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Is the perirhinal cortex involved in working memory?

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Is the perirhinal cortex involved in working memory?

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BA, Reed College, 2005

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An abstract of
A thesis submitted to the Faculty of the
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Abstract
Is the perirhinal cortex involved in working memory?

By Alison R Weiss

The goal of this research was to characterize the nature of working memory (WM) deficits in monkeys with neonatal ibotenic acid lesions of the perirhinal cortex (PRh). Neonatal lesions of the PRh transiently impaired learning performance in a delayed non-match to sample task using session-unique stimuli at a short (5-sec) delay, but this mild impairment was not seen when the animals were re-tested with longer delays of 30s. In contrast, the same neonatal lesions severely impacted acquisition of a self-ordered object task (Obj-SO). Furthermore, the source of the errors from the Neo-PRh monkeys on the Obj-SO task differed from controls: although both groups made more primary errors on trial 3 than trial 2, the number of perseverative errors increased across trials only in the Neo-PRh group. Thus, the results indicate that neonatal perirhinal lesions had a greater impact on WM monitoring processes than on WM maintenance processes.

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INTRODUCTION

Working memory (WM) is a term that encompasses the psychological and neural processes responsible for keeping active a limited set of cognitive representations, and the executive capacity that acts upon those transiently stored representations. There are many facets of this executive capacity and aspects of its 'central' processes regulate attention, maintain knowledge about goals, contingencies, or stimuli, and inhibit habitual/routine behaviors (Baddeley & Della Sala, 1998). In any instance of WM, representations of objects, places, ideas, goals, or rules must be maintained in a manner flexible enough to cooperate with simultaneous/parallel process that monitor or manipulate the representations being kept 'in mind.' For example, if a person is given a list of digits and asked for the sum, the person will hold active a memory of the list, *maintenance,* while attending selectively to each of the numbers, *monitoring,* in order to perform the mental arithmetic for summation, *manipulation* (Petrides, 1991a; 1991b; 1995; D'Esposito, Postle, Ballard, & Lease, 1999; Owen et al., 1999; Petrides, 2000; Cannon et al., 2005). In this way, these different WM processing domains interact to support mechanisms of non-associative learning.

Domain-specific models of WM propose that the prefrontal cortex (PFC) has a topographical organization separated by executive processing domains (i.e. a certain area is the 'monitor' and a different area the 'manipulator'). Evidence from functional imaging research with healthy human adults (D'Esposito, Postle, Ballard, & Lease, 1999; Owen et al., 1999), and lesion studies in monkeys (Mishkin, Vest, Waxler, & Rosvold, 1969; Passingham, 1975; Mishkin & Manning, 1978; Kowalska, Bachevalier, & Mishkin, 1991; Petrides, 1991a; 1995), strongly supports this distinction, and has led to the proposal that maintenance is associated with ventrolateral PFC (vlPFC) activity, whereas monitoring/manipulation is associated with

dorsolateral PFC (dlPFC) activity. However, a question that remains to be addressed is whether these processing domains are uniquely PFC-dependent or whether they require interaction between the PFC and other neural structures.

Although the involvement of the lateral PFC fields in WM processes has been well demonstrated in both humans and animals (Machado & Bachevalier, 2003), recent functional imaging studies in healthy humans and monkeys has shown that medial temporal lobe (MTL) structures are also recruited during many WM task (Davachi & Goldman-Rakic, 2001; Stern, Sherman, Kirchhoff, & Hasselmo, 2001; Libby, Ekstrom, Ragland, & Ranganath, 2012; Ranganath, Cohen, Dam, & D'Esposito, 2004). Lesion studies have confirmed this relationship; patients with hippocampal damage and monkeys with hippocampal lesions are severely impaired on tasks dependent on dlPFC integrity (Kimble & Pribram, 1963; Petrides, 1991a; 1995; 2000). In contrast, there have been inconsistent results on the effects of hippocampal damage on WM tasks dependent on the vlPFC (Diamond, Zola-Morgan, & Squire, 1989; Jeneson, Mauldin, & Squire, 2010). Furthermore, in a recent report, Heuer and Bachevalier (2011) demonstrated that neonatal damage to the hippocampus in monkeys resulted in severe loss of WM-monitoring abilities while sparing WM-maintenance abilities. Thus, it appears that the MTL may contribute differentially to WM processing domains. This is interesting in light of the anatomical connectivity of the hippocampus with the PFC. The only direct inputs of the hippocampus to the PFC target the ventromedial PFC via the fornix but not the dlPFC (Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000; Croxson et al., 2005). Thus, if the hippocampus provides bottom-up information to the dlPFC, this will need to be realized via a multisynaptic pathway. Yet, the dlPFC projects back to the posterior hippocampus (Goldman-Rakic, Selemon, & Schwartz, 1984; Morris, Pandya, & Petrides, 1999) and could provide a top-

down mechanism regulating hippocampal-dependent WM processes. By contrast, within the MTL, the perirhinal cortex (PRh) is well positioned to have a more prominent role in WM processes, given that it has direct reciprocal connections not only with the hippocampus but also with both lateral PFC fields (Lavenex, Suzuki, & Amaral, 2002; Suzuki & Amaral, 1994; Saunders, Mishkin, & Aggleton, 2005). The extensive anatomical interactions between the PRh and the lateral PFC fields suggest that the PRh cortex may provide critical bottom-up inputs to the PFC in support of WM. So, is there evidence that PRh activity is at all related to WM? Electrophysiological and functional imaging studies have reported increased activity in PRh during object-based WM tasks, and give credibility to the theory that this cortical area supports object representations used in WM. Also, cells in the PRh of adult macaques are highly activated during WM tasks requiring the temporary maintenance of object representations (i.e. small-set delayed-match-to-sample). Interestingly, these changes are not observed in other temporal visual area, such as area TE (Lehky & Tanaka, 2007). Likewise, 2-Deoxyglucose imaging studies indicate increased activity in PRh during a delayed object alternation task; a task requiring the maintenance and monitoring of information in WM. The same increase was not seen in ERh (Davachi & Goldman-Rakic, 2001). Taken together, these results point to a unique contribution of the PRh to performance on tasks that require the active/flexible representation of familiar objects, that is in fact strengthened by the concurrent lack-of-contribution of both the primary afferents (area TE/TEO) and primary efferents (ERh) to the PRh.

During the last decade, the interplay between PRh and the hippocampus in support of long-term memory processes has been well documented (Brown & Aggleton, 2001; Warburton & Brown, 2010; Lavenex, Suzuki, & Amaral, 2004; Lee et al., 2006). Thus, the PRh is known to be critical for recognition memory as well as for memory of stimulus-stimulus associations. Yet, its

participation in WM processes remains untested despite theories suggesting that it provides higher-order object representations to lateral PFC, and the functional evidence that PRh activity is recruited by certain WM tasks. Given that PRh projects to both the vlPFC and dlPFC involved in WM maintenance and WM manipulation processes, respectively, we conjectured that both of these processes would be affected by selective damage to the PRh.

To test this hypothesis, we took advantage of the availability of two groups of adult rhesus macaques. One group consisted of monkeys that had received neonatal ibotenic acid lesions of the perirhinal cortex (Neo-PRh) and the second consisted of monkeys that had received sham surgeries (Neo-Sham) or no surgeries and served as controls. As adults, all animals were tested in two object-based working memory tasks: Session-Unique Delayed Non-Match to Sample, SU-DNMS (Mishkin & Delacour, 1975), requiring the maintenance of object representations in WM and Object Self-Ordered Task, Obj-SO (Petrides, 1995), requiring maintenance and monitoring of object representations in WM.

METHODS

Subjects

Fifteen adult rhesus macaques (*Macaca mulatta*), 9 females and 6 males, participated in this study. Between postnatal days 10-12, the animals underwent surgery to create bilateral lesions of the perirhinal cortex, or sham operations. Six infant monkeys (3 females, 3 males) were given MRI-guided ibotenic acid injections into perirhinal areas 35 and 36 (Group Neo-PRh), seven monkeys (5 female, 2 male) underwent the same surgical procedures withholding any injections (Group Neo-C), and two additional monkeys (1 female, 1 male) served as unoperated

controls. At the time of this study, all animals were 6-7 years old and housed individually in a room with a 12hour light/dark cycle (7AM/7PM). Monkeys were fed Purina Old World Primate chow (formula 5047) and supplemented with fresh fruit enrichment. During behavioral testing, chow was restricted and the weight of the animals was monitored and maintained at or above 85% of the full feed weight. Water was given ad libitum.One cohort of subjects were born at the YNPRC breeding colony (Lawrenceville, Georgia), and a second cohort were born at the breeding colony of the University of Texas, M.D. Anderson Cancer Center Science Park (Bastrop, TX). At both institutions, all animals received similar rearing and behavioral procedures, including social interactions with age-matched peers and human caregivers as described previously, see Goursaud & Bachevalier (2007). Briefly, infants were individually housed in the primate nursery in adjacent wire cages that allowed for multisensory contacts between individuals (i.e. visual, auditory, olfactory, tactile) and surrogate-nursery reared according to procedures established by Sackett and colleagues (Sackett, Ruppenthal, & Davis, 2002; Burbacker et al., 2013). For the first 3-4 weeks, a primary human caregiver hand-fed the infants Similac formula. Once able to self-feed, they were pair-housed and their diet was supplemented with banana pellets (190mg, P.J. Noyes, Cleveland, OH). From 3 to 9 months of age, animals were socialized for 3-4 hours daily with age- and sex-matched peers in a large cage containing toys, and, at 12 months of age, they lived in tetrads in a large enclosure 24 hrs/day. Thereafter, animals were maintained in pairs.

All animals had received extensive but similar cognitive testing before they participated in this experiment. Briefly, this cognitive testing included incidental recognition memory (visual paired comparison at 1, 6 and 18 months), oddity learning (3 and 15 months), concurrent discrimination learning with devaluation (48 months), object and spatial memory (60 months).

All protocols were approved by the Institutional Animal Care and Use Committee at Emory University in Atlanta, Georgia and conformed to the NIH Guide for the care and use of Laboratory Animals (HHS publication 85-23, 1985).

Neuroimaging and Surgical Procedures

All neuroimaging and surgical procedures were described in detail by Goursaud & Bachevalier (2007) and are summarized below.

Neuroimaging

To determine injection coordinates, subjects were given MRIs immediately prior to surgery. Initially, animals were sedated with Ketamine HCl (10mg/kg of 7:3 Ketamine Hydrochloride, 100mg/ml, and Xylazine, 20mg/ml, administered i.m.) and intubated to allow inhalation of isoflurane (1%-3%, v/v) in order to maintain an appropriate plane of anesthesia during the duration of the scan. YNPRC veterinary staff monitored vital signs (heart and respiration rates, body temperature, blood pressure, body temperature and expired CO_2) during the scan. A stereotaxic apparatus held the animal's head in a constant position throughout the MRI and surgery, enabling precise head alignment between the MR images and the stereotaxic injection coordinates.

The brain was imaged with a 3T Siemens Magnetom Trio system (Siemens Medical Solutions, Malvern, PA at YNPRC) and two sets of pre-surgical scans were obtained: 1) a structural image used to calculate the injection sites (3D T1-weighted fast spoiled gradient (FSPGR)-echo sequence, TE=2.6ms, TR=10.2ms, 25° flip angle, contiguous 1mm sections, 12cm FOV, 256 x 256 matrix); and 2) a Fluid Attenuated Inversion Recovery, FLAIR, image sequence as

a baseline for future lesion extent measurements (TE = 140ms, TR = 1000ms, inversion time (TI) = 2200ms, contiguous 3mm sections, 12cm FOV, 256 x 256 matrix; image sequences acquired in 3 series offset 1mm posterior). Animals in Group Neo-PRh group had the same two sets of scans repeated one week after surgery using the methods described below.

Surgical

All surgical procedures were performed under deep anesthesia and aseptic conditions. Animals were maintained with Isoflurane gas (1%-2%, v/v, to effect) during the surgery. Fluid support (IV drip 0.45% NaCl and dextrose) was given to maintain normal hydration, and a heating pad placed underneath the animal prevented hypothermia. YNPRC veterinary staff monitored all vital signs during surgery and recovery.

The scalp was shaved and cleaned with chlorhexidine diacetate (Nolvasan, Pfizer). A long-lasting local anesthetic, Bupivacaine Hydrochloride (Marcaine 25%, 1.5ml), was injected along the planned incision line. An incision was cut along the midline of the scalp. The galea was retracted and held in place with hemostats. Moist gauze was placed over the retracted galea to prevent the tissue from desiccating during the procedure. Bilateral craniotomies (1cm wide x 2.5cm long) were made with an electric drill above the areas to be injected, and bone wax (Ethicon, Inc., Somerville, NJ; 2.5g size) was applied as necessary to prevent bone bleeding. Using a scalpel, the dura was opened. Three injection sites, spaced in 2mm intervals, were selected along the rostral-caudal length of the perirhinal cortex bilaterally (see Figure 1 for injection sties in two representative cases). Hamilton syringes were held by Kopf electrode manipulators (David Kopf Instruments, Tujunga, CA) and lowered simultaneously into each hemisphere at each injection site. A volume of 0.4µl ibotenic acid (Biosearch Technologies,

Novato, CA, 10mg/ml in PBS, pH 7.4) was injected into each site at a rate of 0.4µl/min. The needle remained in place for 2 min after each injection to ensure that the total intended volume had diffused into the surrounding tissue and to prevent unintended damage caused by dragging ibotenic acid back through the needle track when withdrawing. Sham operated controls (Neo-C) underwent the same procedures, however once the dura was cut, no needles were lowered.

The dura, galea, and skin were closed in anatomical layers and the animal was removed from isoflurane and extubated. Veterinary staff monitored the recovery of each animal closely. Analgesic (acetaminophen, 10mg/kg, p.o.) was given QID for 3 days after surgery. Additionally, animals received dexamethazone sodium phosphate (0.4mg/kg, i.m.) to reduce edema, and Cephazolin (25 mg/kg, i.m.) to prevent infection once a day starting 12h prior to surgery and ending 7 days after.

Lesion Assessment

Histological evaluations are unavailable, as all animals are currently participating in other experiments. Instead, lesion extent was evaluated using methods based on those described in (Nemanic, Alvarado, Price, Jackson, & Bachevalier, 2002; Malkova, Lex, Mishkin, & Saunders, 2001). Briefly, coronal FLAIR image sequences acquired 1-week post-surgery were used to assess lesion extent. Edema induced by cell death are seen on the FLAIR images as water hyper-signal. The areas of hyper-signal in each coronal section were drawn onto corresponding coronal sections of a normal 1-week old rhesus monkey brain (J. Bachevalier, unpublished atlas) using Adobe Photoshop. These images were then imported into Image J® and the surface area of the lesion was calculated in pixels^2. This surface area was multiplied by image thickness (1mm) to calculate the volume. The percent of damage to brain regions of interest (PRh, visual area TE/

TEO, ERh, Para H, amygdala, and hippocampus) were calculated by dividing the volume of the lesion by the volume of each structure in the control atlas and multiplying by 100.

Apparatus and Stimuli

All behavioral tasks were conducted using the Wisconsin General Testing Apparatus (WGTA) located in a dark room with a white-noise generator. Monkeys were transferred from their home cages and positioned in the WGTA facing a tray with 3 recessed food wells (2cm diameter, 1cm deep, spaced 13cm apart). This study made use of a collection of 1,000 junk objects that differed in size, shape, color, and texture. Correct responses were rewarded with preferred food rewards (i.e. mini-marshmallow, jelly bean, M&M etc.)

Session-Unique Delayed Nonmatch-to-Sample (SU-DNMS)

Session-Unique Delayed Nonmatch-to-Sample (SU-DNMS) measures the maintenance of information in working memory, and, based on lesion studies, is considered to be dependent on vlPFC, (Mishkin & Manning, 1978; Mishkin, Vest, Waxler, & Rosvold, 1969; Passingham, 1975). Procedures for this task replicated those used by Heuer & Bachevalier (2011) and allowed for comparisons between the effects of neonatal PRh lesions to those of neonatal hippocampal lesions.

Each trial consists of two phases: sample presentation and choice. During the sample phase, the monkey is presented with a single object, followed by a delay. In the choice phase, two objects, the sample object and a second object, are presented to the monkey and a reward is obtained if the monkey displaces the object that was not rewarded during the sample phase. In SU-DNMS the same two objects are used in all trials throughout the daily session, and the

object selected for the sample presentation phase on each trial alternates using a pseudorandom sequence. In the first trial, the two objects are novel, but as the daily session progresses, the two stimuli become highly familiar and generate retroactive interference. Thus, in SU-DNMS familiarity/novelty judgments cannot be used to guide responses, rather subjects are required to generate responses based upon recency memory and inhibit responses based on memories of previous trials.

Daily training sessions consisted of 30 trials with 5s delays, presented at 30s inter-trial intervals. A new pair of objects was used for each daily session. Learning criterion was set at 90% or better (27 out of 30) in one session, followed by a performance of 80% or better (24 out of 30) in the consecutive training session. Training was discontinued after a maximum of 1,000 trials if criterion was not met. Once subjects met learning criterion at the 5s delay, testing was continued in the same way using a 30s delay and a 30s inter-trial interval. At this longer delay, subjects performed 20 trials per day until a learning criterion of 85% averaged over two consecutive testing sessions (34 out of 40) was achieved, or to a maximum of 500 trials.

Object Self-Ordered Task (Obj-SO)

Tasks that involve memory for serial order have been used in both NHPs with selective PFC lesions and humans with PFC damage. Serial order tasks like the Object Self-Ordered task (Obj-SO) measure both maintenance and monitoring of cognitive representations and have been shown to dissociate WM-processes dependent on the dlPFC from those that are dependent on vlPFC (e.g. SU-DNMS) (Petrides, 1991a; 1995; D'Esposito, Postle, Ballard, & Lease, 1999).

Procedures for this task replicated those used to test the effects of neonatal hippocampal lesions on WM monitoring memory processes (Heuer & Bachevalier, 2011)for comparisons with the neonatal perirhinal lesions. On each daily session, monkeys choose 3 objects, one at a time, during 3 successive trials. At the start, all three objects are baited with a food reward, Trial 1. Once the monkey makes a first choice, the position of the objects on the tray is shuffled and only the two objects unselected objects in Trial 1 are baited in Trial 2. After the second choice, the positions of the objects are once again shuffled and only the single remaining (unselected) object is baited on Trial 3. The same 3 objects were used in all daily testing sessions and were presented at 10s inter-trial intervals. If, at any time during Trial 2 or 3, the monkey selected an unbaited object, this initial error was scored as a *primary error* and a correction procedure was initiated. Correction procedures involved reordering the objects and re-presenting them to the monkey until a rewarded object was selected. The number of times the correction procedure is repeated was used to measure *perseverative errors*. For analyses, primary and perseverative errors were calculated separately for Trial 2 or Trial 3.

Learning criterion for the Obj-SO task was met when subjects scored 85% correct across 10 consecutive testing sessions (3 primary errors or fewer), or testing was discontinued if subjects reached a maximum of 50 training sessions. Thus, in Obj-SO monkeys are rewarded for making choices based on the temporal sequence of their own object selections in previous trials of the daily session.

Statistical Analyses

T-tests were used to compare the scores of the control animals (n = 5) from the Texas cohort and control animals (n = 4) of the Georgia cohort across all measures. None reached

significance, and so these groups were collapsed in a single control group for all subsequent analyses.

Repeated-measure ANOVAs were used to compare the scores of the Neo-PRh and Neo-C groups on these two WM-based learning tasks. For SU-DNMS, 2 x 2 ANOVA (Group x Delay) using delay as the repeated-factor were performed on the 2 parameters (trials to reach criterion, and errors to reach criterion). For Obj-SO, Primary and Perseverative Errors were calculated separately for Trial 2 and Trial 3 (Trial2-Trial3). Thus, comparisons were made using 3-way ANOVA (Group x Primary Error Trial2-Trial3 x Perseverative Error Trial2-Trial3) with repeated measures for the last 2 factors.

RESULTS

Lesion Extent

All monkeys received extensive bilateral damage to the PRh, averaging 73.6% (min=67.1%, max=83.3%) as summarized in Table 1. Unintended damage occurred in all cases, mostly in ERh (average=20.6%, min=5.4%, max=34.5%) but also minimally in area TE (average=2.5%, min=0.1%, max=7.11%). Four of the six Neo-PRh subjects had negligible damage to the anterior hippocampus (average=0.8%), and three of the six subjects had minimal damage to the amygdala (average=2.5%). Figure 1 shows pre-surgical and post-surgical MR images of two representative cases and illustrates the extent of hypersignals seen in these two cases one-week after the ibotenic acid injection.

Session-Unique Delayed Nonmatch-to-Sample (SU-DNMS)

The numbers of trials and errors to reach the learning criterion at each delay, 5-sec and 30-sec, are shown in Figure 2. All animals reached criterion at both the short and long delays. However, at the 5-sec delay, animals in Group Neo-PRh made significantly more errors than sham-operated controls, (Neo-PRh =73.0, Neo-C = 30.2; t(13)=2.207, p=0.046). The Neo-PRh animals also took more trials to reach the learning criterion at the 5-sec delay than controls (Neo-PRh = 270.0, Neo-C = 123.3), and this difference approached significance (t(13)=1.935, p=0.075). At the 30-sec delay, the Neo-PRh animals needed more trials (Neo-PRh=120, Neo-C=60) and made more errors (Neo-PRh=34.8, Neo-C=18.4) than controls, but these differences did not reach significance (Trials: t(13)=-0.999, p=0.336; Errors: t(13)=-0.811, p=0.432).

A 2 x 2 (Group x Delay) ANOVA for Trials and Errors respectively, with repeated measures for the delay factor, revealed a significant main effect of group for both the number of trials [F(1,13)=5.208, p=0.040] and errors to reach criterions [F(1,13)=5.156, p=0.041]. The main effect of delay was not reliable for both trials [F(1,13)=4.331, p=0.058] and errors [F(1,13)=2.803, p=0.118], nor was the interaction [Trials: F(1,13)=0.715,p=0.413; Errors: F(1,13)=0.783, p=0.392]. Thus, as shown in Figure 2, animals with neonatal perirhinal cortex lesions acquired the task more slowly at 5-seconds, but performed similarly to sham operated controls at the longer delay, 30-seconds.

Correlations between the extent of PRh lesion and scores at the two delays did not reach significance [Trials: 5-sec r=-0.049, p=0.927; 30-sec r=-0.512, p=0.299. Errors: 5-sec r=0.022, p=0.966; 30-sec r=-0.461, p=0.357].

Object Self-Ordered Task (Obj-SO)

The number of daily sessions as well as the number of primary and perseverative errors to reach criterion are shown in Figure 4. The sham-operated control animals reached criterion in an average of 12.7 daily sessions. In contrast, all but one of the 6 animals with neonatal perirhinal cortex lesions (Neo-PRh-5) failed to reach criterion within the limit of testing, thus averaging 43 daily sessions. These group differences reached significance [$t(13)=-3.454$, $p=0.004$]. This learning impairment was also reflected by the greater number of primary and perseverative errors on Trial 2 and Trial 3 made by the Neo-PRh animals as compared to the Neo-C animals [Trial 2 Primary: Neo-PRh=15.17, Neo-C=3.89 ; Trial 3 Primary: Neo-PRh=27.00 , Neo-C=9.44; Trial 2 Perseverative: Neo-PRh=5.50 , Neo-C=0.78; Trial 3 Perseverative: Neo-PRh=45.00, Neo-C=12.44].

A 3-way MANOVA, with repeated measures for Primary Errors and Perseverative Errors revealed a significant main effect of group [$F(1,13)=9.597$, $p=0.008$], and a significant effect of Perseverative Errors [$F(1,13)=22.716$, $p<0.001$], but not Primary Errors [$F(1,13)=2.819$, $p=0.117$]. There was also a significant interaction between group and Perseverative Errors [$F(1,13)=5.624$, $p=0.034$], but not between group and Primary Errors [$F(1,13)=2.974$, $p=0.108$]. In addition, the interaction between Primary and Perseverative Errors reached significance [$F(1,13)=25.892$, $p<0.001$], as well as the 3-way interaction [$F(1,13)=10.545$, $p=0.006$]. This 3 way interaction revealed that, although both groups made more primary and perseverative errors on Trial 3 than on Trial 2, Group Neo-PRh made more primary and perseverative errors than Group Neo-C on both trials [Trial 2 Primary: $t(13)=-3.44$, $p=0.004$; Trial 3 Primary: $t(13)=-2.647$, $p=0.020$; Trial 2 Perseverative: $t(13)=-3.385$, $p=0.005$; Trial 3 Perseverative: $t(13)=-2.901$, $p=0.012$]. In addition, for Group PRh, the increase in perseverative errors from Trial 2 to Trial 3 was greater in magnitude than the increase in primary errors from Trial 2 to Trial 3. Thus, the increase in

Primary Errors across trials for group Neo-PRh was similar to that of group Neo-C, as revealed by no significant Group by Primary Errors interaction (see above), whereas the increase in Perseverative Errors across trials for group Neo-PRh was significantly greater than that observed in group Neo-C, as revealed by the significant group by Perseverative Errors interaction (see above).

Correlations between the extent of PRh lesion and all measures of task performance did not reach significance [Sessions: r=0.184, p=0.727; Trial 2 Primary Errors: r=0.198, p=0.706; Trial 3 Primary Errors: r=0.184, p=0.727; Trial 2 Perseverative Errors: r=-0.042, p=0.936; Trial 3 Perseverative Errors: r=0.232, p=0.658].

DISCUSSION

The goal of this study was to investigate the effects of neonatal PRh-lesions on WM processes. The results indicate that neonatal perirhinal lesions have a greater impact on WM monitoring processes (Experiment 2: Obj-SO) than on WM maintenance processes (Experiment 1: SU-DNMS). These findings will be discussed in turn.

Maintaining representations in WM

Monkeys with Neo-PRh lesions initially learned SU-DNMS more slowly than controls. However, the slight impairment at the short delay was not evident with further training at the longer delay of 30s. The same groups of animals were tested on several other memory tasks from infancy through adulthood, and their performance on these tasks can help us reject several interpretations of the transient impairment in the SU-DNMS task. For example, animals

with neonatal perirhinal lesions did not differ from controls in learning a trial-unique delayed nonmatching task indicating no significant impact of the Neo-PRh on perceptual abilities, formation of object representation, learning reward contingencies, or motivation to perform a task. Furthermore, the impairment at the 5 s of the SU-DNMS could not be explained by an inability to maintain object representation across the short delay, given their normal performance at delays up to 600s in the delayed nonmatching task as well as at the delay of 30 s in the SU-DNMS. However, one distinct feature of the SU-DNMS task that has not been addressed with prior memory tasks given to these groups of animals, but could be relevant to their impairment in the SU-DNMS, is the increased interference encountered by the animals while responding to successive trials. Indeed, in contrast to all other memory tasks performed by the animals, SU-DNMS uses the same two stimuli on every trial of a daily session, generating increased proactive interference as the animals progressed through the task. Thus, the learning impairment observed in animals with Neo-PRh lesions at the 5s delay could be the result of an inability to suppress or inhibit interference.

A large body of work has already demonstrated that the hippocampus may be critical to reduce proactive interference (Butterly, Petroccione, & Smith, 2012; Shapiro & Olton, 1994; but see Aggleton, Hunt, & Rawlins, 1986; Bachevalier, Wright, & Katz, 2013). Given that the majority of sensory inputs reaching the hippocampus are relayed through the perirhinal cortex, the Neo-PRh lesions could have disconnected the hippocampus from receiving this flow of information and yielded decreased resistance to interference. However, this explanation seems implausible given that direct damage to the hippocampus does not impair performance on the SU-DNMS (Heuer & Bachevalier, 2011). An alternative explanation may relate to the important interconnections of the perirhinal cortex with the inferior prefrontal convexity (Petrides &

Pandya, 2001). Lesion studies have already indicated that damage to the inferior prefrontal convexity (IC) in monkeys yielded deficits in rule-learning that were attributed to perseverative interference generated from competition between well-established responses (Butter, 1969; Mishkin & Manning, 1978; Passingham, 1975). Furthermore, like performance of Neo-PRh monkeys, monkeys with IC lesions require more trials than controls to acquire the DNMS rule, tending to make perseverative errors, but after learning the task, they performed normally on subsequent tests with longer delays (Kowalska, Bachevalier, & Mishkin, 1991). Thus, we speculate that the transient deficit in learning the SU-DNMS may have resulted from a disconnection of the IC from the PRh. That is, removal of the PRh in infancy could prevent IC from accessing object-representations generated by PRh, resulting in impaired interference suppression. Yet, the learning deficit in the SU-DNMS after the neonatal PRh lesions was only transitory as was the learning deficit following IC lesions. This suggests that with further training, animals with such lesions can overcome or suppress their perseverative habits, presumably, by developing alternative strategies.

In sum, the results suggest that neonatal perirhinal cortex lesions have little effect on the ability to learn SU-DNMS, and therefore this cortical area may not be critical to support maintenance of object representations in WM.

Monitoring representations in WM

As compared to the transient impairment on the WM maintenance task, SU-DNMS, the same neonatal perirhinal lesions severely impacted acquisition of the Obj-SO task in all but one of the Neo-PRh monkeys. Furthermore, the source of errors during Obj-SO acquisition differed between the Neo-PRh and Neo-C groups. The Neo-PRh monkeys made more primary errors

than the controls, but the increase in primary errors from trial 2 to trial 3 was similar for both groups. Furthermore, although the Neo-PRh monkeys made also more perseverative errors than controls, the increase in perseverative errors from trial 2 to trial 3 was greater in magnitude for animals with Neo-PRh lesions than for controls. This pattern of results indicates that monkeys with neonatal perirhinal lesions may be unable to monitor the order of self-generated responses. Alternatively, as for the slight learning impairment reported above for the SU-DNMS task, the inability of animals with Neo-PRh lesions to solve the Obj-SO task could also be due to interference. The Obj-SO task uses the same three stimuli from trial to trial, and across all sessions, resulting in high levels of interference. Thus, the severe impairment on the Obj-SO task following neonatal perirhinal lesions is due either to an inability to monitor information in WM and/or to an inability to suppress interference. Further empirical studies are needed to assess whether one or both of these alternative roles of the perirhinal cortex in memory is correct. One possible way to distinguish between these alternatives will be to train animals with Neo-PRh lesions in a serial order memory task that uses novel objects in each trial, such as the serial-order memory task (Petrides, 1991a; Heuer & Bachevalier, 2013). The use of trial-unique stimuli will minimize the impact of interference, and thus task performance should depend only on the ability to monitor the temporal order of stimuli.

Comparison to Neo-H

To test whether the effect of Neo-PRh were similar to Neo-H, we compared the scores of our Neo-PRh group with the scores of the Neo-H group tested on the same two tasks in our lab by Heuer & Bachevalier (2011). Results indicated that the Neo-PRh group were slightly more impaired in learning the SU-DNMS task at the 5-sec delay than the Neo-H group, although not

significantly. Thus, early hippocampal lesions appear to effect SU-DNMS acquisition to a smaller degree than early lesions to the perirhinal cortex. In contrast, our Neo-PRh group was equally impaired in learning the Obj-SO task as the Neo-H group tested by Heuer & Bachevalier (2011). Thus, the effect of early perirhinal lesions appears to have an equally significant an effect on Obj-SO task performance as early hippocampal lesions.

Early-damage vs Adult-damage

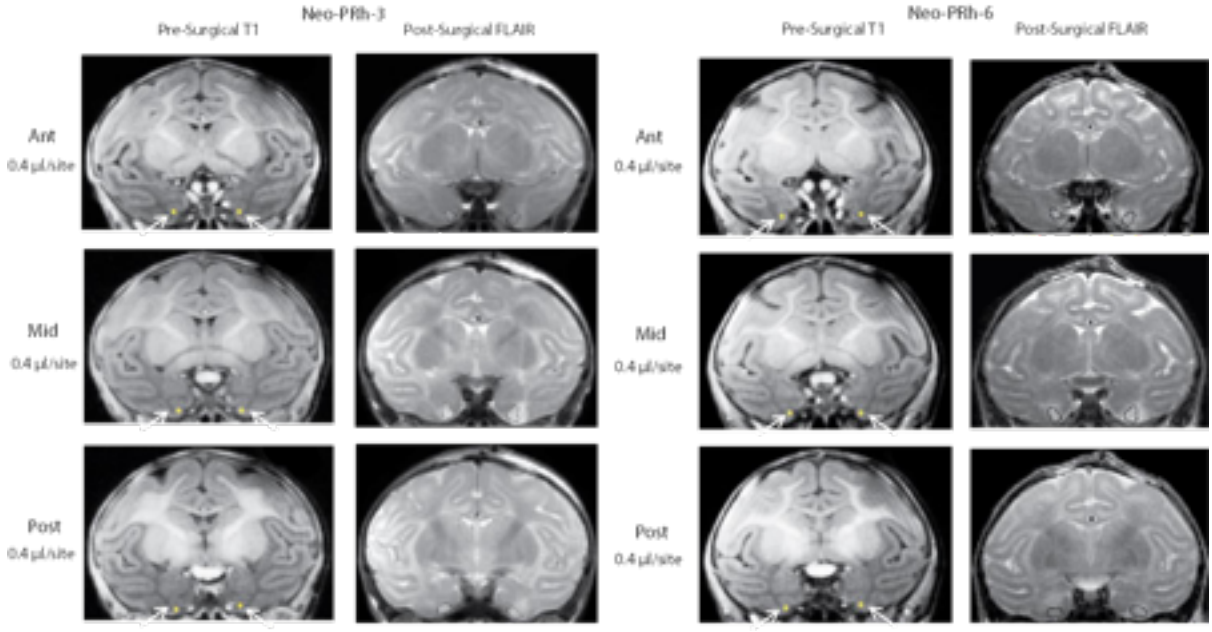
Although the results suggest that the perirhinal cortex may be particularly important to suppress interference and/or monitor information in WM, there are some caveats with this conclusion. Because the perirhinal lesions were done in infancy and no data exist on the effects of adult-onset perirhinal cortex lesions on the WM tasks, it is not clear whether the deficits we observed resulted from direct damage to the perirhinal cortex or from downstream effects of the PRh lesions on the normal maturation of other neural structures, especially those with a protracted development, such as the prefrontal cortex (Fuster, 2002). Developmental studies in rodents (Tseng, Chambers, & Lipska, 2009) and monkeys (Chlan-Fourney, Webster, Felleman, & Bachevalier, 2000; Chlan-Fourney, Webster, Jung, & Bachevalier, 2003; Bertolino et al., 1997; Meng et al., 2013a; Meng et al., 2013b) have already demonstrated significant morphological and neurochemical changes in the lateral PFC as a result of early damage to the MTL structures. Given that the lateral PFC is critical for performance on the WM tasks, the WM deficits after the neonatal PRh lesions may have resulted from maldevelopment of the lateral PFC following disruption of inputs it receives from the PRh rather than damage to PRh per se. Clearly, disentangling these alternative interpretations of the results will require the replication of the

current experiments in a group of monkeys that will have received the same PRh lesions in adulthood.

FIGURES/TABLES

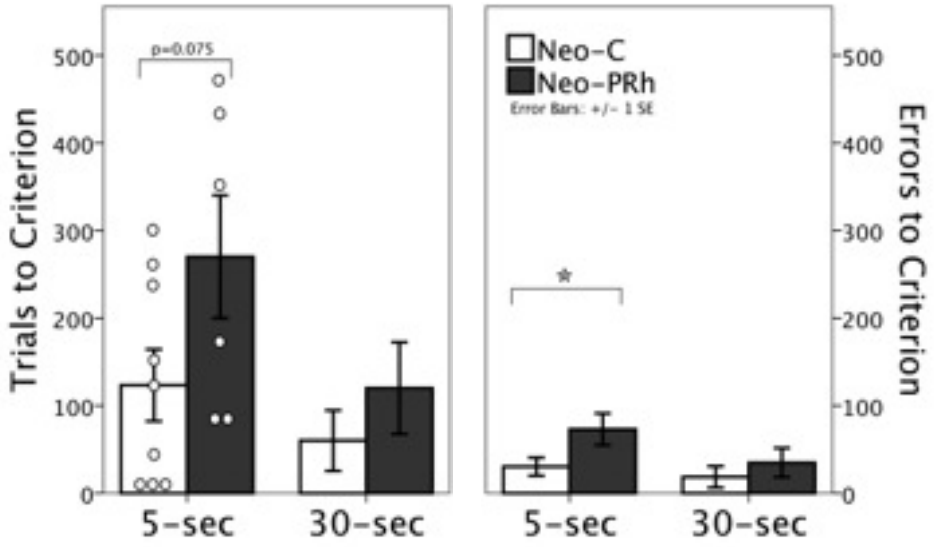
<u>Figure 1:</u> MR Images

Coronal MR images from two representative cases (Neo-PRh-3 and Neo-PRh-6). For each case, high-resolution T1 images at three levels through the anterior temporal lobe (left columns) indicate the sites of ibotenic acid injections in the perirhinal cortex (white arrows and stars). Post-surgical coronal FLAIR images (right columns) illustrate the extent of hypersignals indicative of edema and cell death (white area). The dashed lines delineate the anatomical borders of the perirhinal cortex.



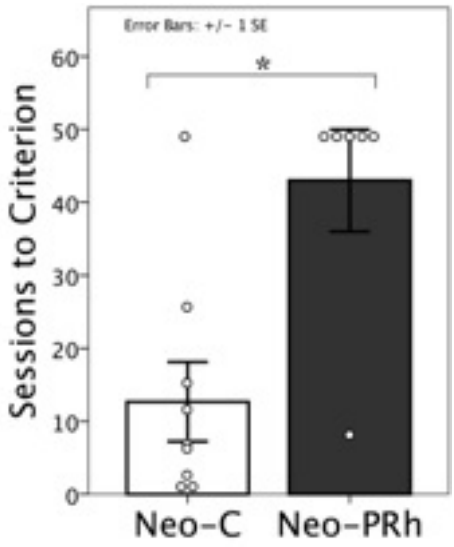
<u>Figure 2:</u> Trials and Errors to criterion, SU-DNMS

Mean trials (left panel) and errors (right panel) to criterion in the SU-DNMS task at the 5-sec and 30-sec delay for monkeys with neonatal perirhinal cortex lesions (Neo-PRh, filled bars) and controls (Neo-C, open bars). *p<0.05.



<u>Figure 3:</u> Sessions to reach criterion, Obj-SO

Average number of sessions to reach criterion in the Obj-SO task in monkeys with neonatal perirhinal lesions (Neo-PRh, filled bars) and controls (Neo-C, open bars). *p<0.05.



<u>Figure 4:</u> Primary and Perseverative Errors across delays, Obj-SO

Number of Primary Errors (left panel) and number orz Perseverative Errors (right panel) for Trial 2 and Trial 3 of the Obj-SO task for monkeys with neonatal perirhinal lesions (Neo-PRh, filled bars) and controls (Neo-C, open bars). *p<0.05

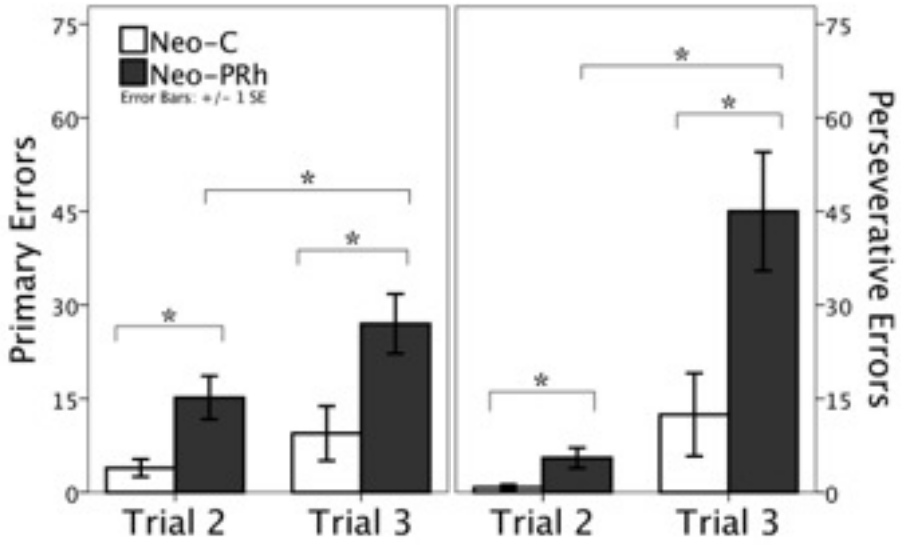


Table 1: Extent of Neo-PRh lesions

	Intended Damage Perirhinal				Unintended Damage Entorhinal			
Cases	**L%**	**R%**	**X%**	**W%**	**L%**	**R%**	**X%**	**W%**
Neo-PRh-1	89.8	76.9	83.3	69.0	28.5	2.3	15.4	0.6
Neo-PRh-2	68.2	70.6	69.4	48.1	17.7	20.7	19.2	3.7
Neo-PRh-3	65.4	81.0	73.2	53.0	7.7	3.1	5.4	0.2
Neo-PRh-4	59.4	74.7	67.1	44.4	11.5	17.8	14.7	2.1
Neo-PRh-5	75.9	66.8	71.4	50.7	38.6	29.9	34.2	11.5
Neo-PRh-6	74.1	80.3	77.2	59.5	25.3	43.6	34.5	11.1
Average	***72.1***	***75.1***	***73.6***	***54.1***	***21.6***	***19.6***	***20.6***	***4.9***

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% X R%)/100). (Courtesy of A. Zeamer and B. Bachevalier).

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