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Human memory development and its dysfunction after early hippocampal injury

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Cognitive memory involves long-term memories for facts (semantic memory) and personal experiences (episodic memory) that can be brought to mind. There is consensus that the hippocampus and related medial temporal lobe (MTL) structures are crucial for adult cognitive memory, but much less is known about their contribution to memory during infancy and childhood. We argue that the MTL is involved in memory from early in life, supporting recognition memory within the first postnatal months and recall memory within the first year. We propose that normal development involves a sequence in which a form of semantic-like memory emerges first, whereas the characteristics of episodic memory develop only later with progressive development of the hippocampus. Early bilateral injury to the hippocampus disrupts this normal pattern such that memory skills cannot develop beyond the stage of semantic memories. This review is part of the *INMED/TINS* special issue *Nature and nurture in brain development and neurological disorders*, based on presentations at the annual *INMED/TINS* symposium (http://inmednet.com/).

Introduction

Memory is among the most fundamental aspects of cognitive development, enabling individuals to amass knowledge about the world and recall everyday events. Most neuroscientists believe that there are two types of long-term memory: non-cognitive and cognitive. Non-cognitive memories are typically described as unconscious or automatic, and include motor skills, conditioned responses and priming. By contrast, cognitive memories are those that can be consciously brought to mind and include knowledge of facts and of specific events. Cognitive memory can be further subdivided into episodic memory for personal experiences and semantic memory for general knowledge and facts [1]. Recall of items from episodic memory is by definition associated with retrieval of contextual details related to the encoding (e.g. I went to Paris with my family last summer), whereas recall of items from semantic memory is not (e.g. Paris is the capital of France). A similar distinction applies to recognition, whereby it can occur with retrieval of contextual details related to encoding ('recollection-based recognition') or without these additional details ('familiarity-based recognition' [2,3]). There are different views about the relationship between the episodic and semantic components of cognitive memory. One view is that semantic memories reflect the context-free 'residue' of many episodes, and thus depend on episodic memory for their formation [4]. By contrast, another view is that information enters cognitive memory in a serial fashion, and must first be encoded semantically before it can be encoded episodically [1].

The different types of long-term memory appear to rely on different brain circuits. Cognitive memories are mediated by a medial temporal lobe (MTL) circuit, involving the hippocampus and the perirhinal, entorhinal and posterior parahippocampal cortices, whereas non-cognitive memories are mediated by other brain regions. The neural basis of the semantic and episodic components of cognitive memory is more controversial. According to one view [5–7] (Figure 1), the structures involved in cognitive memory function in a hierarchy, wherein perceptual information first enters the parahippocampal regions mediating semantic memory (and familiarity-based recognition) and only then passes to hippocampal regions necessary for episodic memory (and recollection-based recognition). Others acknowledge the possibility of a division of labour within the MTL memory system, but contend that the hippocampus itself is involved in both semantic and episodic memory [8,9] (Figure 1).

Developmental studies are an important tool for understanding the organization of the cognitive and neural mechanisms underlying memory. One fundamental question is when the organization of the components of cognitive memory that are present in adults becomes observable. If different types of memory and their neuroanatomical substrates become functional at

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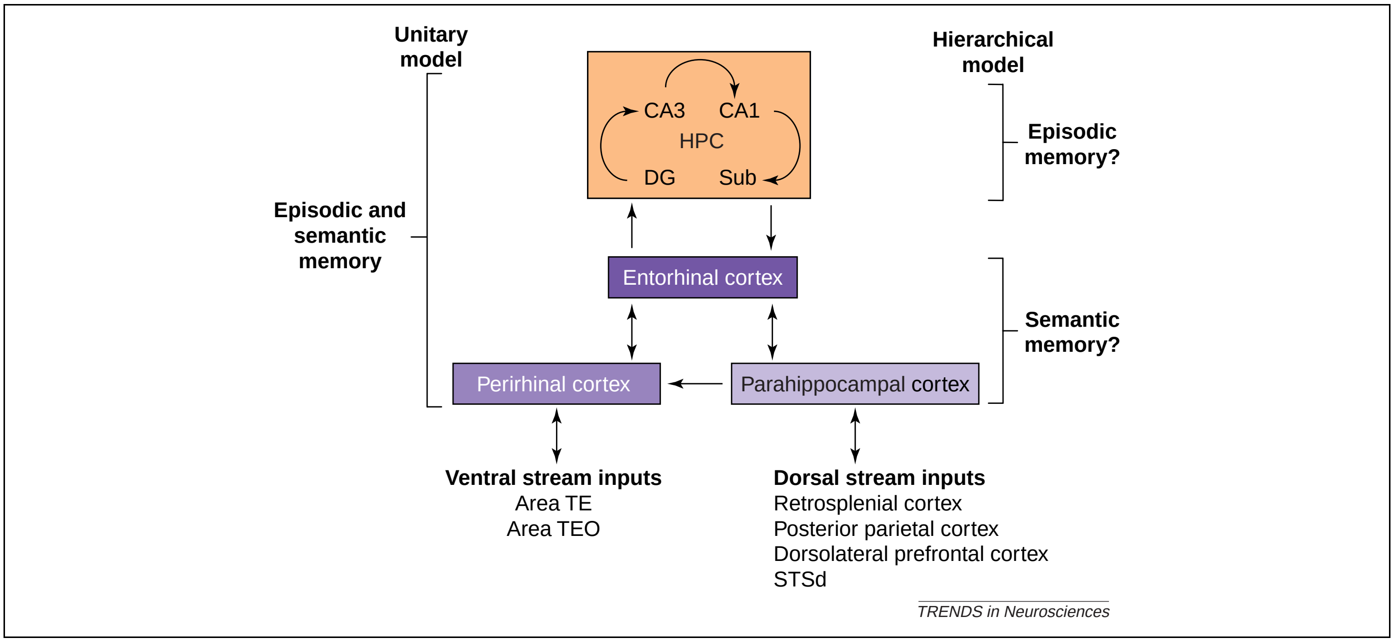

Figure 1. The hierarchical and unitary models provide different accounts for the neural basis of the semantic and episodic components of cognitive memory. According to the hierarchical model, information from the 'what' (ventral) and 'where' (dorsal) visual streams first enters the perirhinal and parahippocampal cortices, respectively, and then can pass via the entorhinal cortex to the hippocampus. In this model, semantic memory is mediated by the perirhinal, entorhinal and posterior parahippocampal regions whereas episodic memory relies on the hippocampus; thus, information is first encoded in semantic memory before it can pass on in the hierarchy to be encoded in episodic memory. This model therefore predicts that selective damage to the hippocampus can result in impaired episodic memory but that semantic memory can remain intact, whereas damage to the surrounding cortical regions would impair both types of memory. In the unitary model, both semantic and episodic memory rely on the hippocampus and the surrounding cortices. Thus, damage to any of these components should affect both semantic and episodic memory. Abbreviations: Area TE and Area TEO, regions of the inferior temporal cortex; DG, dentate gyrus; HPC, hippocampal complex; STSd, dorsal superior temporal sulcus; Sub, subiculum.

different rates, they can be studied in isolation or when interacting in ways that are not easily observed in the mature system. Studies of the effects of early injury to the neural substrates of cognitive memory can also provide important information. For example if, as proposed by the hierarchical model, the hippocampus is crucial for formation of episodic memories but not for formation of semantic memories, children with early injury to this structure should be able to acquire a normal knowledge base despite impairments in episodic memory. This review aims to examine both normal development of cognitive memory and its dysfunction following early hippocampal injury in humans, with a view to providing an account of the developmental emergence of the different features of cognitive memory.

Development of recognition memory

Recognition is the first form of memory to emerge, appearing within the first days of postnatal life. This has been shown using the visual paired-comparison task, in which participants are first familiarized with one visual stimulus and then their memories tested by presenting the familiar stimulus alongside a novel one. Adult humans [10–12] and monkeys [13,14] with bilateral MTL lesions, including those restricted to the hippocampus [15,16], show the normal pattern of looking for longer at novel than at familiar stimuli when there is little or no delay between familiarization and test, but their responses are impaired if a delay is imposed. Unlike these adults with lesions, human infants show evidence of delayed memory: 3–4-day-old children look longer at a novel face than a familiar one even when a 2 min delay is imposed [17], and 3-month-old children can do the same over a 24 h delay [18]. It is not known whether infants show evidence of recognition memory even before full-term gestational age (40 weeks). Existing studies of pre-term infants using the visual paired-comparison procedure do not provide the relevant information because they have examined pre-term infants only after term gestational age and have not included delays (e.g. Ref. [19]).

Two neuroanatomical proposals assign either the hippocampus [20,21] or the perirhinal cortex [22] as the crucial structure for early recognition memory. In the first view, infants' recognition memory is initially mediated by the hippocampus and primarily reflects novelty detection rather than recognition of familiarity *per se* [20,21]. The observation in adult neuroimaging studies that the hippocampus is involved in novelty detection [23] is consistent with this argument, although other regions, notably the perirhinal cortex, also respond to novelty [23]. Progressive development of the hippocampus, the medial temporal cortex and their interconnections enables a more mature form of recognition memory to emerge by 8–12 months; this supports recognition over longer delays and across modalities (the model does not differentiate familiarity and recollection).

In the second view, infants' recognition is initially mediated by regions of the MTL (perirhinal cortex) involved in familiarity-based recognition in adults [22]. With time, the hippocampus becomes progressively more involved in recognition, presumably enabling recollection-based recognition and abilities of self-awareness in memory to emerge [2]. In support of this view, novelty preferences in the visual paired-comparison task at 1 and