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Research report

Object and spatial memory after neonatal perirhinal lesions in monkeys

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HIGHLIGHTS

• Object and location memory was assessed in monkeys with neonatal perirhinal lesions.
• Recognition of objects after delays longer than 30 s was impaired.
• No functional sparing after the early-onset perirhinal lesions.
• By contrast, recognition of spatial locations was left intact.

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ABSTRACT

The contribution of the perirhinal cortex (PRh) to recognition memory is well characterized in adults, yet the same lesions have limited effect on recognition of spatial locations. Here, we assessed whether the same outcomes will follow when perirhinal lesions are performed in infancy. Monkeys with neonatal perirhinal (Neo-PRh) lesions and control animals were tested in three operant recognition tasks as they reached adulthood: Delayed Nonmatching-to-Sample (DNMS) and Object Memory Span (OMS), measuring object recognition, and Spatial Memory Span (SMS), measuring recognition of spatial locations. Although Neo-PRh lesions did not impact acquisition of the DNMS rule, they did impair performance when the delays were extended from 30 s to 600 s. In contrast, the same neonatal lesions had no impact on either the object or spatial memory span tasks, suggesting that the lesions impacted the maintenance of information across longer delays and not memory capacity. Finally, the magnitude of recognition memory impairment after the Neo-PRh lesions was similar to that previously observed after adult-onset perirhinal lesions, indicating minimal, or no, functional compensation after the early PRh lesions. Overall, the results indicate that the PRh is a cortical structure that is important for the normal development of mechanisms supporting object recognition memory. Its contribution may be relevant to the memory impairment observed in human cases of temporal lobe epilepsy without hippocampal sclerosis, but not to the memory impairment found in developmental amnesia cases.

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1. Introduction

The perirhinal cortex (PRh), a thin strip of cortex lying in the rhinal sulcus within the medial temporal lobe, provides one of the main inputs to the hippocampus (see for review [1]). Its crucial role in recognition memory was initially discovered from lesion studies in both monkeys [2–6,43,45], and rats [7,8], when recognition memory was assessed using either incidental recognition tasks, such as the visual paired comparison (VPC) task, or operant memory tasks, such as delayed nonmatching-to-sample (DNMS). Subsequent electrophysiological studies in monkeys [9,10] and rodents [11–13] as well as neuroimaging studies in humans [14–16] provided further evidence of the significant contribution of the PRh to recognition memory. Furthermore, the anatomical evidence that at birth the PRh can be clearly identified cytoarchitecturally and displays adult-like chemo-anatomical characteristics [17], we recently demonstrated that the PRh is also required to support recognition memory in early infancy.

In a longitudinal study tracing the development of recognition abilities in infant monkeys from 1.5 months to 18 months with the VPC task, we found that normally developing monkeys (Neo-C) showed robust recognition memory across short and long delays, as measured by VPC, with a delay-dependent performance emerging.
only at 18 months of age [18]. These recognition memory abilities were severely compromised in infant monkeys that had received bilateral neurotoxic damage to the PRh (Neo-PRh) in the first 2 weeks after birth [19]. This memory loss was mild but emerged as early as 1.5 months, became more pronounced in adolescence (18 months), and remained present in adulthood (48 months). However, the degree of incidental recognition memory loss after the neonatal PRh lesions was less severe than that observed when the same lesions were incurred in adulthood [6], suggesting that the development of incidental recognition memory processes can be supported, at least in part, by other MTL structures (such as the entorhinal cortex and hippocampus) despite the absence of intact/functional inputs from PRh.

Given that adult-onset PRh lesions impacted object recognition memory performance not only using the incidental VPC task [6] but also using operant recognition tasks [4], in the present study we investigated whether similar to the adult-onset PRh lesions, the early-onset PRh lesions will impact performance on operant object recognition tasks, namely DNMS and Object memory Span (OMS) tasks. Finally, contrary to its significant contribution to object recognition memory, the PRh has a less critical role in memory for spatial locations [20–27], especially when delays are kept short [28,29]. Thus, memory for spatial locations was also measured in animals with Neo-PRh lesions using a Spatial Memory Span (SMS) task. In sum, as they reached adulthood, monkeys with Neo-PRh lesions and their controls (Neo-C) were tested in three operant recognition tasks: Delayed Nonmatching-to-Sample (DNMS) and Object Memory Span (OMS), measuring object recognition; and Spatial Memory Span (SMS), measuring recognition of spatial locations.

2. Methods

All protocols were approved by the Institutional Animal Care and Use Committee at Emory University in Atlanta, Georgia and are in accordance with the NIH Guide for the care and use of Laboratory Animals [30].

2.1. Subjects

Seventeen adult rhesus macaques (Macaca mulatta), 9 female and 8 male (average weight 7.5 kg), participated in this study. Fourteen animals received surgery on postnatal days 10–12, either bilateral ibotenic acid lesions of the perirhinal cortex (Neo-PRh; 3 females, 3 males), or sham-surgery and served as surgical controls (Neo-C; 4 females, 4 males). Three others served as un-operated controls (Neo-C; 2 female, 1 male).

As infants, the animals were surrogate-nursery reared according to procedures established by Sackett and colleagues [31] and received similar rearing environments that included social interactions with age-matched peers and human caregivers (for details see [32]). From 3–9 months of age, environmental and social enrichment was provided by allowing the animals to socialize with age- and sex-matched peers in a large cage containing toys for 3–4 h each day. Once reaching 12 months of age, the animals were placed into same-sex tetrad and housed in a large indoor enclosure. Between 18–48 months, animals were maintained in pairs. Upon reaching adulthood, they were housed individually.

At the time of this study, all animals were 48–52 months old. They were housed in a room with a 12–h light/dark cycle (7AM:7PM), fed Purina Old World Primate chow (formula 5047), and supplemented with fresh fruit. Water was given ad libitum. During behavioral testing, chow was restricted and the weight of the animals monitored and maintained at or above 85% of the full feed weight.

2.2. Neuroimaging and surgical procedures

MR images were acquired with a 3T Siemens Magnetom Trio system (Siemens Medical Solutions, Malvern, PA at YNPRC). Two sets of pre-surgical scans were obtained: (1) structural T1-weighted image sequence used to calculate the injection sites (3D T1-weighted fast spoiled gradient (FSPGR)-echo sequence, TE = 2.6 ms, TR = 10.2 ms, 25° flip angle, contiguous 1 mm sections, 12 cm FOV, 256 × 256 matrix); and (2) Fluid Attenuated Inversion Recovery (FLAIR) image sequence as a baseline for future lesion extent measurements (TE = 140 ms, TR = 1000 ms, inversion time (TI) = 2200 ms, contiguous 3 mm sections, 12 cm FOV, 256 × 256 matrix; image sequences acquired in 3 series offset 1 mm posterior). The same two scans were repeated 1 week post-surgically and were used to evaluate lesion extent using the methods described below. For the scans, the animals were sedated with Ketamine HCl (10 mg/kg of 7:3 Ketamine Hydrochloride, 100 mg/ml, and Xylazine, 20 mg/ml, administered i.m.), intubated to allow inhalation of isoflurane (1–3%, v/v), and instrumented with an IV drip (0.45% NaCl and dextrose) to maintain normal hydration. The head was secured in a stereotoxic apparatus and vital signs (heart and respiration rates, blood pressure, expired CO2, and temperature) were monitored for the duration of the scans. Using the T1-weighted coronal images, three injection sites spaced 2 mm along the rostral–caudal length of the perirhinal cortex were selected bilaterally and their MR coordinates were transformed into stereotoxic coordinates.

Immediately after the pre-surgical scans, the anesthetized animals were transported to the surgical suite and prepared for the aseptic surgical procedures. The skin was opened, underlying tissues were retracted, and two small craniotomies were made (1 cm wide × 2.5 cm long) with an electric drill above the injection sites. For each injection site, two Hamilton syringes held by Kopf electro manipulators (David Kopf Instruments, Tujunga, CA) were simultaneously lowered into each hemisphere and a volume of 0.4 µl ibotenic acid (Biosearch Technologies, Novato, CA, 10 mg/ml in PBS, pH 7.4) was injected at a rate of 0.4 µl/min. The sham-operated controls (Neo-C) underwent the same anesthetic and surgical procedures but no needles were lowered. At the end of the surgical procedures, the wound was sutured in anatomical layers and animals were closely monitored until complete recovery.

Algescin (acetaminophen, 10 mg/kg, p.o.) was given QID for 3 days after surgery. Animals also received dexamethasone sodium phosphate (0.4 mg/kg, i.m.) to reduce edema, and Cephazolin (25 mg/kg, i.m.) to prevent infection, once a day starting 12 h prior to surgery and ending 7 days after.

2.3. Lesion assessment

All Neo-PRh animals are currently participating in an ongoing longitudinal developmental project. Thus, post-mortem histological evaluations of the lesions are unavailable at this time. Lesion extent was estimated using coronal FLAIR images acquired 1-week post-surgery. Cell death caused by the ibotenic acid induces edema that is detected as a hyper-signal on the FLAIR images. To estimate the extent of the lesion, areas of hyper-signal in each coronal FLAIR images 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 [3] and the surface area of the lesion was calculated in pixels 2. The volume of the lesion was calculated by summing the surface area of each coronal section and multiplying by image thickness (1 mm). The percent of damage to the intended site (PRh) as well as adjacent structures (visual area TE/TEO, entorhinal and parahippocampal cortex, 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 (see for more details [33,34]).

Lesion extents have already been described in detail (see [19]) and are summarized in Table 1. Briefly, the ibotenic acid injections resulted in extensive bilateral damage to the PRh in all cases (average = 73.6%, min = 67.1%, max = 83.3%). Slight unintended damage to the entorhinal cortex (average = 20.6%, min = 5.4%, max = 34.5%) as well as area TE (average = 2.5%, min = 0.1%, max = 7.11%) occurred in all cases. Additionally, there was minor damage to the hippocampus (average = 0.8%) in 4 cases, and to the amygdala (average = 2.5%) in 3 cases. Fig. 1 shows pre-surgical and post-surgical MR images of a representative case (Neo-PRh-2; see also case Neo-PRh-3 illustrated in [19]).

2.4. Behavioral procedures

All 17 monkeys participated in cognitive testing starting early in infancy, continuing throughout adolescence and into adulthood as part of a longitudinal developmental study. Prior testing included tests of incidental recognition memory (visual paired comparison at 1, 6, 18 and 48 months [19]), oddity learning (3 and 15 months), and concurrent discrimination learning with devaluation (48 months).

2.5. Apparatus and stimuli

All 3 behavioral tasks were conducted in the Wisconsin General Testing Apparatus (WGTA). A stimulus tray made from opaque plexiglass with 3 food wells arranged in a single centered row (2 cm diameter, 1 cm deep, 13 cm apart) was used for the DNMS. A similar stimulus tray containing 19 wells arranged in 3 rows (middle row of 7 wells with 6 wells on the other two rows) was used for the memory span tasks. The three rows of wells were staggered (instead of being in-line as in [35]) to ensure that objects positioned on the row closest to the animal did not block the view of objects positioned on the rows further away from the animal (see Fig. 1 in [36]). Animals were rewarded for correct responses with preferred food rewards (i.e. mini-marshmallow, raisin, etc.).

2.6. Delayed Nonmatching-to-Sample (DNMS)

The Delayed Nonmatching-to-Sample task (DNMS) measures the ability of the monkey to identify novel objects from those seen few seconds earlier [36]. On each trial, the subject was presented with a single object covering the center well of the tray, which was baited with a food reward. Once the subject displaced the sample object and retrieved the reward, a 10 s delay was imposed, following which the sample object (now un-baited) and a baited novel object were presented covering the lateral wells of the testing tray. Animals received 20 trials per day using new objects on each trial. The left/right position of the baited novel object varied pseudo-randomly, and a 30 s interval was imposed between trials. Testing continued until animals reached a criterion of 90 correct trials out of 100 trials over 5 consecutive testing days or to a maximum of 1000 trials. Monkeys were then given a performance test with increasing delays of 30 s, 60 s, 120 s, and 600 s. Each delay condition was administered for 20 trials per day for 5 consecutive testing days, resulting in 100 trials at each delay, except for the longest delay of 600 s that were administered for 5 trials per day for 10 consecutive testing days, resulting in 50 trials. All stimuli were selected from a collection of 1000 junk objects that differed in size, shape, color, and texture. The objects were divided in 25 bins of 40 objects each and each bin was selected for testing one at a time until all 25 bins were used before re-using the first bin. Thus, objects only reappeared about once per month.

2.7. Memory span tasks

Procedures for the Object and Spatial Memory Span tasks (OMS and SMS, respectively) replicated those used in Heuer & Bachevalier [36].

Object Memory Span (OMS). In this task, new objects were added one by one on the 19 wells tray and monkeys had to place the novel object to receive a reward. Monkeys were tested on 8 novel spans and 2 repeat spans in each testing day for 10 consecutive days. Thus, animals received a total of 80 novel spans and 10 repetitions of each of the 2 repeat-spans. The novel spans included sets of 19 novel stimuli on each day, whereas the repeat spans included two sets of 19 stimuli used on each testing day with the order of presentation held constant. The stimuli were sampled without replacement from a separate pool of 1500 junk objects. During each daily testing session, the two repeat spans were randomly intermixed with the 8 novel spans, and a 30 s interval separated the spans. The animals were prevented from using a spatial strategy to solve the OMS task by shifting the location of the objects on the tray between each trial of a given span.

For each object span, the first trial began with the first object placed on one of the 19 wells covering a reward. After displacing the first object and retrieving the reward, a 10 s delay was imposed, during which the now familiar object was moved to a different un-baited location and a novel object was added to another location on the tray with a reward underneath. Once the animal made its choice, another 10 s delay was imposed, the locations of the now 2 familiar objects were shuffled, and a third novel object was added to another location of the tray and baited. Objects were added until the animal made an error by selecting a previously presented object. The number of objects correctly selected before making an error was recorded as a measure of object memory span.

Spatial Memory Span (SMS). After completing the OMS task, all monkeys were subsequently trained on the SMS task. This task used similar procedures as the OMS task except that nineteen identical red plastic disks were used instead of objects, and their locations on the tray held constant. Thus, in SMS, monkeys were rewarded for selecting a new location on each trial. Testing occurred on 10 consecutive days, during which they received 8 novel spans and 2 repeat spans per day (e.g. 80 novel spatial spans and 10 repetitions of each of the 2 repeat spans). For the repeat spans, the sequence of locations was held constant for each presentation of the span. For the novel spans, locations were selected randomly prior to daily testing. During each daily testing session, the two repeat spans were randomly intermixed with the 8 novel spans. A 30 s interval separated the spans.

For each spatial span, the first trial began with one disc covering a baited well. After displacing the disc and retrieving the reward, a 10 s delay was imposed. The same well (this time un-baited) was re-covered by the disc and a new well was baited and covered by a second disc. Once the animal made its choice, a third disc was introduced in a new location with the previous locations now un-baited. Another disc was added for each subsequent trial until a previously rewarded location was erroneously selected. The number of locations correctly selected before making an error was recorded as a measure of spatial memory span.

2.8. Data analyses

For all measures, the Shapiro–Wilks test was used to verify normal distributions of the data. Two of our ordinal variables differed significantly from the normal distribution, i.e. number of trials and number of errors to criterion in the DNMS, so group differences were tested with Mann–Whitney U-test. Additionally, performance on DNMS was not normally distributed for two of the delays, thus an arcsine transformation was applied to scores obtained at all delays
### Table 1

Extent of intended and unintended damage.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>PRh</th>
<th>ERh</th>
<th>TE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L%</td>
<td>R%</td>
<td>X%</td>
</tr>
<tr>
<td>Neo-PRh-1</td>
<td>89.76</td>
<td>79.91</td>
<td>83.34</td>
</tr>
<tr>
<td>Neo-PRh-2</td>
<td>68.16</td>
<td>70.58</td>
<td>69.37</td>
</tr>
<tr>
<td>Neo-PRh-3</td>
<td>65.45</td>
<td>81.02</td>
<td>73.23</td>
</tr>
<tr>
<td>Neo-PRh-4</td>
<td>59.40</td>
<td>74.73</td>
<td>67.06</td>
</tr>
<tr>
<td>Neo-PRh-5</td>
<td>75.90</td>
<td>66.81</td>
<td>71.35</td>
</tr>
<tr>
<td>Neo-PRh-6</td>
<td>74.12</td>
<td>80.31</td>
<td>77.22</td>
</tr>
<tr>
<td>Average</td>
<td>72.13</td>
<td>75.06</td>
<td>73.60</td>
</tr>
<tr>
<td>Subjects</td>
<td>TH/TF</td>
<td>AMY</td>
<td>HF</td>
</tr>
<tr>
<td></td>
<td>L%</td>
<td>R%</td>
<td>X%</td>
</tr>
<tr>
<td>Neo-PRh-1</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Neo-PRh-2</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Neo-PRh-3</td>
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<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Neo-PRh-4</td>
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<td>3.93</td>
<td>5.47</td>
</tr>
<tr>
<td>Neo-PRh-5</td>
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<td>0.00</td>
</tr>
<tr>
<td>Neo-PRh-6</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Average</td>
<td>1.17</td>
<td>0.66</td>
<td>0.91</td>
</tr>
</tbody>
</table>

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). 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. [19].

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**Fig. 1.** Coronal MR images from a representative case (Neo-PRh-2). Pre-surgical structural T1-weighted images (left column) at three rostro-caudal levels through the perirhinal cortex. Post-surgical coronal FLAIR images (right column) show the extent of hypersignals (white areas) indicative of edema and cell damage caused by injection of ibotenic acid. Arrows point to the rhinal sulcus on the left and to the hypersignals on the right.
to normalize the distributions [37]. After this correction, 2-way repeated measures ANOVAs were used with Group as the between subject factor and Delay as the repeated within-subject factor.

Given that the data obtained from the memory span tasks followed a normal distribution, the performances of the Neo-C and Neo-PRh groups were compared using a 2 (Group: Neo-PRh vs Neo-C) × 2 (Span: Novel vs Repeat) ANOVA with repeated measures for span type. These analyses were conducted separately for the object and spatial versions of the memory tasks. To determine whether there were any female/male differences among the groups, all analyses were also run using sex as a second independent factor. Although females had scores slightly lower than males in the DNMS performance test and the OMS task, none of the analyses revealed significant sex effects. Thus, both sexes were combined for the statistical analyses presented in the Results section.

For all ANOVAs, effect sizes are reported using eta squared ($\eta^2$). This statistic was calculated by dividing the sums of squares for the effect of interest by the total sums of squares [38–40].

Finally, Pearson correlations were used to determine the relationship between the extent of neonatal perirhinal lesions and performance on all three tasks.

3. Results

3.1. Delayed Nonmatching-to-Sample

The numbers of trials and errors to reach the learning criterion for each subject are displayed in Table 2. Monkeys with Neo-PRh lesions learned the DNMS rule as proficiently as control animals, requiring an average of 267 trials (61 errors) to reach the 90% learning criterion as compared to an average of 196 trials and 53 errors for the controls. Mann–Whitney U Tests indicated that neither learning measures differed significantly between the groups [Trials: $U = 19.0$, $p > 0.05$; Errors: $U = 26.0$, $p > 0.05$].

Performance at increasing delays are given in Table 2 and illustrated in Fig. 2. Animals with Neo-PRh lesions performed more poorly than controls across all delays, except for the longest delay of 600 s. Their performance across the four delays averaged 82.6% correct as compared to 89.6% correct for the controls. However, this group difference did not reach significance [$F(1,15) = 3.796$, $p > 0.05$, $\eta^2 = 0.30$], but the main effect of delay did [$F(3,45) = 3.646$, $p = 0.019$, $\eta^2 = 0.13$]. The interaction was not significant [$F(3,45) = 0.418$, $p > 0.05$, $\eta^2 = 0.02$], indicating that performance of both groups slightly decreased across lengthening delays. As shown in Table 2, two of the Neo-C animals (Neo-C-3 and Neo-C-10) had behavioral problems during testing with the longer delays and thus, had poorer scores than the nine other control animals. Thus, re-running the statistical analyses without these two cases revealed a significant group difference [$F(1,13) = 6.026$, $p = 0.029$, $\eta^2 = 0.42$] and the effect of delay approached significance [$F(3,39) = 2.548$, $p = 0.070$, $\eta^2 = 0.09$], but the interaction was not significant [$F(3,39) = 0.276$, $p > 0.05$, $\eta^2 = 0.01$].

The extent of PRh lesion was not significantly correlated with either measures of DNMS task acquisition [Trials: $r = 0.339$, $p > 0.05$; Errors: $r = 0.064$, $p > 0.05$] or with DNMS performance at any of the delays [30 s: $r = 0.670$, $p > 0.05$; 60 s: $r = 0.294$, $p > 0.05$; 120 s: $r = -0.378$, $p > 0.05$; 600 s: $r = -0.204$, $p > 0.05$].

3.2. Memory Span tasks

The length of novel and repeat spans obtained for each animal for both versions of this task (object and spatial) and averaged across all 10 testing days are displayed in Table 2.

OMS.Neo-PRh monkeys obtained object spans of 4.3 and 2.8 for the novel and repeat spans, respectively, comparable to those obtained by control animals (4.0 and 3.0, respectively). Analyses revealed no main effect of Group on object span length [$F(1,15) < 0.01$, $p > 0.05$, $\eta^2 < 0.01$], but a highly significant main effect of span type [$F(1,15) = 67.313$, $p < 0.001$, $\eta^2 = 0.80$] and no interaction [Group*Type: $F(1,15) = 0.302$, $p > 0.05$, $\eta^2 = 0.02$], such that performance on novel spans tended to be better than repeat spans for both groups.

SMS. The average spatial span lengths of Neo-PRh monkeys were 2.1 and 1.8 for the novel and repeat spans, respectively similar to those found in control animals (2.2 and 1.9, respectively). Thus, the group effect did not reach significance [$F(1,15) = 0.635$, $p > 0.05$, $\eta^2 = 0.05$]. However, there was a significant main effect of span type such that both groups had lengthier spans for novel as compared to repeat spans [$F(1,15) = 7.069$, $p = 0.018$, $\eta^2 = 0.30$]. The interaction was not significant [Group*Type: $F(1,15) = 0.014$, $p > 0.05$, $\eta^2 < 0.01$].

Correlations between the extent of PRh lesion and Span Lengths did not reach significance [Novel Object Span: $r = -0.070$, $p > 0.05$; Repeat Object Span: $r = -0.140$, $p > 0.05$; Novel Spatial Span: $r = 0.459$, $p > 0.05$; Repeat Spatial Span: $r = 0.199$, $p > 0.05$].

3.3. Effects of age at surgery

In order to determine whether the age at which PRh lesions were incurred influenced recognition memory, we compared the scores of Groups Neo-PRh and Neo-C from the present study with those of monkeys that had received similar PRh lesions in adulthood (Adult-PRh) and their controls (Adult-C) and were tested on the DNMS task [36]. Given that the effects of adult-onset PRh lesions have never been assessed for the memory span tasks, the comparison between early and late lesions were performed only on the DNMS performance test using the 3 delays (30s, 60s, and 120s) in which all animals were tested. As illustrated in Figure 3, both early-onset and late-onset PRh lesions similarly impacted performance scores at all delays. Thus, the 3-way ANOVA revealed a significant main effect of Group [$F(1,23) = 9.714$, $p = 0.005$, $\eta^2 = 0.32$] and a significant main effect of Delay [$F(2,46) = 7.239$, $p = 0.002$, $\eta^2 = 0.24$] but no main effect of Age at lesion [$F(1,23) = 0.455$, $p = 0.05$, $\eta^2 = 0.02$]. Also, none of the interactions reached significance [Delay*Group: $F(2,46) = 0.966$, $p > 0.05$, $\eta^2 = 0.02$; Delay*Age:
Table 2

<table>
<thead>
<tr>
<th>Groups</th>
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<th>Percent correct at delay</th>
<th>Object span</th>
<th>Spatial span</th>
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<td></td>
<td>Trials</td>
<td>Errors</td>
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<td>60s</td>
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<td>85</td>
</tr>
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<td>134</td>
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<td>67</td>
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<td>60.8</td>
<td>86.5</td>
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</tbody>
</table>

Scores are number of trials and errors to criterion and performance at each of the delays on the DNMS task and span lengths for the OMS and SMS tasks for animals with neonatal perirhinal lesions (Neo-PRh) and controls (Neo-C). Data from Neo-C-1 thru Neo-C-6 previously reported in Heuer & Bachevalier [36].

Fig. 3. Average percent correct (±SEM) on DNMS at delays of 30s, 60s, and 120s for animals with early-onset perirhinal lesions (Neo-PRh: open squares, dashed line) and their controls (Neo-C: filled circles, solid line) and those with late-onset perirhinal lesions (Adult-PRh: open diamonds, dashed line) and their controls (Adult-C: filled triangles, solid line). Chance is at 50%.

F(2,46)=0.940, p>0.05, \( \eta^2=0.02 \); Group\*Age: F(1,23)=0.286, p>0.05, \( \eta^2=0.01 \); Delay\*Group\*Age: F(2,46)=0.008, p>0.05, \( \eta^2<0.01 \).

4. Discussion

This developmental study assessed for the first time the effects of early-onset PRh lesions on the ability to recognize objects and spatial locations. The results indicate that, although neonatal PRh lesions did not impact acquisition of the DNMS rule, they impaired DNMS performance at all delays. In contrast, the neonatal PRh lesions had no impact on either memory span tasks using short 10s delays. Importantly, the magnitude of the DNMS performance after the neonatal PRh lesions was similar to that reported following adult-onset lesions. These results will be discussed in turn.

4.1. Object recognition memory

Animals with Neo-PRh lesions were mildly, but not significantly, retarded during the acquisition of the DNMS rule using a short 10s delay. The relatively normal rule-learning during acquisition phase of the DNMS task contrasts with the learning impairment reported earlier in animals that had received similar PRh lesions in adulthood [3]. It is possible that the remaining PRh tissue, as well as other structures such as the entorhinal cortex and prefrontal cortical areas, could support DNMS rule learning. This idea is supported by data from monkeys with adult-onset lesions that encompass both perirhinal and entorhinal cortices and indicate that this combined lesion produces more severe deficits in DNMS rule learning than PRh lesion alone [3] and adult-onset lesions of the ventrolateral prefrontal cortex also alter DNMS acquisition [44,46,47]. In addition, neonatal lesions of the ventrolateral prefrontal cortex also yield severe deficits in DNMS learning [48]. Alternatively, it is also possible that some saving of function occurred as a result of the early lesion due to increased brain plasticity during infancy.

However, when delays were extended beyond 10s, the same Neo-PRh animals were impaired on the DNMS task as compared to controls. This recognition impairment is similar to that reported in monkeys with adult-onset PRh lesions [3; see Fig. 3] and is reminiscent of a similar recognition memory impairment reported in the same Neo-PRh animals when tested on an incidental visual recognition task, the Visual Paired Comparison (VPC) [19]. However, it is interesting to note that the drop in DNMS performance after Neo-PRh lesion was significant but scores remained above chance levels. This functional sparing may have resulted either from intact PRh tissue remaining after the lesions, or from plasticity and functional reorganization in other structures as discussed above.

4.2. Object and Spatial Memory Span

The neonatal PRh lesions did not impact performance on the object memory span task (OMS), which measures memory capaci-
ity. Results showed that Neo-PRh and Neo-C groups had equivalent object span lengths. Given the normal performance of Group Neo-PRh at the short delays in the DNMS task, the lack of impairment in the OMS task likely resulted from the short delays used. Similarly, neonatal PRh lesions spared performance on the spatial memory span task. As for the OMS task, the lack of impairment could be due to the short delay of 10s used in the present study. Other studies of monkeys with adult-onset lesions restricted to the PRh have also reported a sparing of spatial memory [20,26], even when tested using delays as long as 10 min [41]. In fact, only one study in monkeys has reported impairment on a spatial scene learning task following perirhinal lesions [42]. It is possible that the spatial scene task had additional nonspatial demands, such as recognizing complex stimuli, that could be critically supported by the PRh [1]. Alternatively, since the aspersion lesions in this later study included the entorhinal cortex in addition to the perirhinal cortex, the spatial memory impairment may also have resulted from combined damage to both cortical fields. Therefore, findings from the present study uphold evidence from other studies indicating that the perirhinal cortex is not, or less so, critical for the recognition of spatial locations.

4.3. Relation with neurodevelopmental disorders

The dissociation of the effects of neonatal damage to the hippocampus and perirhinal cortex on recognition memory replicate what has already been reported when the same damage occurs in adulthood. Both early-onset and late-onset lesions of the perirhinal cortex yield significant impairment in recognition memory [3,5,6,49,50], whereas early- and late-onset hippocampal lesions do not [6,36]. Thus, the present findings strengthen the proposal that the perirhinal cortex is more critical than the hippocampus for recognition memory processes when assessed with operant recognition tasks (or Yes/No recognition tasks for humans). The present developmental data may shed light on the neural source of the recognition memory deficits frequently reported in patients with neurodevelopmental disorders resulting from medial temporal lobe damage.

For example, memory deficits have been reported in patients with temporal lobe epilepsy and have mostly been ascribed to neuropathological changes in the hippocampus [51–54]. Yet, a recent review of the literature [55] indicated a volumetric reduction of the perirhinal cortex in a subset of patients affected by temporal lobe epilepsy in spite of normal hippocampal volumes as well as a presence of selective neuronal loss and synaptic reorganization in the perirhinal cortex in the absence of hippocampal sclerosis. Interestingly, Guedj and colleagues [15] showed that performance on recognition tests in patients with temporal lobe epilepsy was correlated with interictal metabolism of entorhinal/perirhinal cortex but not with the hippocampus. The present data support the view that the recognition memory impairment seen in patients with temporal lobe epilepsy may be related to neuropathological changes in the perirhinal cortex rather than changes in the hippocampus.

A second example relates to recognition memory performance of patients with developmental amnesia caused by early hypoxic hippocampal damage. These patients have relatively intact recognition memory measured with Yes/No recognition tasks [56], but show delay-dependent recognition deficits when tested with incidental recognition memory tasks, such as the VPC [57]. Their pattern of deficits on the two recognition tasks differs from that seen in monkeys with neonatal perirhinal lesions (impaired in both tasks), but is reminiscent to that observed in monkeys with neonatal hippocampal lesions, i.e. intact performance on DNMS [36], but impaired performance on the VPC task [58]. Neuroimaging data on these patients have revealed significant reduction in hippocampal volume with no observable changes in the perirhinal cortex [59], although there is still some debate on whether other cortical areas of the medial temporal lobe are involved in the recognition deficits. The present data tend to support the view that the perirhinal cortex must be unaffected in these specific cases.

4.4. Conclusions

The present data showed that early damage to the perirhinal cortex produced object recognition memory deficits that persisted into adulthood. Yet, memory for spatial locations was not impacted. These findings strengthen the view that the perirhinal cortex is not, or less so, critical for spatial memory processes and suggest that lesions impacted the ability to maintain information across long delays, but not memory capacity. Finally, sparing of object recognition memory was not observed despite the fact that the neonatal perirhinal lesions occurred at an age when the brain possesses significant plasticity and neural reorganization. Taken together with previous data on the effects of neonatal hippocampal lesions on object recognition memory, the present results suggest that recognition deficits in patients with temporal lobe epilepsy could solely result from damage to the perirhinal cortex, whereas memory deficits in patients with developmental amnesia could solely result from damage to the hippocampus.

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