to the medial temporal lobe (i.e., perirhinal cortex) occurring within several weeks after birth. These aims were achieved by using the visual paired comparison task, which has been shown across species to reliably measure different memory abilities and is reliant on an intact medial temporal lobe (Bachevalier & Nemanic, 2008; Munoz et al., 2011; Pascalis et al, 2009). This paradigm has also been used across development in both humans and non-human primates (Blue & Colleagues, 2009a, b; Haaf et al., 1996; Jones et al, 2011; Richmond & Nelson, 2009; Robinson & Pascalis, 2004).

Development of relational memory has been studied in both humans and non-human animals (Blue & Colleagues, 2009a, b; Galea et al, 1994; Green & Stanton, 1989; Haaf et al., 1996; Jones et al, 2011; Overman et al, 1996; Richmond & Nelson, 2009; Robinson & Pascalis, 2004; Rudy & Paylor, 1988; Rudy et al, 1987; Sluzenski et al, 2006) albeit not extensively in either populations. Therefore the current study aimed to investigate the development of different relational memory in order to determine whether they followed the same trajectory. What we found was that overall relational abilities seemed to have a very long development.

### **Object-Location Relations**

In human children, spatial relational memory abilities relying seem to develop late, generally after age 7 (Lehning et al., 1998, 2003; Overman et al, 1996; Pentland et

al, 2003). In non-human primates, a previous study by Blue and Bachevalier (2009) found that spatial relational memory abilities were not fully mature even in adolescence, suggesting an even later development which may continue well into adulthood. The current findings in both studies suggest a very late development of spatial relational memory as measured by the conditions in which the objects were rearranged within a spatial array. Pre-school children did not exhibit clear memory for spatial relations. Furthermore, even school-aged children had difficulties. Adults, however, appeared to have trouble in their memory for objects rearranged in an array only when multiple arrays were present. Moreover, these difficulties were only observed for males. However, when the objects shifted positions within a scene, adults regardless of gender exhibited clear memory for the spatial relations.

These patterns of results imply that memory for spatial relations take a long time to mature, and may be related to development in the prefrontal cortex, which continues to develop well into adulthood and has been shown to support spatial relational abilities (Alvarado & Bachevalier, 2000; Kim, Delcasso, & Lee, 2011). The pattern in young adults are in line with findings that women have better memory for object locations within arrays than men (Voyer et al., 2007), whereas girls and boys under age 13 do not differ.

**Potential differences in processing.** In addition, the differences observed between the rearrangement (experimental) and replacement (controls) conditions of the spatial relational task may be related not to the relational/non-relational properties, but to some fundamental differences in the processing demands in these tasks. For instance, the object replacement conditions may contain a single unit of to-be-processed information,

the identity of the objects, whereas, the rearrangement conditions, may contain two units of to-be-processed information, the identities of the objects and the relative location of the objects. Therefore, the rearrangement condition may be providing an additional challenge to the viewer making it a more demanding task. The current findings that novelty preference for the rearrangement conditions was lower than novelty preference for the replacement conditions could be due to these inherent differences.

However, the initial processing of the information was similar in both the rearrangement and replacement conditions. Essentially the only difference was whether three of the objects were replaced or rearranged during the subsequent presentation. Furthermore, the novel stimuli in both types of conditions still contained old information, two objects within previously experienced locations, which could potentially make both tasks relational. Therefore both the rearrangement and replacement conditions could potentially have multiple units of to-be-processed information, old information as well as new information, and location information. Another plausible explanation is that the replacement conditions may measure object-object relations, which may be at a lower level of processing than the object-location relations in the replacement conditions. Even still, it could be possible that the object replacement conditions do not measure relations at all.

It is currently unclear what might be underlying the differences observed in the rearrangement and replacement conditions and whether these differences can be contributed to relational properties of the tasks, especially because the definition of relational memory is imprecise. The current working definition is that there should be some combination of stimulus elements and that these elements are flexibly held and

represented across episodes or events (Cohen et al., 1997; Cohen & Eichenbaum, 1993). This broad definition seems to fit both the rearrangement and replacement conditions making it difficult to suggest that one is relational whereas the other is not, or to ascertain why there might be processing differences.

### **Object-Context Relations**

The current findings suggest that in humans, memory for object-context relations appeared to develop fairly early. In fact, a number of researchers have argued this using the visual paired comparison paradigm (Jones et al., 2011, Robinson & Pascalis, 2004). However, with further inspection, we found that children might be processing object-context relations in a different way than adults. It appeared that children might have been utilizing object information more than context information, whereas, adults may be more able to make memory judgments based on object-context relations. Conversely, the initial findings of Haaf et al. (1996) suggest that the object-context features are by default bound yet inflexible in infants. It is important to note that the age tested in the present study was far from the 6-months old tested by Haaf and colleagues.

Support for early development of object-context relations come from Robinson and Pascalis, who tested older infants and toddlers, and suggested that object-context flexibility develops around 18-months. However, Robinson and Pascalis, failed to separate memory for the object from memory for the background. We added a condition that measured these elements separately and found that children did not exhibit memory for the background when the object remained the same. Therefore, we concluded that the robust performance on the background change condition could be attributed to children utilizing information about changes in the object features (such that they are able to



detect the novelty of the object), hence not needing the background information. Thus, the task demands would appear similar to the condition in which the background remained the same.

### **Eye Movements and Processing**

Measuring changes in eye movements is accepted as a sufficient, yet indirect measure of memory and has been linked to underlying memory processing (Cohen et al., 1997). Many studies, including the current investigation, measure novelty preference as the time spent attending to a novel stimulus as a proportion of time spent attending to all stimuli presented (Bachevalier & Nemanic, 2008; Pascalis et al, 2009; Richmond & Nelson, 2009; Robinson & Pascalis, 2004). Research findings have suggested that prior familiarity with or exposure to stimuli could change eye movement patterns during subsequent encounters (Cohen et al., 1997). Cohen and colleagues argued that they were able to measure the nature of behavior during subsequent encounters by measuring the number and duration of fixations to target stimuli, by utilizing predictability measure of whether the stimuli was previously encountered, and by measuring reaction times to memory questions. They found that individuals without memory impairments were able to distinguish differences between new and old items, and between unchanged old items and manipulated old items, in which relations among items had changed. In addition, other researchers have concluded that eye movements provide a sensitive measure of previously experienced item relations even when they cannot be explicitly recalled (Hannula et al, 2009).

In the series of studies in this paper, we utilized overall looking times as a measure of memory for objects, object arrays, and objects presented within contexts.

Whereas, measurements of looking times may provide valuable information concerning changes in the eye movement patterns of individuals who encounter stimuli with prior familiarity, it is not able to fully address questions of processing within the preferential viewing task or changes in viewing patterns that may occur over time. It also cannot address the point in the processing of the stimuli at which a sense of recognition of a stimulus occurs; whether it happens rapidly during the subsequent encounter or whether it takes some time. Indeed, previous research demonstrated relatively rapid processing of relations using eye movement data, suggesting that recognition might occur within the first 1000ms of stimulus presentation (Richmond & Nelson, 2009). Therefore, utilizing sensitive time-course related measurements rather be more suitable for understanding how different types of relational memories are processed over time than overall viewing behaviors. Conversely, viewing behaviors in the current study was able to provide information on whether individuals are generally identify changes in the relations of previously encountered stimuli.

### **Early MTL Damage and Relational Memory**

This paper is one of the first to investigate early lesions to a medial temporal lobe structure outside of the hippocampus in primates. Although the perirhinal cortex has recently received heavy interest in the memory literature, due to its role in object recognition and perception (Buckley, 2005; Holdstock, 2005; Murray, Bussey, & Saksida, 2007), early lesions to this area has not been studied. Many cases of damage to the medial temporal lobe include pronounced damage to the parahippocampal gyrus (Alessio et al., 2006; Scoville & Milner, 1957; Zola-Morgan, Squire, & Amaral, 1986), which includes the perirhinal cortex. Consequently, many cases of early and long-term

temporal lobe epilepsy show damage to the perirhinal cortex (Alessio et al, 2006). Furthermore, some researchers have reported the deficits in memory following selective perirhinal cortex damage, may be more detrimental than selective hippocampal lesions (for example see Murray, Baxter, & Gaffan, 1998). However, the contributions of the perirhinal cortex to relational memory have not been extensively investigated (Gaffan & Parker, 1996; Jo & Lee, 2010a, b; Bachevalier & Nemanic, 2008). Therefore, the current investigation is important as it attempted to fill a gap within the literature by evaluating both the development and neural substrates (outside of the hippocampus) underlying the development of relational memory.

We can conclude from the findings that relational memory abilities appear to have some sort of protracted development, even if the trajectory is different in each. However, the roles of the underlying neural structures are still elusive. In the current investigation, relational memory developed so late in non-human primates that we were unable to measure the developmental trajectory past 3 years of age. The late development of the tri-synaptic pathway of the hippocampus might be contributing to spatial relational memory abilities (Alvarado & Bachevalier, 2000). Furthermore, the connections between the hippocampus and neocortex surrounding it (which includes the perirhinal cortex) may still be developing after age 3 in monkeys. Even still, we cannot preclude the development of the connections between the medial temporal lobe structures and the prefrontal cortex in supporting relational memory (see Alvarado & Bachevalier, for more complete argument). In order to clarify the development of neural structures underlying relational memory future research must target these areas early in development and track their progression (structural, as well as functional).

## **Conclusion**

Understanding the development and neural correlates of relational memory are especially important since relational abilities are impaired in many disorders. The medial temporal lobe is especially susceptible to early insult from ischemic events and traumatic brain injuries (Vargha-Khadem, personal communication). These events occur more often than commonly acknowledged and can be detrimental throughout life.

Developmental amnesia is only one example of early insult that results in long term memory deficits. Another such example is temporal lobe epilepsy. Abnormalities in the medial temporal lobe (which can result in disorders like autism, schizophrenia, Alzheimer's) occurring during development may also impact relational memory abilities.

Even still, developmental changes in this area occur throughout life. Therefore, understanding how relational memory processes further differ in younger and older adults can provide insight into understanding what sorts of changes could be occurring in the brain during the latter part of development. Simply put, we still have a great deal to do in order to understand the development of relational memory as well as the neural structures that support this process throughout life.

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Table 1

*Average Familiarization Times across Tasks*

Ages	Object-Context Relation Conditions			
	Background Change	Novel Object	Novel Background	Mean
4-Year-Old	6.29(.85)	5.82(1.02)	6.04(1.20)	6.07(1.12)
8-Year-Old	7.15(1.35)	6.74(1.44)	6.68(1.16)	6.86(1.11)
Adult	8.19(1.21)	8.15(1.30)	8.04(1.21)	8.13(1.11)

Ages	Object -Location Relation Conditions		
	Object-in-Place	Object-Control	Mean
4-Year-Old	7.04(1.36)	7.09(.95)	7.07(1.12)
8-Year-Old	7.54(1.24)	7.72(1.26)	7.67(1.12)
Adult	8.30(1.30)	8.46(.98)	8.38(1.03)

Ages	Object-Location within Semi-Naturalistic Scenes Condition		
	Object Rearrangement	Object Replacement	Mean
4-Year-Old	6.66 (1.27)	6.78(1.48)	6.72 (1.36)
8-Year-Old	7.57 (1.29)	7.57 (1.49)	7.57 (1.37)
Adult	8.68 (.85)	8.36 (1.18)	8.52 (1.03)

*Note:* Standard deviations are in parentheses. Mean – average across tasks for each age.

Table 2

*Average Total Looking Times across Tasks*

Ages	Object-Context Relation Conditions			
	Background Change	Novel Object	Novel Background	Mean
4-Year-Old	6.29 (.87)	5.97(1.20)	6.00(1.13)	6.08(1.09)
8-Year-Old	6.67 (1.33)	6.45(.94)	6.49(1.28)	6.55(1.08)
Adult	8.09(1.33)	7.79(1.40)	7.97(1.31)	7.96(1.14)

Ages	Object -Place Relation Conditions		
	Object-in-Place	Object-Control	Mean
4-Year-Old	6.57(.83)	6.75(1.20)	6.68(.90)
8-Year-Old	6.83 (1.22)	7.60(1.00)	7.22(.90)
Adult	7.99 (.93)	8.45(.94)	8.22(.89)

Ages	Object-Location within Semi-Naturalistic Scenes Condition		
	Object Rearrangement	Object Replacement	Mean
4-Year-Old	5.76 (1.11)	5.76 (1.31)	5.76 (1.20)
8-Year-Old	6.97 (1.32)	7.28 (1.33)	7.12 (1.32)
Adult	8.73 (.80)	8.51 (1.00)	8.62 (.90)

*Note:* Standard deviations are in parentheses. Mean – average across tasks for each age.

Table 3

*Familiarization Time by Task, Group, and Age*

Group/Case	Spatial Location			
	8 Months	18 Months	24 Months	36 Months
Neo-C 1	66	115	73	130
Neo-C 2	88	160	75	122
Neo-C 3	123	91	75	77
Neo-C 4	289	84	81	76
<i>Mean</i>	<i>142</i>	<i>113</i>	<i>76</i>	<i>101</i>
Neo-PRh 1	152	84	80	99
Neo-PRh 2	306	271	68	96
Neo-PRh 3	74	121	96	122
Neo-PRh 4	93	91	65	71
Neo-PRh 5	126	95	67	66
Neo-PRh 6	75	126	93	84
<i>Mean</i>	<i>138</i>	<i>131</i>	<i>78</i>	<i>90</i>
Group/Case	Object-In-Place			
	8 Months	18 Months	24 Months	36 Months
Neo-C 1	84	111	96	110
Neo-C 2	81	170	81	138
Neo-C 3	104	139	104	66
Neo-C 4	234	126	86	83
<i>Mean</i>	<i>126</i>	<i>136</i>	<i>92</i>	<i>99</i>
Neo-PRh 1	81	114	116	158
Neo-PRh 2	233	146	73	108
Neo-PRh 3	104	155	114	142
Neo-PRh 4	69	76	55	72
Neo-PRh 5	80	76	67	61
Neo-PRh 6	69	94	120	86
<i>Mean</i>	<i>106</i>	<i>110</i>	<i>91</i>	<i>104</i>
Group/Case	Object-Control			
	8 Months	18 Months	24 Months	36 Months
Neo-C 1	64	117	72	112
Neo-C 2	61	126	96	134
Neo-C 3	101	86	96	69
Neo-C 4	228	120	99	87
<i>Mean</i>	<i>114</i>	<i>112</i>	<i>91</i>	<i>100</i>
Neo-PRh 1	101	109	65	92
Neo-PRh 2	195	134	81	123
Neo-PRh 3	86	149	97	117
Neo-PRh 4	52	67	63	73
Neo-PRh 5	59	73	70	58
Neo-PRh 6	67	81	81	66
<i>Mean</i>	<i>93</i>	<i>102</i>	<i>76</i>	<i>88</i>

Table 4

*Total Looking Time at Both Images by Task, Group, and Age*

Group/Case	Spatial Location			
	8 Months	18 Months	24 Months	36 Months
Neo-C 1	3.7	2.4	2.0	3.0
Neo-C 2	3.8	1.9	2.0	2.4
Neo-C 3	3.2	3.1	2.9	3.4
Neo-C 4	2.5	2.4	2.3	2.1
<i>Mean</i>	3.3	2.5	2.3	2.7
Neo-PRh 1	2.2	4.1	3.6	4.7
Neo-PRh 2	2.2	1.5	2.9	2.5
Neo-PRh 3	3.2	2.2	2.7	2.0
Neo-PRh 4	3.3	2.1	2.2	3.2
Neo-PRh 5	3.6	2.0	1.7	3.2
Neo-PRh 6	3.0	1.8	2.4	2.6
<i>Mean</i>	2.9	2.3	2.6	3.0

Group/Case	Object-In-Place			
	8 Months	18 Months	24 Months	36 Months
Neo-C 1	6.4	4.6	3.2	4.1
Neo-C 2	6.3	3.4	3.3	1.9
Neo-C 3	7.6	5.7	5.3	5.6
Neo-C 4	5.2	3.5	3.7	3.3
<i>Mean</i>	6.4	4.3	3.9	3.8
Neo-PRh 1	3.9	3.6	5.3	3.8
Neo-PRh 2	5.6	3.4	4.0	1.5
Neo-PRh 3	6.2	2.7	2.2	3.8
Neo-PRh 4	6.4	3.2	3.7	3.2
Neo-PRh 5	7.0	3.6	3.3	3.6
Neo-PRh 6	7.5	2.8	2.6	2.6
<i>Mean</i>	6.1	3.2	3.5	3.1

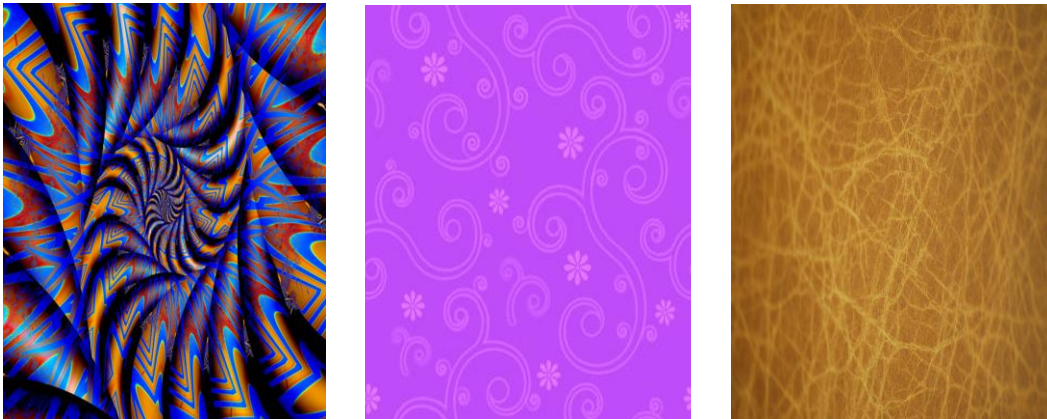
  

Group/Case	Object-Control			
	8 Months	18 Months	24 Months	36 Months
Neo-C 1	8.6	5.1	7.1	5.9
Neo-C 2	7.7	3.7	4.9	4.4
Neo-C 3	8.4	5.2	5.2	6.4
Neo-C 4	8.7	3.8	4.8	4.9
<i>Mean</i>	8.4	4.5	5.5	5.4
Neo-PRh 1	6.9	6.1	5.7	4.4
Neo-PRh 2	3.9	3.3	4.4	2.2
Neo-PRh 3	6.7	3.7	3.7	4.5
Neo-PRh 4	6.1	5.4	5.9	4.9
Neo-PRh 5	7.7	4.5	4.2	5.7
Neo-PRh 6	7.7	5.8	4.8	3.3
<i>Mean</i>	6.5	4.8	4.8	4.2

### A. Examples of Objects



### B. Examples of Backgrounds



*Figure 1.* Examples of stimuli used for preferential looking paradigm. Objects included clipart and photo object images of household items, toys, vehicles, animals etc. (A), and backgrounds included fractal images and patterns (B). Note: The objects were similar in size and all stimuli were trial unique. Therefore, each stimulus presentation included new object and background configurations.

### A. Tobii Eye Tracker



### B. Eye Tracker Setup (with Secondary Monitor)

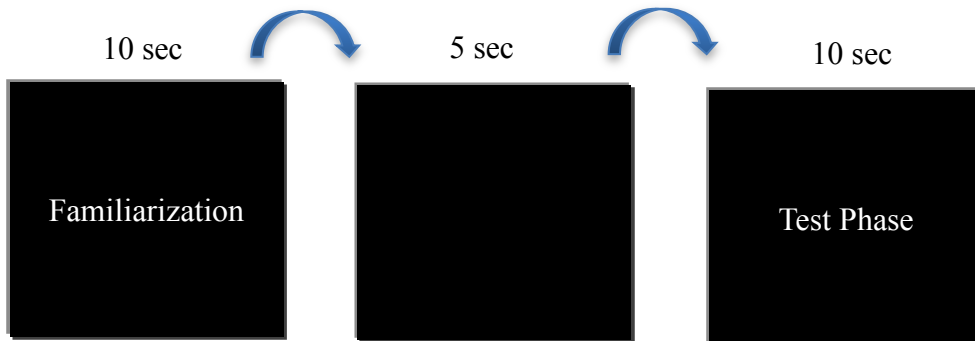


### C. Live Viewer

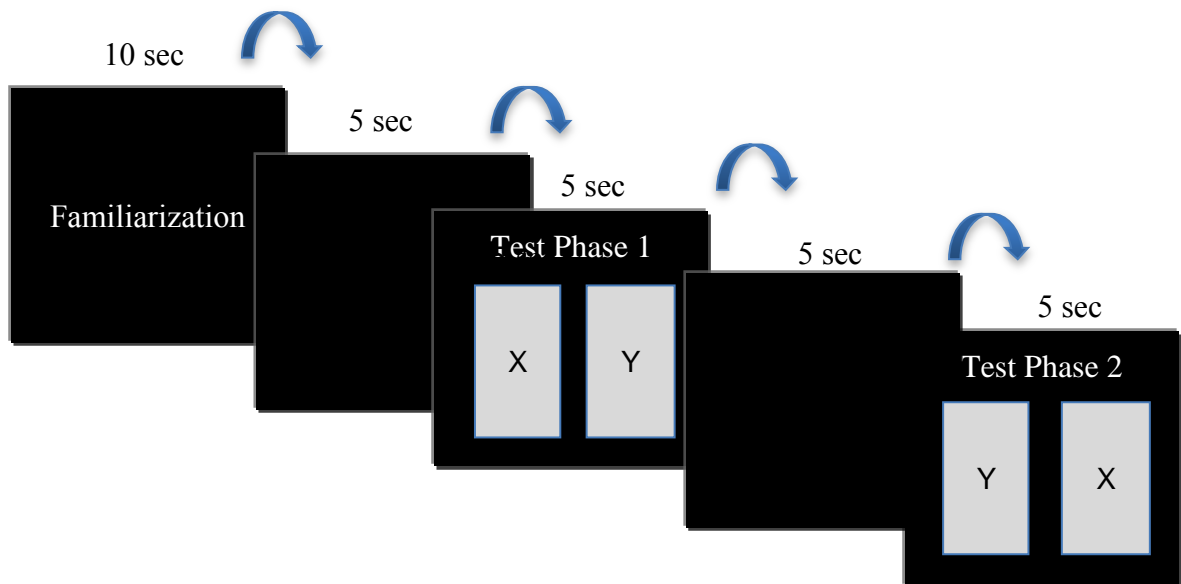


*Figure 2.* Eye tracker setup. Tobii eye tracker (A), secondary monitor (B), and live viewer (C). This setup allowed the researcher to view real-time gaze data overlay on the secondary monitor.

### A. Schematic Representation of Task with One Test Phase

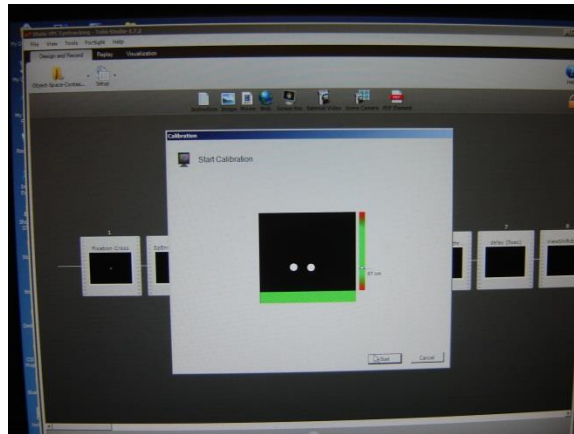


### B. Schematic Representation of Task with Two Test Phases

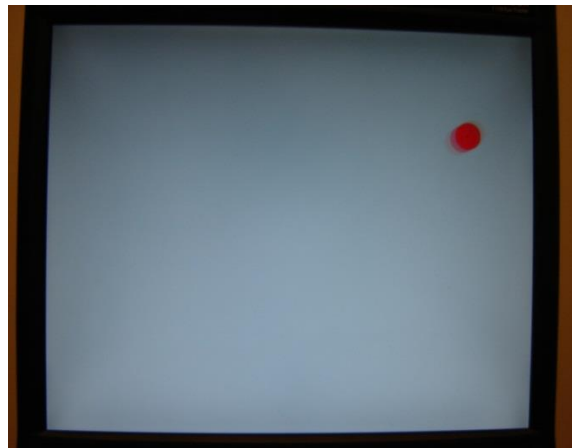


*Figure 3.* Schematic representation of (A) trials in which only one test phase is presented and (B) trials in which two test phases are presented. Note: The right/left position of the stimuli change in the trials with two test phases. X and Y represent images.

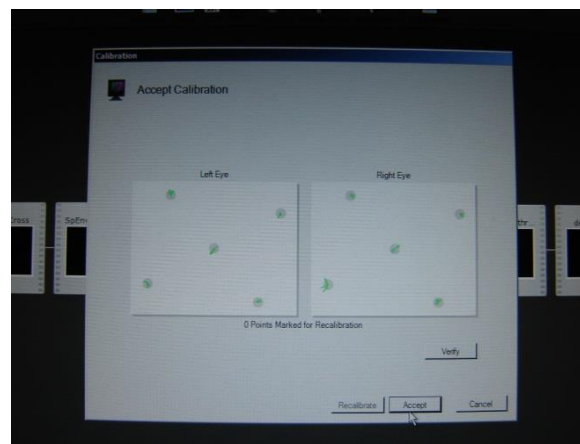
### A. Calibration Start Screen



### B. Moving Calibration Dot



### C. Acceptance of Calibration



*Figure 4.* Calibration sequence. Once the calibration is started (A), the calibration dot appears and moves around the screen to specific locations (B). Finally, the calibration is accepted (C). Note: Green lines on acceptance screen indicate viewed locations.



### Object-Location Relations (No Background)

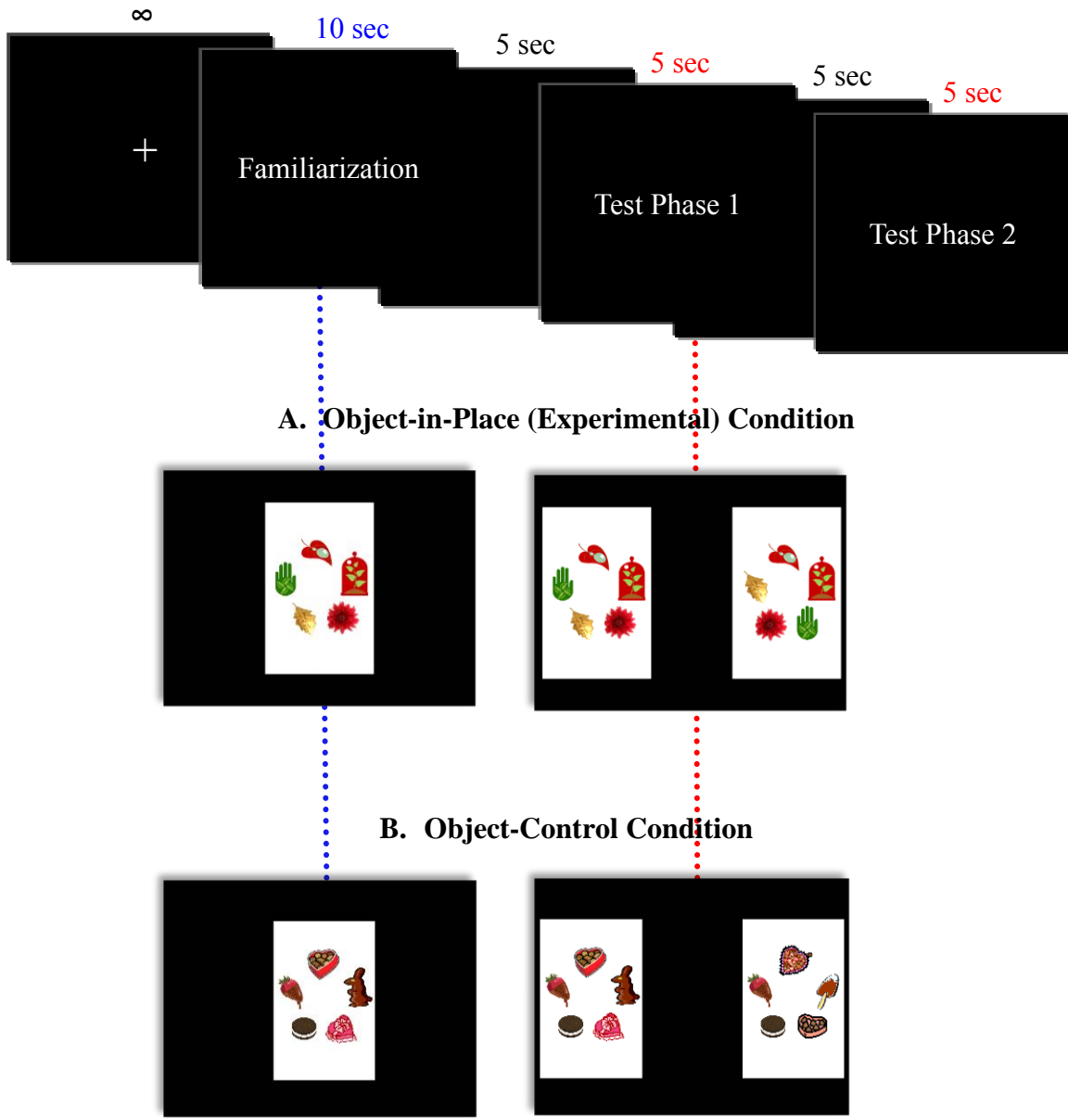
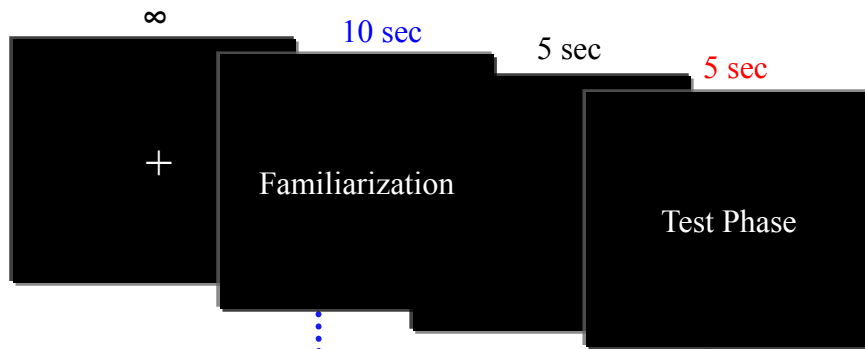
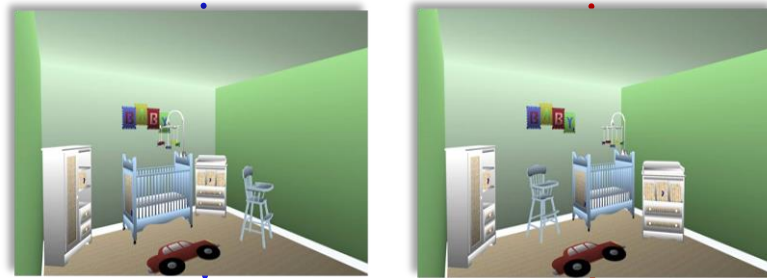


Figure 5. Stimulus presentation for *Object-Location* relational trials. Stimulus presentation is from left to right. Two different trial types were presented. In both types of trials an array of five objects are presented during the familiarization phase. During the test phases, the novel image either consisted of three of the objects rearranged (A, Object-in-Place) or replaced (B, Object-Control). Note: Left/right position changes between test phase 1 and 2. Dotted blue line- familiarization phase; dotted red line- test phases. Black text- length of inter-stimulus interval; blue text- length of familiarization period; red text- length of test period. The symbol  $\infty$  denotes a undefined time.

## Object Location Relations (Semi-Naturalistic Scenes)



### B. Object Rearrangement (Experimental) Condition

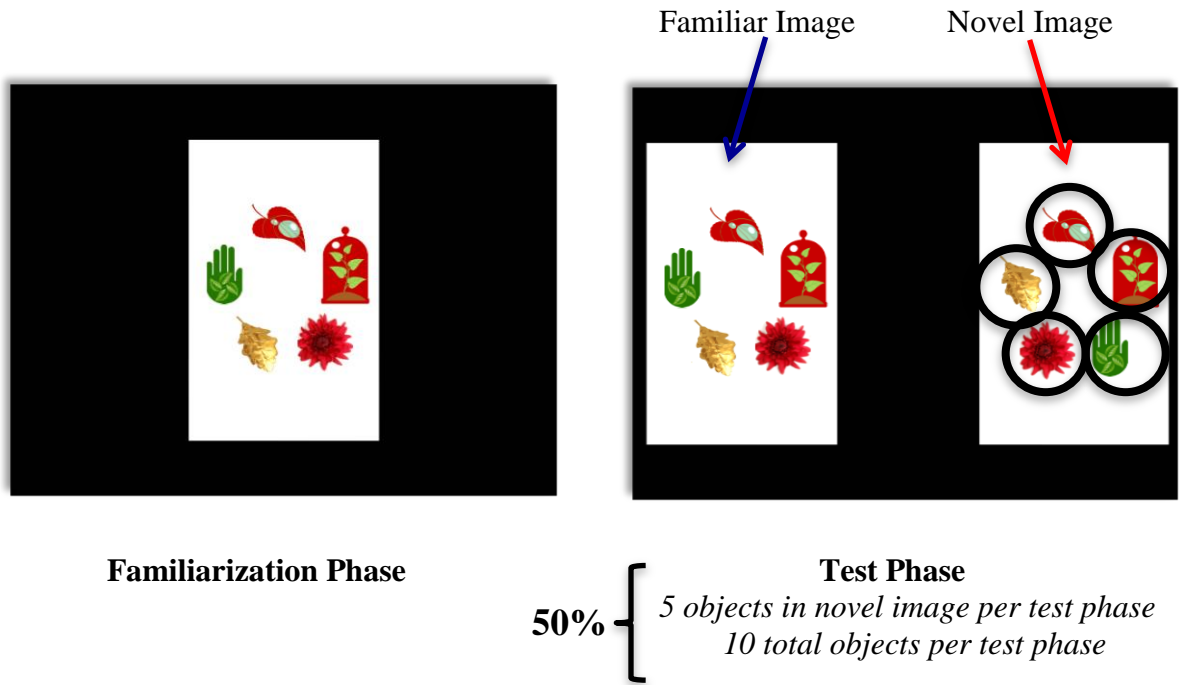


### C. Object Replacement (Control) Condition

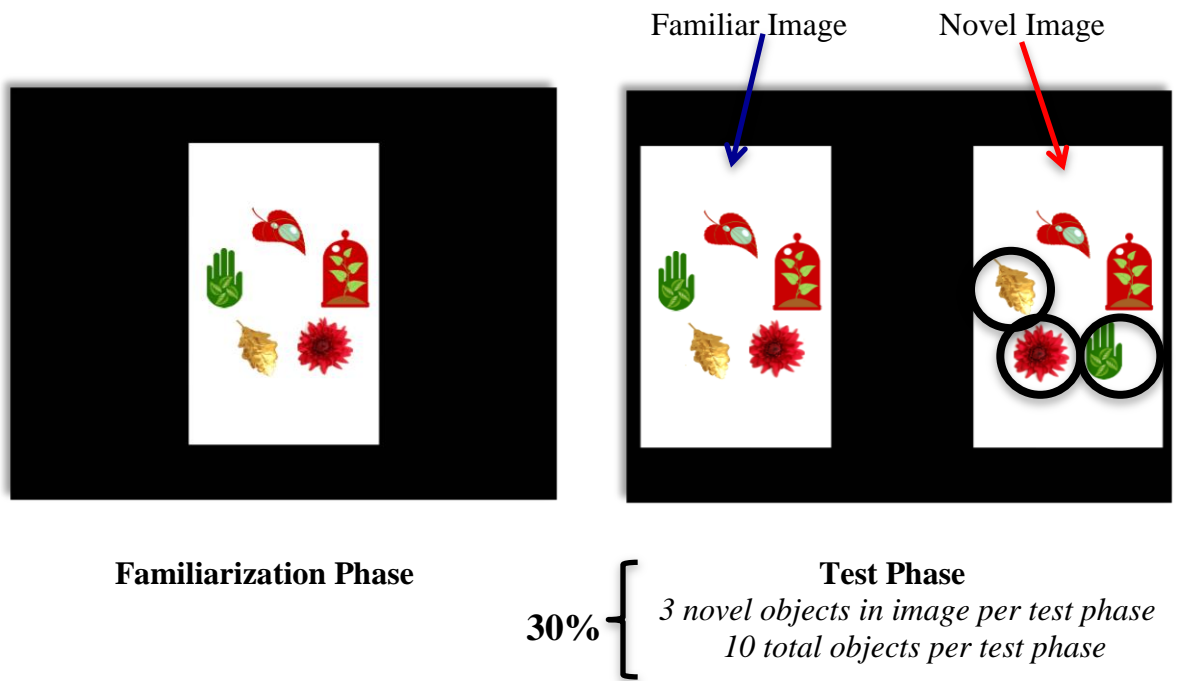


*Figure 6.* Stimulus presentation for Object-Location within Semi-Naturalistic Scene conditions. Note that there is only one test phase, which lasts 10 second. A blank screen is displayed during a 5-second delay period. Dotted blue line- familiarization phase; dotted red line- test phases. Black text- length of inter-stimulus interval; blue text- length of familiarization period; red text- length of test period. The symbol  $\infty$  denotes a undefined time.

**A. Object-Location (No Background): Chance for Novel Image Preference**



**B. Object-Location (No Background): Chance for Novel Object Preference**



### C. Object-Location (Scene): Chance for Novel Object Preference



**Familiarization Phase**



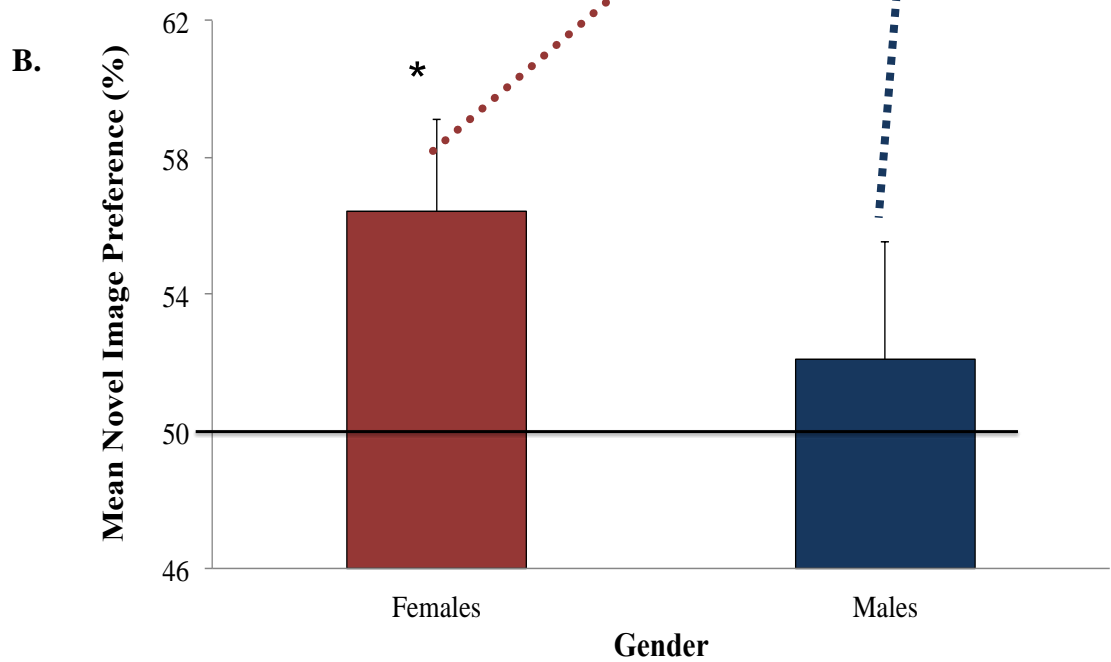
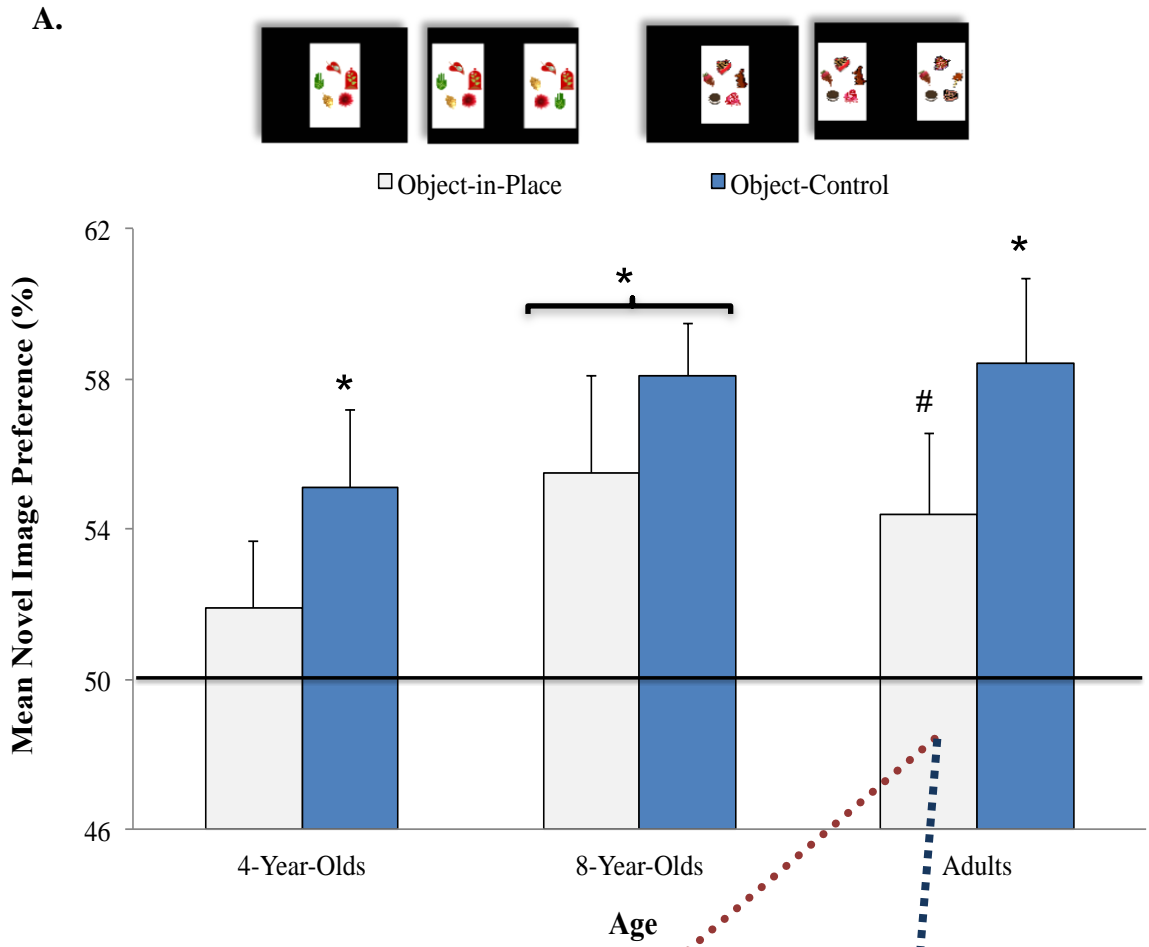
**Test Phase**

60%

{ 3 novel objects in each scene  
5 foreground objects

*Figure 7.* Calculation of chance performance for novelty preference scores. Novel image preference (A) and novel objects preference (B) for the No Background condition, and novel object preference for the Semi-Naturalistic Scene condition (C) of Experiment 1 are depicted above. Novel objects are circled in black. The total number of novel objects per test phase divided by the total number of objects per test phase calculates chance performance.

**Object-Location (No Background): Mean Novel Image Preference**



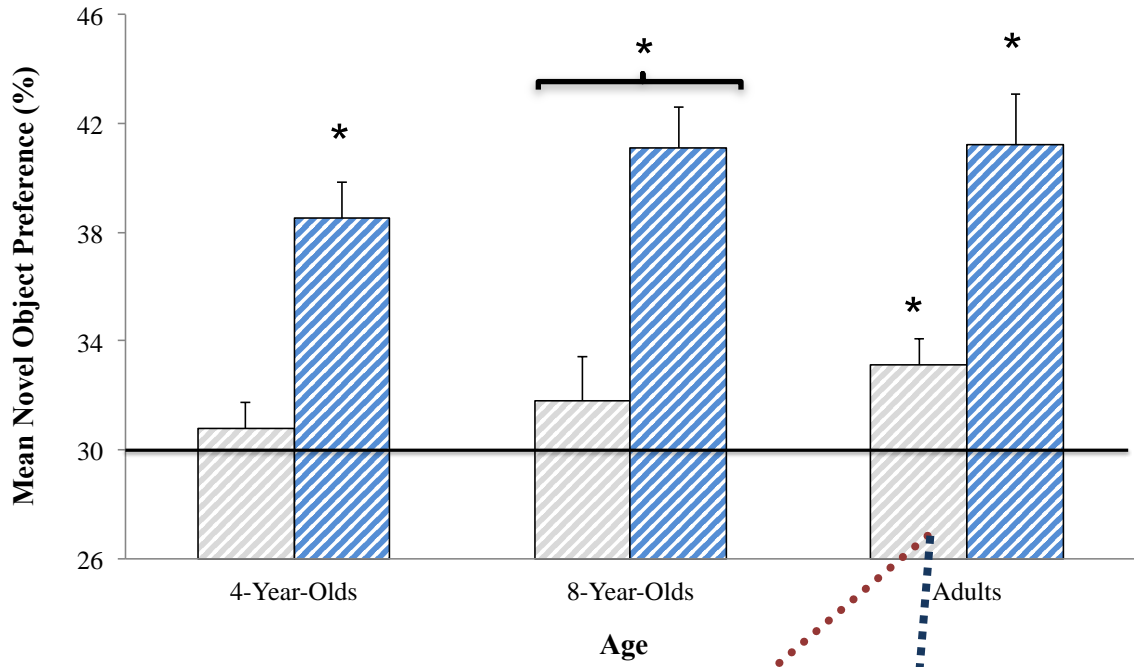
*Figure 8.* Panel A depicts the mean novel image preference for *Object-Location* relational trials for 4- and 8-year olds, and adults. The light gray bars represent the Object-in-Place experimental trials, and the blue bars represent the Object-Control trials. Above the legend for each trial type is an example of the stimuli. Panel B depicts the mean novel image preference for females (red) and males (dark blue) in the Object-in-Place task. The solid black horizontal line represents chance, set at 50 percent. Asterisks represents significant difference from chance ( $p < .05$ ). Pound represents a marginal effect ( $p < .10$ ).

**Object-Location (No Background): Mean Novel Object Preference**

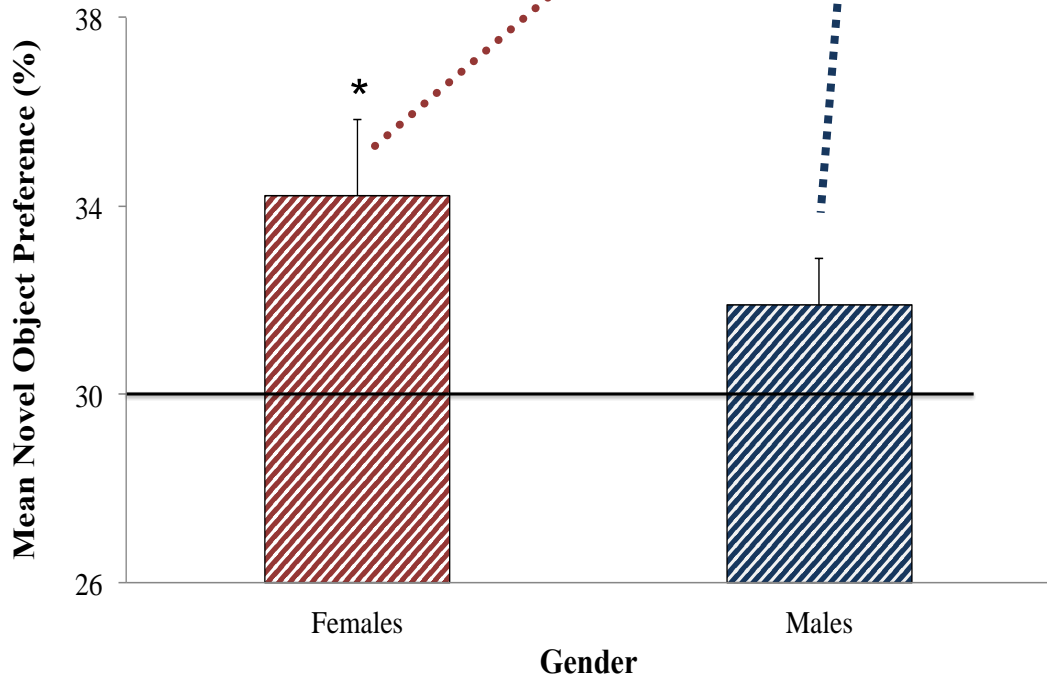
**A.**



□ Object-in-Place      ■ Object-Control



**B.**



*Figure 9.* Panel A depicts the mean novel object preference for *Object-Location* relational trials for 4- and 8-year olds, and adults. The light gray diagonal striped bars represent the Object-in-Place experimental trials, and the blue diagonal striped bars represent the Object-Control trials. Above the legend for each trial type is an example of the stimuli. Panel B depicts the mean novel object preference for females (red diagonal stripes) and males (dark blue diagonal stripes) in the Object-in-Place task. The solid black horizontal line represents chance, set at 50 percent. Asterisks represents significant difference from chance ( $p < .05$ ).



### Object-Location (Scene): Mean Novel Object Preference

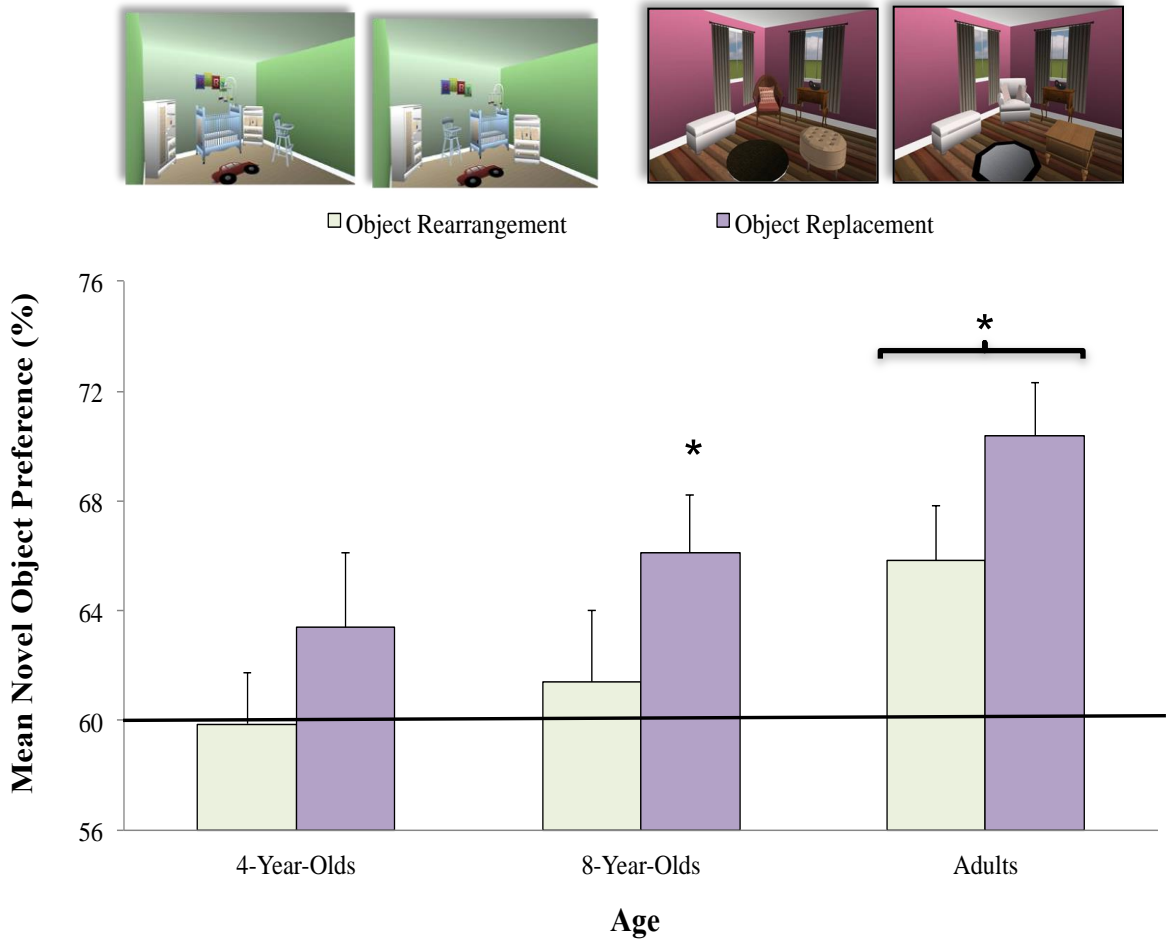
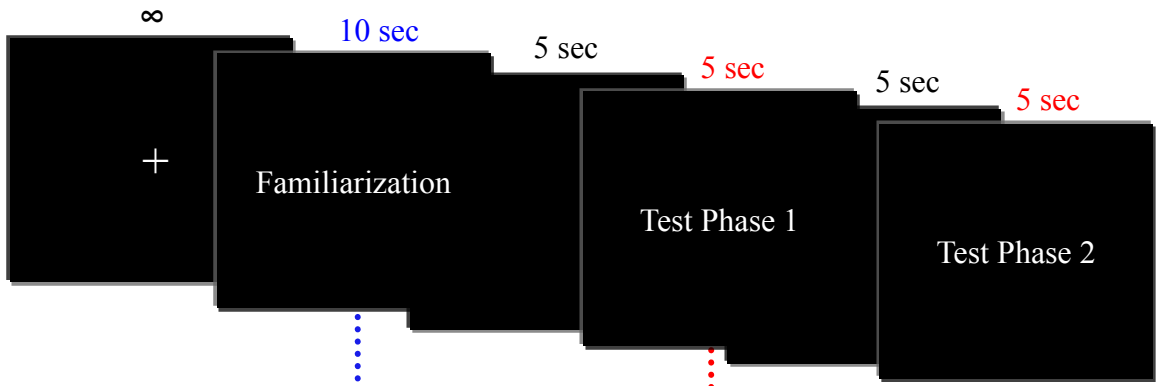
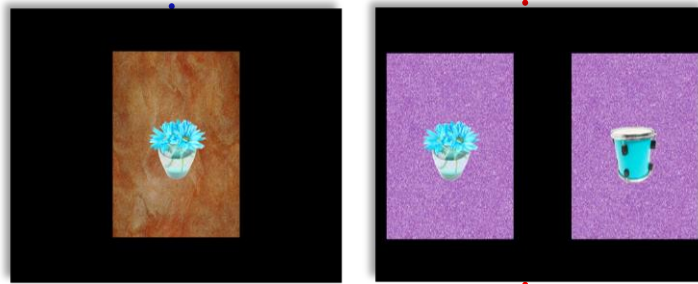


Figure 10. Mean novel object preference for *Object-Location* within *Semi-Naturalistic Scene* trials for 4- and 8-year olds, and adults. The light green bars represent the Object Rearrangement experimental trials, and the light purple bars represent the Object Replacement control trials. Above the legend for each trial type is an example of the stimuli. The solid black horizontal line represents chance, set at 50 percent. Asterisks represents significant difference from chance ( $p < .05$ ).

# Object-Context Relations



## A. Background Change (Experimental) Condition



## B. Novel Object (Control) Condition

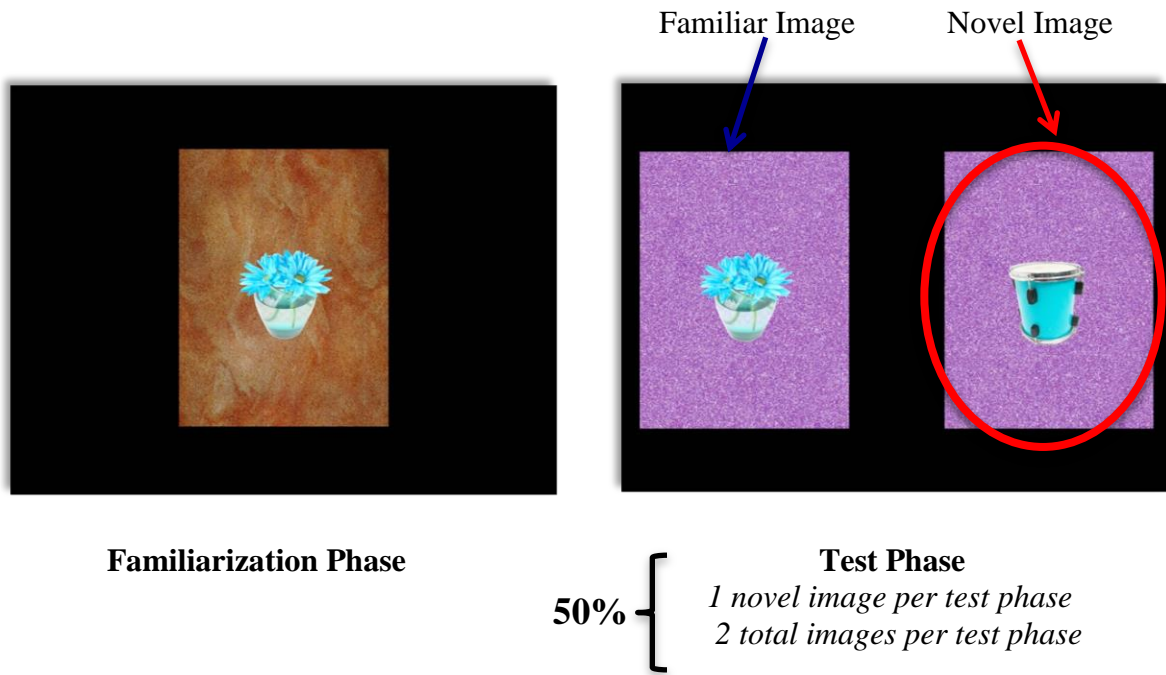


## C. Novel Background (Control) Condition



*Figure 11.* Stimulus presentation for *Object-Context* relational trials. Black boxes at the top represent the order of stimulus presentation (from left to right). Three different trial types were presented. In the background change experimental condition (A), the background between familiarization and test changed for both the familiar and novel object. In the novel object control condition (B), the background remained the same and a novel object was presented with the familiar object. In the novel background control condition (C), the familiar object was presented on either a familiar or novel background. Note: In test phase 2 the stimuli are similar to test phase 1 with the exception of the left/right position. Dotted blue line- familiarization phases; dotted red line- test phases. Black text- length of inter-stimulus interval; blue text- length of familiarization period; red text- length of test period. The symbol  $\infty$  denotes a undefined time.

## Object-Context: Chance for Novel Image Preference



*Figure 12.* Calculation of chance for novel image preference for trials in Experiment 2. The novel image is circled in red. The total number of novel images per test phase divided by the total number of images per test phase calculates chance performance.

### Object-Context: Mean Novel Image Preference

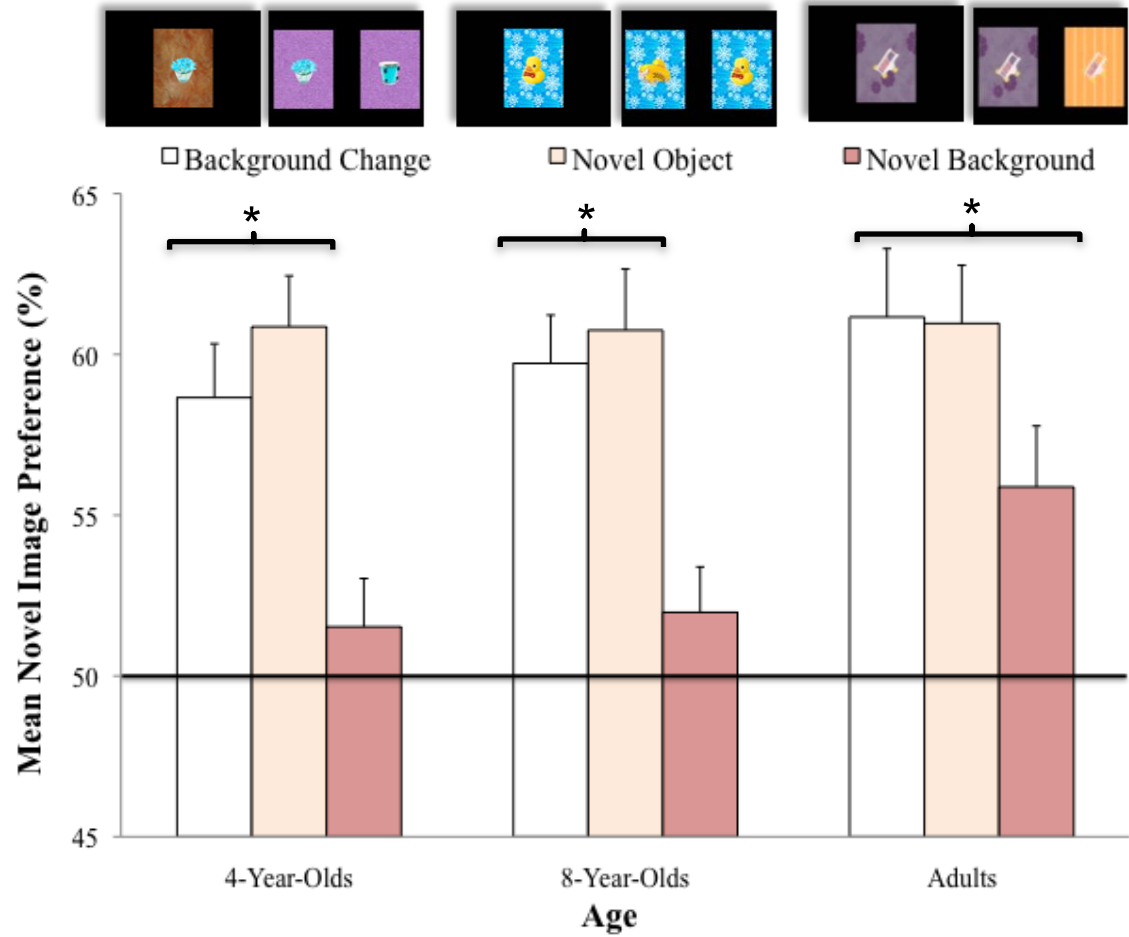


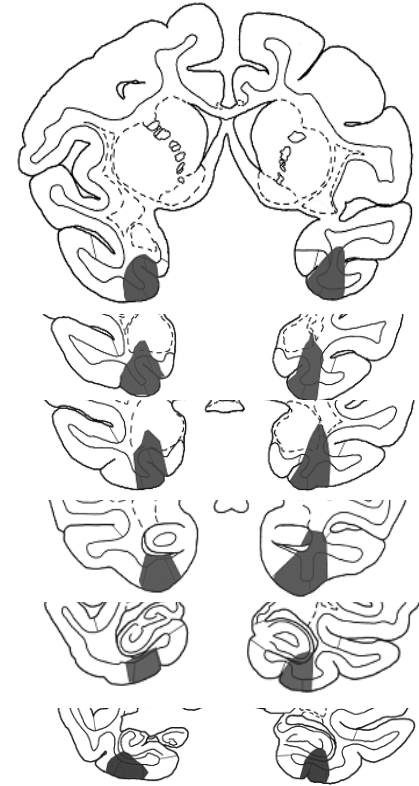
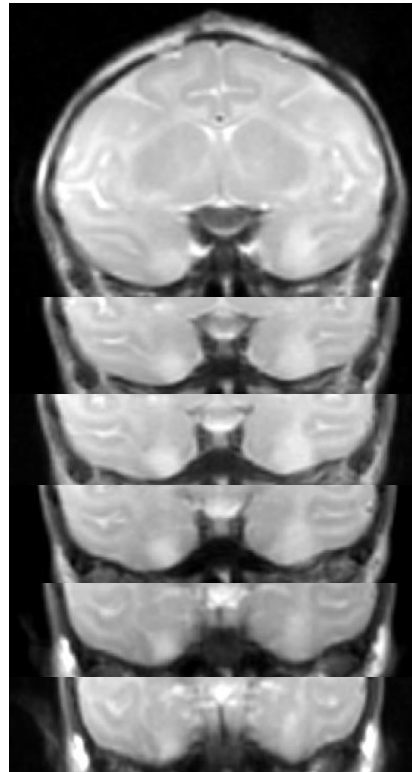
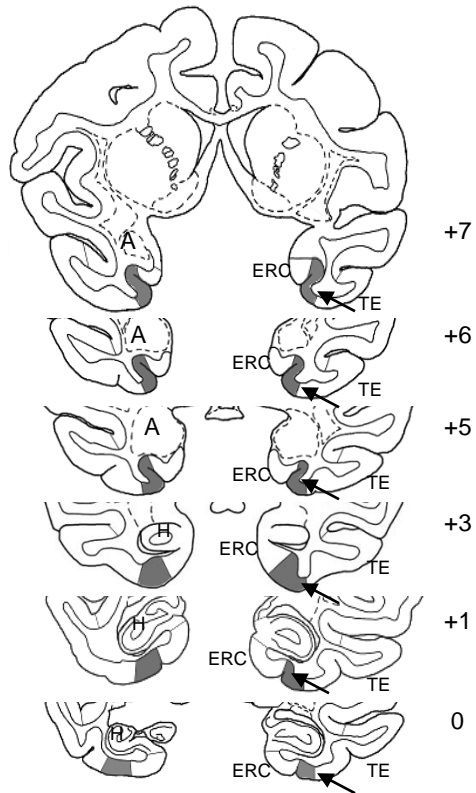
Figure 13. Mean novel image preference for *Object-Context* relational trials for 4- and 8-year olds, and adults. White bars represent the background change experimental trials, peach colored bars represent the novel object control trials, and the pink bars represent the novel background control trials. Above the legend for each trial type is an example of the stimuli. The solid black horizontal line represents chance, set at 50 percent. Asterisks represents significant difference from chance. Pound sign represents significant group difference (Age) for the particular trial type.

Neo-PRh-1

Intended Lesion Extent

1-Week Post Surgical FLAIR

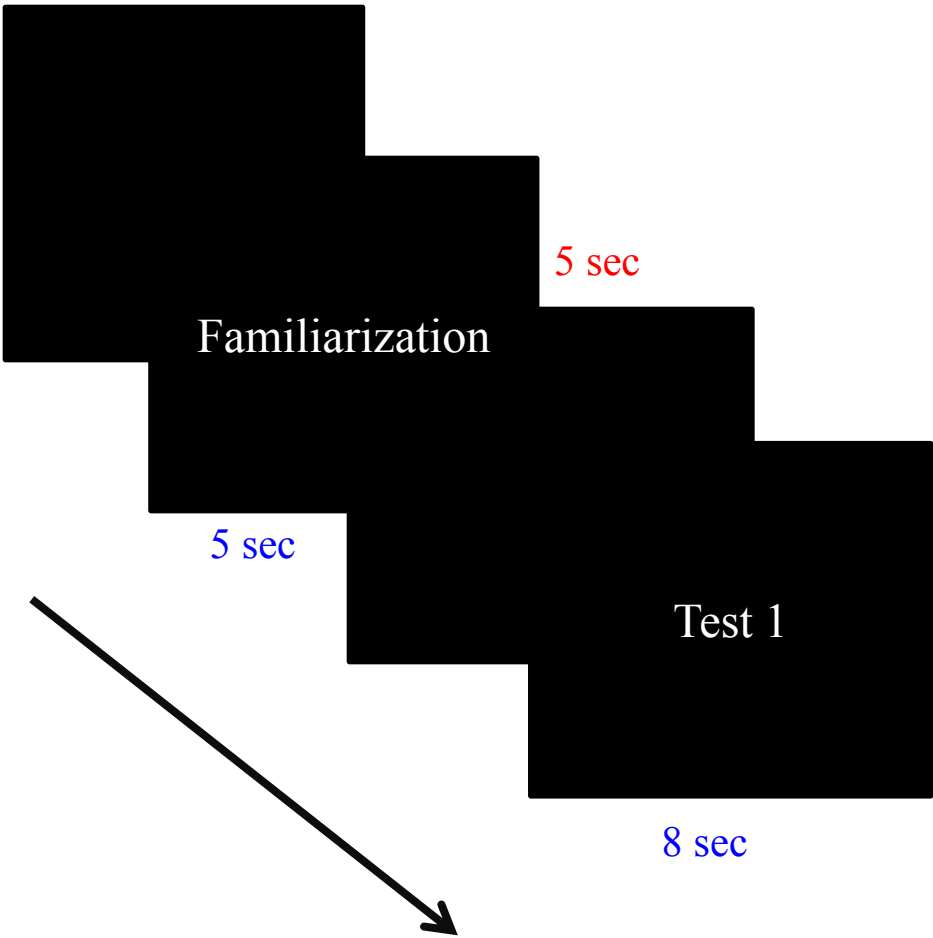
Reconstructed Lesion Extent



Representative Case

*Figure 14.* Coronal drawing sections through the perirhinal cortex of a normal macaque brain (left column) depict intended damage (gray area). Arrows indicate areas of intended damage. Coronal FLAIR images at corresponding levels (middle column) illustrate hypersignals (white area) resulting from edema caused by cell death. Reconstruction of the extent of hypersignals set onto corresponding coronal sections of the normal monkey brain (right column). Abbreviations: ERC – entorhinal cortex; A- amygdala; H- hippocampus; and TE, temporal cortical area as defined by von Bonin and Bailey (1947).

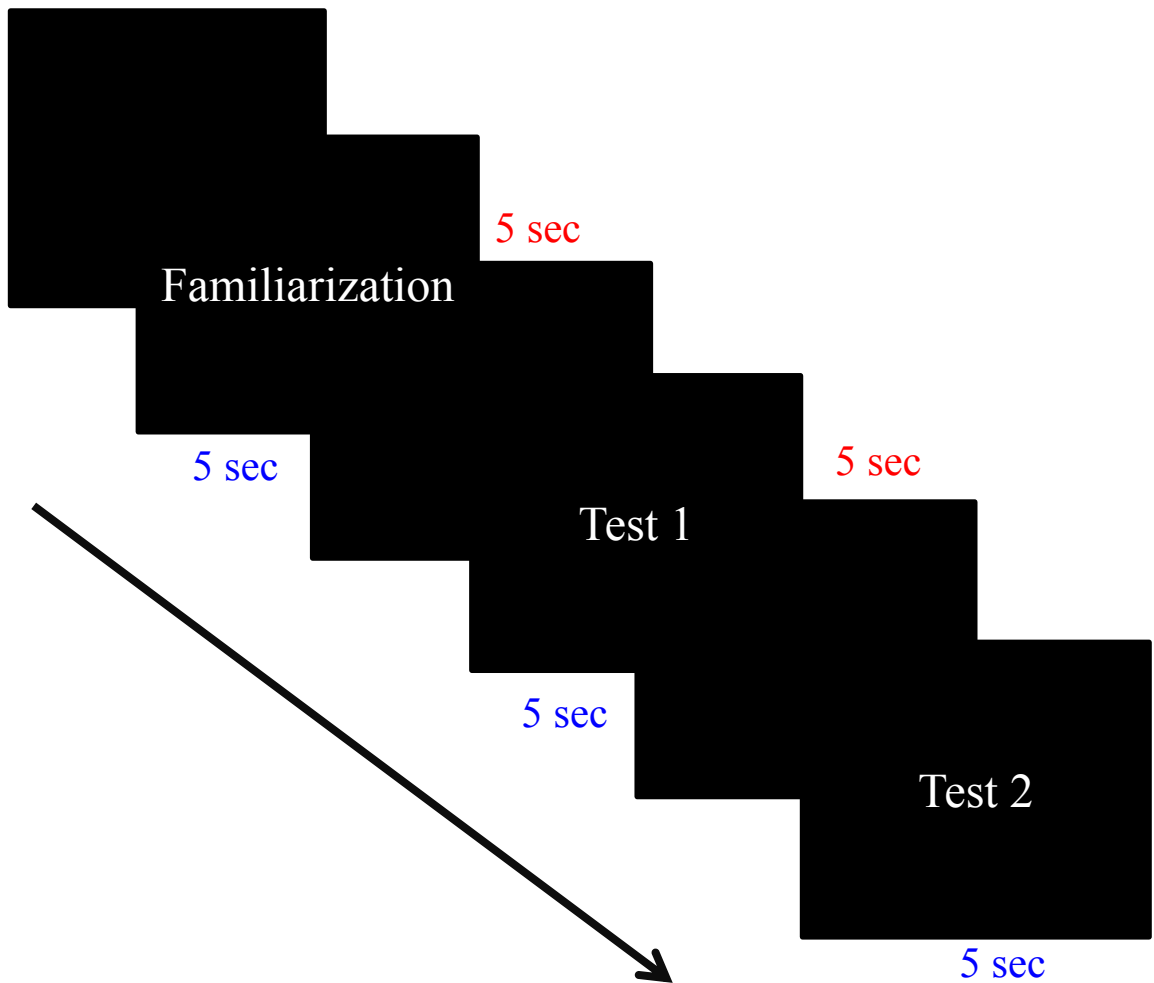
**Spatial Location Stimulus Presentation**



*Figure 15.* Stimulus presentation for the VPC-Spatial-Location tasks. Note that there is only one delay period totaling 8 secs in length. Red numbers- delay periods (in secs); blue numbers- familiarization and test periods (in secs).



## Object-In-Place/Object-Control Stimulus Presentation



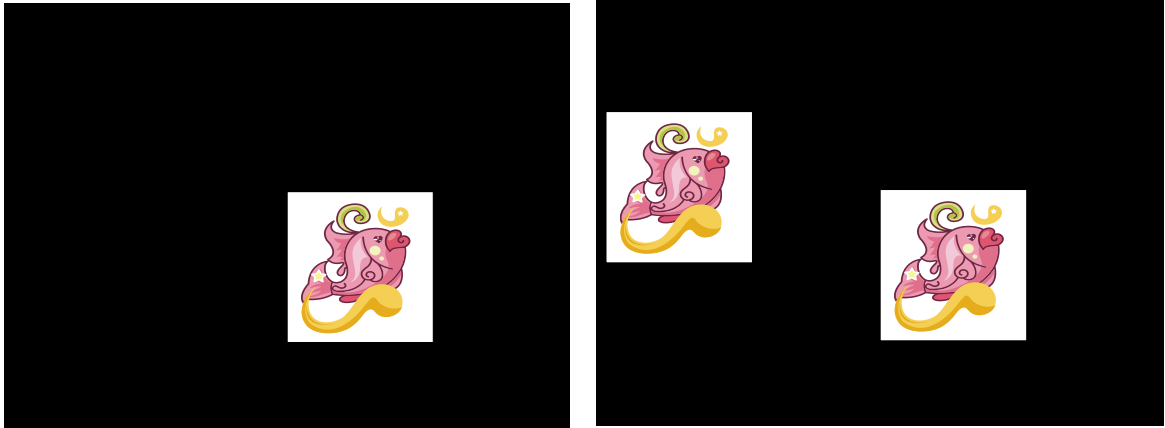
*Figure 16.* Stimulus presentation for the VPC-Object-in-Place and VPC-Object-Control tasks. Note that each delay period is 5 secs in length. Two test phases are represented in this image, however, not all trials have two retention tests (see above). Red numbers- delay periods (in secs); blue numbers- familiarization and test periods (in secs).

### A. Spatial-Location

Familiarization Phase

Delay (5s)

Test Phase

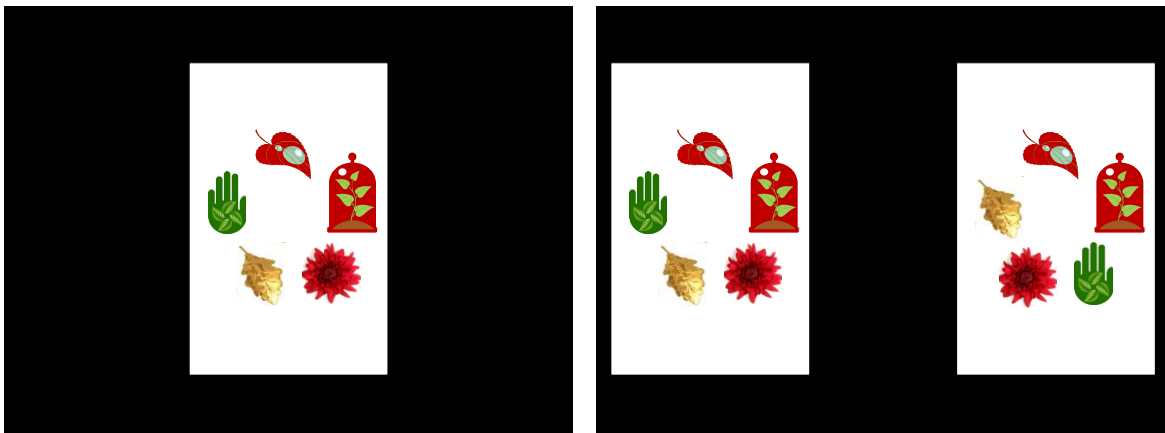


### B. Object-In-Place

Familiarization Phase

Delay (5s)

Test Phase



### C. Object-Control

Familiarization Phase

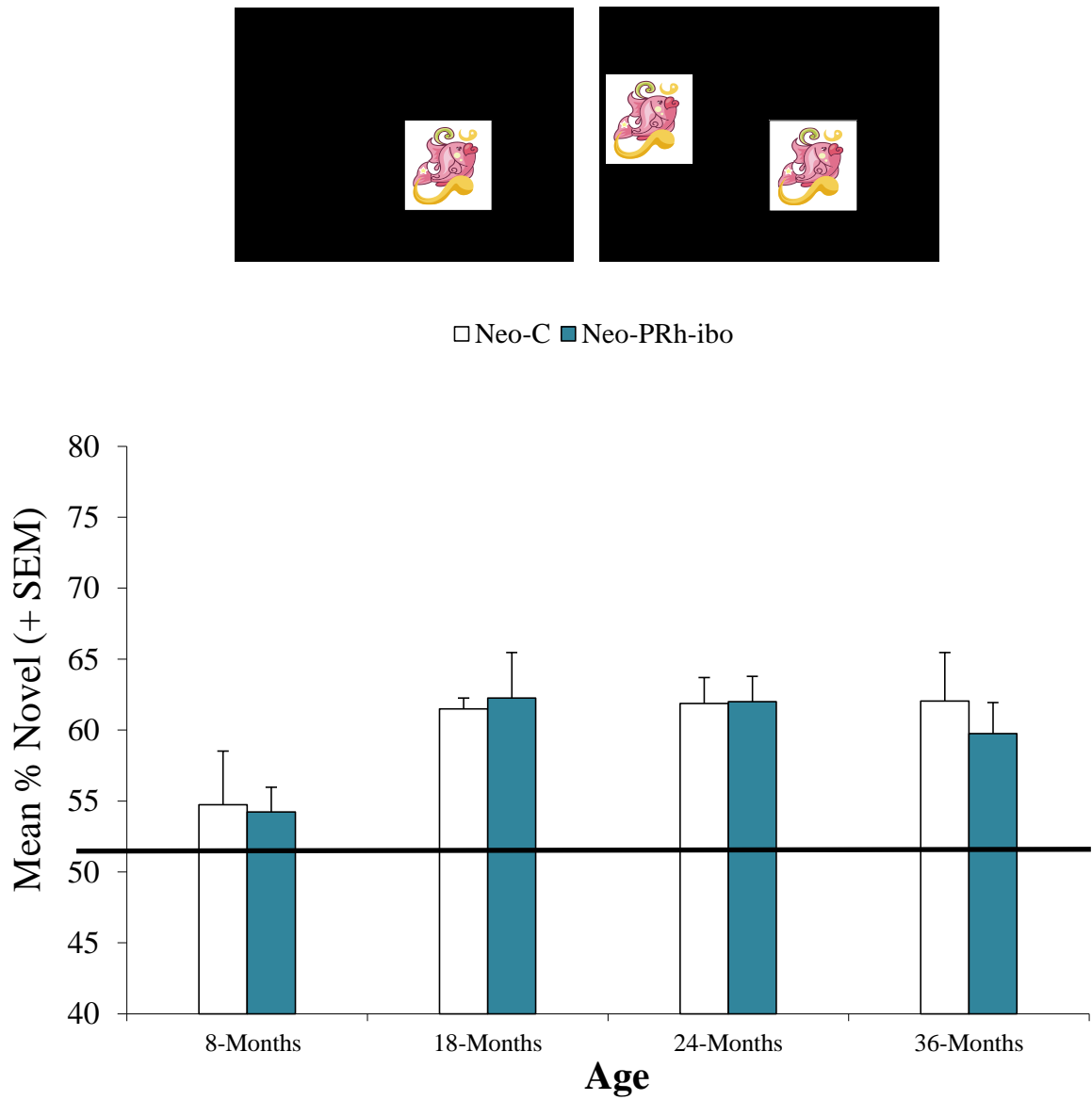
Delay (5s)

Test Phase



*Figure 17.* Spatial and non-spatial visual paired comparison (VPC) tasks. Examples of trials for the VPC-Spatial-Location (A), the VPC-Object-in-Place (B), and the VPC-Object-Control (C) tasks. Note that for the Spatial-Location task, the novel image is the same as the familiar image but is placed in a different position on the screen. For the Object-in-Place tasks the novel image differed from the familiar image only in the location of the 5 objects forming the images. In the VPC-Object-Control task, the novel image consisted of replacing three objects of the familiar image with three new objects.

### VPC-Spatial-Location: Mean % Novel



*Figure 18.* Mean percent of time looking at the novel image ( $\pm$  SEM) in the VPC-Spatial-Location, for sham-operated controls (White Bars: Group Neo-C) and monkeys with perirhinal lesions (Teal Bars: Group Neo-PRh-ibo) at 8-, 18-, 24-, and 36-months of age. The black horizontal line represents chance performance. Asterisk defines significant difference from chance ( $p < .05$ ) and pound represents significant difference between ages ( $p < .05$ ).

VPC-Object-in-Place: Mean % Novel

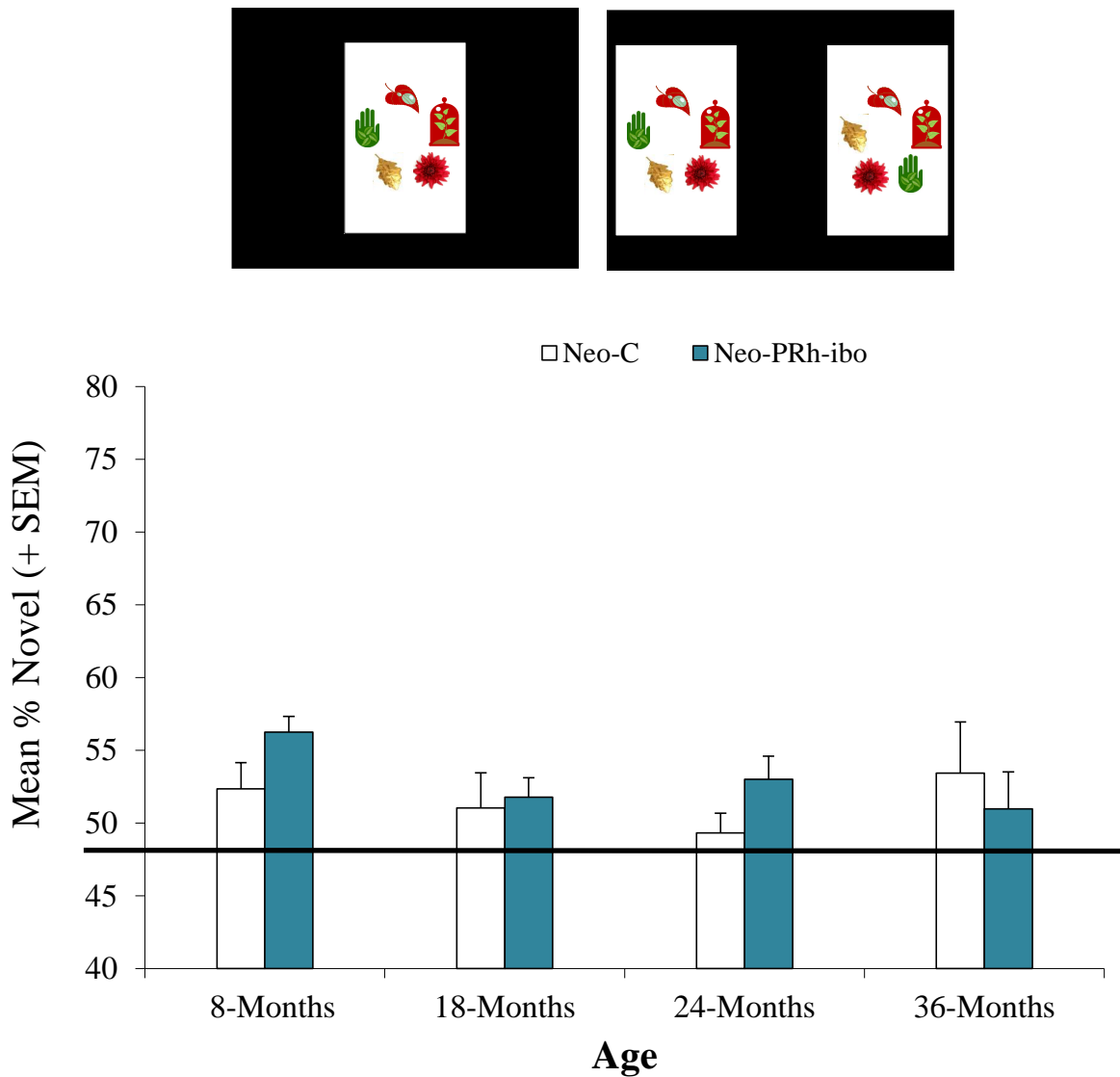


Figure 19. Mean percent of time looking at the novel image ( $\pm$  SEM) in the VPC-Object-in-Place, for sham-operated controls (White Bars: Group Neo-C) and monkeys with perirhinal lesions (Teal Bars: Group Neo-PRh-ibo) at 8-, 18-, 24-, and 36-months of age. The black horizontal line represents chance performance. Asterisk defines significant difference from chance ( $p < .05$ ) and pound represents significant difference between ages ( $p < .05$ ).

VPC-Object-Control: Mean % Novel

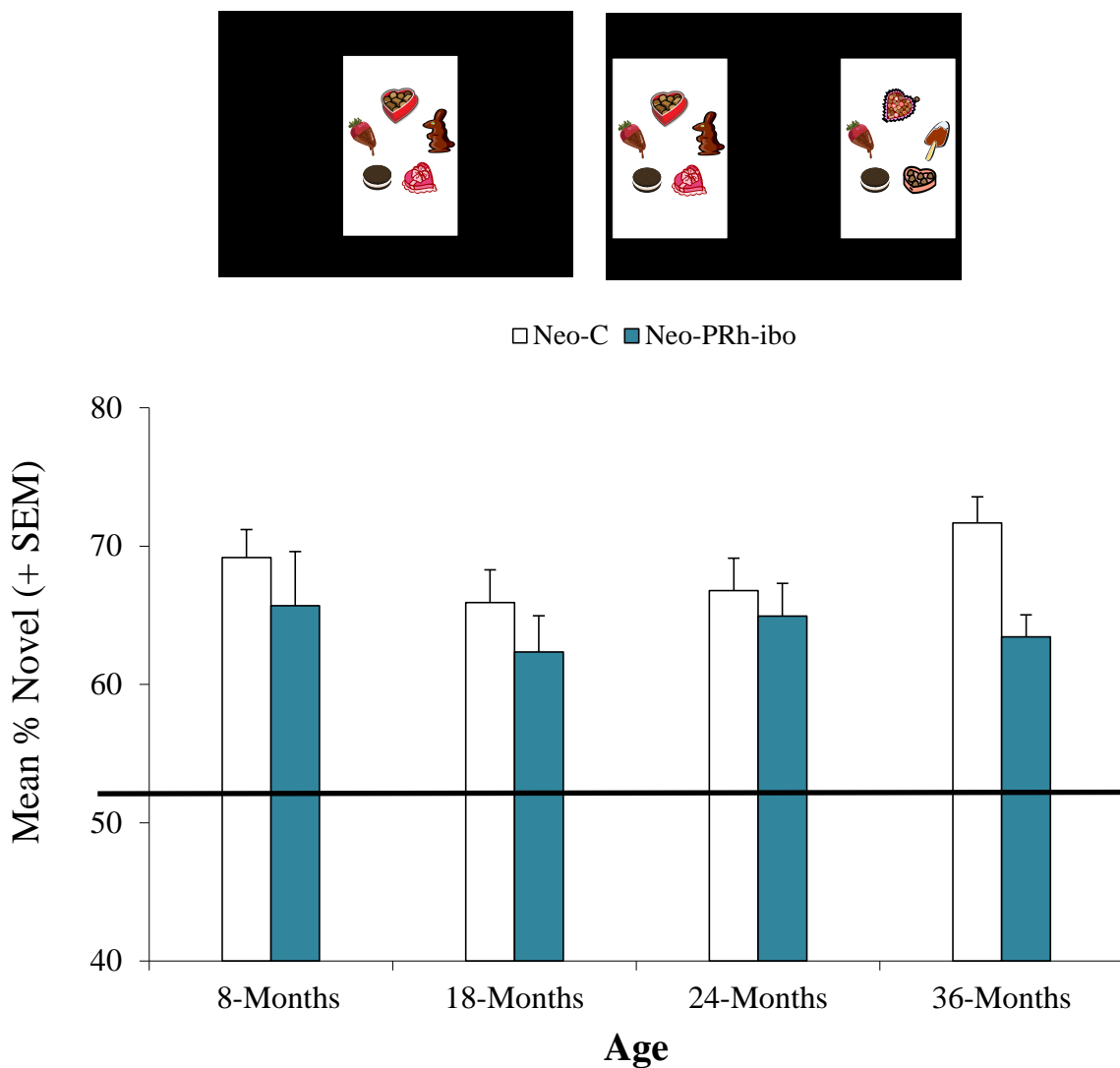
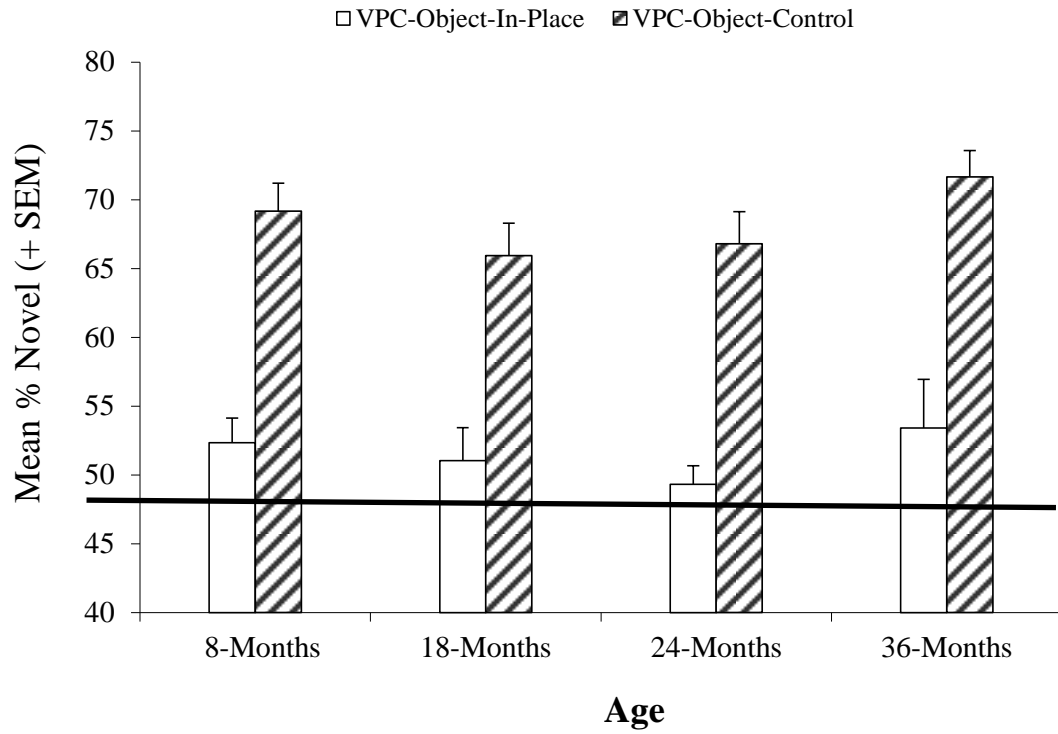
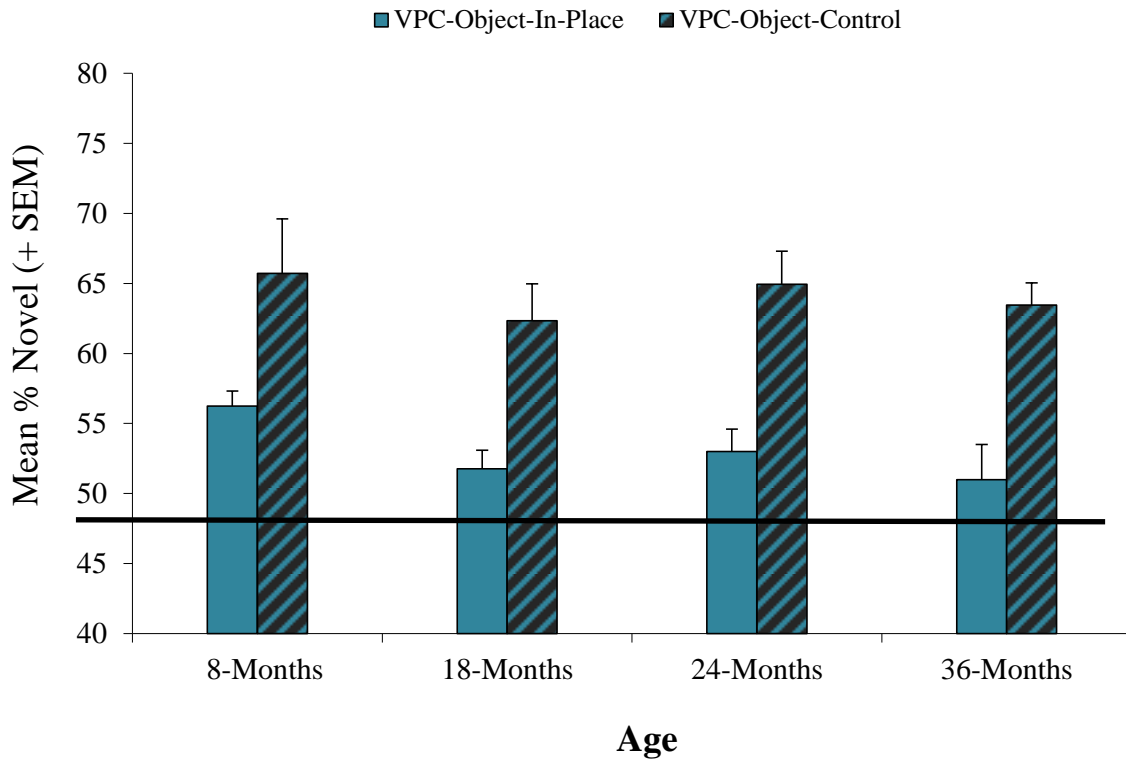


Figure 20. Mean percent of time looking at the novel image ( $\pm$  SEM) in the VPC-Object-Control, for sham-operated controls (White Bars: Group Neo-C) and monkeys with perirhinal lesions (Teal Bars: Group Neo-PRh-ibo) at 8-, 18-, 24-, and 36-months of age. The black horizontal line represents chance performance. Asterisk defines significant difference from chance ( $p < .05$ ) and pound represents significant difference between ages ( $p < .05$ ).

### A. VPC-Object-in-Place/Object Control Analysis: Group Neo-C



### B. VPC-Object-in-Place/Object Control Analysis: Group Neo-PRh



*Figure 21.* Mean percent of time looking at the novel image in the VPC-Object-In-Place (solid bars) and VPC-Object-Control (diagonal bars) tasks for sham-operated controls (White Bars: Group Neo-C) and monkeys with perirhinal lesions (Teal Bars: Group Neo-PRh-ibo) at 8-, 18-, 24-, and 36-months of age. The black horizontal line represents chance performance. Asterisk defines significant difference from chance ( $p < .05$ ) and pound represents significant difference between ages ( $p < .05$ ).