



Review

Developmental studies of the hippocampus and hippocampal-dependent behaviors: Insights from interdisciplinary studies and tips for new investigators



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ABSTRACT

The hippocampus is not fully developed at birth and, with respect to spatial cognition, only begins to show signs of adult-like function at three postnatal weeks in rodents. Studying the developmental period spanning roughly two to four weeks of age permits an understanding of the neural framework necessary for the emergence of spatial navigation and, quite possibly, human episodic memory. However, due to developmental factors, behavior data collection and interpretation can be severely compromised if inappropriate designs are applied. As such, we propose methodological considerations for the behavioral assessment of hippocampal function in developing rats that take into account animal size, growth rate, and sensory and motor ability. We further summarize recent key interdisciplinary studies that are beginning to unravel the molecular machinery and physiological alterations responsible for hippocampal maturation. In general, hippocampal development is a protracted process during which unique contributions to spatial cognition and complex recognition memory come “on line” at different postnatal ages creating a unique situation for elucidating the neural bases of specific components of higher cognitive abilities.

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1. Introduction

Episodic memory constitutes the “what,” “when” and “where” aspects of personal experiences and is subserved by the hippocampus and associated neural structures (Nyberg et al., 1996). Episodic memory allows us to relate past experiences to current situations, to plan future scenarios, to create narratives and, in large part, defines who we are as individuals. In rodents, the hippocampus sits at the top of a perceptual and cognitive system that permits rapid spatial memory formation and spatial navigation (Dumas and Rudy, 2010). Due to similarities in architecture, cellular physiology and network dynamics across species, research into spatial navigation and spatial memory in rodents serves as an ideal model to understand the physiological bases of episodic memory in humans (Squire, 1992; Squire and Zola, 1998). Moreover, the protracted development of the hippocampus during the late postnatal period allows for examination of discrete hippocampus-dependent functions as they come on line, beginning with contextual encoding at two weeks and ending with the ability to form and retrieve long-term episodic memories at after four weeks of age.

In humans, spatial memory emerges at about three years of age (Aadland et al., 1985; Huttenlocher, 2008). In rodents, as judged by performance in spatial learning and memory tasks, the hippocampus does not show signs of adult-like function until at least the end of the third postnatal week (Blair et al., 2013; Douglas et al., 1973; Dumas, 2004; Kraemer and Randall, 1995; Rudy et al., 1987). Reliance of spatial learning and memory on well-developed motor and distal sensory systems (Rudy, 1992) may partially explain why the hippocampus matures late in the postnatal period, so that information fed to the juvenile hippocampus is an accurate, high fidelity representation of the environment (Fagiolini et al., 1994; Göb et al., 1987; Schachtele et al., 2011; Stanton, 2000). This notion is substantiated by studies that have demonstrated that the trajectory for hippocampal maturation can be modified *via* experimental manipulation of visual experience (Dumas, 2004; Foreman and Althaus, 1992; Kenny and Turkewitz, 1986), gain-of-function pharmacological treatment (Blair et al., 2013), and genetic mutation of neurotransmitter receptors (Sanders et al., 2013). Such approaches permit creation of a holistic model of hippocampal construction and identification of the specific neural processes that underlie various aspects of spatial cognition and episodic memory.

To fully understand episodic memory in adulthood, it is important to understand how the hippocampus is built during postnatal development and how it gains the ability to influence behavior (Wills et al., 2013). Because developmental approaches to investigation of hippocampal function are on the rise, this mini-review is intended to define appropriate behavioral tests for younger animals (often referring back to pioneering literature) and highlight recent mechanistic experiments that are beginning to create a unified model of the neural bases of hippocampal maturation.

2. Considerations for behavioral tests in immature rodents

Behavioral testing in juvenile rodents is very similar to that performed in adults with a few considerations, including smaller body size and accelerated growth rate of young rodents, continued refinement of sensory and motor systems, and interpretation complications produced by multiple-day training procedures. Attention paid to such details reduces experimental variability and increases the ability to resolve age-related differences in spatial learning and memory.

2.1. Issues related to size, diet, and rapid growth

Developing rats and mice are smaller than adults and remain in a phase of rapid growth as they approach three weeks of age (Fig. 1). Because juveniles are smaller, maze dimensions need to be adjusted (Bulut and Altman, 1974; Carman and Mactutus, 2002; Carman et al., 2003; Dumas, 2004). Also, during the third postnatal week, developing rodents still feed from the dam while transitioning to solid food. Thus, appetitive tasks that require food deprivation, whether spatial or not, are likely to produce excessive metabolic and/or psychological stress prior to training, impact growth trajectory, and are not appropriate (Bronstein and Spear, 1972). As well, appetitive rewards that are salient to older animals may not be so to younger animals, impeding analysis of learning and memory abilities (Smith and Bogomolny, 1983). Furthermore, appetitive and aversive tasks that require multi-day training procedures produce temporal confounds that hinder interpretation of results. For instance, if behavior changes from day one to day two of a multi-day procedure, without single exposure controls, it is not possible to know if any behavioral alteration observed during day-two performance was influenced by day-one training or emerged independently on day two.

2.2. Environmental considerations

Finally, while sensory and motor abilities are largely well-developed at three weeks of age, some degree of continued refinement is apparent (Moye and Rudy, 1987; Prusky and Douglas, 2003). It is likely that, at three weeks, young animals cannot see as far as more mature animals (Fagiolini et al., 1994; Liao et al., 2004). Thus, given testing environments of the same size, contextual cue patterns should be larger for juveniles (Rudy et al., 1987) (Fig. 2). Finally, three-week-old rodents are not as strong as adults nor have they produced as thick a coat of fur. Therefore, special attention should be paid to environmental temperature and number of trials administered, especially in wet mazes where these animals do not float as well and may be more adversely affected by excessive number or duration of trials and inter-trial temperature changes (Iivonen et al., 2003; Kraemer and Randall, 1995).

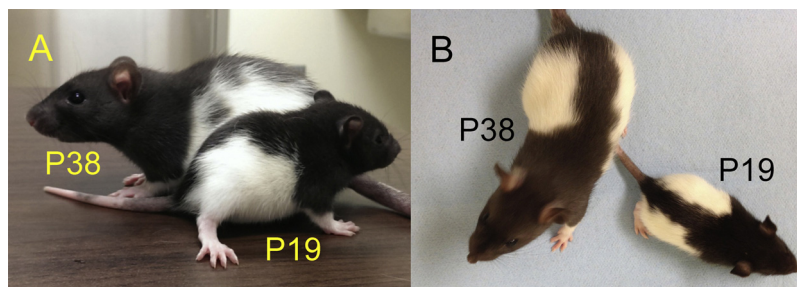


Fig. 1. Long-Evans rats at P19 and P38. Both height (A) and length (B) differ dramatically between these age groups. Behavioral testing conditions must account for differences in size and step length in relation to the animal's age.

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