Chapter 1
Introduction

At birth, infants have fully developed brains—at least from a macroscopic point of view—and the constituents of the brain are easily recognizable in both humans (Arnold and Trojanowski 1996) and nonhuman primates (Rakic and Nowakowski 1981). However, many events need to occur in various areas of the brain once the child is born in order for it to achieve full maturity, and the human hippocampal formation (HF) is no exception. Although the HF is almost completely developed—macroscopically and structurally—by the time of birth, it does mature. This process of maturation includes absolute growth through the expansion of its constituents (Gogtay et al. 2006; Evans 2006), and the functional refinement of its circuitry at both the anatomic and physiologic levels.

However, even given this period of protracted development until full maturity, the anatomical appearance of the infant HF differs from that of the adult in only rather subtle ways. This fact does not preclude the development and maturation of a system that is most strongly associated with memory function, while, from a pathological point of view, epilepsy probably accounts for most of the clinical problems related to the HF.

For the sake of concision and brevity, we will not provide basic notions of the cell layers and fiber tracts that reside in the HF here, but we will assume that the reader knows how to navigate along its anterior–posterior dimension (the rostrocaudal axis, more commonly known as the septotemporal axis, especially in the rodent-related literature; i.e., Amaral and Witter 1989). Likewise, the medial-to-lateral axis implies a starting point in the dentate gyrus (DG), and unfolds from the medial extreme to the most lateral point, which is marked in humans by the border near to the transition with the neocortex. This lateral border of the HF varies along the anterior–posterior dimension such that the entorhinal cortex (EC) occurs rostrally and the parasubiculum caudally, and the presubiculum occurs near the end of the hippocampus (i.e., Fig. 23.15 in Insausti and Amaral 2004).

It seems reasonable to start by defining what is included under the term HF. As is the case in the adult human brain, we recognize a number of structures that are mainly linked by unidirectional connections. These have a starting point, namely

the DG, and an end point, the EC. This scheme, which was laid out by the great Spanish neuroanatomist Santiago Ramón y Cajal, is still valid today. Axons of the superficial cellular layers of the EC (layers II and III) innervate the DG and field CA3 of the hippocampus proper through the perforant path, and form the main source of afferents to the DG. DG cells project to CA3 through the mossy fiber system that forms the stratum lucidum, a special stratum that is specific to CA3. CA3, in turn, projects to CA1 through the system of Schaffer collaterals. CA1 projects to the subiculum, and this in turn projects to the presubiculum and parasubiculum. Finally, a converging input terminates in the EC, at the deep layers (layers V and VI) from CA1 (but not CA3) and the subiculum, while the presubiculum and very likely the parasubiculum project to layer III. Under normal circumstances no cells in CA3 innervate the DG, CA3 does not receive innervation from CA1, and CA1 is not innervated by the subiculum. In this way, the hippocampal input and output follows a defined stepwise set of connections that reach the EC, to be ultimately distributed to the neocortex. This system lies at the core of the declarative memory system.

The layout of the neural circuits that subserve the declarative memory system has been derived largely from experimental studies, mostly of rodents and to a lesser extent the nonhuman primate brain. There are a number of reviews in the literature that describe the details of this basic circuitry (Witter et al. 1989; rodent: Witter and Amaral 2004; human: Insausti and Amaral 2004) that have been applied to the human infant by extrapolating the experimental data, particularly from studies carried out in nonhuman primates (Lavenex et al. 2007) as the homology is closer than with rodent species, although the basic mechanisms may be similar.

Although the whole set of macroscopic components of the HF is complete when a child is born, a number of connectivity maturation phenomena occur after this that are extremely important in normal development. Another important phenomenon that may take place in humans, and has been known about for several decades in rodents (Sidman and Rakic 1973), is neurogenesis in the DG of the hippocampus. Although this has been demonstrated in humans (Eriksson et al. 1998), little is known about its contribution to the postnatal development of the human HF.

Yet another important issue is the presence of pathologies related specifically to neurodevelopmental disorders. Those disorders, which have been recognized for a long time, manifest themselves as epileptic seizures in the temporal lobe (cryptogenetic seizures), and more subtle disorders such as developmental amnesia (Vargha-Kadem at al. 1994, 1997), schizophrenia (Arnold et al. 1991a, b; Conrad et al. 1991; Heckers et al. 1991; Abel et al. 1992; Cannon et al. 1994; Arnold et al. 1995), autism (Bauman and Kemper 1985; Raymond et al. 1996; Saitoh et al. 2001), Down syndrome (Insausti et al. 1998c; Uecker et al. 1993; de la Monte and Hedley-Whyte 1990; Ferrer and Gullotta 1990; Weis 1991; Raz et al. 1995; Tanzi

1996), fetal alcohol syndrome (West et al. 1994), Williams syndrome (Galaburda et al. 1994), as well as other less frequent syndromes associated with genetic causes, such as velo-cardio-facial syndrome (22q11 deletion syndrome), where memory function impairment and a higher risk for schizophrenia are observed in association with decreased hippocampal volume (Debbane et al. 2006a, b).

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