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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 30s 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 with human cases of temporal lobe epilepsy without hippocampal sclerosis, but not to the memory impairment found in developmental amnesia cases.

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, on 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

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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 tetrads 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-weighed 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 stereotaxic 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 stereotaxic 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 electrode 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.

Analgesic (acetaminophen, 10 mg/kg, p.o.) was given QID for 3 days after surgery. Animals also received dexamethazone 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® 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