pointer for future research. Most prominently, a notable gap in our understanding of feature-based attention exists as to from where and how its allocation is controlled. While the FEF is an appealing possibility, the dorsolateral prefrontal cortex, which builds representations of learned visual features or objects (Funahashi, 2006) might also play a role. Similarly, the integration of the various types of attention identified so far (e.g., spatial, feature-based, surface-based, object-based, etc.) at the level of single neurons requires more research.

The excellent agreement between the new functional imaging data from human cortex with the result of previous electrophysiological recordings from single cells in monkey cortex nicely demonstrates how both approaches inform each other and how true progress in modern neuroscience depends on an integrative approach harnessing the abilities of a broad range of techniques. Future progress on the open questions most likely will depend on just such an approach.

REFERENCES


Enigmas of the Dentate Gyrus

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We are rapidly approaching a better understanding of the mechanisms that allow our brains to form distinct representations for similar events or episodes. McHugh et al. have brought that goal one step closer by showing that NMDA receptor-dependent synaptic plasticity in the dentate gyrus is necessary for immediate differentiation between environments with similar features.

How does the brain distinguish between memories that are similar, such as this year’s birthday compared to last year’s? How do you remember that Kristin helped your daughter open presents during her garden party when she became 4, whereas it was Erika who had that job when she turned 5 (Figure 1)? The hippocampus, a key structure involved in the storage of episodic and declarative memories (Tulving and Markowitsch, 1998; Squire et al., 2004), may have just the properties required to deal with these challenges.

A critical step in the encoding of a new episodic memory is the amplification of the differences between the new representation and representations that already exist in the network, a process termed “pattern separation.” Lesion studies in behaving rodents have suggested that a neuronal pattern-separation mechanism may be located within a subregion of the hippocampal formation, more specifically in the granule cell population of the dentate gyrus (Rolls and Kesner, 2006). This interpretation has been supported by studies of place cells in the hippocampus. Place cells signal the animal’s location by firing specifically when the animal is in a specific part of the environment (O’Keefe and Dostrovsky, 1971). One well-characterized feature of these cells is their tendency to substantially change their firing patterns after only minor changes in the sensory input or the motivational context, a phenomenon referred to as “remapping” (Muller et al., 1991). Studies of remapping have provided important clues to the neuronal network mechanisms for pattern separation. Two forms of remapping have been identified in the CA3-dentate network of the hippocampus (Leutgeb et al., 2005, 2007). During “global remapping,” there is a complete redistribution of both firing locations and firing rates in the cell population. This form of remapping is invariably associated with a shift in the spatial inputs from the entorhinal cortex (Fyhn et al., 2007). During “rate remapping,” only the rates of the active hippocampal cells change.

References


while the location of firing is maintained, a process that is thought to result from neurons in the assembly changing their input weights rather than by a change in the recruitment of cells to the currently active ensemble. Recent work has shown that the coactivity patterns of only a small subset of active granule cells in the dentate gyrus are sufficient to immediately distinguish small changes in sensory input during rate remapping in CA3 (Leutgeb et al., 2007). The fact that there is no detectable change in simultaneous recordings from the medial entorhinal cortex under these circumstances (Fyhn et al., 2007; Leutgeb et al., 2007) raises the possibility that rate-based pattern-separation mechanisms originate in the dentate gyrus.

In a recent article in Science, McHugh and colleagues (McHugh et al., 2007) have provided the latest insights into understanding the mechanisms of hippocampal pattern separation. Previously, the same group was able to use targeted genetic manipulations to determine the role of synaptic plasticity in the CA3 pyramidal cell population during pattern completion, a process complementary to pattern separation and thought to take place in neural networks when memories are retrieved from a subset of the cues that defined the original event (Nakazawa et al., 2002, 2003). They now use similar techniques one synapse upstream to investigate the mechanisms of pattern separation. Using mice with floxed NRI subunits of the NMDA receptor and crossing them with mice that expressed Cre recombinase selectively in granule cells of the dentate gyrus, the authors were able to generate a mouse line with NMDA receptors abolished specifically in the dentate granule cells. These mutant animals lacked long-term potentiation (LTP) in the perforant-path-to-granule-cell synapses but had intact LTP in other synapses of the hippocampus. McHugh et al. used this mouse line to determine the possible role of the dentate gyrus in neuronal and behavioral pattern separation.

The absence of NMDA receptors in the dentate gyrus did not affect the performance of DG-NR1 knockout mice in the Morris water maze or in standard contextual fear conditioning. Both knockout and control mice were also able to distinguish changes in context when freezing was assessed in a second chamber with different sensory cues. However, when the two chambers were made less distinct and the conditioning took place over time, the knockout mice showed a deficit in discriminating the nonconditioned chamber from the chamber that was repeatedly associated with the foot shock. Control animals learned to discriminate between the two contexts after several days of repeated exposure, while the DG-NR1 knockout mice took 10 days longer to acquire the task.

The absence of NMDA receptors in the dentate gyrus also disrupted the redistribution of firing rates in downstream CA3 place cells in a rate-remapping paradigm. The activity of hippocampal neurons in both CA1 and CA3 were recorded while mice were allowed to explore two environments that differed in contextual cues, but not location. In control mice, CA3 neurons showed the expected change between the two environments, indicated by a dramatic change in firing rates in the first context compared to the second. There was no change in the place code of the CA3 cells. The rate change was retained the second day. In the DG-NR1 knockout mice, the change in the rate distribution did not emerge on day 1, but was seen with continued training on the second day when it was no longer different from controls. In combination, these results suggest that NMDA receptor-dependent synaptic plasticity in the dentate gyrus is necessary for fast rate coding in CA3 during first-time exposure to environments with similar features.

This study represents a significant advance in our understanding of how the dentate gyrus contributes to pattern separation during the encoding of memory in the hippocampus. Theoretical studies have long pointed to a possible role for the dentate gyrus in pattern separation, based, in particular, on the sparse firing of granule cells in this area and the formation of one-to-one detonator synapses between granule cells and CA3 pyramidal cells (Rolls and Treves, 1998). This prediction has been verified by recent work showing that rate orthogonalization in CA3 is accompanied by pronounced changes in the coactivity pattern of granule cells in the dentate gyrus (Leutgeb et al., 2007). Whether these differences are instrumental in decorrelating memory representations further downstream in the hippocampus has not been determined, however. The present work shows that...
the dentate gyrus is necessary for pattern separation to occur in the CA3 area. Blockade of pattern separation is associated with poor discrimination between memories. The results also reveal that NMDA receptor-dependent plasticity is part of the cellular mechanism for pattern separation. This is interesting because pattern separation can, in principle, emerge merely from the unique connectivity patterns and firing thresholds of dentate granule cells. The results suggest that the formation of distinct memories may involve rewiring already at the level of the perforant path synapses.

The findings reported by McHugh and colleagues raise a number of questions that will guide research in the years to come. We will highlight three of them. First, it is important to determine to what extent the absence of rate change in the knockout mice reflects only a deficit in pattern separation or also an impairment in the encoding of novel information more broadly. Previous work has provided evidence for two independent changes in firing rates in CA3 cells during exploration of distinct novel environments. In addition to the expression of a new rate pattern in the cell population, which is immediate and tied to the reconfiguration of the sensory cues (Leutgeb et al., 2006), the ensemble of active CA3 cells is also changed at a slower time scale, with some cells fading out and others coming in as the animal is exploring the environment (Leutgeb et al., 2004). It may take 20–30 min until a stable CA3 representation is formed in a constant environment. If a rat is placed into the same recording box on separate sequential trials, each lasting only 10 min, the change in firing rates continues on the second trial and sometimes even longer (Leutgeb et al., 2004). Both the fast and the slow process seem to be impaired in the DG-NR1 knockout mice of McHugh et al. Not only were CA3 representations for different boxes more correlated than in control animals, but the knockout also reduced the rate difference between early and late parts of the first trial, in the same box (their Figure S5). It will be important to determine whether separate network mechanisms are responsible for the impairments in disambiguation and development of CA3 representations in a novel environment. One way to find out would be to test the animals on multiple or extended trials in the same environment.

Second, it will be interesting to determine whether the impairments in fast rate remapping and contextual discrimination can be attributed to possible effects of a continued NMDA receptor loss on neurogenesis and maturation of granule cells. Cre-loxP recombination was detected in newly born dentate granule neurons. Coupled with the observation that NR1 RNA was nearly absent by postnatal week 16 in the DG-NR1 knockout mice, we can assume that neurogenesis occurs but that dentate granule neurons born in adult animals lack functional NMDA receptors. This is of particular interest because it has been shown that NMDA receptor function is needed for the survival and integration of newborn granule neurons into the dentate circuit (Tashiro et al., 2006). Without the continued integration of new granule neurons, the dentate network in the DG-NR1 knockout mice could be different than the control network. How the potential lack of fully integrated cells would influence the formation of new distinct representations is not known, although the absence of neurogenesis has been shown to influence the behavior of rodents in some, but not all, hippocampal-dependent learning tasks (Leuner et al., 2006).

The final and ultimate challenge will be to understand how the dentate-dependent disambiguation processes translate into behavior. What mechanisms exist to rate-orthogonalize CA3 representations over longer periods, and how are such changes accelerated by plastic response patterns in the granule cell population? It is striking that while rate differentiation in place cells was impaired only on the first recording day in the McHugh study, the behavioral impairment was not expressed until after multiple days of continued training. This slow development is quite different from the fast learning normally associated with hippocampal function (Nakazawa et al., 2003; Squire et al., 2004). Yet the impairment of hippocampal circuitry in the McHugh study was very selective, suggesting that NMDA receptor-dependent plasticity in the dentate gyrus is the first step of a longer chain of events that, in the end, leads to impaired discrimination of spatial environments. Discerning the elements of this cascade will be crucial for an ultimate understanding of the relation between neuronal and behavioral pattern separation.

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