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Review

An analysis of dentate gyrus function (an update)

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ABSTRACT

In this review there will be a description of the dentate gyrus (DG) neural circuitry that mediates the operation of a variety of mnemonic processes associated with dorsal and ventral DG function in rats. Dysfunction of the dorsal DG can be shown to mediate mnemonic processing of spatially based information including a) the operation of conjunctive encoding of multiple sensory inputs to determine spatial representations, b) pattern separation based on reducing interference between similar spatial locations and spatial contexts for horizontal distance between objects, vertical distance for height of objects, slope or angle of motor movements, c) importance of spatial context in object recognition and processing of shades of grey associated with the walls of the box d) temporal integration in the creation of remote memory based in part on DG neurogenesis and function of the CA3 subregion of the hippocampus. Dysfunction of the ventral DG can be shown to mediate mnemonic processing of odor and reward value based information including a) pattern separation for odors and reward value, and b) social recognition.

1. Structure and circuitry of the dentate gyrus subregion of the hippocampus

The dentate gyrus (DG) is primarily composed of granule cells which are located in the molecular and granule cell layers. Between the granule cell layers and area CA3c, there is the hilus which contains the granule cell axons which are labeled mossy fibers, mossy cells and a variety of GABAergic interneurons. The DG has been shown to receive multiple sensory inputs, including vestibular, olfactory, visual, auditory, and somatosensory, from the perirhinal and lateral entorhinal cortex in conjunction with spatially organized grid cells from the medial entorhinal cortex [1] to represent memory based metric spatial representations. The perforant path input of the dorsal dentate gyrus (dDG) can be divided into medial and lateral components. The medial component processes spatial information which is mediated by NMDA receptors and the lateral component processes non-spatial (e.g., objects, odors) information are mediated by opioid receptors [2,3]. The granule cell axons are labeled mossy fibers which innervate CA3a,b,c and mossy cells. The mossy cells are modulated by CA3c axons and in turn project to granule and interneurons to provide for inhibition and/or excitation of granule cells. This may be a critical circuit for the operation for a pattern separation process. It is important to note that CA3c neurons do not have recurrent collateral connections and the axons can bypass CA3 a,b via a direct connection to CA1. Finally, stem cells are located in the subgranular zone and migrate to the granule cell layer. A schema of the circuitry of the DG and other subregions of the hippocampus is shown in Fig. 1. For a more detailed description see [4,5].

2. Conjunctive encoding

The dDG has by Ref. [6]. been shown to receive multiple sensory inputs, including vestibular, olfactory, visual, auditory, and somatosensory, from the perirhinal and lateral entorhinal cortex in conjunction with spatially organized grid cells from the medial entorhinal cortex to represent metric spatial representations. The perforant path input of the dDG can be divided into medial and lateral components. The medial component processes spatial information and the lateral component processes nonspatial (e.g., objects, odors) information [2,3]. On that basis demonstrating the existence of a dDG mediation of an object-place conjunction would be of great importance. In a recent study [7] the effects of dorsal dentate gyrus (dDG) lesions in rats were tested on recognition memory tasks based on the interaction between objects, features of objects, and spatial features. The results indicated that the rats with dDG lesions did not differ from controls in recognition for a change within object feature configuration and object recognition tasks. In contrast, there was a deficit for the dDG lesioned rats relative to controls in recognition for a change within object-spatial feature configuration, complex object-place feature configuration and spatial recognition tasks. It is suggested that the dDG subregion of the hippocampus supports object-place and complex object-place feature information via a conjunctive encoding process. Based on the idea that the medial perforant path input into the dDG mediates spatial

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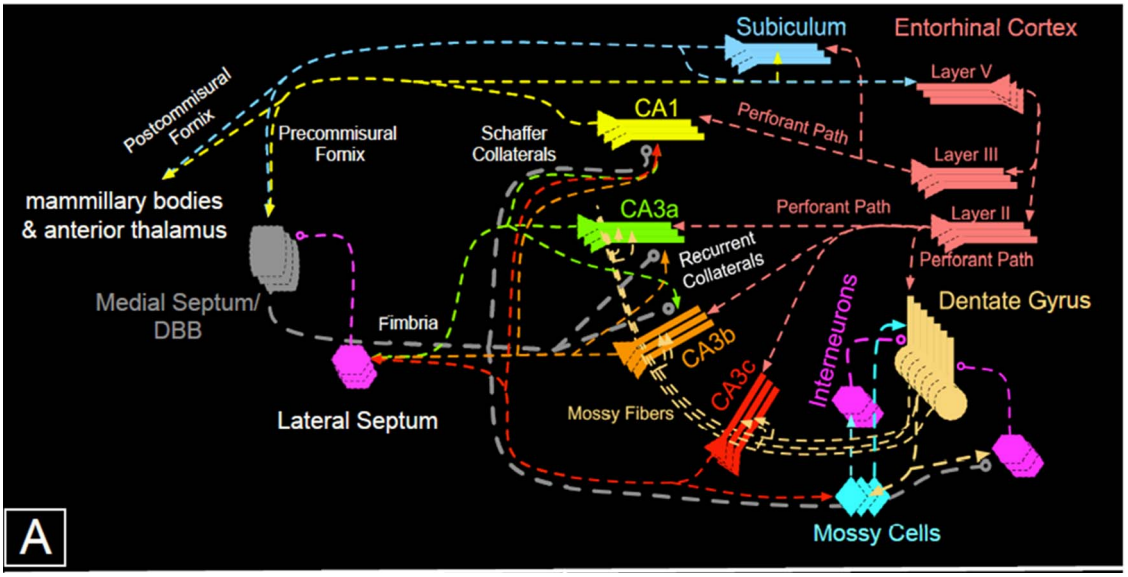

Fig 1. A schema of the circuitry of the DG and other subregions of the hippocampus.

information via activation of NMDA receptors and the lateral perforant path input into the DG mediates visual object information via activation of opioid receptors, the following experiment was conducted. Using a paradigm developed by Poucet [8], rats were tested for detection of a novel spatial change and detection of a novel visual object change while under the influence of direct infusions of AP5 (an NMDA antagonist) or naloxone (an opiate antagonist) into the dDG. Naloxone infusions into the dDG disrupted both novelty detection of a spatial location and a visual object, whereas AP5 infusions into the dDG disrupted only detection of a novel spatial location, but had no effect on detection of a novel object [9]. These results are consistent with the results of the Kesner et al. [7] experiment described above, suggesting an important role for the dorsal DG in supporting object-place conjunctive processes.

3. Spatial pattern separation in rodents

It can clearly be demonstrated that single granule cells within the hippocampus are activated by most sensory inputs, including vestibular, olfactory, visual, auditory, and somatosensory, as well as higher-order integration of sensory stimuli [9]. An important question is whether these sensory inputs via conjunctive encoding have a memory representation within the dDG subregion of the hippocampus. One possible role for the dDG in processing all sensory information might be to provide sensory markers to demarcate a spatial location, so that the dDG can more efficiently mediate spatial information. Thus, it is possible that one of the main processing functions of the dDG is to encode and separate spatial events from each other; this ensures that new highly processed sensory information is organized within the dDG and enhances the possibility of encoding and temporarily remembering one place as separate from another place, while reducing spatial interference. It should also be noted that the mossy cells which form an intricate circuit with granule cells are generally more active than the granule cells in a variety of spatial situations [10,11].

Rolls' [1,6] model proposes that pattern separation is facilitated by sparse connections in the mossy fiber system, which connects dDG granular cells to dorsal dCA3 pyramidal neurons. Separation of patterns is accomplished based on the low probability that any two dCA3a,b,c neurons will receive mossy fiber input synapses from a similar subset of dDG cells. Mossy fiber inputs to dCA3a,b,c from dDG are suggested to be essential during learning and may influence which CA3 neurons fire based on the distributed activity within the dDG. Cells of the dDG are suggested to act as a competitive learning network with Hebb-like modifiability to reduce redundancy and produce sparse, orthogonal outputs. O'Reilly and McClelland [12] and Shapiro and Olton [13] also suggested that the mossy fiber connections between the dDG and dCA3 may support pattern separation.

If disruption of dDG function results in inefficient pattern separation, then deficits involving spatial tasks may occur when there is increased overlap or similarity among distal cues and presumably increased similarity among representations within the dDG. Remembering a specific location in, for example, an eight-arm maze or a water maze may be influenced by the degree of overlap among critical distal spatial cues. dDG-lesioned rats demonstrate deficits similar to complete hippocampal lesions when tested on a working memory version of the radial eight-arm maze [14–17]. In addition, rats with dDG lesions also showed deficits comparable to rats with complete hippocampal lesions when tested on the Morris water maze task if the start location was varied on each trial [18–21].

To examine the contribution of the dDG to spatial pattern separation, Gilbert et al. [22] tested rats with dDG lesions using a paradigm that measured short-term memory for spatial location information as a function of spatial similarity between spatial locations. Specifically, the study was designed to examine the role of the dDG subregion in discriminating spatial locations when rats were required to remember a spatial location based on distal environmental cues and to differentiate between the to-be-remembered location and a distracter location with different degrees of similarity or overlap among the distal cues. Rats were tested using a cheeseboard maze apparatus (the cheeseboard is similar to a dry land water maze with 177 circular, recessed holes on a 119-cm-diameter board) on a delayed match-to-sample for a spatial location task. Animals were trained to displace an object that was randomly positioned to cover a baited food well in 1 of 15 locations along a row of food wells. Following a short delay, the rats were required to choose between objects that were identical to the sample-phase object: one object was in the same location as the sample-phase object and the second object was in a different location along the row of food wells. Rats were rewarded for displacing the object in the same spatial location as the sample-phase object (correct choice), but they received no reward for displacing the foil object (incorrect choice). Five spatial separations, from 15 cm to 105 cm, were used to separate the correct object and the foil object during the choice phase. The results indicated that rats with dDG lesions were significantly impaired at short spatial separations; however, during the choice phase performance of dDG-lesioned animals increased as a function of greater spatial