

Intact perceptual ability, but impaired familiarity judgment, after neonatal perirhinal lesions in rhesus macaques

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ABSTRACT

The perirhinal cortex is known to support high-level perceptual abilities as well as familiarity judgments that may affect recognition memory. We tested whether poor perceptual abilities or a loss of familiarity judgment contributed to the recognition memory impairments reported earlier in monkeys with PRh lesions received in infancy (Neo-PRh) (Weiss and Bachevalier, 2016; Zeamer et al., 2015). Perceptual abilities were assessed using a version of the Visual Paired Comparison task with black&white (B&W) stimuli, and familiarity judgments were assessed using the Constant Negative task requiring repeated familiarization exposures. Adult monkeys with Neo-PRh lesions were able to recognize B&W stimuli after short delays, suggesting that their perceptual abilities were within the range of control animals. However, the same Neo-PRh monkeys were slower to acquire the Constant Negative task, requiring more exposures to objects before judging them as familiar compared to control animals. Taken together, the data help to account for the differential patterns of functional compensation on previously reported recognition tasks following neonatal versus adult-onset PRh lesions, and provide further support to the view that the PRh is involved in familiarity processes.

1. Introduction

The developmental consequences of early medial temporal lobe damage is of major clinical interest given the learning and memory deficits that are associated with many developmental neuropsychiatric disorders (e.g. schizophrenia, autism, ADHD, Fragile X, Down's and Williams syndromes). These disorders share common factors (developmental components, genetic predisposition, and medial temporal lobe pathology) with similarly impaired cognitive functions, but have different time courses and severity. Thus, a critical step towards creating effective interventions and treatments will require better understanding of the neural basis of perception, learning, and memory, and of the outcomes of early insult at different nodes along this network across development. Although a large body of work has linked structural and functional changes of the hippocampus to these disorders (for review see Machado and Bachevalier, 2007), recent studies have indicated that the perirhinal (PRh) cortex, and its interactions with the hippocampus, plays a critical role in perception and memory (Murray and Wise, 2012; Ranganath, 2006) and may likewise be associated with components of the cognitive deficits in these disorders.

The perirhinal cortex (PRh), a cortical area within the medial temporal lobe, provides representations of objects in support of visual

perception and recognition memory (for review see Suzuki and Naya, 2014). In adult monkeys, the impact of PRh damage on object recognition has been well characterized. Selective PRh lesions in adult monkeys resulted in delay-dependent impairment on the delayed non-matching-to-sample task (DNMS) (Meunier et al., 1993), and abolished novelty preferences on the Visual Paired Comparison (VPC) (Nemanic et al., 2004). A growing number of studies have led researchers to propose that, in contrast to the hippocampus that is thought to support recollection, the PRh is thought to support recognition by detecting familiarity among objects (Eichenbaum et al., 2007; Schoemaker et al., 2014; Tu et al., 2011; Warburton and Brown, 2010; Yonelinas et al., 2002). Additional studies in monkeys with adult-onset PRh lesions revealed a mild perceptual impairment when the test stimuli were black and white (B&W) or had overlapping/similar features (Bussey et al., 2002, 2003, 2005, 2006; but see Hampton, 2005), suggesting that this cortical area may also contribute to higher-order visual processes. However, no studies to date have reported on the impact of neonatal PRh damage on similar cognitive processes.

New data from a recent longitudinal study tracking the development of memory in infant rhesus monkeys indicated that bilateral neurotoxic PRh lesions created before 2 weeks of age (Neo-PRh) produced mild impairment in novelty preference on the VPC task that emerged at 1.5

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months, became more severe during adolescence (18 months), and remained present in adulthood (48 months) (Zeamer et al., 2015). Furthermore, this recognition memory impairment was also present when the same Neo-PRh monkeys were tested in another recognition memory task, the DNMS task, as adults. Animals with Neo-PRh lesions were able to normally learn the DNMS rule and accurately remembered familiar objects after short (10s) delays, but were increasingly impaired when tested with delays of 30 s and longer (Weiss and Bachevalier, 2016; Zeamer et al., 2015). Taken together, these two studies provided further support to the view that PRh is involved in recognition and highlighted its early emerging role during development. However, as will be further discussed below, the difference in the magnitude of the deficit obtained with the two recognition tasks led us to question whether the deficit following the Neo-PRh lesions truly reflected a recognition deficit per se or could rather be interpreted as a deficit in familiarity judgment, or simply as poor perceptual abilities.

1.1. Impact of stimulus similarity on incidental object recognition

An interesting feature of the recognition memory impairment found after Neo-PRh lesions as measured by the VPC task was the lack of the typical delay-dependent forgetting curve reported after adult-onset PRh lesions (Nemanic et al., 2004). That is, although this delay-dependent performance was observed in the control animals, the scores of the Neo-PRh animals were worse than those of controls but comparable at all delays. (Zeamer et al., 2015, and see Fig. 3A). A lack of motivation to look at stimuli could be rejected because Neo-PRh animals took the same amount of time to familiarize with stimuli and had the same amount of looking time during the two retention tests as the control animals. However, this pattern of results suggested that the cause of the poor performance on the VPC task by Neo-PRh animals may not be a loss of memory per se or motivation but rather difficulty with other processes, such as poorer perceptual ability. Indeed, the PRh receives strong inputs from sensory cortical regions of the brain, with the densest afferents originating in ventral visual areas TE/TEO (Suzuki and Amaral, 1994; Suzuki, 1996). In addition, lesion studies in adult monkeys show that selective damage to the PRh yields severe visual discrimination impairment, mainly when stimulus complexity is high or perceptual overlap between stimuli is extensive (i.e. feature ambiguity), but not when stimuli are distinctive (Bussey et al., 2002, 2003, 2005, 2006; Murray and Richmond, 2001).

To assess whether the poor perceptual abilities might be the source of the recognition memory deficits found in the VPC task after the Neo-PRh lesions, Neo-PRh monkeys and their controls were tested on a new version of the VPC task using highly similar black and white (B&W) stimuli (Experiment 1). We conjecture that the presence of a delay-dependent recognition deficit after Neo-PRh lesions in this new version of the VPC task (i.e. normal performance at short delays but impairment at long delays) will indicate that Neo-PRh animals have perceptual abilities in the normal range and that early PRh lesions impact recognition memory processes rather than perceptual abilities.

1.2. Familiarity discrimination

An additional important distinction in the recognition memory impairment following Neo-PRh lesions comes from a comparison of the effects of the Neo-PRh lesions on the two recognition memory tasks (i.e. VPC vs DNMS) with those obtained after adult-onset PRh lesions on the same two tasks. Adult-onset PRh lesions result in similar recognition deficits in both tasks (Meunier et al., 1993; Nemanic et al., 2004). By contrast, the Neo-PRh lesions yield different outcomes in the two tasks. Although the magnitude of the recognition deficits in the DNMS task were similar after Neo-PRh or adult onset lesions (Weiss and Bachevalier, 2016), the magnitude of the recognition memory deficits in the VPC task were less severe after the Neo-PRh lesions than after the adult onset lesions (Zeamer et al., 2015). Thus, the evidence of a

moderate functional sparing following the neonatal lesions when recognition was measured with the VPC task contrasts with the lack of functional sparing when recognition was measured with the DNMS. Several factors may have led to this pattern of results.

First, given the plasticity of the brain across development (for review see Kolb et al., 2013), it is possible that other MTL cortical areas could have compensated for the absence of the PRh. In addition, because the animals were tested at several time points during development with the VPC task, albeit with novel stimuli each time, practice on the task together with neural compensation mechanisms could have led to improved performance as the animals were re-tested as adults. Alternatively, the different outcomes of the Neo-PRh lesions may relate to important procedural differences in the familiarization phase in the two tasks. That is, in VPC, monkeys are familiarized with the stimulus for a cumulative looking time of 30s, whereas in DNMS the monkeys view the stimulus for the number of seconds it takes to displace an object (usually 3–7 s). Thus, greater familiarization with the sample stimuli in the VPC task could have resulted in stronger recognition than with DNMS. Length of familiarization phase has already been shown to impact the strength of novelty preference in the VPC task (Richmond et al., 2004; Zeamer et al., 2011), and in recent years, a number of electrophysiological studies in monkeys (Erickson et al., 2000; Liu and Richmond, 2000) and rats (Albasser et al., 2010; Zhu et al., 1997; Burke et al., 2012), as well as neuroimaging studies in humans (Dew and Cabeza, 2013; Guedj et al., 2010; Vilberg and Davachi, 2013) have linked activity of PRh neurons with mechanisms of familiarity judgment. To assess whether the different outcomes of the Neo-PRh lesions in the two recognition memory tasks relate to the amount of exposures that animals were given to the sample stimulus, Experiment 2 measured performance of the animals with Neo-PRh lesions and their controls in the Constant Negative task, which requires discriminations between novel objects and objects with which the animals had repeated previous exposures (Browning et al., 2013).

We conjecture that normal performance on this task will indicate normal familiarity judgment after Neo-PRh lesions, whereas deficit will confirm that the difference in the magnitude impairment between the two recognition tasks may be due to a difficulty of Neo-PRh animals to form familiarity judgments.

2. General methods

All protocols were approved by the Institutional Animal Care and Use Committee at Emory University in Atlanta, Georgia and were in accordance with the NIH Guide for the care and use of Laboratory Animals (National Research Council (US), 2011).

2.1. Subjects

Sixteen adult rhesus macaques (*Macaca mulatta*), 8 female and 8 males, participated in this project. Fourteen received surgery on post-natal days 7–12, either bilateral ibotenic acid injections of the perirhinal cortex (Neo-PRh: 3 females, 3 males), or sham-surgery (Neo-C: 4 females, 4 males). Two additional monkeys (1 female, 1 male) did not undergo surgery but experienced the same rearing conditions (Neo-UC). One cohort of the Neo-C subjects (Neo-C-1 to Neo-C-6) was born at the University of Texas M.D. Anderson Cancer Center Science Park (Bastrop, TX), and a second cohort of the Neo-C subjects (Neo-C-7 to Neo-C-10) was born at the Yerkes National Primate Research Center (Lawrenceville, GA). At both institutions, monkeys received identical rearing procedures that included extensive opportunities for social interactions with age-matched peers and with human caregivers (for details see Goursaud and Bachevalier, 2007; Raper et al., 2013). Independent sample *t*-tests revealed no significant differences between the GA and TX cohorts on any measure collected for this study. Additional independent-sample *t*-tests compared the Neo-C and Neo-UC groups and indicated also that these groups did not differ significantly.

Table 1
Summary of Lesion Extents.

Subjects	PRh				ERh				TE			
	L%	R%	X%	W%	L%	R%	X%	W%	L%	R%	X%	W%
Neo-PRh-1	89.76	79.91	83.34	69.04	28.51	2.28	15.39	0.65	4.53	9.70	7.11	0.44
Neo-PRh-2	68.16	70.58	69.37	48.11	17.72	20.65	19.19	3.36	0.14	0.06	0.10	0.00
Neo-PRh-3	65.45	81.02	73.23	53.02	7.72	3.12	5.42	0.24	0.26	3.39	1.82	0.01
Neo-PRh-4	59.40	74.73	67.06	44.39	11.55	17.84	14.69	2.06	0.72	2.62	1.67	0.02
Neo-PRh-5	75.90	66.81	71.35	50.71	38.60	29.86	34.32	11.53	0.72	0.41	0.57	0.00
Neo-PRh-6	74.12	80.31	77.22	59.53	25.34	43.64	34.49	11.06	0.37	2.93	1.65	0.01
Average	72.13	75.06	73.60	54.13	21.57	19.57	20.57	4.87	1.12	3.19	2.15	0.08

Subjects	TH/TF				AMY				HF			
	L%	R%	X%	W%	L%	R%	X%	W%	L%	R%	X%	W%
Neo-PRh-1	0.00	0.00	0.00	0.00	8.24	10.86	9.55	0.89	0.13	2.39	1.26	0.00
Neo-PRh-2	0.00	0.00	0.00	0.00	0.00	2.76	1.38	0.00	0.00	0.00	0.00	0.00
Neo-PRh-3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.27	0.14	0.00
Neo-PRh-4	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Neo-PRh-5	7.02	3.93	5.47	0.28	0.00	0.00	0.00	0.00	3.37	0.00	1.68	0.00
Neo-PRh-6	0.00	0.00	0.00	0.00	3.78	4.17	3.97	0.16	3.32	0.32	1.77	0.01
Average	1.17	0.66	0.91	0.05	2.00	2.96	2.48	0.18	1.12	0.50	0.81	0.00

Scores are estimates of intended and unintended damage following Neo-PRh lesions for each case. L% = percent damage to left hemisphere; R% = percent damage to right hemisphere; X% = average damage to both hemispheres; W% = weighted damage to both hemispheres ($W\% = (L\% \times R\%) / 100$). PRh, perirhinal cortex; ERh, entorhinal cortex, TE, temporal cortical area; TH/TF, parahippocampal cortex; AMY, amygdala; HF, hippocampal formation. Lesion extents from cases Neo-PRh-1 thru Neo-PRh-6 were previously reported by Zeamer et al. (2015).

Thus, for all analyses reported below, data from all 10 Control animals were combined into a single Neo-C group.

At the time of Experiment 1, the animals were an average of 6.9 years old. All monkeys had similar experience with cognitive testing, having previously completed tests of object recognition (Weiss and Bachevalier, 2016; Zeamer et al., 2015), working memory (Weiss et al., 2016), and emotional reactivity (Ahlgren et al., 2017). At the time of Experiment 2, the animals had reached 9.7 years old on average, and had additional experience with tasks of Concurrent Discrimination/Reinforcer devaluation, and Safety Signal Learning.

2.2. Neuroimaging and surgical procedures

All neuroimaging and surgical procedures were previously described in detail (Zeamer et al., 2015) and are briefly summarized below. To create the selective PRh lesions, two series of MR images (structural T1 and Fluid Attenuated Inversion Recovery, FLAIR) were acquired pre-surgically to calculate injection sites and served as a baseline for lesion extent measurements, respectively. The same series were repeated one week post-surgery to estimate extent of lesions. Images were acquired using a Siemens 3.0 T/90 cm whole body scanner and a 3" circular surface coil. First, a T1-weighted scan (spin-echo sequence, echo time [TE] = 11 ms, repetition time [TR] = 450 ms, contiguous 1 mm section, 12 cm field of view [FOV], 256 × 256 matrix) was acquired in the coronal plane. Additionally, three fluid attenuated inversion recovery (FLAIR) scans (3D T2-weighted fast spoiled gradient [FSPGR]-echo sequence, TE = 2.6 ms, TR = 10.2 ms, 25° flip angle, 12 cm FOV, 256 × 256 matrix) were obtained in the coronal plane at 3.0 mm (each offset of 1 mm posteriorly) throughout the brain.

Throughout the duration of the scans and surgery that followed, the animals were under gas anesthesia (1.0–3.0%, v/v, to effect) and their head was secured in a stereotaxic apparatus. An IV drip containing dextrose and 0.45% sodium chloride was used to maintain normal hydration, a heating pad was placed under the animals to prevent hypothermia, and vital signs (heart and respiration rates, expired CO₂, and temperature) were recorded during the neuroimaging and surgical procedures.

Upon completion of pre-surgical scans, the animals were moved to

the surgical suite where they were prepared for injections using aseptic surgical procedures. Three sites were selected bilaterally and their MR coordinates transformed into stereotaxic coordinates. These sites were spaced in 2 mm intervals along the anterior-posterior axis of the PRh, and each site was injected with 0.4 μl ibotenic acid (Biosearch Technologies, Novato, CA, 10 mg/ml in PBS, pH 7.4) at a rate of 0.2 μl/min. Sham-operated controls underwent the same anesthetic, imaging, and surgical procedures, except no needles were lowered in the brain. After completion of the surgical procedures, animals were closely monitored until they fully recovered from anesthesia.

Analgesic (acetaminophen, 10 mg/kg, p.o.) was given QID for 3 days after surgery. Additionally, all animals received dexamethazone sodium phosphate (0.4 mg/kg, i.m., SID) to reduce edema, and Cephazolin (25 mg/kg, i.m., SID) to prevent infection starting 12 h prior to surgery and ending 7 days after.

2.3. Lesion assessment

All monkeys are participating in an ongoing longitudinal study, and so post-mortem histological evaluations of the lesions are unavailable at this time. Instead, lesion extents were estimated using coronal FLAIR images acquired 1-week post-surgery. Ibotenic acid injection causes cell death and induces edema that are detected as hypersignals (increased fluids) on the FLAIR images. Using Adobe Photoshop, these areas of hypersignals were drawn onto corresponding coronal sections of a normal 1-week old rhesus monkey brain (J. Bachevalier, unpublished atlas). These images were imported into Image J[®] and the lesion surface area was calculated in pixel² for each slice. The volume of the lesion was then calculated by summing the surface area of the lesion on each coronal section and multiplying by image thickness (1 mm). Finally, the percent damage to the intended area (PRh), and unintended damage to adjacent structures (visual areas TE/TEO, entorhinal and parahippocampal cortex, amygdala, and hippocampus), was calculated by dividing the volume of the lesion by the volume of each structure in the control atlas and multiplying by 100 (for details see Nemanic et al., 2004).

A summary of the extent of intended and unintended damage resulting from the ibotenic acid injections for each surgical case is

Case Neo-PRh-5

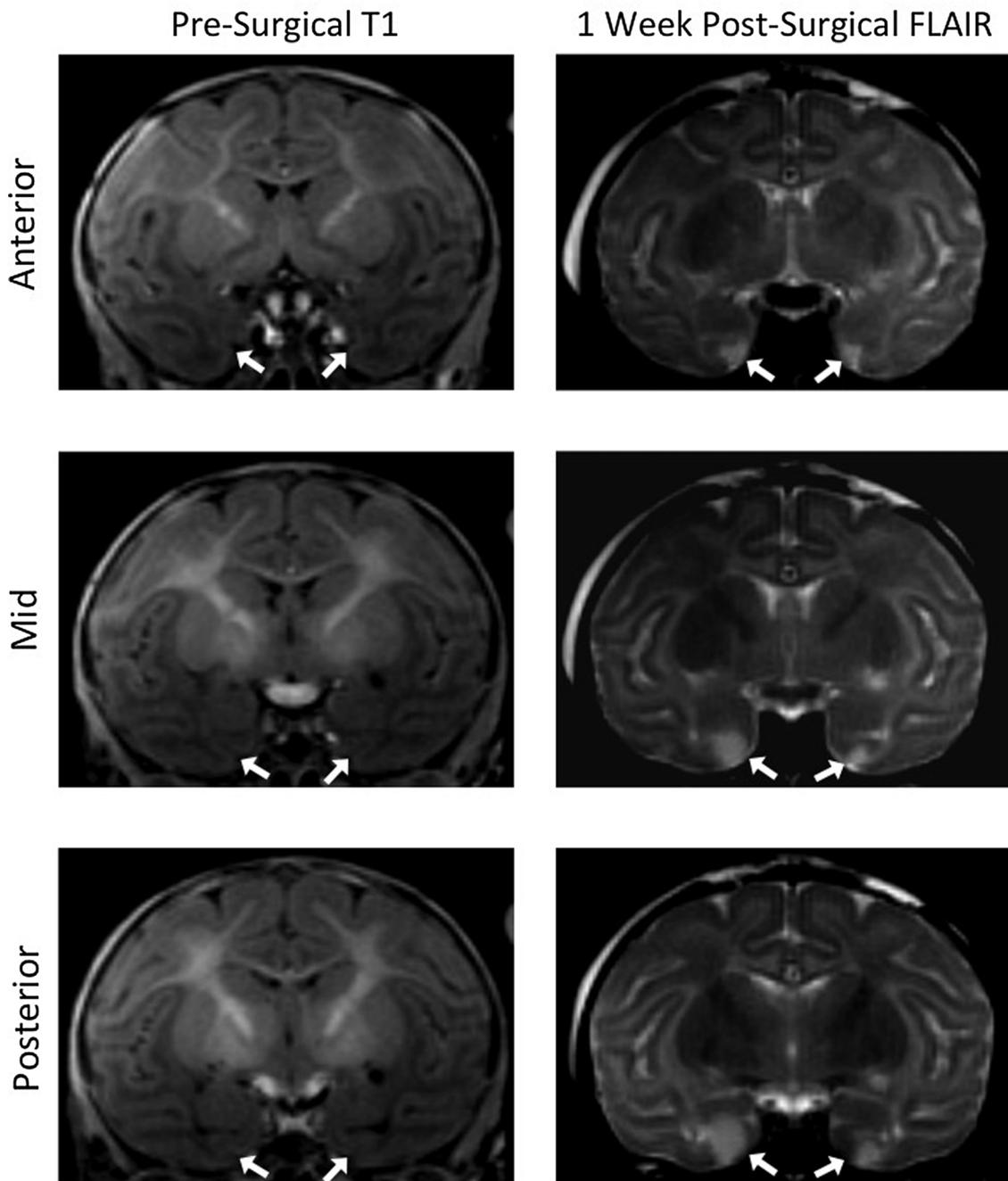


Fig 1. Coronal MR images from a representative case (Neo-PRh-5).

Pre-surgical structural T1-weighted images (left column) and Post-surgical FLAIR images (right column) at three rostro-caudal levels through the perirhinal cortex from a representative case (Neo-PRh-5). Post-surgical FLAIR images show regions of hypersignals (white areas) indicative of edema and cell damage caused by the injection of ibotenic acid. In the left column, arrows point to the rhinal sulcus. In the right column, arrows point to regions of hypersignals.

presented in Table 1. Briefly, extensive bilateral lateral damage to the PRh was observed for all cases (average = 73.60%, min = 67.06%, max = 83.34%). In addition, ibotenic acid injections caused mild unintended damage to the entorhinal cortex (average = 20.57%, min = 5.42%, max = 34.49%). Fig. 1 shows pre-surgical and post-surgical MR images of a representative case. Images from additional cases have been previously published (Weiss and Bachevalier, 2016; Weiss et al., 2016; Zeamer et al., 2015; Ahlgrim et al., Ahlgrim et al. submitted; Weiss et al., Weiss et al., in prep).

3. Impact of stimulus similarity on incidental object recognition

As adults, monkeys with Neo-PRh lesions showed impaired novelty preference when tested with the VPC task (see Fig. 3A reproduced from Zeamer et al., 2015). However, inspection of the pattern performance revealed that Neo-PRh monkeys performed similarly at all delays, indicating the absence of the typical forgetting curve (normal performance at short delays but impairment at longer delays) typically observed after adult-onset PRh lesions (Zeamer et al., 2015). This lack of delay-dependent performance suggests that the reduced novelty preference after Neo-PRh lesions may have resulted from impairment in

processes other than memory. Given the evidence that PRh lesions alters perceptual processes in adult monkeys (Bussey et al., 2002, 2003, 2005, 2006; Murray and Richmond, 2001), the Neo-PRh animals and their controls were tested on a version of the VPC task that used B&W stimuli designed to have overlapping features.

3.1. Methods

3.1.1. Apparatus

During all testing sessions, monkeys were seated in a custom-made Plexiglas primate chair. The subjects viewed stimuli on a 19" monitor placed approximately 40 cm away. To encourage the animals not to look away from the monitor, their head movements were restricted using a custom molded thermoplastic helmet (Machado and Nelson, 2011). An experimenter controlled the stimulus presentation via a Dell laptop connected to the monitor. A digital video camera was mounted above the monitor and focused on the eyes such that the experimenter had a clear view of the looking behavior throughout the entire testing session. Looking behavior during each testing session was recorded onto a memory card for later coding.

3.1.2. Task

The VPC task is a preferential looking paradigm that takes advantage of the natural inclination of monkeys to look at novel stimuli. In this version, the stimuli consisted of pairs of images of highly similar black and white objects and were identical to those used by Zeamer and Bachevalier (2013). Fig. 2 provides examples of the stimuli, and a schematic representation of a VPC trial. Each trial consisted of a Familiarization during which monkeys fixated on a centrally presented stimulus until a cumulative looking time of 30 s was achieved. Then, the screen went black for a variable delay (10s, 60s, or 120s), which was followed by two 5-s Retention Tests (each separated by a 5 s delay). In the retention tests, the familiarized object was paired with a novel of the same category, shape and color. Variable delays were randomly intermixed within a daily session. The left-right position of the novel and familiar stimulus varied pseudo-randomly across trials and was reversed between the first and second Retention Tests. Trials were separated by 30-s inter-trial intervals during which the screen remained black and the monkey was offered a preferred treat (i.e. raisin, jelly bean, marshmallow). A white noise generator was used throughout testing to reduce external noise and minimize disruptions. Monkeys completed between 3 and 7 trials per testing day, and were tested until they completed 10 trials at each delay (30 trials total).

3.1.3. Data analysis

Preferential looking towards the novel stimuli is an index for recognition of the familiarized stimulus. Novelty preference scores were calculated for each trial using frame-by-frame analysis of the eye movements recorded during testing (see details in Pascalis and Bachevalier, 1999). A trained observer (with inter-observer reliability:

Pearson $r = 0.931$), who was blind to experimental condition and the location of the novel image, scored the videos. From each trial three measures were calculated: 1) *familiarization time*, defined as the time to accumulate 30 s of fixation in the familiarization phase; 2) *total looking time*, defined as the total amount of time spent looking at each stimulus during both retention tests; and 3) *percent novel*, defined as the time spent looking at the novel stimulus during the two retention tests divided by the total looking time and then multiplied by 100. Trials for which the total looking time was less than 1 s were excluded from the analysis, but this occurred on less than 6% of trials (30 out of the total 580).

Group X Delay ANOVAs, using repeated measures for the second factor, tested the effects of the lesion and delay-length on familiarization time, total looking time, and novelty preference for the B&W stimuli. Planned independent-sample *t*-tests were subsequently used to compare scores between the Neo-C and Neo-PRh groups at each delay. To determine whether there were any female/male differences among the groups, all analyses were also run using sex as a second independent factor. None of the analyses revealed significant sex effects, and so both sexes were combined for all analyses reported in the Results section. For all ANOVAs, effect sizes were reported using partial eta squared (η_p^2). For all *t*-tests, effect sizes were reported using Cohen's *d* (d_{Cohen}).

To determine if the size of the lesion could have impacted performance on the B&W VPC, additional bivariate Pearson correlations were performed between extent of PRh damage, or unintended damage of the adjacent entorhinal cortex (ERh), and novelty preference at each delay.

3.2. Results

3.2.1. Familiarization time

Analysis of the Familiarization Time revealed that Neo-C and Neo-PRh groups required similar amounts of time to accumulate the 30 s of looking time required during the familiarization phase of the B&W VPC task [Group: $F(1,14) = 0.094$, $p = 0.766$, $\eta_p^2 = 0.007$; Delay: $F(2,28) = 1.382$, $p = 0.268$, $\eta_p^2 = 0.090$; Group X Delay: $F(3 = 2,28) = 0.376$, $p = 0.690$, $\eta_p^2 = 0.026$]. Table 2 summarizes the average familiarization times for the two groups at each of the three delays tested.

3.2.2. Total looking time

The average total looking times are reported in Table 2 for each group at each of the three delays tested. Analysis of the Total Looking Time (TLT) indicated that the Neo-C group had significantly higher TLTs than the Neo-PRh group [$F(1,14) = 8.264$, $p = 0.012$, $\eta_p^2 = 0.371$]. Analyses also revealed a significant effect of Delay [$F(2,28) = 12.637$, $p < 0.001$, $\eta_p^2 = 0.474$], and a significant interaction [$F(2,28) = 3.605$, $p = 0.040$, $\eta_p^2 = 0.205$]. Planned independent-sample *t*-test revealed that group Neo-C had significantly longer TLTs than group Neo-PRh during all delays [10s: $t(14) = 3.115$, $p = 0.008$, $d_{\text{Cohen}} = 1.609$; 60s: $t(14) = 2.708$, $p = 0.017$, $d_{\text{Cohen}} = 1.398$; 120s: t

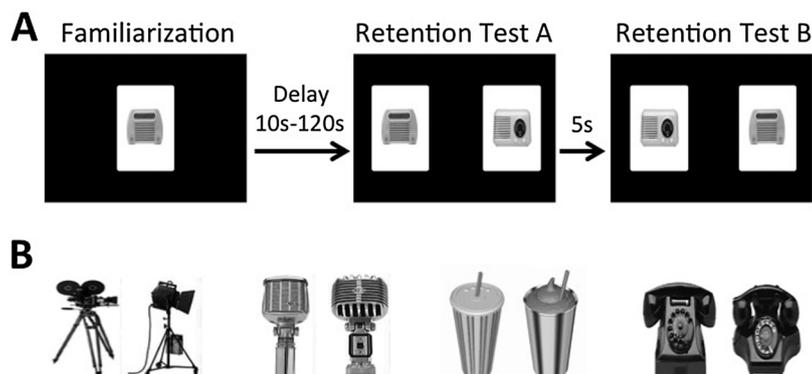


Fig. 2. Schematic of B&W Visual Paired Comparison (VPC) Task.

In [A], a representative trial of the VPC task that consisted of a cumulative familiarization phase of 30 s followed by delays from 10, 60 and 120s, after which two Retention tests of 5 s each were given separated by a 5 s delay. In the Retention tests, the now familiar stimulus was paired with a novel, but similar, stimulus. Inter-trial-intervals of 30 s separated the trials. Examples of the stimuli used in this task are shown in [B].

Table 2
Summary of Visual Paired Comparison with B&W stimuli.

Dependent Measures	Group			
	Neo-C		Neo-PRh	
	Average	SEM	Average	SEM
<i>Familiarization Time (s)</i>				
10 s delay	194.5s	52.5	216.5s	14.3
60 s delay	188.9s	54.1	198.6s	17.0
120 s delay	191.3s	52.3	207.7s	13.1
<i>Total Looking Time (s)</i>				
10 s delay	5.5s	1.1	2.5s	0.3
60 s delay	4.8s	1.0	2.2s	0.2
120 s delay	4.5s	1.0	2.2s	0.2
<i>Novelty Preference (%)</i>				
10 s delay	66.0%	8.2	62.6%	2.8
60 s delay	65.0%	7.8	57.2%	3.2
120 s delay	64.4%	7.9	56.6%	3.1

Scores for Familiarization and Total Looking Time are reported in seconds. Scores for Novelty Preference are the percent of the total looking time spent viewing novel stimuli. SEM, standard error.

(14) = 2.686, $p = 0.018$, $d_{\text{Cohen}} = 1.387$]. Additional planned paired-sample t -tests indicated that the TLT of group Neo-C was significantly higher for the 10 s delay than the 60 s [$t(9) = 4.386$, $p = 0.002$, $d_{\text{Cohen}} = 0.286$] and 120 s [$t(9) = 8.200$, $p \ll 0.001$, $d_{\text{Cohen}} = 0.441$], but did not differ between the 60 s and 120 s delays [$t(9) = 1.495$, $p = 0.169$, $d_{\text{Cohen}} = 0.141$]. In contrast, TLT for the Neo-PRh group did not differ between any of the delay conditions [10 s vs 60s: $t(5) = 1.150$, $p = 0.302$, $d_{\text{Cohen}} = 0.359$; 10 s vs 120s: $t(5) = 1.513$, $p = 0.191$, $d_{\text{Cohen}} = 0.467$; 60 s vs 120s: $t(5) = 0.290$, $p = 0.784$, $d_{\text{Cohen}} = 0.106$].

3.2.3. Novelty preference

The average novelty preferences of Neo-PRh and Neo-C groups are illustrated for each of the 3 delays in Fig. 3B, and reported in Table 2. A 2-way repeated measures ANOVA revealed significant main effects of Group [$F(1,14) = 6.637$, $p = 0.022$, $\eta_p^2 = 0.322$] on Novelty Preference, but no significant main effect of Delay [$F(2,28) = 2.374$, $p = 0.112$, $\eta_p^2 = 0.145$] and no interaction between these factors [$F(2,28) = 0.908$, $p = 0.415$, $\eta_p^2 = 0.061$]. Planned group comparisons of novelty preferences at each delay separately revealed significant group differences in Novelty Preference at the 60 s and 120 s delays [60s: $t(14) = 2.582$, $p = 0.022$, $d_{\text{Cohen}} = 1.334$; 120s: $t(14) = 2.358$, $p = 0.033$, $d_{\text{Cohen}} = 1.218$], but not at the 10 s delays [$t(14) = 0.989$, $p = 0.339$, $d_{\text{Cohen}} = 0.511$]. Finally, one-sample t -tests indicated that the novelty preferences of group Neo-C differed from chance (50%) at all delays tested [10s: $t(9) = 7.529$, $p \ll 0.001$, $d_{\text{Cohen}} = 2.381$; 60s: $t(9) = 10.697$, $p \ll 0.001$, $d_{\text{Cohen}} = 3.384$; 120s: $t(9) = 8.077$, $p \ll 0.001$, $d_{\text{Cohen}} = 2.531$], whereas the novelty preferences of group Neo-PRh differed significantly from chance at the 10 s delay [$t(5) = 4.572$, $p = 0.006$, $d_{\text{Cohen}} = 1.867$] but not at the 60 s and 120 s delays [60s: $t(5) = 2.266$, $p = 0.073$, $d_{\text{Cohen}} = 0.925$; 120s: $t(5) = 2.159$, $p = 0.083$, $d_{\text{Cohen}} = 0.882$].

3.2.4. Correlation with lesion extent

The extent of PRh damage was not correlated with novelty preference at any of the delays tested [1s: $r = 0.542$, $p = 0.267$; 10s: $r = 0.309$, $p = 0.551$; 60s: $r = -0.629$, $p = 0.181$; 120s: $r = -0.415$, $p = 0.414$]. Similarly, the extent of unintended entorhinal cortex damage was not correlated with any measures of task performance [1s: $r = 0.372$, $p = 0.527$; 10s: $r = 0.328$, $p = 0.526$; 60s: $r = -0.122$, $p = 0.817$; 120s: $r = 0.667$, $p = 0.148$]. However, it must be acknowledged that the lesions in the Neo-PRh monkeys were similar in extent, ranging only between 70%–85% (see Table 1). This lack of variability

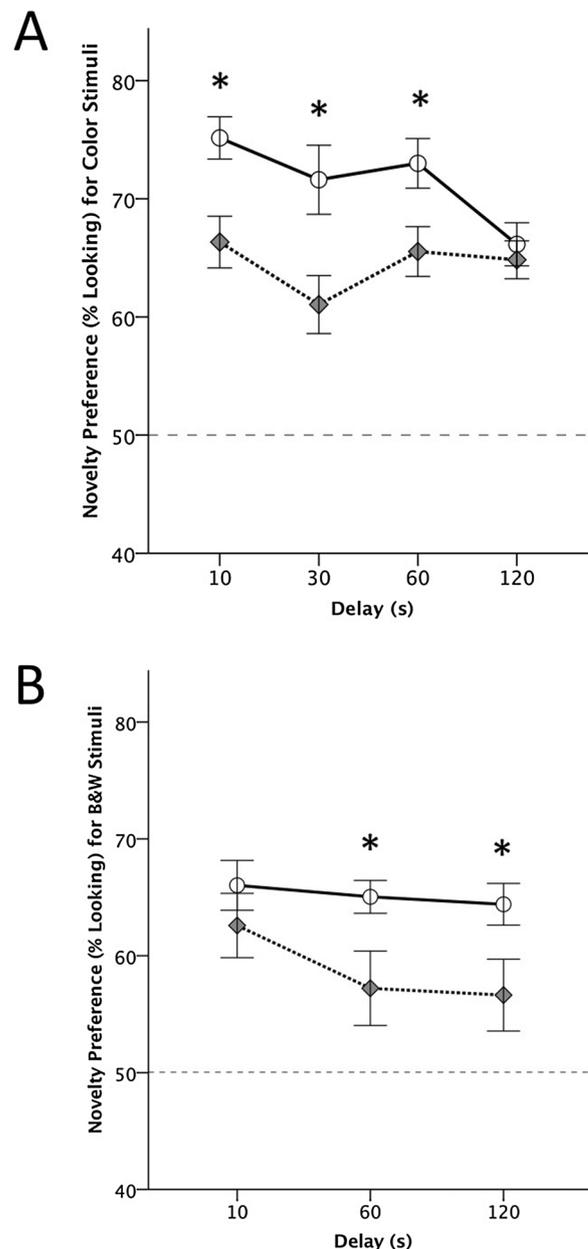


Fig. 3. Black and White VPC.

Average novelty preference (\pm SEM) across the delays in animals with neonatal perirhinal cortex lesions (Neo-PRh: shaded diamonds, dashed lines) and sham operated controls (Neo-C: open circles, solid line). Graph in [A] illustrates performance of the animals tested at 48 months in the VPC tasks using color stimuli (from Zeamer et al., 2015). Graph in [B] illustrates performance of the same animals on the B&W VPC task. Chance is at 50%. *indicates significant group differences ($p \ll 0.05$).

may have contributed to the lack of correlations between extent of lesions and task performance.

3.3. Summary

Experiment 1 tested whether poor perceptual abilities contributed to the recognition memory deficits reported previously in the Neo-PRh monkeys (Weiss and Bachevalier, 2016; Zeamer et al., 2015) with a new version of the VPC task using perceptually similar B&W stimuli. The results indicated that both groups had similar levels of novelty preference when the delays were kept short (10s), but that Neo-PRh animals had significantly lower novelty preferences when the delays were extended to 60 s and 120s. Additionally, Neo-PRh monkeys had similar

Total Looking Time (TLT) at all delays as compared to controls that had greater TLTs at the shorter delay (10s) than at the longer delays (60s and 120s). The group difference indicated that Neo-PRh monkeys attended less frequently to the stimuli during the retention tests than Neo-C monkeys. This decrement in TLTs did not seem to directly impact novelty preference scores, first because Neo-PRh monkeys had novelty preference scores in the normal range at the short delay despite low TLTs, and second because Neo-C monkeys had significant novelty preference scores at the longer delays even though their TLTs at these long delays were lower than at the shorter delay. Given the normal levels of novelty preference of group Neo-PRh at the 10s delay but not at the longer delays, these data replicate the previously reported recognition memory deficits in the same animals (Zeamer et al., 2015; Weiss and Bachevalier, 2016) and suggest that Neo-PRh monkeys have perceptual abilities within the normal range.

4. Familiarity discrimination

Adult monkeys with Neo-PRh lesions were impaired on two object recognition tasks: VPC and DNMS (Weiss and Bachevalier, 2016; Zeamer et al., 2015). However, compared with adult-onset PRh lesions, the Neo-PRh lesions resulted in a partial sparing of recognition memory when measured using VPC, but not when measured using DNMS. An important procedural difference between the two memory tasks is the length of the familiarization time. Although the VPC task requires a 30 s cumulative familiarization time, the DNMS task requires a shorter amount of time, that is the time the monkeys takes to displace the object (usually 3–7s). Therefore, one possible explanation for the recognition memory sparing observed with the VPC task is that Neo-PRh animals were exposed for longer time to the stimulus. To test whether animals with Neo-PRh may require longer time to become familiarized with a stimulus, they were trained as well as their controls in the Constant Negative task (Browning et al., 2013), which required them to discriminate a novel object from an object for which the animals have been familiarized with.

4.1. Methods

4.1.1. Subjects

All 6 of the Neo-PRh animals (Neo-PRh-1–Neo-PRh-6) participated in this experiment. However, at the time of this experiment, only 3 of the Neo-C animals were available to participate: Neo-C-1, Neo-C-7, and Neo-C-9 (Neo-C-2 through Neo-C-6 and Neo-C-10 were euthanized prior to this study. Neo-C-8 could not be tested due to illness).

4.1.2. Apparatus and stimuli

In our version of the Constant Negative task, monkeys were positioned in the Wisconsin General Testing Apparatus (WGTA) facing a tray with 3 recessed food wells (2 cm diameter, 1 cm deep, spaced 13 cm apart). A collection of 960 junk objects that differed in size, shape, color, and texture were used as familiar stimuli and repeated every day or as novel stimuli, which were sampled without replacement each day until completion of the task. Correct responses were rewarded with preferred food rewards (i.e. mini-marshmallow, jelly bean, M&M etc.). Animals were mildly food deprived prior to testing, and their weight monitored carefully and maintained at least 85% of normal body weight.

4.1.3. Task

The Constant Negative task was based on the paradigm developed by Browning et al. (2013), and is illustrated in Fig. 4. During a daily session, monkeys were given a set of 60 unique discrimination problems in which they chose between two objects. For each problem, one object was designated the unrewarded “constant negative” stimulus (S-) and another never-before-seen (novel) object was designated the rewarded stimulus (S+). The 60 S- objects were presented once during every

daily session, and became familiar over several days of testing. In contrast, the S+ objects presented together with the S- were always novel, and were drawn from the pool of the remaining 900 junk objects without replacement. The order in which the 60 S- stimuli were presented was shuffled each session and a 30-s intertrial interval was used. Monkeys were trained daily in this task until they reached the learning criterion of 90% (54/60) correct followed by a score of 85% (51/60) or better the subsequent training session.

4.1.4. Comparison with concurrent discrimination task

Like the VPC and DNMS tasks, the Constant Negative task is designed to encourage the discrimination of novel objects among a set of familiar objects. However, the use of alternative strategies may also support performance on the task. For example, although it is possible that performance was driven by a mnemonic-based strategy of responding to novel stimuli (accomplished by using memory traces to discriminate novel from familiar stimuli), performance could also have been driven by a habit-based learning systems (see Bachevalier, 1990). If so, monkeys may have instead learned to avoid the Constant Negative objects because they were consistently associated with non-reward, as is the case in traditional habit learning paradigms, such as the Concurrent Discrimination task (see Mishkin et al., 1984), rather than because the familiar objects were explicitly remembered and avoided. In the Concurrent Discrimination task, monkeys are shown a list of 30 pairs of objects, one of which is always rewarded and the other not. The same two objects are always paired together and presented once every 24 h. Over several testing sessions, monkeys gradually learn by trial-and-errors which objects are rewarded, and which ones are to be avoided. This task has been previously shown to depend on striatal circuitry and not the medial temporal lobe structures (Mishkin and Appenzeller, 1987; Teng et al., 2000; Fernandez-Ruiz et al., 2001). Given that the Neo-PRh and Neo-C groups had also previously completed a 60-pair Concurrent Discrimination task using the same testing apparatus and similar but different stimuli (personal communication, J. Bachevalier), we compared the scores the animals obtained in both tasks to gain insight into the types of strategies the animals may have used to support their performances. It should be noted that, although all Neo-C monkeys completed the Concurrent Discrimination task, only those who participated in Experiment 2 (Neo-C-1, Neo-C-7, and Neo-C-9) were included in these comparisons. For full methodological details of the Concurrent Discrimination paradigm, please see Kazama et al. (2014). Given the large body of work reporting preserved visual habit learning following MTL damage (Squire, 2004; Squire and Zola, 1996; Bachevalier, 1990), we predicted that the Neo-PRh monkeys would perform as well as controls.

4.1.5. Data analyses

The numbers of trials and errors to reach the learning criterion were used as the dependent measures, and independent sample *t*-tests were used to compare the performance of the Neo-PRh monkeys with that of the Neo-C. The same analyses were also re-run using a Group X Sex ANOVA to determine whether there were any female/male differences among the groups. None of the analyses revealed significant sex effects, and so both sexes were combined for all analyses reported in the Results section.

Additionally, to investigate whether the speed at which the Neo-PRh animals became familiar with the S- objects differed from that of the Neo-C animals, we calculated the learning curves for each group. A multiple regression model was used to determine whether the slopes of the learning curves differed between the two groups.

Bivariate Pearson correlations were performed to examine the relationship between the scores on the Constant Negative task and the extent of PRh damage or unintended damage to adjacent areas.

Finally, to compare performance on the Constant Negative task with that of the Concurrent Discrimination task, a Group x Task repeated measures ANOVA was used to compare the number of errors needed to

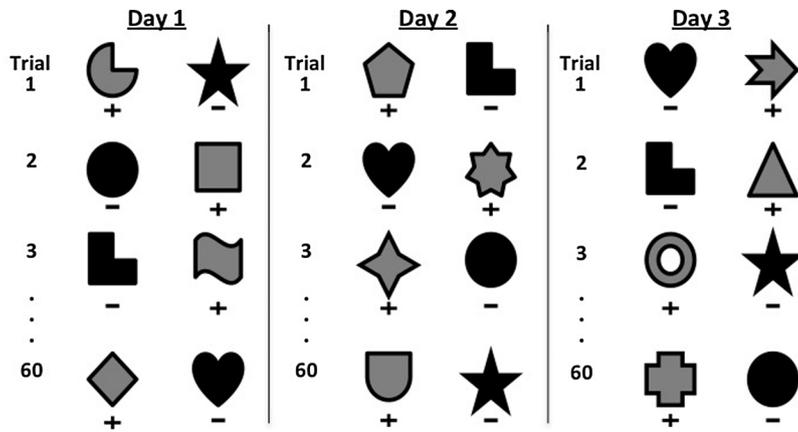


Fig. 4. Schematic diagram of the Constant Negative task.

Schematic diagram of the Constant Negative Task adapted from Browning et al. (2013). During each daily session, monkeys were given a set of 60 unique discrimination problems and chose between a rewarded novel object (S+ shown in gray) and an unrewarded object that was repeated in each daily session (S- shown in black). A 30-s interval separated each discrimination problem.

reach the same learning criterion (54 out of 60) on the two tasks.

For all ANOVAs, effect sizes were reported using partial eta squared (η_p^2). For all T-tests, effect sizes were reported using Cohen's d (d_{Cohen}).

4.2. Results

The average number of errors made by the Neo-C and Neo-PRh groups (92 and 110 respectively) before reaching the learning criterion did not significantly differ [$t(7) = -1.07$, $p = 0.321$, $d_{\text{Cohen}} = 0.755$; see Fig. 5B]. However, as illustrated in Fig. 5A, the Neo-PRh group required significantly more trials than the Neo-C group (450 and 320 respectively) prior to achieving the learning criterion [$t(7) = -2.54$, $p = 0.039$, $d_{\text{Cohen}} = 1.798$].

A multiple regression model using Group, Session, and their interaction, was found to significantly predict Errors [$F(3,67) = 39.726$, $p \ll 0.0001$, $R^2 = 0.640$]. Results of this analysis indicated that Group [$\beta = -0.578$, $t(67) = -3.584$, $p = 0.001$] and Session [$\beta = -1.405$, $t(67) = -7.102$, $p \ll 0.001$] were both reliable predictors of Errors on the Constant Negative task. Importantly, the interaction between Group and Session was also significant [$\beta = 0.967$, $t(67) = 3.637$, $p = 0.001$], suggesting that the slopes of the learning curves (Fig. 6) differed between the groups, with the Neo-C group having steeper (faster) learning curves than the Neo-PRh group.

4.2.1. Correlations with lesion extent

The extent of PRh damage was not correlated with any measures of task performance [Errors: $r = -0.557$, $p = 0.251$; Trials: $r = -0.574$, $p = 0.234$]. Similarly, the extent of entorhinal damage was not correlated with any measures of task performance [Errors: $r = -0.186$, $p = 0.724$; Trials: $r = -0.716$, $p = 0.109$]. This indicates that the extent of the damage caused by the neonatal ibotenic acid injections is not likely to be related to task performance, however this conclusion should be tempered with the observation that the lesions in the Neo-PRh monkeys had limited variability, ranging only between 70%–85% (see Table 1).

4.2.2. Comparisons with concurrent discrimination task

A comparison of the number of errors each group made in the Constant Negative and Concurrent Discrimination tasks is illustrated in Fig. 7. The Group \times Task interaction [$F(1,7) = 8.346$, $p = 0.023$, $\eta_p^2 = 0.544$], as well as the main effect of Task [$F(1,7) = 10.418$; $p = 0.014$, $\eta_p^2 = 0.598$] reached significance, but the effect of Group did not [$F(1,7) = 5.050$, $p = 0.059$, $\eta_p^2 = 0.419$]. Planned paired-sample t -tests revealed that the Neo-PRh group made similar numbers of errors in both tasks (average = 110 vs 117 errors for Constant Negative and Concurrent discrimination tasks respectively; $t(5) = -0.364$, $p = 0.731$, $d_{\text{Cohen}} = 0.217$). By contrast, the Neo-C group made fewer errors in the Constant Negative task than in the

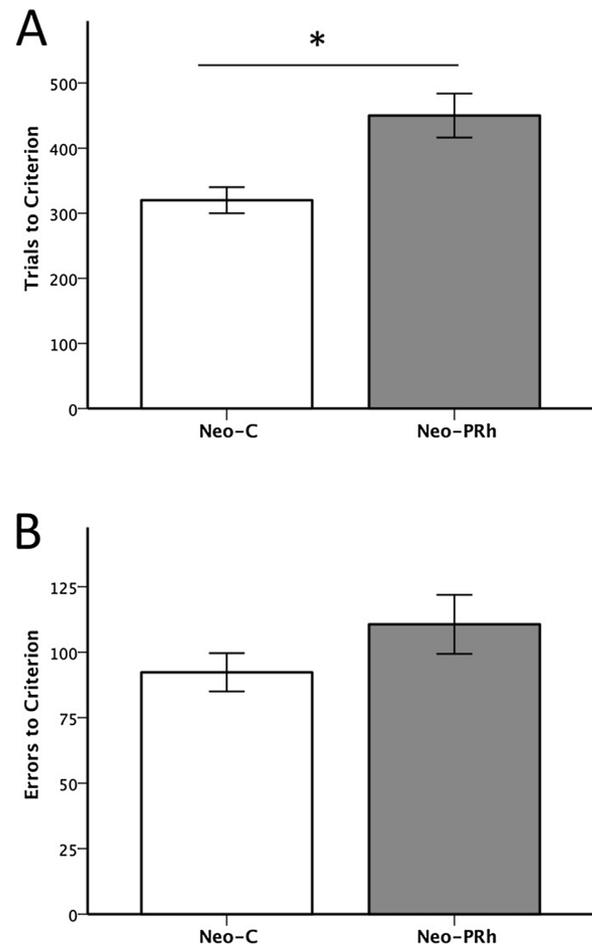


Fig. 5. Constant Negative Trials and Errors to Criterion.

Average number of Trials [A] and Errors [B] for group Neo-PRh (shaded bars) and sham operated Controls (open bars) to meet the 90% correct learning criterion on the Constant Negative task. Bars represent \pm SEM, and * indicates significant group differences ($p \ll 0.05$).

Concurrent discrimination task (average = 92 vs 212, respectively), but this difference did not reach significance, [$t(2) = -2.739$, $p = 0.111$, $d_{\text{Cohen}} = 2.452$]. Finally, planned comparisons indicated that, although both groups had the same number of errors in the Constant Negative task, group Neo-PRh made significantly less errors than group Neo-C on the Concurrent Discrimination task [$t(7) = 2.919$, $p = 0.022$, $d_{\text{Cohen}} = 2.064$].

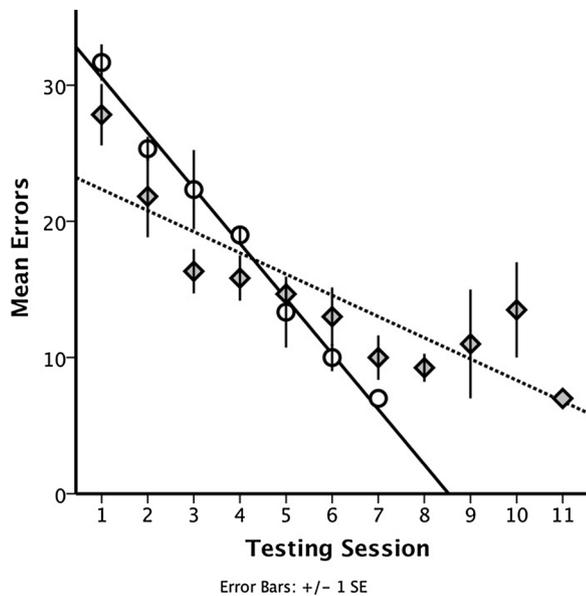


Fig. 6. Errors by testing sessions.

Average number of errors plotted across each testing session for group Neo-PRh (shaded diamonds) and group Neo-C (open circles) on the Constant Negative task. Bars represent \pm SEM.

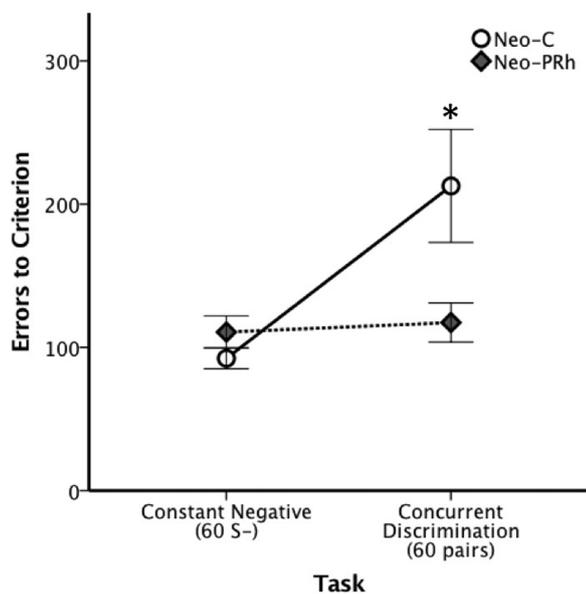


Fig. 7. Comparison between Constant Negative and Concurrent Discrimination.

Average number of Errors for group Neo-PRh (shaded diamonds, dashed line) and group Neo-C (open circles, solid line) to meet the 90% correct criterion for the Constant Negative task versus the Concurrent Discrimination Task. Data for the concurrent discrimination task were generously provided by A. Kazama and J. Bachevalier. Bars represents \pm SEM, and * indicates significant group differences ($p < 0.05$).

4.3. Summary

Experiment 2 assessed the effects of Neo-PRh lesions on familiarity judgment using the Constant Negative task. Neo-PRh monkeys required significantly more trials to reach the learning criterion, yet they made similar numbers of errors as controls. Further analysis revealed that the speed at which the Neo-PRh animals became familiar with the Constant Negative S- objects was slower than the Neo-C animals. These differential learning rates suggest that Neo-PRh monkeys were slower to familiarize with the constant negative (S-) objects as compared to controls. Finally, unlike control animals, those with Neo-PRh lesions performed similarly in both the Constant Negative and Concurrent

Discrimination tasks.

5. Discussion

This study revealed several original findings on the long-term effects of neonatal PRh lesions. First, although these early lesions had minimal, or no, impact on perceptual abilities, they did affect the speed with which animals became familiar with stimuli. Second, a comparison between performance on the Constant Negative task and the Concurrent Discrimination task also suggests that animals with Neo-PRh lesions may have developed strong habit learning strategies to compensate for their poor recognition memory abilities. These findings are discussed in turn.

5.1. Perirhinal cortex and perceptual abilities

Previous lesion studies in adult monkeys have provided evidence for a critical role of the PRh in perceptual abilities (for review see Murray et al., 2007). Experiment 1 sought to determine whether neonatal lesions of the PRh would lead to similar perceptual impairment. Using a version of the VPC task with highly similar B&W stimuli, adult monkeys with neonatal PRh lesions displayed normal levels of novelty preference on the B&W VPC task after short delays, but were impaired as compared to controls when delays extended to 60 s and 120s. This pattern of performance disproves the proposal that perceptual impairments may account for the poor recognition memory performance of Neo-PRh monkeys reported earlier (Weiss and Bachevalier, 2016; Zeamer et al., 2015). Instead, these data indicate that Neo-PRh monkeys have perceptual abilities within the normal range but have impaired recognition memory.

The normal perceptual ability after neonatal PRh lesions contrasts with data from a series of studies in adult-onset PRh lesions reporting perceptual impairments using B&W photographic stimuli with highly overlapping features (Bussey et al., 2002, 2003, 2005, 2006; Hampton, 2005). One possible explanation for the lack of perceptual impairments after Neo-PRh lesions may relate to the stimuli used, which may not have been sufficiently ambiguous as compared to those used in adult-onset lesions in both monkeys and humans. For example perceptual impairment in adult human neuropsychiatric patients with PRh damage has been reported when tested using abstract B&W stimuli (Barense et al., 2012; Neusome et al., 2012), but not color (Hales et al., 2015). However, perceptual impairment was found in patients with brain damage that included the PRh when tested with B&W line drawings similar to those used in the current study (Newsome et al., 2012). Thus, differences in the types of stimuli used may not entirely explain the different outcomes between early-onset and adult-onset PRh lesions in perceptual abilities. Another, more likely, interpretation relates to the early timing of the PRh lesions in the current study. Given the levels of neural plasticity normally occurring during infancy (for reviews see Kolb and Gibb, 2011; Takesian and Hensch, 2013), it is possible that other structures could have compensated for the perceptual abilities in the absence of a fully functional PRh. For example, neuroimaging data in healthy adults have indicated that V2 activation mimics the activity of the PRh during perceptual tasks that involve difficult visual discriminations (Peterson et al., 2012). These data highlight the broader network of brain areas that are recruited during perceptual learning tasks, and point to another structure that could potentially mediate visual processing after neonatal PRh lesions.

5.2. Perirhinal cortex and familiarity judgments

The data indicate that neonatal PRh lesions slightly retarded the learning of the Constant Negative task. Given that the effects of adult-onset PRh lesions have never been investigated in this task, it is unknown at this time whether the mild impairment in familiarity judgments noted after the Neo-PRh lesions may be due to a partial sparing of

functions. However, this mild impairment may have provided a way by which the Neo-PRh lesions affected more severely performance on the DNMS task (with short exposure to objects; Weiss and Bachevalier, 2016) than on the VPC task (with longer exposure to stimuli; Zeamer et al., 2015).

Although it is still unclear whether the mild deficit in familiarity judgments after the Neo-PRh lesions may be the result of compensatory processes due to the early lesions, another factor that could have mitigated the deficit is whether monkeys developed alternative cognitive strategies to solve the task. For example, developing a habit of avoiding the familiar objects, not because they are recognized but because they are consistently associated with non-reward, could also support performance on the Constant Negative task. To examine this possibility, performance of Neo-PRh and Neo-C animals on the Constant Negative task was compared to performance of the same animals on the 60-pair Concurrent Discrimination task, a habit-learning paradigm (see Mishkin et al., 1984). Neo-C monkeys made fewer errors on the Constant Negative task than on the Concurrent Discrimination task, suggesting that they were using different strategies to solve the two tasks. This finding corroborates prior research reporting that healthy adult monkeys also make fewer errors on the Constant Negative task than on the Concurrent Discrimination task (Browning et al., 2013), and indicates that normal monkeys tend to use familiarity-based strategies to solve the Constant Negative task but habit-based strategies to solve the Concurrent Discrimination. In contrast, the Neo-PRh group made a similar number of errors on the Constant Negative and Concurrent Discrimination tasks, suggesting that these monkeys may have used habit-based strategies to guide their responses on both tasks.

An intriguing additional finding is the better performance of the Neo-PRh monkeys on the 60-pair Concurrent Discrimination task than the Neo-C monkeys. Therefore, another interpretation of the mild impairment of the Neo-PRh monkeys on the Constant Negative task is that Neo-PRh monkeys may have developed more robust habit-learning strategies than control animals, and these strategies may have helped them to compensate for their poor recognition memory as an alternate strategy to solve the Constant Negative Task. There exist a number of studies that have already demonstrated that damage to the medial temporal lobe (fornix transection or hippocampal lesions) in monkeys known to impair recognition memory, significantly facilitates learning of visual discrimination reversal (Zola and Mahut, 1973), transverse patterning (Saksida et al., 2007), and concurrent discrimination (Machado and Bachevalier, 2007). Additional studies are needed to fully assess the source of the impairment in the Constant Negative task and to disentangle the different competing cognitive systems available for performance on this memory task.

5.3. Conclusion

Ample data have demonstrated the significant recovery of sensorimotor and visual functions following early injury (for review see Cioni et al., 2011). Yet, there have been comparably fewer studies that extended recovery of functions in cognitive systems (Goldman et al., 1970; Kolb and Gibb, 2011; Kolb et al., 2013; Miller et al., 1973). The data from the current study indicate robust recovery in perceptual ability following neonatal PRh lesions, whereas the mild deficit in familiarity judgment will need to be confirmed with further assessment of the effects of adult-onset PRh lesions on the Constant Negative Task. The data also has helped clarify previous interpretations of the pattern of recognition impairment reported in adult rhesus monkeys with neonatal PRh lesions (Weiss and Bachevalier, 2016; Zeamer et al., 2015). More broadly, these results enhance our understanding of the development of recognition memory and of early brain plasticity within this system. Future studies are needed to determine the timing of critical periods during development with increased potential for functional recovery, and the factors that influence those trajectories.

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Conflict of Interest

None.

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