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SYMPOSIUM-INTRODUCTION

The Hippocampus and Episodic Memory in Children

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One of the central tenets of cognitive neuropsychology, arising in large measure from the seminal studies of Brenda Milner (Milner, 1972), is that the hippocampus is crucial to episodic memory. Those foundational studies were based on the effects of temporal-lobe epilepsy (TLE) and resections on learning and retention of novel information. Yet, a striking observation in this literature is that the typical profiles of memory dysfunction seen in adults with TLE are not apparent in children with this disorder. In adults, there is a robust association between left TLE and verbal memory impairment, with somewhat weaker findings for right TLE and visuospatial memory deficits (McAndrews & Cohn, 2012). In contrast, memory deficits are less likely to be related to hemispheric or material specificity in children with TLE and more likely to be secondary to attentional problems (Engels & Smith, 2010; Mabbott & Smith, 2003). These apparent differences between the developing and mature brain in the relationship between the functional integrity of the hippocampus and memory abilities in TLE may reflect important maturational changes and plasticity at both behavioral and structural levels.

This symposium presents a sample of papers that address the question of hippocampal-memory relationships in the developing brain from different perspectives and techniques, including imaging memory operations in typically developing children and examining the effects of neonatal injury that can disrupt both structure and function in children and primates. Collectively these papers provide new information regarding the developmental trajectory of hippocampally based memory processes.

IMAGING MEMORY IN CHILDREN AND ADOLESCENTS

The past several decades have seen a large number of studies using functional MRI (fMRI) to probe the involvement of the hippocampus, through both focal activation and connectivity with other regions, in various aspects of episodic memory. Many of these studies have been directed at changes in memory networks with adult aging, and there has been much less attention to the other end of the developmental curve. Several studies have shown differences between children and adults in patterns of hippocampal activation during encoding and retrieval which are consistent with the general proposition that the hippocampus plays an increasingly specialized role in memory for event details with development (Chiu, Schmithorst, Brown, Holland, & Dunn, 2006; DeMaster & Ghetti, 2013; Ghetti, DeMaster, Yonelinas, & Bunge, 2010).

Research by one of our contributors has examined developmental changes in the ability to distinguish veridical memories from false memories. Using a paradigm that induces high levels of false recognition to lures that are semantically associated with studied items, they reported that anterior hippocampal activation associated with veridical memory increased from 8 years of age to adulthood, with no distinction between activation to hits and critical lures in the youngest group (Paz-Alonso, Ghetti, Donohue, Goodman, & Bunge, 2008). Extending those findings, the paper by Paz-Alonso et al. (in this issue) focuses on the interaction of hippocampus and frontal and parietal cortices in children (ages 8–9 years) and adults (ages 19–27 years) in veridical *versus* false recognition. The study reports different strengths of coupling between hippocampus and cortical regions; connectivity with dorsal prefrontal and parietal cortices increases with age for veridical recognition whereas connectivity with ventral prefrontal areas decreases with age for false recognition. In the context of the current symposium, the crucial finding is a developmental change in the role of the anterior hippocampus in network dynamics during memory retrieval, which may reflect differential access to or engagement of episodic and semantic memory processes.

Magnetoencephalography (MEG) is another brain imaging technique that has recently been shown to identify hippocampal signals associated with specific memory processes. Importantly, MEG can also provide information about temporal dynamics in brain activation. Using a transverse patterning paradigm as a prototype of relational learning, Hopf et al. (in this issue) examined developmental patterns of hippocampal

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activity in relation to performance in children and adolescents. Specifically, as adults typically show a more right-lateralized pattern of hippocampal activity, they were interested in whether better performance in children would be associated with a similar pattern (i.e., maturation) *versus* a bilateral pattern of hippocampal engagement (i.e., compensation). Their data supported the former hypothesis, and are consistent with functional imaging studies of language that show that developmental progression toward greater lateralization is associated with increased capability (Brown et al., 2005).

EFFECTS OF EARLY DAMAGE/DISRUPTION TO THE HIPPOCAMPUS

Several of the papers in the symposium have taken the more classical neuropsychological approach of investigating the atypical brain and the effect of early onset medial temporal lobe abnormalities on memory. One of these studies evaluates the effects of neonatal hippocampal lesions in rhesus macaques on the development of spatial memory (Blue et al., this issue). Two of these papers are on human clinical populations, children born prematurely (Omissolo et al., this issue) and children with temporal lobe epilepsy (Gascoigne et al., this issue). While they focus on different aspects of memory and to differing degrees on structural metrics, they all speak to the question of whether medial temporal lobe damage incurred early in life is associated with memory impairment. The human studies are cross-sectional in design whereas the animal study is longitudinal. Thus, these study designs complement one another in what they can reveal about developmental trajectories.

Despite the large body of evidence demonstrating the role of the hippocampus in spatial memory in humans, monkeys, rodents, and birds (Bachevalier & Nemanic, 2008; Burgess, Maguire, & O'Keefe, 2002; Mayer, Watanabe, & Bischof, 2013; O'Keefe & Nadel, 1978), to date there has not been a longitudinal study of the development of spatial memory after hippocampal lesions in early life. The study by Blue et al. in this issue fills that gap by evaluating the development of two aspects of spatial memory (one involving an egocentric frame of reference and the other dependent on allocentric cues) in monkeys who had neonatal lesions (incurred between 10 and 15 days of age). These animals were tested at three points in time: as infants (8 months), juveniles (18 months) and adults (5–6 years), and compared with sham-operated controls; at the oldest age, their performance was also compared with that of animals with adult-onset lesions of the hippocampus. Their control monkey results confirmed previous data indicating that the formation of spatial representations based on the different reference frames (egocentric *vs.* allocentric) has different developmental time courses, the former emerging in the juvenile stage and the latter reaching performance above chance only in adulthood. As juveniles, the hippocampally lesioned animals had a deficit on the egocentric spatial location task; by adulthood they were indistinguishable from controls, suggesting some form of compensation that emerges later in development. On the allocentric task, the early lesions resulted in chance performance at all ages, with deficits relative to control animals apparent in adulthood. There are two notable features of these findings. First, the developmental time course in the control monkeys has parallels in the literature on the development of spatial memory in humans, confirming the value of the comparative neuropsychological approach to understanding memory systems across development. Second, the findings also map the development of spatial memory to the morphologic maturation of the hippocampus in monkeys, and the authors speculate that, in humans, structure-function (hippocampus/spatial memory) development emerges concurrently.

Another paper in this issue focusing on early brain dysfunction by Omizzolo et al. investigated children born very preterm (VPT; before 32 weeks gestation). Up to 60% of this population have structural brain damage (Inder, Warfield, Wang, Huppi, & Volpe, 2005; Ment, Hirz, & Huppi, 2009), and VPT children are also at risk for delayed brain growth (Taylor et al., 2011). Several studies have demonstrated that hippocampal volume is reduced in VPT children, yet surprisingly few studies have looked at hippocampal structural integrity and memory abilities. Here, Omizzolo and colleagues examined the relationship between hippocampal volume and performance on measures of verbal and visual working memory, verbal and visual learning and recall in children at the age of 7 years. The strengths of their study lie in their relatively large cohort of VPT children ($N = 145$) and the use of precise and reliable techniques to measure the hippocampus. Intracranial volume was found to be smaller in the VPT group than in the term born controls, as were the volumes of the left and right hippocampus; however, when the analyses were corrected for sex, intracranial volume and a brain abnormality score, differences between the hippocampi of VPT children and controls were not significant. Although the VPT group had deficits on the memory tasks (Omizzolo et al., 2013), there were no significant associations between left or right hippocampal volumes and performance on any of the cognitive measures. The failure to replicate previous findings could be due to differences in VPT cohorts over time due to changes in medical practices, differences in hippocampal measurement techniques, or both. The authors discuss their findings in light of the observation that the VPT brain is not a typically developing brain; it is important to consider the impact of the alteration in function in other areas of the brain in addition to the hippocampus as it is possible that other brain structures may be recruited to assist with memory processing.

The final paper in this issue describing memory in a clinical population addresses autobiographical memory in children with temporal lobe epilepsy. As noted above, the study of memory impairments in adults with TLE has stimulated the collection of a rich and large body of data (Bell, Lin, Seidenberg, & Hermann, 2011; Leritz, Grande, & Bauer, 2006). Much of that literature has been concerned with laboratory-based episodic memory tasks, and only more recently have investigators addressed autobiographical memory (see McAndrews, 2012), which involves both

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semantic (knowledge of facts about one's past and oneself) and episodic information (details of personally experienced events). The study by Gascoigne et al. in this issue is the first to examine autobiographical memory in a pediatric sample with TLE. Children with TLE remembered significantly fewer episodic details from past personal events than did demographically-matched controls under conditions of free recall but not when prompts were provided, which is more consistent with a retrieval rather than a storage impairment. There was no difference in performance between children who did and did not have structural abnormalities in the hippocampus (as revealed by MRI); however, it is possible that the seizures may have disrupted function of the mesial temporal lobe structures even if structural anomalies were not apparent (Blake, Wroe, Breen, & McCarthy, 2000; Muhlert et al., 2011).

DEVELOPMENTAL HINDRANCE

Within the field of Developmental Neuropsychology there is an adage that children with early brain dysfunction can "grow into their deficit". This statement refers to the fact that children may not show deficits in many areas of cognition and behavior at a young age, but that such impairments become apparent as they grow older (see Anderson, Spencer-Smith, & Wood, 2011, for review). For example, after neonatal stroke, it has been shown that, as preschoolers, children did not differ from developmental expectations for intellectual skills, but by school age showed evidence for emerging deficits in nonverbal reasoning, working memory, and processing speed (Westmacott, MacGregor, Askalan, & deVeber, 2009). This pattern may emerge from several possible factors. First, there may be other regions outside of the damaged area that are capable of subserving such functions at early stages of development, but when the tasks that a child can do become more complex, these regions are no longer sufficient for their execution. Somewhat related to this idea is the possibility that these functions are supported by other regions outside of the damaged area early in typical development, with the latter region taking on those functions as age increases (change in functional specialization with time). It may also be that environmental demands on cognitive systems increase as the child gets older, resulting in a gap between the child's level of performance and that expected for age.

Two of the papers comprising this symposium had findings consistent with this notion that hippocampal damage in childhood could result in the delayed appearance of a deficit. In the study by Blue et al., the monkeys with neonatal lesions did not differ from controls in their performance of the allocentric task at ages 8 and 18 months, in that all groups were at chance, but were impaired as adults when the controls had achieved good performance. The authors argued that their results indicated that the hippocampus is critical for spatial relational memory, but that its involvement emerges after 18 months (the juvenile period) when the hippocampus reaches its morphological maturity. In the study on autobiographical memory, Gascoigne et al. found that episodic recall increased with age in the healthy control group, but not in the children with TLE, such that the gap in performance between the two groups became apparent only at older ages. This phenomenon has previously been described on tests of verbal memory in children with TLE (Gonzalez, Mahdavi, Anderson, & Harvey, 2012), which has led to the concept of "developmental hindrance" in memory (Helmstaedter & Elger, 2009). We note that Omizzolo et al.'s report in this issue of no association between hippocampal volume and memory is potentially consistent with this notion, but this is not conclusive as their sample was relatively young (age 7 years) when tested. Therefore, further longitudinal study of the cohort will be needed to determine if the findings represent another instance of "developmental hindrance", in that correlations between structure and function could emerge later.

FUTURE DIRECTIONS

Although the papers in this issue vary in their techniques and specific questions, they generally underscore a developmental trend toward increased specialization in hippocampal engagement, anatomic localization, and connectivity in supporting episodic memory. The symposium papers also raise several issues for future research. First, the possibility that anterior and posterior hippocampal regions (and their connections) support different types of memory abilities was noted by Paz-Alonso and colleagues. There is increasing interest in probable functional dissociations in the neuroimaging literature (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013), and evidence of a developmental trend in hippocampal volume with decreasing anterior and increasing posterior volumes with age (Gogtay et al., 2006). It may be that this trajectory relates to increasing capacity for recovery of the fine-grained detail and episodic richness we associate with recollection, a capacity that appears to increase from childhood to adulthood and that seems to be reliant on the posterior hippocampus and interconnected regions. Thus, developmental neuroimaging studies of children should provide fertile ground for exploring and expanding on some of the theoretical constructs that have been proposed in the adult literature. Second, potential advances in both cognitive and clinical neuroscience could be made by combining imaging and lesion methods, that is, by imaging patients with focal hippocampal damage (see Kipp et al., 2012). The adult literature has documented how *different networks* can support memory in the context of hippocampal damage and, like the imaging papers in this issue that examine developmental changes in hippocampal engagement and connectivity, we could learn a tremendous amount about compensation and reorganization during this period of high plasticity. A final and related point is that we need longitudinal studies in both healthy and disordered cohorts, given most of our inferences now are based on cross-sectional studies. While the resource barriers to longitudinal research are considerable, that approach will enable us to best harness the rich data from cognitive neuroscience studies of memory development toward understanding and potentially remediating effects of early damage to the hippocampus.

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CLINICAL IMPLICATIONS

Early lesions do result in memory disorders; early neuroplasticity does not appear to be sufficient to allow memory to develop normally. Because the role of the hippocampus in memory becomes increasingly specialized as age increases, the appearance and/or severity of deficits can change over time. Both of these points indicate that individuals with early dysfunction involving the hippocampus should be evaluated for memory disorders and that it may be necessary to follow their progress over childhood. The neuroimaging findings suggest that other cortical areas interact with the hippocampus in ways that change with age and it should be recognized that early lesions to the frontal and parietal lobes may also impact on memory in a dynamic way over time.

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