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Review

An analysis of the dentate gyrus function

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HIGHLIGHTS

- The dorsal dentate gyrus supports conjunctive encoding processes.
- The dorsal dentate gyrus supports spatial pattern separation.
- The dorsal dentate gyrus supports context pattern separation.
- The dorsal dentate gyrus supports remote memory associated with neurogenesis.
- The ventral dentate gyrus supports odor pattern separation.

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ABSTRACT

In this review article the emphasis will be on the role of the DG (dorsal and ventral) in supporting memory based on the operation of specific processes. Based on the development of computational models of dorsal dentate gyrus (dDG) and behavioral evidence based on dysfunction of dDG, this review will show that the dDG mediates mnemonic processing of spatial information. The processes subserved by dDG include (a) the operation of conjunctive encoding of multiple sensory inputs, implying an integration of sensory inputs to determine a spatial representation, and (b) pattern separation of spatial (especially metric) information, involving the reduction of interference between similar spatial locations (c) pattern separation of context (d) importance of context in object recognition, and (e) temporal integration and remote memory and spatial pattern separation based in part on neurogenesis. In addition the ventral dentate gyrus (vDG) mediates mnemonic processing of odor information as indicated by odor pattern separation.

Contents

1. An analysis of the dentate gyrus function

In recent years there has been an emphasis in exploring the dynamic properties of the subregions (dentate gyrus, CA3, and CA1) of the hippocampus rather than examining the hippocampus as a homogeneous structure. In this review article the emphasis

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will be on the role of the DG (dorsal and ventral) in supporting memory based on the operation of specific processes. Based on the anatomy of the dorsal dentate gyrus (dDG), its input and output pathways, and the development of a computational model, Rolls [1] and Rolls and Kesner [2] have suggested that the dDG supports three major processes, including conjunctive encoding of multiple sensory inputs, spatial pattern separation, and facilitation of encoding of spatial information based on its outputs to dorsal CA3 (dCA3). These processes are based on a competitive learning network with Hebb-like modifiability to remove redundancy from the inputs and to produce a more orthogonal, sparse, and categorized set of outputs. Based on the discovery of neurogenesis in the DG, an additional process involving temporal integration of remote memory has been proposed by Ref. [3].

2. Conjunctive encoding

The dDG 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 [4] 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 [5,6]. Based on the idea that the medial perforant path input into the dDG mediates spatial 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 [7], 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 (a μ 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 [8]. These data suggest that the dDG uses conjunctive encoding of visual object and spatial information to provide for a spatial representation that may be based on metric information. Additional support for the idea that the dDG contributes to the organization of spatial information based on conjunctive encoding was provided in the following experiment that emphasized acquisition of an association between a context and an odor cue [9]. In this experiment, dDG lesions as well as controls were trained in two Plexiglas boxes that represented two different contexts: Context 1 and Context 2. A context was defined as the total of all of the environmental cues in the apparatus, including floor texture, color of walls, and visual cues on the walls. Each animal was assigned two pseudo-randomly selected odors (Odor A and Odor B), which were used throughout all testing procedures. The task required that the rat learn to associate Odor A with Context 1 and Odor B with Context 2 in order to receive a food reward. Animals with dDG lesions demonstrated impairments in the ability to acquire the cue–context associations compared with the controls. Results from follow-up odor- and context-discrimination tests suggest that all rats acquired the discrimination tasks at similar rates. Therefore, it is unlikely that deficits in performance on the contextual associative learning task were due to an inability to discriminate between odors or contexts. The present findings suggest that the dDG may play an important role in conjunctive encoding of spatial paired with olfactory information.

3. Spatial pattern separation

It can clearly be demonstrated that single 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 [10]. An important question is whether these sensory inputs via conjunctive encoding have a memory representation within the hippocampus. One possible role for the hippocampus in processing all sensory information might be to provide sensory markers to demarcate a spatial location, so that the hippocampus can more efficiently mediate spatial information. Thus, it is possible that one of the main processing functions of the hippocampus is to encode and separate spatial events from each other; this ensures that new highly processed sensory information is organized within the hippocampus and enhances the possibility of encoding and temporarily remembering one place as separate from another place, while reducing spatial interference. Even though there have been a number of review articles describing functions of the dDG in supporting pattern separation [11–15], this paper covers new topics including the determination of a role for the DG in context and odor pattern separation.

Rolls' [1] 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 dCA3 neurons will receive mossy fiber input synapses from a similar subset of dDG cells. Mossy fiber inputs to dCA3 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 [16] and Shapiro and Olton [17] 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, a water maze, or a spatial context in fear conditioning 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 [18–21]. 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 [22–25].

Lee and Kesner [26] tested rats with dDG lesions on acquisition and retrieval of contextual fear conditioning. Rats with dDG lesions showed initial impairments in freezing behavior during acquisition of the task, but they eventually reached the freezing level of controls with subsequent testing. When retrieval of contextual fear was examined in rats with dDG lesions 24 h after acquisition, the animals showed a significant deficit in freezing compared to controls. Based on these studies it is clear that dDG lesions impair spatial memory. dDG-lesioned animals may be impaired as a result of impaired pattern separation; however, it is difficult to determine whether a particular memory process is impaired in these animals using these three paradigms.

To examine the contribution of the dDG to spatial pattern separation, Gilbert et al. [27] 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 distractor location with different degrees of similarity or overlap among the distal cues.

Animals 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 animals 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 separation between the correct and foil objects. The performance of rats with dDG lesions matched control rats at the largest spatial separation. The graded nature of the impairment and the significant linear improvement in performance as a function of increased separation illustrate a deficit in pattern separation [27]. Based on these results, it was concluded that lesions of the dDG decrease the efficiency of spatial pattern separation, which results in impairments on trials with increased spatial proximity and increased spatial similarity among working memory representations. Thus, the dDG may function to encode and to separate events in space producing spatial pattern separation. Such spatial pattern separation ensures that new highly processed sensory information is organized within the hippocampus, which in turn enhances the possibility of encoding and temporarily remembering one spatial location as separate from another.

Based on the observation that cells in dCA3 and dCA1 regions respond to changes in metric and topological aspects of the environment [28,29], one can ask whether these different features of the spatial environment are processed via the dDG and then subsequently transferred to the dCA3 subregion or if these features are communicated via the direct perforant path projection to the dCA3 subregion. In both cases, information may then be transferred to the dCA1 subregion. To answer this question, Goodrich-Hunsaker et al. [30] examined the contributions of the dDG to memory for metric and topological spatial relationships. Using a modified version of an exploratory paradigm developed by Ref. [7]), rats with dDG, dCA3, and dCA1 lesions as well as controls were tested on tasks involving a metric spatial manipulation. In this task, a rat was allowed to explore two different visual objects separated by a specific distance on the cheeseboard maze mentioned above [27]. On the initial presentation of the objects, the rat explored each object. However, across subsequent presentations of the objects in the same spatial locations, the rat habituated and eventually spent less time exploring the objects. Once the rat had habituated to the objects in their locations, the metric spatial distance between the objects was manipulated so that the two objects were either closer together or farther apart. The time the rat spent exploring each moved object was recorded. The results showed that rats with dDG lesions spent significantly less time exploring the two objects that were displaced relative to controls, indicating that dDG lesions impair the detection of metric distance changes. Rats with dCA3 or dCA1 lesions displayed mild impairments relative to controls.

In addition, the detection of a topological change was investigated. In the topological manipulation condition, rats were allowed to explore four different visual objects that were positioned in a square on the cheeseboard maze. The rats were again allowed to explore the objects and eventually habituated to the objects with subsequent exposure. However, following habituation, the locations of two of the four objects were switched, and the time the rat spent exploring each object was recorded. The results showed that dCA1 lesions may impair, whereas dDG or dCA3 lesions do not impair, the rats' detection of the topological manipulation. The results suggest that neurons in the dDG may be critically involved in processing spatial information on a metric scale, but they may not be necessary for representing topological space. The results of both experiments provide empirical validation for the role of dDG in spatial pattern separation and support the predictions of computational models [1,2].

There are other studies in the literature that have demonstrated that hippocampal lesions, including the dDG, can result in deficits for spatial tasks that can be interpreted as a function of increased interference and impairment in the utilization of a spatial pattern separation process. One example will suffice. McDonald and White [31] used a place preference procedure in an eight-arm maze. Two of the arms were selected and food was placed at the end of one arm and not at the end of the other arm. Fornix-lesioned rats acquired the place preference task as quickly as controls if the arm locations were opposite each other, but the fornix-lesioned rats were markedly impaired if the locations were adjacent to each other. Clearly, there would be greater spatial interference when the locations are adjacent to each other rather than far apart. In a more recent study [32], the role of the dDG was tested in mediating spatial pattern separation using a similar place-learning paradigm described by [31]. The results indicate that rats with dorsal dDG lesions and control lesions acquired the spatial discrimination for separate locations at similar rates. However, for the adjacent condition, dDG-lesioned rats required significantly more trials to reach the learning criterion than did controls.

4. Pattern separation and neurogenesis

Based on the observation that neurogenesis occurs in the DG and that new DG granule cells can be formed across time, it has been proposed that the dDG mediates a spatial pattern separation mechanism as well as generates patterns of episodic memories within remote memory [3]. Thus far, it has been shown in mice that disruption of neurogenesis using low-dose X-irradiation was sufficient to produce a loss of newly born dDG cells. Further testing indicated impairments in spatial learning in a delayed non-matching-to-place task in the radial-arm maze. Specifically, impairment occurred for arms that were presented with little separation, but no deficit was observed when the arms were presented farther apart [33], suggesting a spatial pattern separation deficit. These results are similar to those described for rats in the Morris et al. [32] study. Another study in mice provided evidence that the disruption of neurogenesis using lentivirus expression of a dominant Wnt protein produced a loss of newly born dDG cells; and these mice were tested in an associative object-in-place task with different spatial separations and observed to be impaired as a function of the degree of separation, again suggesting a spatial pattern separation deficit [29]. In a more recent study (Kesner and Fanselow, unpublished observations) it can be shown that DNA methyltransferase 1-c knockout mice are impaired relative to controls in the Goodrich et al. (2005) spatial pattern separation task. These data suggest that neurogenesis in the dDG may contribute to the operation of spatial pattern separation. Thus, spatial pattern separation may play an important role in the acquisition of new

spatial information, and there is a good possibility that the dDG may have been the subregion responsible for the impairments in the various tasks described above.

5. Temporal integration and remote memory neurogenesis

A novel role for the dDG in temporal processing for spatial information has begun to emerge based on the development of a computational model of neurogenesis [3]. According to this model, adult born granule cells in the dDG contribute to a temporal associative integration process for events presented within the same time frame. Currently, there is a paucity of behavioral evidence to support the temporal integration theory. Therefore, we developed a novel behavioral paradigm to investigate the role of the dDG in temporal integration for proximal and distal spatial events [34]. Male Long-Evans rats were randomly assigned as control animals or to receive bilateral intracranial infusions of colchicine into the dDG. Following recovery from surgery, each rat was tested on a novel cued-recall of sequence paradigm for different spatial locations. In this task, the study phase was conducted across 2 consecutive days (Day 1 and Day 2) and consisted of two 5-min exploration sessions separated by a 3-min intersession interval (ISI) per day. The rats were allowed to explore the same object placed in designated spatial locations on a cheeseboard maze across 2 days (e.g., Day 1: spatial location A and 3 min later spatial location B; Day 2: spatial location C and 3 min later spatial location D). One week later, on the first day of the test phase (Day 8), animals were placed on the maze and allowed to explore an object positioned at spatial location A or C (A and C were used as recall cues) for 1 min followed by a 3-min ISI. After this interval, animals were given a 5-min preference test between spatial location B and D (positioned 106 cm apart). On the second day, rats that received A as the recall cue on Day 8 were tested on Day 9 with C as the recall cue. Similarly, if C was uses as a recall cue on Day 8, then A would be used as a recall cue on Day 9. The presentation order of spatial location recall cue for spatial location A and spatial location C was counterbalanced across subjects and across days. Control animals showed a significant preference for the spatial location previously paired with the cue (the temporal associate), but dDG lesioned animals did not show a preference for either spatial location during the preference test. These findings suggest that selective colchicine-induced dDG lesions are capable of disrupting the formation of temporal associations between spatial events presented within a 3 min time frame.

6. Context- pattern separation for geometry of the environment

Do other subregions of the hippocampus engage in spatial pattern separation? Early research suggested that the dCA3 region may also engage in spatial pattern separation processes for a spatial representation of the geometry of the environment. This idea is supported by the finding of [35], who showed that dCA3c place cells were able to maintain distinct representations of two visually identical environments and to selectively reactivate either one of the representation patterns depending on the experience of the rat. Also, Leutgeb et al. [36] recently showed that when rats experienced a completely different environment, dCA3c place cells developed orthogonal representations of the different environments by changing their firing rates between the environments, whereas dCA1 place cells maintained similar responses.

To further test the role of dCA3 in mediating pattern separation, an experiment was conducted to determine whether the dDG or dCA3 regions cooperate to perform spatial pattern separation operations for specific spatial locations as well as the spatial geometry of the environment or whether the dDG performs spatial pattern separation on the basis of specific locations in space and the dCA3 performs spatial pattern separation on the basis of the geometry of the environment [37]. Rats with lesions of dDG and dCA3a,b were given the opportunity to explore a white or black circular or square box of the same size as reported by [36], which contained two objects spaced 68 cm apart. After habituation to the box and objects, the rats received one of two transfer tests. In the first test, objects were changed to a 38-cm distance, but the box shape (geometry of the environment) remained the same; in the second test, the box shape (geometrical environment) was changed, but the distance between objects remained the same. Efficacy of the transfer test in terms of re-exploration of the metric change was based on a comparison between the degree of object exploration during the transfer session versus the degree of object exploration during the last session of habituation. Similarly, the efficacy of the transfer test in terms of re-exploration of the geometry of the environment was based on the number of grid crossings (activity level) and rearings during the transfer session versus the number of grid crossings and rearings during the last session of habituation. The results indicated that lesions of the dDG, but not dCA3a,b, disrupted both detection of metric changes in the spatial location of objects and changes in a geometrical environment [37]. Thus far, these data are consistent with the prediction of the Rolls [1] computational model that the dDG is the critical substrate for spatial pattern separation. These data are not consistent with other [35,36] findings of a pattern separation function within CA3a,b for geometrical environments.

It has been shown that the CA3 region can be divided into a CA3a,b, and c sub-areas [38,39]. The CA3a,b region has recurrent collaterals, but the CA3c region does not have recurrent collaterals. Also, there is a direct connection from CA3c to CA1 which means that the Ca3c region can bypass the Ca3a,b region. Finally, based on previous research of [38,40]), it has been proposed that mossy cells receive excitatory inputs from granule cells and dCA3c pyramidal cells and integrate their inputs, which, in turn via excitatory recurrent axonal projections, activate many dDG cells. Such a circuit could integrate spatial location information and form representations of geometrical environments. Most of the recording of cells that respond to different environments reported by [35,36] were based on electrode placements in the dCA3c area. The lesion data were based on lesions within dCA3a/b, but not dCA3c. Additional experiments with dCA3c lesions in contrast to dCA3a/b lesions were carried out [37]. The results indicated that dorsal dCA3c lesions disrupted pattern separation processes only when the animal was required to detect a metric change in object location, but there was no apparent effect during the environmental change task. It must be noted, however, that dorsal dCA3c lesions never caused effects as dramatic as those caused by dDG lesions. One interpretation may be that the dDG selectively recruits dCA3c to assist in metric detection and not detection of the overall environmental change. The present experiment [37] provides behavioral evidence that the dCA3c and the dDG may interact for spatial information processing. This effect was seen only in the condition under which the animal was required to detect a discrete metric change in object location, a task that has been shown to be particularly sensitive to dDG. Interestingly, this deficit was observed in object exploration but not rearing behaviors. Although the present behavioral data do not show any effects of dCA3a,b lesions, the dDG effect is clear. Additionally, the dorsal dCA3c lesion data suggest that there is a circuit involving the dCA3c and the dDG that is perhaps important for preprocessing spatial information prior to dorsal dCA3a,b processing stages.

7. Context-pattern separation for color of the environment

In addition to a role for dDG in supporting context based on the geometry of the environment, it has been suggested that the

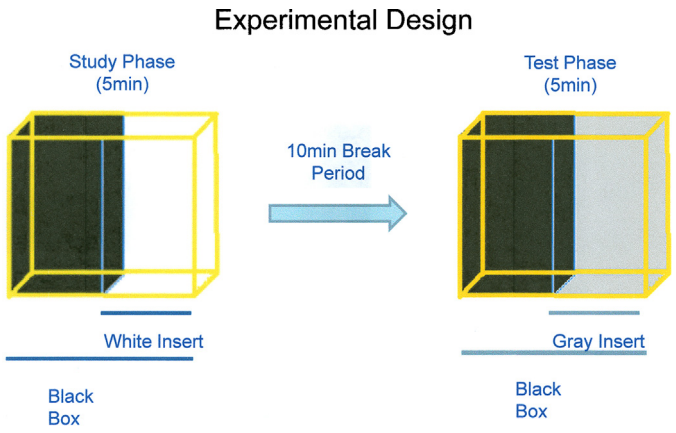

Fig. 1. An illustration of the boxes and inserts that were used for the experiment and the experimental design associated with context pattern separation for color of the environment.

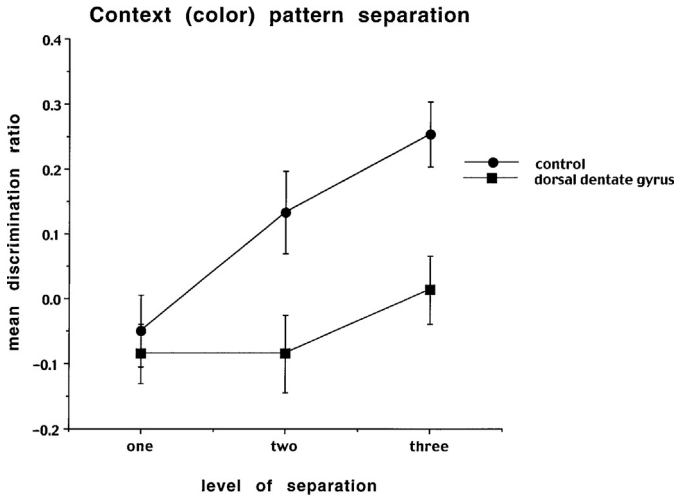

Fig. 2. Mean discrimination ratio for context (color) based on level of separation for controls and dorsal dentate gyrus lesioned rats.

hippocampus also processes context based on background cues, such as colors [41,42]. In order to test whether the dDG plays an important role in processing of context based on colors and whether it is possible to generate a pattern separation effect based on different shades of black and white. Four shades of color boxes were constructed—white, light gray, dark gray and black and four shaded inserts were constructed to fit inside each box—white, light gray, dark gray and black. The inserts were constructed to cover half of each box, such that the two sides of each box had different shades of color. On the test day during the study phase dDG lesioned rats and controls were placed in one of the colored boxes, with a colored insert that was different than the color of the box for a 5 min period. Then the rat was placed into its home cage for ten minutes. During the 10 min retention interval either the insert or box color was changed to generate the context of the test phase (see Fig. 1 for experimental design). The study phase had a duration of 5 min. Context exploration was measured throughout the study and the test phase by the number of observed rearings each subject exhibited on the insert side and the box side (the side without the insert). Each rear constitutes removing both front paws from the ground. Each subject was tested for 12 days, using the number of rearings to measure novelty detection. Each experimental day was followed by a rest day or a 48 h break period, taking a total of 24 days for each subject to complete the task. Three context gradient levels were measured, taking the difference of the novel color (introduced during the test phase) and the familiar from the study phase (Fig. 2). Level 1 context gradient was a slight color change—white to light gray, light gray to dark gray, dark gray to black, or the reverse of any of the former. Level 2 context was a medium color change—white to dark gray, light gray to black or the reverse of any of the former. Level 3 context was the maximum color change—white to black or the reverse. Each subject completed four trials at level 1, level 2 and level 3 context gradient transitions. These levels were used to establish the degree to which subjects noticed the context change. The results of the experiment indicates that control rats displayed a color pattern separation effect across levels of separation of context (shades of color), but the dDG lesioned rats did not display a color pattern separation across levels 1, 2, and 3 (Kesner and Musso, unpublished observations). To support the idea that rats in this task primarily process recognition for the color context, it can be shown that during the study phase there is a preference for the darker color for both groups, but during the test or recognition memory phase there is no preference for the darker color for both groups. Thus, the dDG plays an important role in context recognition for colors by reducing interference between shades of color.

8. A role for context in object recognition

It has been suggested that the hippocampus may provide contextual information by combining object and place information [2,43]. Previous research has shown that the dorsal dentate gyrus (dDG) subregion of hippocampus may play an important role in combining object and place information via conjunctive encoding [44]. In one of the most common paradigms to measure the importance of context associated with object recognition, two groups of animals are allowed to explore two similar objects during a study phase and then after a short delay (s to min) the animals are tested either in the same context but with of one of the two objects changed (labeled object recognition) or with one of the two objects changed and a context (a different color box or a different room) labeled (object-context recognition). Control animals explore the novel object more than the familiar in both the object and object-context situation. Hippocampal lesioned rats have no problems exploring the novel object more than the familiar object in the object recognition situation, but fail to explore the novel object more than the familiar object in the object-context recognition situation [45–48]. Spanswick and Sutherland [49] reported the same results following a loss of granule cells in the dDG following adrenalectomy. A different approach is to examine the effects of context in object recognition memory by using a black box (object recognition)) and using a clear box with available cues that define a spatial context (object-context recognition) (Dees and Kesner, unpublished observations). Based on a 10 min retention interval between a study phase and a test phase, the results indicated that dDG lesioned rats are impaired when compared to controls in the object–context recognition test in the clear box. However, there were no reliable differences between the dDG lesioned rats and the control group for the object recognition test in the black box. Even though the dDG lesioned rats were more active in object exploration and activity within the boxes based on rearing responses, the familiarization gradients did not differ. These results suggest that the dDG lesioned rats are clearly impaired when there is an important contribution of context.

9. Odor pattern separation and ventral dentate gyrus

It can be shown that the hippocampus is critical for pattern separation for olfactory cues when a mnemonic component is included. A recent report from Kesner et al. [50] demonstrated that for a series

of straight carbon chain alcohols that form an aliphatic series (i.e., the differences among chemicals is a linear series of carbons) [51], the ventral, but not dorsal, hippocampus is critical for solving a task requiring the rat choose which of two odors was previously encountered during a working memory paradigm. Importantly, rodents performed more poorly on this task as the number of carbons separating the odors was reduced, suggesting increased olfactory interference. To verify there was not a deficit at the perceptual level, rats trained to discriminate odors, even as similar as one carbon apart, were able to do so long as the mnemonic contribution to task performance was minimized (i.e., no delay or memory demand required flexible use of the olfactory information).

To specifically assay pattern separation during this task, and more specifically the role of the ventral dentate gyrus (vDG) for odor processing, working memory and pattern separation for odor information was assessed in rats using a matching-to-sample for odors paradigm. Odor separations of 1, 2, 3 or 4 were selected for each choice phase and represented the carbon chain difference between the study phase odor and the test phase odor. Once an animal reached a criterion of 80–90% correct across all odor separations based on the last 16 trials, rats received a control or vDG lesion and were retested on the task. On postoperative trials, there were no deficits at 15 s delay for either the controls or the vDG lesioned rats. However, when the delay was increased to 60 s rats with vDG lesions were significantly impaired at short odor separations, but performance of rats with ventral dentate gyrus lesions matched control rats at the largest odor based separation. The graded nature of the impairment and the significant linear improvement in performance as a function of increased separation illustrate a deficit in odor pattern separation. Based on these results, it was concluded that lesions of the vDG decrease the efficiency of odor based pattern separation, which results in impairments on trials with increased odor proximity and increased odor similarity among working memory representations [52]. The data suggest that the ventral hippocampus, especially the vDG, but not the dorsal hippocampus, support pattern separation for odor information along the domain of carbon length in aliphatic series.

It is important to note that other forms of pattern separation do not involve the dDG subregion of the hippocampus. For example, temporal pattern separation is mediated by the dCA1 but not the dDG [27]. Furthermore, hippocampal lesions including dDG do not produce a deficit for pattern separation of visual objects, reward values, or motor responses [53,56,57,58]. Instead, the perirhinal cortex subserves pattern separation for visual objects [53–55], the amygdala subserves pattern separation for reward value [57], the caudate nucleus subserves pattern separation for motor responses [58], and the pyriform cortex as well as ventral DG subserve pattern separation for odors [52,59].

10. Conclusion

In conclusion, based on the development of computational models of dDG and behavioral evidence based on dysfunction of dDG, it appears that the dDG mediates mnemonic processing of spatial information. The processes subserved by dDG include (a) the operation of conjunctive encoding of multiple sensory inputs, implying an integration of sensory inputs to determine a spatial representation, and (b) pattern separation of spatial (especially metric) information, involving the reduction of interference between similar spatial locations (c) pattern separation of context (d) importance of context in object recognition, and (e) temporal integration and remote memory and spatial pattern separation based in part on neurogenesis. In addition the vDG mediates odor pattern separation.

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