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Familiarity Discrimination in Rhesus Macaques with Neonatal Perirhinal Lesions

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Abstract

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By Wendi Guo

Studies in both humans and monkeys have demonstrated that the perirhinal cortex (PRh) is involved in recognition memory. However, the consequences of neonatal perirhinal lesions on recognition memory later in adulthood are not fully understood. Differences in performance seen on recognition memory tasks (better performance on VPC than DNMS) have suggested that differences in the length of familiarization time between the two tasks may be responsible for their different outcomes. To test this possibility, we tested monkeys with neonatal perirhinal lesions (Neo-PRh) on the Constant Negative task. In this task, animals were presented with repeated familiarization trials of 60 unrewarded objects. The 60 unrewarded objects (constant negatives) were paired with novel objects every testing day. As testing proceeded, the constant negative objects became familiar over the course several testing days and preference for the novel objects on each trial was used as a measure of familiarity. Neo-PRh animals made a similar number of errors compared to controls before reaching criteria. However, Neo-PRh monkeys needed significantly more trials to reach criteria than control animals. In addition, Neo-PRh animals had a slower rate of learning compared to control animals. Finally, a significant correlation was found between the number of Constant Negative trials needed to reach criteria and DNMS performance at a 30 second delay. Overall, the results suggest that early damage to the PRh causes deficits in recognition memory in adulthood and that repeated familiarization trials may be needed to overcome these deficits in the absence of a functional PRh. The present findings give us some insight on memory deficits seen in human cases of temporal lobe epilepsy.

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Introduction

Earlier studies have reported that patients affected by temporal lobe epilepsy have impairments in recognition memory (Drane et al., 2008; Rosas, Parron, Serrano, & Cimadevilla, 2013). While memory deficits reported in these patients have been mainly attributed to hippocampal loss of function (Merkow, Burke, & Kahana, 2015), there is increasing evidence that this neurological disorder extends beyond the hippocampus (Guedj et al., 2010). The perirhinal cortex has been shown to be crucial for the normal development of recognition memory (Zeamer, Richardson, Weiss, & Bachevalier, 2015). Thus, the deficits in recognition memory seen in patients with temporal lobe epilepsy may be largely attributed to damage to the perirhinal cortex.

The perirhinal cortex (PRh, Brodmann's area 35/36) is a cortical area located in the medial temporal lobe (MTL). This region of the inferotemporal gyrus sits at the boundary between MTL and the ventral visual pathway (Suzuki, 1996; Suzuki & Naya, 2014). The PRh receives significant inputs from visual association cortices important for object discrimination (Suzuki & Amaral, 1994). In turn, the PRh sends strong projections to the hippocampal formation via the entorhinal cortex (Suzuki, 1996), the orbitofrontal cortex (Suzuki & Amaral, 1994) and the lateral prefrontal cortex (Hirata et al., 2013) via the uncinate fasciculus. Thus, the PRh is well positioned to play a critical role in object perception, object discrimination and recognition memory. Studies in rats (Mumby & Glenn, 2000; Mumby & Pinel, 1994), monkeys (Buffalo, Ramus, Squire, & Zola, 2000; Malkova, Bachevalier, Mishkin, & Saunders, 2001; Meunier, Bachevalier, Mishkin, & Murray, 1993; Nemanic, Alvarado, & Bachevalier, 2004) and humans (Aggleton et al., 2005) have reported significant and long-lasting impairments in visual discrimination and recognition after selective damage to the PRh. Although the importance of the

PRh for recognition memory has been well documented in adulthood, the consequences of neonatal lesions of the PRh are less understood.

Recognition memory, the ability to identify previously encountered objects and events, is often assessed by the delayed nonmatching-to-sample (DNMS) task. In this task, a baited sample object is presented, and after a variable delay, the sample object (now unbaited) is presented alongside a baited novel object. Monkeys are rewarded for choosing the novel object, and unique novel objects are used in every trial. After learning the DNMS rule, memory load can be increased by extending the delay interval. Another commonly used method to assess recognition memory is the visual paired-comparison task (VPC). In this task, subjects passively view a stimulus on a screen, and after a variable delay, the same stimulus is presented with a novel stimulus. Typically, monkeys will prefer to look at the novel stimulus; as a result, preference for novelty is considered to be a measure of recognition for the familiarized stimulus. In VPC, the trials are unrewarded and animals passively explore the stimuli. In contrast, for DNMS, the animals actively displace sample objects for a reward, thus, this task involves more purposeful encoding of objects. Therefore, the VPC differs from DNMS in that the VPC involves passive or incidental recognition memory, whereas DNMS involves active (purposeful) recognition memory processes (Nemanic et al., 2004). Studies have shown that monkeys with selective adult-onset PRh lesions displayed significant impairments on DNMS with a 30-sec delay, and further impairment with increasing delays compared to sham-operated controls (Nemanic et al., 2004). Similarly, these operated monkeys also displayed a lack of preference for novelty at all VPC delays except the shortest delay of 1 second (Nemanic et al., 2004). Thus, the PRh appears to be important to support recognition processes in adulthood.

Congruent with adult-onset PRh lesions, monkeys with neonatal PRh lesions (Neo-PRh) displayed a significant delay-dependent decrease in performance in the VPC task compared to sham-operated monkeys. Although, unlike the adult-onset lesions, their performance remained above chance at all delays (Zeamer, Richardson, Weiss, & Bachevalier, 2015). This sparing of novelty preference suggests that other cortical structures may be able to compensate for the absence of the PRh at a young age. However, when recognition memory in the same animals was assessed using the DNMS, the Neo-PRh lesions resulted in recognition loss at all delays, and the magnitude of the impairment was similar to that reported for adult-onset PRh lesions (Weiss & Bachevalier, 2015, in press), suggesting no functional compensation after the early-onset lesions. This difference in magnitude of recognition memory loss obtained when recognition was taxed by the two recognition tasks suggests that DNMS and VPC require different cognitive processes presumably mediated by different cortical areas.

Previous literature suggests that recognition performance as measured by VPC is critically dependent on the interactions between temporal cortical areas. Studies have demonstrated that the hippocampus and the parahippocampal cortex may be sufficient to support incidental recognition memory in the absence of the PRh (Nemanic et al., 2004). Thus, other MTL areas may be able to compensate for the loss of PRh function in infancy, resulting in the pattern of functional sparing seen in Neo-PRh monkeys on the VPC recognition task. However, the lack of functional sparing seen on the DNMS recognition task following neonatal PRh lesions, may indicate that DNMS performance is dependent on interactions between the PRh and the prefrontal cortex (PFC). Due to the strong connections between the PRh and the PFC, it is possible that neonatal MTL damage affects the development of the prefrontal cortex (Bertolino et al., 1997) which may result in the impaired performance seen on DNMS. Thus, the severe

deficits seen in DNMS after neonatal PRh lesions may be caused by the maldevelopment of the PFC resulting from the lack of inputs from the PRh during a critical stage of development. As a result, Neo-PRh monkeys may have only mild recognition impairment on recognition tasks that are not PFC dependent such as the VPC.

Alternatively, better recognition performance in animals with neonatal PRh lesions as measured by VPC compared to DNMS could have resulted from a longer familiarization period. The sample objects presented on each trial of the VPC task are shown for a cumulative time of 30 sec compared to the DNMS in which familiarization time limited to 4-8 sec (i.e. the time taken for the animal to displace the object and retrieve the reward). Given that PRh has been shown to play an important role in familiarity judgment (Bowles et al., 2007), it is possible that, in the absence of a functional PRh, animals may require longer time to familiarize with a stimulus. Hence, the longer familiarization times used in the VPC, as compared to DNMS, may allow for better recognition memory.

Recognition memory is thought to be composed of two key processes: recollection and familiarity. Recollection is typically defined as the ability to vividly recall specific events from episodic memory, whereas familiarity involves a general sense of knowing without the accompaniment of episodic detail (Bowles et al., 2007). Many researchers have proposed that the hippocampus is involved in recollection, whereas familiarity judgements are supported by the perirhinal cortex. For instance, patients with extensive medial temporal lobe damage encompassing both the hippocampus and perirhinal cortex had deficits in recollection and familiarity judgments (Yonelinas et al., 2002). However, selective damage to the hippocampus impaired recollection but spared familiarity (Aggleton et al., 2005; Mayes et al., 2004). Furthermore, electrophysiology studies demonstrate that neuronal firing in the PRh precedes cell

firing in the hippocampus suggesting that there is a rapid familiarity signal mediated by the PRh, which is then followed by a late-onset recollection signal mediated by the hippocampus (Staresina, Fell, Do Lam, Axmacher, & Henson, 2012). Additional neuroimaging studies have found that hippocampal activity increases in response to retrieval of information but not for judgements of familiarity (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Vilberg & Rugg, 2007). Overall, these studies provide strong evidence that there is a functional separation between the hippocampus and the PRh, with the PRh being critical for familiarity judgments.

To test whether the different outcomes on the two recognition tasks may have resulted from reduced familiarity judgment after the Neo-PRh lesions, the present study will use the Constant Negative task created by Browning and colleagues (Browning, Baxter, & Gaffan, 2013). This task involves repeated familiarization exposures to objects which will enable us to measure the number of exposures needed for a novel stimulus to become familiar. Prior research has shown that the Constant Negative paradigm does not rely on prefrontal-temporal lobe interaction, unlike the DNMS task. Monkeys with temporo-prefrontal disconnection were severely impaired on DNMS, but performed normally on the Constant Negative task (Browning et al., 2013; Parker & Gaffan, 1998).

For our experiment, we want will adapt the Constant Negative for Neo-PRh monkeys to determine the effects of Neo-PRh lesions on recognition memory in the absence of PFC input. We predict that when trained in the Constant Negative task, animals with Neo-PRh lesions may require more exposure to a novel object before considering that object as familiar. Consequently, Neo-PRh monkeys will make more errors and take more trials in order to meet criteria compared to control monkeys.

Methods

Subjects

Nine adult rhesus monkeys (*Macaca mulatta*) are participating in this study (3 males and 6 females, all animals are 6-8 years old at the time of this study). Six animals received neurotoxic lesions to the PRh (Neo-PRh) on postnatal days 10-12 using ibotenic acid. Control animals (Neo-C) include two monkeys who received with sham surgeries and one unoperated animal. Neo-PRh and Neo-C monkeys received similar rearing environments with toys and social enrichment at an early age. Upon reaching adulthood, all monkeys were individually housed but had visual contacts with other animals. All animals receive a 12-hr light/dark cycle (7AM:7PM). Water is given ad libitum, and all animals are fed Purina Old World Primate chow (formula 5047). All experimental procedures were approved by the Institutional Animal Care and Use Committee at Emory University at Atlanta and were performed in accordance with the NIH Guide for the care and use of Laboratory Animals.

Neuroimaging and surgical procedures

Before surgery, infant monkeys were sedated with Ketamine HCl (10mg/kg of 7:3 Ketamine Hydrochloride, 100mg/ml) and Xylazine (20mg/ml, administered i.m.) before being placed in an induction box allowing for the inhalation of isoflurane (1%-3%, v/v). The anesthetized infant monkeys were given MRI scans of their brain to identify potential injection sites and to calculate the stereotaxic coordinates of each selected site. A stereotaxic apparatus was used to hold the head of the monkey in place during the duration of the scans. In addition, all vital signs including heart rate, rate of respiration, temperature, blood pressure and expired CO_2 were monitored throughout the procedure. In order to maintain hydration, an intravenous drip (0.45% NaCl and dextrose) was used. MR images were retrieved using a 3T Siemens Magnetom

Trio system (Siemens Medical Solutions, Malvern, PA at YNPRC). Pre-surgical scans included 3D T1-weighted fast spoiled gradient (FSPGR)-echo MR images which were used to identify potential injection sites (TE=2.6ms, TR=10.2ms, 25° flip angle, contiguous 1mm sections, 12cm FOV, 256 x 256 matrix). In addition, Fluid Attenuated Inversion Recovery, FLAIR, scans were also obtained during this time (TE = 140ms, TR = 1000ms, inversion time (TI) = 2200ms, contiguous 3mm sections, 12cm FOV, 256 x 256 matrix).

On the day of the surgery, the anesthetized animals received bilateral injections of 0.4µl ibotenic acid (Biosearch Technologies, Novato, CA, 10mg/ml in PBS, pH 7.4, rate: 0.4µl/min) into three sites spaced 2 mm along the length of perirhinal cortex. For the sham operation, the monkeys went through the same surgical procedures except no needles were lowered in the brain. After completion of the surgery, the animals were allowed to fully recover from anesthesia.

Post-operative care included dexamethazone sodium phosphate (0.4mg/kg, i.m.) to reduce edema, Cephazolin (25 mg/kg, i.m.) to prevent infection, and acetaminophen as an analgesic. One-week post-surgery, the monkeys were given a series of FLAIR and T1 scans which were used for post-surgery lesion assessments.

Lesion Reconstruction

All animals are currently participating in an ongoing longitudinal developmental project. As such, histological evaluation of lesion extent is not available at this time. Instead, coronal FLAIR MR sequences were obtained 1-week post-surgery in order to evaluate lesion extent. Areas of hypersignal were used to estimate the extent of edema and cell death caused by the ibotenic acid injections. To estimate the extent of the lesions, areas of hypersignals were identified in each FLAIR image and plotted onto drawings of a normal 1-week old rhesus

macaque brain. Afterwards, these drawings were imported into ImageJ® and the surface area of the lesion was calculated in pixels. To determine the volume of the intended lesion, the surface area was multiplied by the image thickness (1mm), and the result was then expressed as a percentage of normal volume. Furthermore, volume of unintended damage to the entorhinal cortex was also calculated.

Constant Negative Task

The task is a modified version of the automated Constant Negative task originally performed on a touchscreen (Browning, Baxter, & Gaffan, 2013) and was adapted for manual testing in a Wisconsin General Testing Apparatus (WGTA).

Apparatus and Stimuli: At the start of each daily session, the monkey is transferred from its home cage to the (WGTA) located in a darkened room. A white noise generator is used to mask any environmental noise that could distract the animal. The testing tray consists of three equally spaced wells across the center of the tray (2cm diameter, 1cm deep, 13cm apart). A collection of 960 never-before-seen junk objects serve as stimuli. Sixty objects are selected to become the familiar objects and these select 60 objects are never rewarded (S-). The 900 remaining objects are used as novel objects to be paired alongside the S- objects and these 900 novel objects are always rewarded (S+). For each daily session, the 60 S- are paired with sixty completely novel objects (S+). Thus, after several consecutive sessions, the 60 S- objects will become familiar to the animal.

A daily session starts with transferring the animal from its home cage to the WGTA. For each trial, an opaque screen is lowered to separate the monkey from the stimulus tray. Then, a S- object is paired with a S+ object and both objects are placed on the lateral wells with a reward placed underneath the S+ object. The left/right position of the S+ varies according to a

pseudorandom sequence. The experimenter then lowers a one-way vision screen and raises the opaque screen to allow the animal to select an object. The displacement of a S+ allows the animal to retrieve the reward. After selection of an object, either S+ or S-, the opaque screen is rapidly lowered, and the experimenter records on a testing sheet with a circle indicating a correct choice and a slash indicating a wrong choice. A 30 second timer is started after the opaque screen is lowered during which the experimenter places the next pair of objects (one S- and one S+) as indicated by the testing sheet for the second trial. After the 30 second intertrial interval, the one-way vision screen is lowered and the opaque screen is once again raised to allow the monkey to make a choice between the new pair of objects. This procedure is repeated for the remaining S- objects, resulting in 60 trials per day. The task is run five days per week until the monkey meets the learning criteria of 90% (54 correct choices out of 60 trials) for one session followed by at least 85% (51 correct choices out of 60 trials) on the next session. Testing is discontinued if the monkey fails to meet learning criteria after a maximum of 50 daily sessions.

Data Analysis

After all testing was completed, the total number of errors and trials were counted and averaged for each group. In addition, the average number of errors made for each object was calculated to determine if a particular object had to be excluded from data analysis. Objects were excluded from final analysis if subjects demonstrated a strong bias for selecting or not selecting a particular object. We determined that the number of errors made for each object were similar, therefore, no objects were excluded from final analysis. T-tests were used to compare the average number of errors and trials between the Neo-C and Neo-PRh group until criteria was met. Testing day one was excluded from all statistical analyses since animals would have been unable to discriminate between S- and novel objects during this time. To determine the rate at

which each group became familiarized with constant negative objects, the average number of errors made on each testing day was plotted for Group Neo-C and Group Neo-PRh. Afterwards, a linear regression was performed for each group. The rate of acquisition for the Constant Negative rule was determined by comparing the slopes of each line. A Student's t-test was used to compare the two slopes as described by Zar (1984, Biostatistical Analysis, pages 292-295). Finally, Pearson correlations were used to determine whether Constant Negative performance is indicative of DNMS performance.

Results

Lesion Assessment

A summary of the extent of intended and unintended damage for each animal is presented in Table 1 as previously reported by Zeamer et al., (2015). 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 slight unintended damage to the entorhinal cortex (average=20.57%, min=5.42%, max=34.49%). Pre- and post-surgical MR images of a representative case (Neo-PRh-3) are depicted in Figure 1.

Relationship between extent of damage and performance

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 also not correlated with any measures of task performance [Errors: r= -0.186, p= 0.724; Trials: r= -0.716, p= 0.109].

Constant Negative Performance

Errors per testing day for Neo-PRh and Neo-C monkeys are presented in Table 2. All animals met the learning criteria for the Constant Negative task within the maximum number of testing days allowed. The average number of errors made before meeting criteria for each group are illustrated in Figure 2. Neo-PRh monkeys made a similar number of errors as control animals with an average of 92 errors compared to 111 errors for the Neo-C group. Comparisons between Neo-PRh monkeys and controls revealed no significant difference in the average number of errors made ($t(7)=-1.068$, $p=.321$).

The average number of trials needed to meet the learning criteria for each group are illustrated in Figure 3. Neo-C monkeys required an average of 320 trials to reach criteria while Neo-PRh required an average of 450 trials. This difference reached significance ($t(7)=-2.543$, $p=.039$) indicating that monkeys with Neo-PRh lesions required significantly more trials in order to meet criteria compared to controls.

The comparison of the rate of acquisition of S- objects for Group Neo-C and Group Neo-PRh is presented in Figure 4. A significant difference was observed between the slope of the Neo-C group and slope the Neo-PRh group suggesting that Neo-PRh monkeys were slower at familiarizing themselves with the constant negative objects ($t(67)=5.31$, $p <0.001$). Overall, the slope of the Neo-C learning curve follows a steep and linear pattern indicative of a steady and rapid rate of acquisition (slope= -4.06, $R^2=0.99$). In contrast, lesioned animals were slower than controls to acquire the Constant Negative as indicated by the shallower slope of their learning curve (slope= -1.56, $R^2=0.749$).

DNMS Correlations

A significant correlation was observed between the number of Constant Negative trials and DNMS performance (Figure 5). Monkeys who took more trials to learn the Constant Negative rule displayed a greater impairment on DNMS using a 30 second delay ($R(7)=-0.667$, $p=0.05$). No significant correlations were found for DNMS delays above 30 seconds.

Discussion

In this study, we tested monkeys with neonatal perirhinal lesions on the Constant Negative task to assess whether the lesions altered familiarity judgments. The Constant Negative task required monkeys to discriminate between novel objects and familiar objects over a series of testing sessions. Moreover, we measured the number of exposures needed for a novel stimulus to become familiar. This experiment yielded two main findings. First, Neo-PRh monkeys needed more trials to acquire the Constant Negative rule, thus the monkeys were slower than controls at discriminating between novel objects and familiar objects. This deficit in the rate of learning supports our hypothesis that Neo-PRh animals need extra familiarization time to reach control levels of proficiency. Our findings were consistent with a previous study showing that rats with PRh lesions can overcome recognition deficits with repeated exposures to the target stimuli (Albasser et al., 2011).

The second goal of the study concerned the inconsistencies between Neo-PRh performance on DNMS and VPC. We found that animals requiring more trials to reach criteria in the Constant Negative task also had greater impairments on DNMS. Therefore, the difference in impairment between DNMS and VPC found in the earlier studies (Weiss & Bachevalier, 2015, in press; Zeamer et al., 2015) is most likely due to the fact that the VPC affords a longer familiarization time than the DNMS. Yet, an alternative interpretation for the effects of Neo-PRh

lesions on the two tasks may relate to the maldevelopment of the PFC, a cortical area critical for DNMS but not VPC performance. Indeed, there exists strong interconnections between the PRh, the ventrolateral prefrontal cortex (vlPFC) and the orbitofrontal cortex (Suzuki, 1996; Suzuki & Amaral, 1994). Moreover, severe impairment in DNMS follows disconnections between the PRh and the PFC (Browning, Baxter, & Gaffan, 2013) or orbitofrontal lesions (Meunier, Bachevalier, & Mishkin, 1997). However, the Constant Negative task does not rely on the PFC, and performance on this task is not impaired by prefrontal-temporal disconnection (Browning, Baxter, & Gaffan, 2013). Consequently, the correlation found between the performance on Constant Negative task and DNMS performance indicates that the sparing of recognition memory in the VPC task is likely due to repeated exposures to familiar stimuli. Future studies may be aimed at investigating whether extending the duration of the sample trial in DNMS will compensate for the deficit following PRh lesions.

A limitation of this study is that monkeys may use alternative strategies in order to reach criteria on the Constant Negative task. Like the DNMS, the Constant Negative task is designed to encourage the discrimination of novel objects among a set of familiar objects. However, another possible strategy is based on habit learning through selective reinforcement (Mishkin and Petri, 1984). In this case, monkeys may learn to avoid the constant negative objects as they are consistently unrewarded without being aware that they are familiar. However, it is unlikely that monkeys employed a purely habit based strategy. Given that both Neo-C and Neo-PRh monkeys exhibit steady rates of learning, it is more likely that monkeys used familiarity and novelty cues to guide their responding.

The present findings provide further support that early damage to the PRh causes deficits in recognition memory in adulthood. In terms of neurodevelopmental disorders, advancements in

the study of temporal lobe epilepsy have suggested that the disorder is simply not confined to hippocampus pathophysiology. In contrast, neuroimaging studies have found volumetric reductions of the PRh in spite of normal hippocampal volume (Bernasconi et al., 2000). Similarly, a study by Guedj et al. (2010) found preferential involvement of the PRh in recognition memory in patients with temporal lobe epilepsy (Guedj et al., 2010). These findings, along with the results presented in this study, support the idea that memory impairment seen in human cases of temporal lobe epilepsy is due to neuropathological changes in the perirhinal cortex.

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Table 1. Percent of intended to perirhinal cortex (PRh) and unintended damage to the entorhinal cortex (ERh) as estimated from pre- and post-surgical FLAIR images. L%, percent damage to the left hemisphere; R%, percent damage to the right hemisphere; X%, average damage to both hemispheres; W%, weighted average damage to both hemispheres (W% = (L% × R%)/100).

Subjects	**PRh**				**ERh**			
	L%	R%	X%	W%	L%	R%	X%	W%
Neo-PRh-1	89.76	76.91	83.34	69.04	28.51	2.28	15.39	0.65
Neo-PRh-2	68.16	70.58	69.37	48.11	17.72	20.65	19.19	3.66
Neo-PRh-3	65.45	81.02	73.23	53.02	7.72	3.12	5.42	0.24
Neo-PRh-4	59.40	74.73	67.06	44.39	11.55	17.84	14.69	2.06
Neo-PRh-5	75.90	66.81	71.35	50.71	38.60	29.86	34.23	11.53
Neo-PRh-6	74.12	80.31	77.22	59.53	25.34	43.64	34.49	11.06
Average	72.13	75.06	73.60	54.13	21.57	20.57	20.57	4.87

Table 2. Errors per testing day for Neo-PRh and Neo-C monkeys. Asterisks indicate the days in which criteria was met and were excluded from total errors.

Subjects	Testing Day													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**Total Errors to Criterion**
Neo-PRh-1	29	27	15	18	11	8	7	7	1*	4*	-	-	-	122
Neo-PRh-2	33	22	21	15	14	23	17	9	19	17	7	5*	9*	197
Neo-PRh-3	23	18	17	17	17	10	12	9	7	4*	8*	-	-	130
Neo-PRh-4	21	12	20	11	15	13	7	12	7	10	5*	4*	-	128
Neo-PRh-5	35	33	15	22	16	11	10	5*	7*	-	-	-	-	142
Neo-PRh-6	26	19	10	12	15	13	7	6*	9*	-	-	-	-	112
Neo-C-1	33	25	17	18	13	8	5*	6*	-	-	-	-	-	114
Neo-C-7	29	24	27	19	9	11	6*	2*	-	-	-	-	-	119
Neo-C-9	33	27	23	20	18	11	7	5*	7*	-	-	-	-	139

Figure 1. Coronal pre-surgical T1 and 1-week post-surgical FLAIR images of Neo-PRh-3. Edema caused by cell death is demonstrated by white regions on the post-surgical FLAIR image.

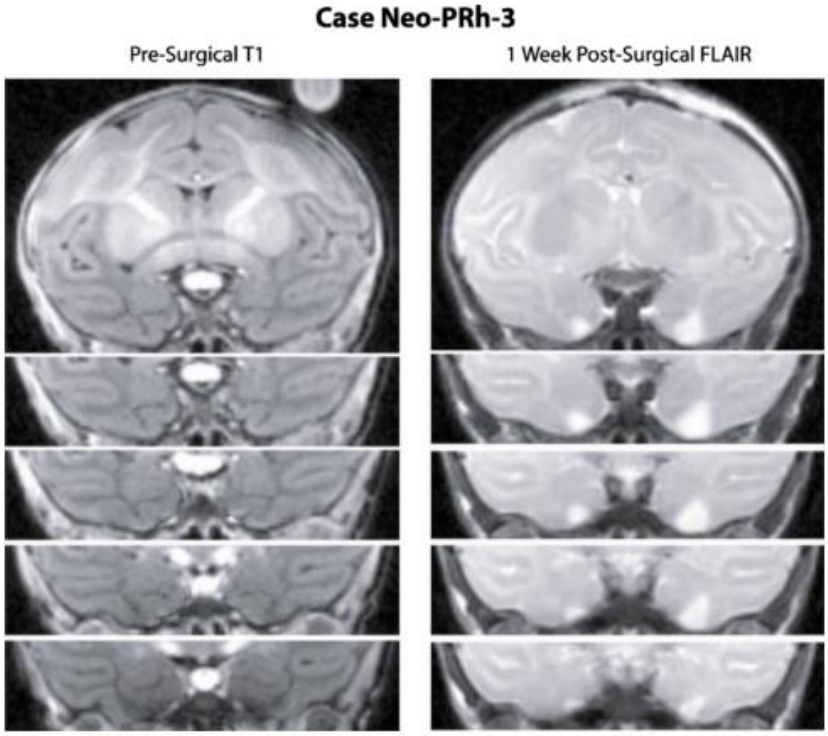

Figure 2. Mean errors made before criteria was met for Group Neo-C (red bar) and Group Neo-PRh (blue bar). No significant differences were found (p>0.05).

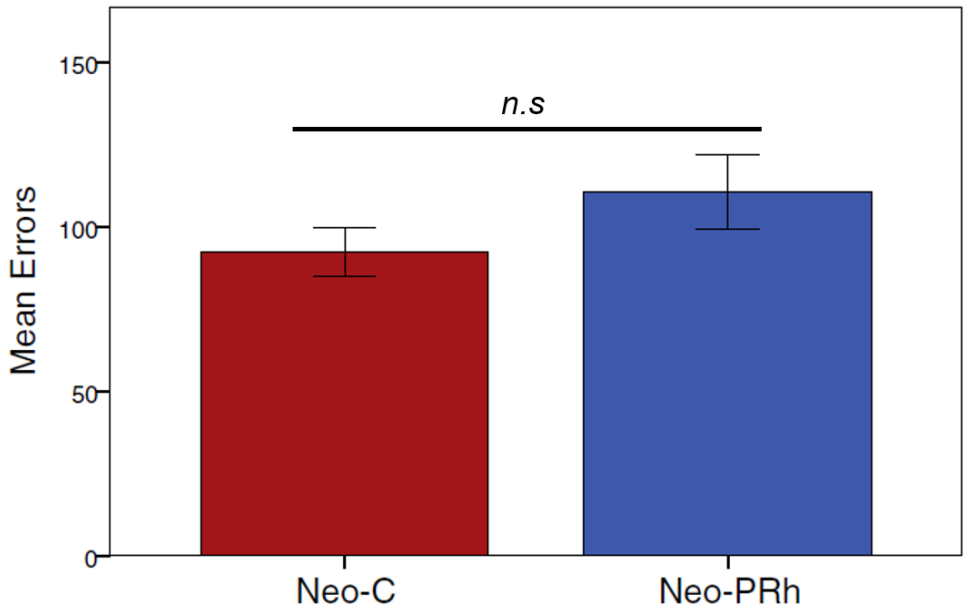

Figure 3. Mean trials completed before criteria was met for Group Neo-C (red bar) and Group Neo-PRh (blue bar). A significant difference was observed between the two groups (p=0.039).

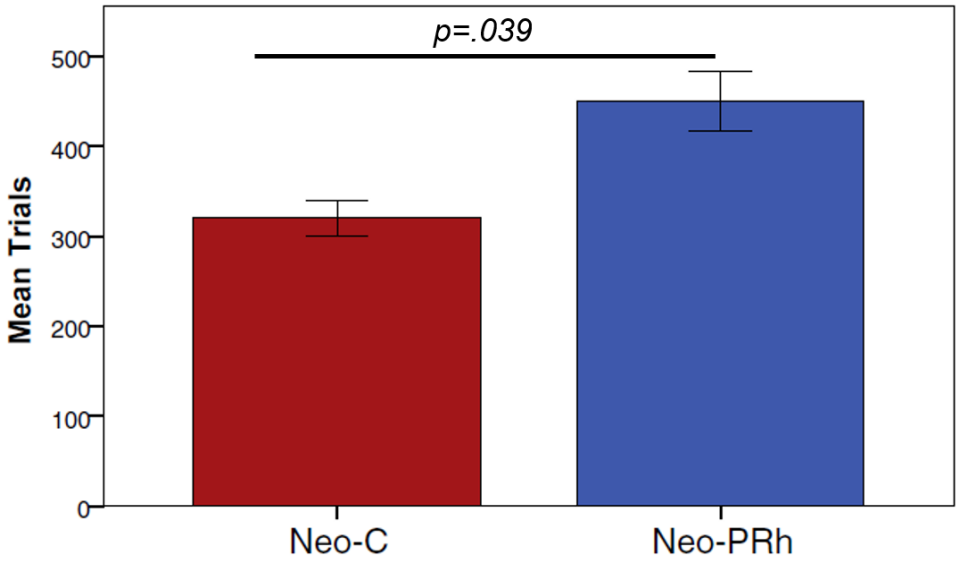

Figure 4. Linear regressions demonstrating the rate of acquisition of the Constant Negative rule. Group Neo-C is depicted in red (slope= -4.06, R^2=0.99); Group Neo-PRh is depicted in blue (slope= -1.56, R^2=0.749). A significant difference in slopes was observed between the two groups (t(67)=5.31, p <0.001).

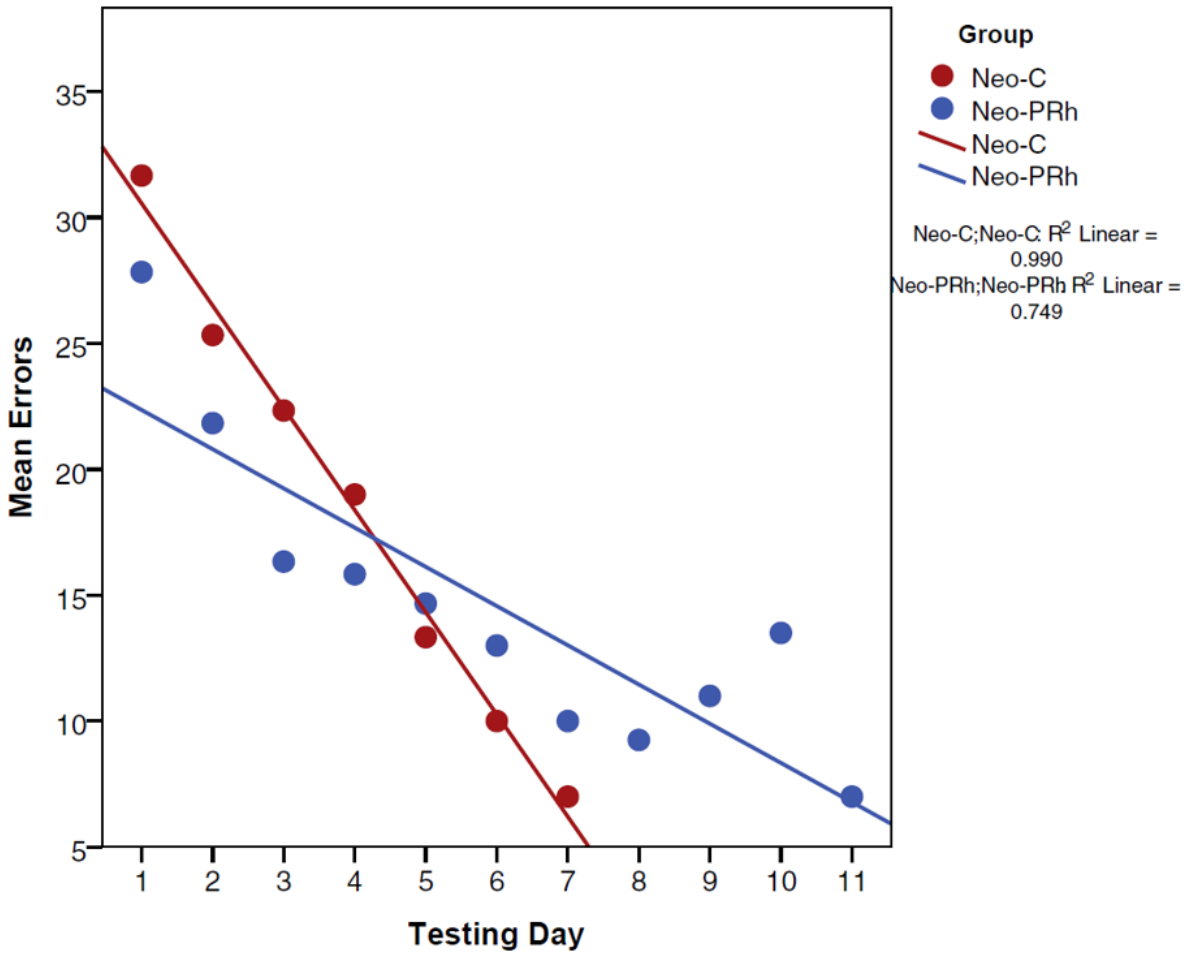

Figure 5. Relationship between Constant Negative trials and DNMS performance at a 30 second delay. Monkeys that took more trials to reach criteria in the Constant Negative task were similarly more impaired on DNMS (R(7)=-0.667, p=0.05).