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Review article

Hippocampal neurogenesis: Learning to remember

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ABSTRACT

Alzheimer's disease, the most prevalent form of dementia in the elderly, is characterized by progressive memory loss and cognitive dysfunction. It has become increasingly clear that while neuronal cell loss in the entorhinal cortex and hippocampus occurs in Alzheimer's disease, it is preceded by a long period of deficits in the connectivity of the hippocampal formation that contributes to the vulnerability of these circuits. Hippocampal neurogenesis plays a role in the maintenance and function of the dentate gyrus and hippocampal circuitry. This review will examine the evidence suggesting that hippocampal neurogenesis plays a role in cognitive function that is affected in Alzheimer's disease, will discuss the cognitive assessments used for the detection of Alzheimer's disease in humans and rodent models of familial Alzheimer's disease, and their value for unraveling the mechanism underlying the development of cognitive impairments and dementia.

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Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; ApoE4, apolipoprotein E ε4; aPKC, atypical protein kinase C; BLBP, brain lipid-binding protein; BrdU, 5-bromo-2′-deoxyuridine; CREB, cAMP response element binding protein; CSF, cerebrospinal fluid; DG, dentate gyrus; DCX, doublecortin; ERK5, extracellular-signal-regulated kinase 5; FAD, familail AD; GFAP, glial fibrillary acidic protein; GCL, granule cell layer; Isx-9, Isoxazole 9; LML/LMI, low memory load/limited interference; Hes5, mammalian hairy and enhancer-of-split homologs; Ascl1, mash1; MAM, methylazoxy-methanol acetate; MCI, mild cognitive impairments; MWM, Morris water maze; Mef2, myocyte-enhancer family of proteins; NPC, neural progenitor cells; NSC, neural stem cells; NeuroD1, neurogenic differentiation1; PSA-NCAM, polysialated neural cell-adhesion molecule; PS1, presenilin 1; PS2, presenilin 2; Prox1, prospero homeobox protein 1; RAWM, radial arm water maze; sox1 and sox2, sex-determining region Y-box 1,2; sAPPα, soluble amyloid percursor protein alpha; SGL, subgranular layer; SVZ, subventricular zone; WWWhen task, What-where-when task; WWWhich task, "What-Where-Which" task.

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1. Introduction

Alzheimer's disease is characterized by a progressive loss of memory, the failure to learn or retain new information and the deterioration of cognitive function. Increasing evidence suggests that memory deficits develop over decades before they are detectable as mild cognitive impairments (MCI). As aging continues some of these MCI patients will progress into Alzheimer's disease (AD) dementia. While extensive research in the last three decades unraveled the genetic constituents that are linked to familial Alzheimer's disease, little is known about how learning and memory impairments develop, and the molecular substrates underlying the vulnerability of the entorhinal–hippocampal circuitry.

The generation of new neurons and glia in the adult hippocampus is increasingly implicated in forms of learning and memory. New neurons are added to the granular cell layer of the dentate gyrus throughout life and are being recruited in greater amounts following experience, learning and exercise (Deng et al., 2010). In turn, deficits in neurogenesis over time may compromise hippocampal function, gradually leading to memory deficits. Numerous studies suggest that neurogenesis is impaired in mouse models of familial AD (for review, Lazarov and Marr, 2010). However it is not clear how hippocampal neurogenesis and its gradual decline with age contribute to the cognitive dysfunction in AD. In search for a connection between AD and adult hippocampal neurogenesis one may struggle with comparative behavioral assessment in humans and mouse models. This review will attempt to connect our basic understanding of mechanisms of learning and memory with memory dysfunction in Alzheimer's disease. In addition, it will critically consider the current evidence concerning the role of neurogenesis in the development of cognitive deficits and Alzheimer's disease.

2. The role of the hippocampus in learning and memory

Memory and learning are essential components of human existence; they provide the framework for everyday activities and invest long-term meaning into significant events. Understanding the mechanism behind how memory works gives us insight into the fundamental nature of humanity. Extensive study has revealed that memory can be divided into functional segments; sensory memory, short term memory (working memory) and long term memory (Fig. 1). Chosen short term memory traces are converted to long-term memory in a process called memory consolidation (McGaugh, 1966; Dudai, 2012; Kitamura and Inokuchi, 2014). How the brain determines that some information is necessary and should be stored, while other information can be discarded, is a fascinating enigma. Such long-term memory for facts (semantic memory) and events (episodic memory) is referred to as explicit

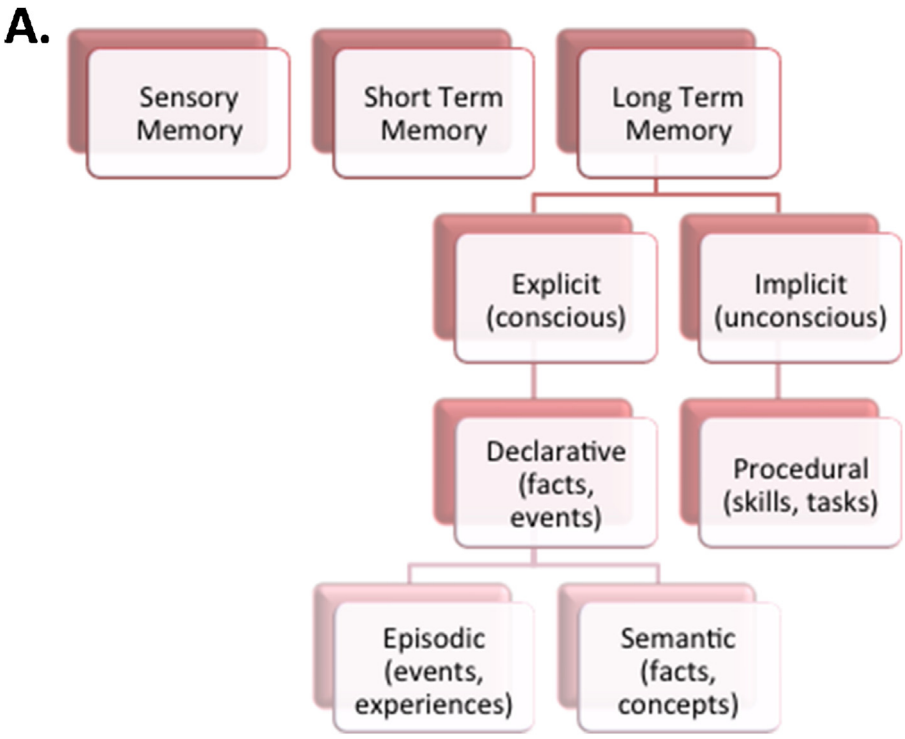

Fig. 1. Human memory domains. (a) Memory is divided into three primary functional domains; sensory memory, short-term memory and long-term memory. Long-term memory in turn can be divided into explicit, or conscious memory, and implicit, or unconscious memory. Implicit memory deals with procedural activities, like walking or tying ones shoe that are performed without conscious thought. In contrast explicit, or declarative, memory is memory for events (episodic memory) and facts (semantic memory).