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The development of object recognition memory in rhesus macaques with neonatal lesions of the perirhinal cortex

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ABSTRACT

To investigate the role of the perirhinal cortex on the development of recognition measured by the visual paired-comparison (VPC) task, infant monkeys with neonatal perirhinal lesions and sham-operated controls were tested at 1.5, 6, 18, and 48 months of age on the VPC task with color stimuli and intermixed delays of 10 s, 30 s, 60 s, and 120 s. Monkeys with neonatal perirhinal lesions showed an increase in novelty preference between 1.5 and 6 months of age similar to controls, although at these two ages, performance remained significantly poorer than that of control animals. With age, performance in animals with neonatal perirhinal lesions deteriorated as compared to that of controls. In contrast to the lack of novelty preference in monkeys with perirhinal lesions acquired in adulthood, novelty preference in the neonatally operated animals remained above chance at all delays and all ages. The data suggest that, although incidental recognition memory processes can be supported by the perirhinal cortex in early infancy, other temporal cortical areas may support these processes in the absence of a functional perirhinal cortex early in development. The neural substrates mediating incidental recognition memory processes appear to be more widespread in early infancy than in adulthood.

1. Introduction

The study of the neural substrates responsible for recognition memory has received increased attention in the last two decades as a result of recent theoretical considerations of the role of the medial temporal lobe (MTL) structures in memory. There is general agreement that, within the MTL, the hippocampus acts in concert with the parahippocampal and perirhinal cortex to support recognition memory. In this view, the hippocampus associates (or binds) contextual information from the parahippocampal cortex with object representations from the perirhinal (PRh) cortex, and encodes and maintains relationships among stimuli (Davachi, 2006; Diana et al., 2007; Eichenbaum et al., 2007; Montaldi and Mayes, 2010; Sutherland and Rudy, 1989). In addition to its role in building representations of objects, the role of PRh in object recognition memory has received growing support from studies in several species including rodents, monkeys and humans (for review see Bachevalier et al., 2002; Brown and Aggleton, 2001; Eichenbaum et al., 2007; Murray et al., 2007; Squire et al., 2007; Wan et al., 1999; Winters et al., 2008). In adult monkeys, selective

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lesions of the perirhinal cortex either alone, or in conjunction with the entorhinal cortex or parahippocampal cortex severely impair performance on object recognition memory tasks, including delayed nonmatching-to-sample and delayed matching-to-sample (Baxter and Murray, 2001; Buffalo et al., 1999, 2000; Gaffan and Murray, 1992; Hadfield et al., 2003; Meunier et al., 1993; Nemanic et al., 2004; Zola-Morgan et al., 1989) as well as the visual paired comparison (VPC) task (Nemanic et al., 2004). In the VPC task, a task known to measure incidental recognition memory processes, the memory deficit emerges at very short delays of only a few seconds and contrasts with the recognition memory impairment seen only at delays longer than 60 s in the same task after selective hippocampal lesions in adults. Similarly, in humans, damage to the medial temporal lobe, which included the perirhinal cortex, impaired performance on a yes/no recognition memory task at delays greater than 6 s, as compared to the impairment seen at longer delays (25 s) in patients with damage limited to the hippocampal formation (Buffalo et al., 1999). In addition, damage to the temporal lobe that included the perirhinal cortex but spared the hippocampus, impaired the ability of human subjects to make familiarity judgments in the remember/know paradigm (Bowles et al., 2007). Finally, neuroimaging studies in humans (Danckert et al., 2007; Pihlajamaki et al., 2004; Ramsøy et al., 2009) have shown that the perirhinal cortex plays a role in processing and encoding novel object information. Although the contribution of the perirhinal cortex to recognition memory processes in adults is well established, its contribution to the early developing recognition memory abilities that have been demonstrated in both humans (Diamond, 1995; Fagan, 1970; Pascalis and de Schonen, 1994) and monkeys (Bachevalier et al., 1993; Gunderson and Sackett, 1984; Zeamer et al., 2009, 2010) remains to be investigated.

We recently tested the normal development of object recognition memory in monkeys using the visual paired comparison (VPC) task (Zeamer et al., 2010) as well as that of infant monkeys that had received selective hippocampal lesions. Infant monkeys received the VPC task at four ages during development (1.5, 6, 18 and 48 months) using delays varying from 10 to 120 s and pictures of color stimuli. At the youngest age of 1.5 months, normal infant monkeys showed novelty preference at all delays and this preference became more robust by 6 months of age. However, at 18 months of age, even when novelty preference remained well above chance level, a delay-dependent effect emerged, such that novelty preference was stronger at the shortest than at the longest delays. In addition, monkeys with neonatal neurotoxic hippocampal lesions performed as well as controls at 1.5 and 6 months of age, and, by 18 months of age, also showed a delay-dependent effect. However, the decrease in novelty preference across the delays was steeper in animals with neonatal hippocampal lesions than in control animals, such that, at the longest delay of 120 s, novelty preference of animals with neonatal hippocampal lesions was significantly weaker than that of controls. This pattern of findings suggested that, in the absence of a functional hippocampus, the intact recognition memory seen at the earlier ages of 1.5 and 6 months in the hippocampal-operated monkeys could be supported by medial temporal cortical areas. One likely candidate is the perirhinal cortex given mounting evidence implicating this temporal cortical area in recognition memory in adults (see above).

Thus, in the present study, we investigated whether the perirhinal cortex could support incidental recognition memory processes in early infancy. Infant monkeys were given neonatal neurotoxic perirhinal lesions and tested in the VPC recognition task at the same time points (1.5, 6, 18 and 48 months) and using the same delays (10–120 s) as in our previous study with neonatal hippocampal lesions (Zeamer et al., 2010; Zeamer and Bachevalier, 2013). We predicted that if the perirhinal cortex mediates recognition memory processes measured with the VPC task at 1.5 and 6 months of age, animals with neonatal perirhinal lesions should be impaired on the task at all ages and with short as well as long delays. Preliminary reports of the findings were published in abstract form (Zeamer and Bachevalier, 2009).

2. Methods

All experimental procedures were approved by the Institutional Animal Care and Use Committee of the University of Texas at Houston where this study began and by Emory University where it was completed. All rearing and behavioral testing procedures were kept constant between the two institutions.

2.1. Subjects

The subjects were sixteen full-term infant rhesus monkeys (*Macaca mulatta*) of both sexes born from multiparous females at the MD Anderson Cancer Center Science Park (Bastrop, TX) and the Yerkes National Primate Research Center (YNPRC) breeding colony (Atlanta, GA), and brought to our primate nursery between 1 and 2 days of age. Between 10 and 12 days postnatally, eight animals underwent a sham operation and two were kept unoperated and were used as controls (Group Neo-C, 5 males, 5 females). The remaining six received MRI-guided neurotoxic injections in the perirhinal cortex (Group Neo-PRh, 3 males, 3 females). At both institutions, all monkeys were reared using similar procedures by the same experimenters and included social interactions with age-matched peers and human caregivers as described previously (see Goursaud and Bachevalier, 2007).

2.2. Surgical procedures

2.2.1. Magnetic resonance imaging (MRI) scans and determination of injection coordinates

All animals received MRI scans immediately prior to surgery. The scans for Group Neo-PRh were used to determine the precise stereotaxic coordinates for injection of ibotenic acid (Nemanic et al., 2002) and the scans for Group Neo-C were used to assess brain maturation using T1 structural images (Payne et al., 2010). The subjects were anesthetized with ketamine hydrochloride and xylazine (10 mg/kg of 7:3 ketamine hydrochloride, 100 mg/ml,