Review article

Separation or binding? Role of the dentate gyrus in hippocampal mnemonic processing

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ABSTRACT

As a major component of the hippocampal trisynaptic circuit, the dentate gyrus (DG) relays inputs from the entorhinal cortex to the CA3 subregion. Although the anatomy of the DG is well characterized, its contribution to hippocampal mnemonic processing is still unclear. A currently popular theory proposes that the primary function of the DG is to orthogonalize incoming input patterns into non-overlapping patterns (pattern separation). We critically review the available data and conclude that the theoretical support and empirical evidence for this theory are not strong. We then review an alternative theory that posits a role for the DG in binding together different types of incoming sensory information. We conclude that 'binding' better captures the contribution of the DG to memory encoding than 'pattern separation'.

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1. Introduction

The dentate gyrus (DG) is an anatomically idiosyncratic structure of the cerebral cortex in several respects (Amaral, 1993; Amaral and Lavenex, 2007; Witter, 2007). First, unlike the case for other regions of the cerebral cortex, its principal cells are granule cells instead of pyramidal cells. Second, its output projections to CA2/CA3 are extremely non-divergent. In rats, each granule cell projects to an average of only 12 CA3 pyramidal cells, so that a precise topography exists in DG-CA3 projections along the septo-temporal axis of the hippocampus. Such non-divergent intracortical projections are rarely found in other areas of the cerebral cortex. Third, DG output fibers (mossy fibers) form unusually large synaptic terminals at proximal apical dendrites of CA3 pyramidal cells with multiple release sites. These features are well suited to exerting strong influences on recipient CA3 pyramidal cells, as has
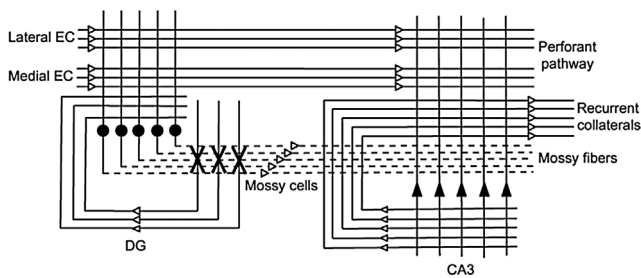
Fig. 1. A schematic diagram of the basic circuit organization of the DG and CA3.

been confirmed by physiological studies (Henze et al., 2002; Salin et al., 1996). These output fibers are also special in that their axon terminals contain high levels of zinc (Frederickson et al., 2000; Haug, 1967). Finally, the DG is different from other cortical regions in that the generation and addition of new neurons in this structure continue into adulthood (Eriksson et al., 1998; Kaplan and Hinds, 1977; van Praag et al., 2002).

What then is the role of such an idiosyncratic hippocampal structure? Several different theories on this issue have been put forward (e.g., Treves and Rolls, 1992; Buckmaster and Schwartzkroin, 1994; Lisman et al., 2005; Aimone et al., 2006; Rangle et al., 2014; Scharfman, 2016) with 'pattern separation' being the dominant theory in the field (Knierim and Neunuebel, 2016; McNaughton and Nadel, 1990; Rolls and Treves, 1998; Yassa and Stark, 2011). In this article, we critically review the theoretical basis and empirical findings related to the pattern separation theory for the DG. We argue that the theoretical support and empirical evidence for pattern separation are not as strong as commonly assumed. We then consider another theory—'binding'—as an alternative account. We argue that, although the two theories are not mutually exclusive, binding better captures the contribution of the DG to hippocampal mnemonic processing than pattern separation.

2. Pattern separation theory

The classic hippocampal trisynaptic circuit consists of the DG, CA3, and CA1 (Fig. 1). Of these, CA3 has occupied center stage in theorizing neural circuit dynamics of hippocampal mnemonic processing since Marr (1971). The CA3 region of the mammalian hippocampus is distinct from other subregions in that it contains massive and extensive recurrent collaterals that connect CA3 neurons together bilaterally (Amaral, 1993; Amaral and Lavenex, 2007; Witter, 2007). CA3 recurrent collaterals also support activity-dependent synaptic plasticity (Harris and Cotman, 1986; Zalutsky and Nicoll, 1990). These features suggest that the CA3 network may operate like a Hopfield network (Hopfield, 1982, 1984), allowing the storage of autoassociative memory (Marr, 1971; McNaughton and Morris, 1987; Rolls and Treves, 1998).

As the first structure in the hippocampal trisynaptic circuit, the DG receives major inputs from the entorhinal cortex (EC) and sends its outputs to CA3 (Amaral, 1993; Amaral and Lavenex, 2007; Witter, 2007) (Fig. 1). Although Marr (1971) focused his theory of the hippocampus on CA3, he proposed that the DG plays the role of increasing "sparseness of representations", which helps increase the storage capacity of CA3. Earlier, in his theory for the cerebellum (Marr, 1969), Marr proposed that the mossy fiber-granule cell network performs pattern separation, transforming highly overlapping representations carried by pontine mossy fibers into largely independent representations in the granular layer, based on the high divergence of mossy fiber projections to granule cells ('expansion recoding'; Albus, 1971). McNaughton and Morris (1987) highlighted expansion recoding as a way of achieving sparse representations that can increase the memory storage capacity of
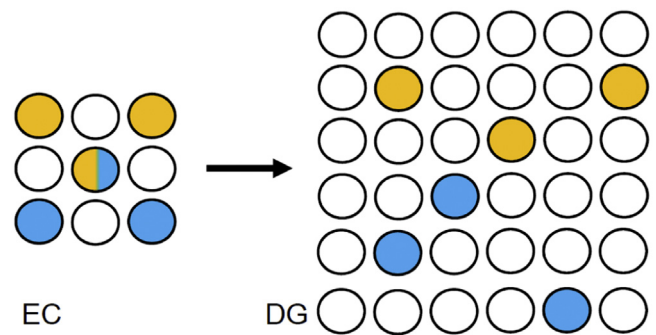

Fig. 2. Pattern separation in the DG. Two overlapping representations (yellow and blue) in the EC (a small network) are transformed into non-overlapping representations in the DG (a large network) by expansion recoding.

the hippocampus, and McNaughton (1989) explicitly proposed that projections from the EC (a smaller network; $\sim 2 \times 10^5$ neurons in rats) to the DG (a larger network; $\sim 10^6$ neurons in rats) reduce overlaps among represented patterns (Fig. 2). The idea that the DG reduces overlaps among input patterns (pattern separation) to help increase storage capacity of CA3 has been adopted by other investigators in developing computational theories of the hippocampus (e.g., Myers and Scharfman, 2009, 2011; O'Reilly and McClelland, 1994; Rolls, 1989; Rolls and Treves, 1998).

In the first empirical study testing the pattern separation theory for the DG, Gilbert et al. (2001) found that rats with colchicine-induced lesions in the DG were impaired in their ability to discriminate two closely spaced locations in a circular arena, but not those that were remotely spaced. This study was followed by two influential studies in 2007. In one study (McHugh et al., 2007), mice lacking N-methyl-D-aspartate (NMDA) receptors specifically in dentate granule cells were impaired in selectively expressing fear responses between two similar contexts. In the other study (Leutgeb et al., 2007), in which the shape of an environment was changed gradually between a cylinder and a square box, DG granule cells showed larger changes than CA3 neurons between two slightly different environments. These results were followed by a large number of subsequent empirical studies. The majority of these studies were behavioral studies, reporting effects of DG manipulation on the animal's ability to discriminate between different stimuli (mostly spatial locations) or contexts (mostly using a contextual fear-conditioning task; reviewed in Knierim and Neunuebel, 2016; Yassa and Stark, 2011). Numerous studies have also tried to link DG adult neurogenesis to pattern separation (reviewed in Hersman et al., 2015; Oomen et al., 2014; Sahay et al., 2011b).

3. Critical assessment of pattern separation theory: theoretical aspects

Theoretically, assuming that the CA3 is where associative memory is stored, a pattern-separation function of the DG could enhance the memory storage capacity of CA3. Given that humans are known to have an enormous capacity for declarative memory, it is plausible that the DG contributes to the increased memory capacity of the hippocampus by performing pattern separation. It is also consistent with the physiology of the DG. DG granule cells show particularly low mean discharge rates in behaving rats (Jung and McNaughton, 1993; Leutgeb and Leutgeb, 2007), probably owing to strongly hyperpolarized resting membrane potentials (Lambert and Jones, 1990) and strong influences of inhibitory interneurons (Ewell and Jones, 2010; Scharfman, 1991). Low activity would reduce the chance for granule cells to be activated by multiple pat-