

disease pathophysiology of neuropsychiatric disorders. After all, we are a unique species, and for understanding our own individual phenotypic variability, we must first decipher what is specific about *Homo sapiens*.

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CA3 Sees the Big Picture while Dentate Gyrus Splits Hairs

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The dentate gyrus (DG) and area CA3 of the hippocampus have been long hypothesized to perform pattern separation and pattern completion, respectively. A new study published in this issue of *Neuron*, Neunuebel and Knierim (2014), provides strong empirical support for this functional dissociation.

The striking pattern of principal cell connectivity within the hippocampus has inspired many theorists to attribute each hippocampal subregion with distinct roles in neural information processing (Marr, 1971; McNaughton and Morris, 1987; Treves and Rolls, 1994; Hasselmo and Wyble, 1997). These striking connectivity patterns include a feedforward trisynaptic loop (entorhinal cortex → DG → CA3 → CA1) with strong divergence at the first step and recurrent connections within area CA3. The number of granule cells in the DG is five times larger than the number of entorhinal cells projecting into the DG (1,000,000 versus 200,000 in the rat [Amaral et al., 1990]). Such divergent connectivity, together with very sparse activity in the DG (i.e., less than 3% of all granule cells activate in a given testing enclosure [Chawla

et al., 2005]), led to the hypothesis that small changes in the entorhinal input pattern could result in large changes in the pattern of activation across the DG as shown in Figure 1 (O'Reilly and McClelland, 1994). The amplification of small differences into large differences is referred to as *pattern separation*. Area CA3 receives input from the DG, the entorhinal cortex, and, most strikingly, itself. The fact that CA3 projects to itself implies that it has the ability to perform autoassociation (Marr, 1971; McNaughton and Morris, 1987). That is, synaptic plasticity mechanisms could strengthen the connections among constellations of coactive CA3 neurons, later allowing a subset of the same constellation to provide excitatory drive to the remaining portion of the original set and thereby reactivate, or *pattern complete*,

the full original constellation as shown in Figure 1.

In this issue of *Neuron*, Neunuebel and Knierim (2014) show strong evidence of pattern separation in the DG and pattern completion in CA3. To do so, they tracked how the activity of multiple single units in the DG and CA3 changed as the testing environment was distorted to varying degrees. The rationale was that pattern separation would be identifiable as large changes in the neural representation following small changes in the testing environment. Pattern completion, in contrast, would be identifiable as relatively minor changes of the neural representation. The testing environment in their task was comprised of a circular track, upon which rats foraged for chocolate sprinkles in a clockwise direction, which was surrounded by a circular black

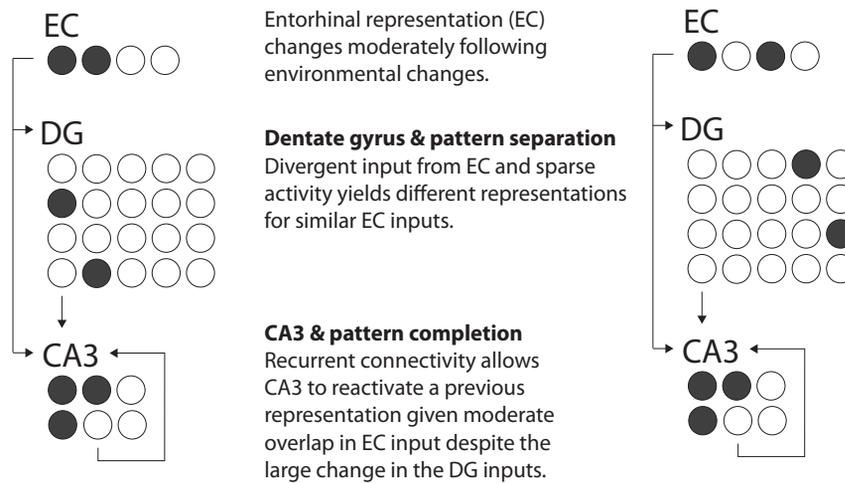


Figure 1. Schematic of How Representations Compare between the Dentate Gyrus and Area CA3 in Two Similar, yet Distinct, Environments

Circles represent neurons in each area and dark fill reflects elevated activation of those neurons. The patterns shown on the left and right reflect the state of the network in two environmental configurations. The differences between the environments are reflected in the representation of the entorhinal cortex (EC) by representations that overlap by one unit. In the dentate gyrus (DG), this is transformed into a highly nonoverlapping representation, reflected here by representations that do not overlap. The amplification of small differences is referred to as pattern separation. In CA3, the moderate overlap in the EC allows for the reactivation of the same representation in both environmental configurations. The collapse over small differences into the same representation is referred to as pattern completion.

curtain. Critically, there were both local spatial cues, in the form of odor and texture cues on the track, and distal spatial cues positioned around the curtained area. After familiarizing the animals to the testing environment, [Neunuebel and Knierim \(2014\)](#) leveraged the well-established “double-rotation task” to parametrically manipulate the degree of conflict between the spatial cues. That is, the local and distal cues were rotated in equal but opposite directions such that the relative offset totaled 45°, 90°, 135°, or 180°. In the DG, both single-unit and population-level analyses demonstrated a rapid decorrelation of the neural representation following any distortion of the testing enclosure, consistent with the existence of a pattern separation process. In CA3, however, the same analyses showed that the representation remained relatively coherent over the varying levels of distortion (usually tracking the movements of the local cues).

The observation of pattern separation in the DG and of pattern completion in area CA3 provides additional support for the long-standing hypotheses regarding the functional properties of these areas ([Marr, 1971](#); [McNaughton and Morris, 1987](#); [Treves and Rolls, 1994](#); [Hasselmo](#)

[and Wyble, 1997](#)). These findings are compatible with existing reports on the nature of the representations in these areas and relative importance of each area for the performance of behavioral tasks (for recent reviews, see [Yassa and Stark, 2011](#); [Kesner, 2013](#); [Rolls, 2013](#)).

A particular strength of the new report, however, is that [Neunuebel and Knierim \(2014\)](#) were able to address the question of whether the pattern separation-like tuning dynamics of the DG and pattern completion-like dynamics of area CA3 were locally generated by comparing the neural representations in these areas to the representations in upstream areas in the same task. A previous study by the same group using the same task found that the medial entorhinal cortex (MEC) coherently tracked the global cues and the lateral entorhinal cortex (LEC) weakly tracked the local cues ([Neunuebel et al., 2013](#)). As such, the rapid decorrelation of the DG representations observed in the present study was not a simple reflection of the tuning of the representations observed in the entorhinal cortex. Likewise, the observation that the CA3 representation remained coherent with respect to the positions of the local cues, a feature that appeared to be

weakly represented in the upstream areas, at best, indicated that area CA3 was able to pattern complete a previously learned neural representation given noisy inputs.

A question raised by the results described in this new report is why the activity of the entorhinal cortices, as the primary cortical outputs of the hippocampus, does not reflect the successful pattern completion performed by CA3 to a greater extent? A report by [Lee et al. \(2004\)](#) demonstrated that this pattern completion is already largely lost one synapse later, in area CA1, particularly on the first day that the environment is modified. Such findings are striking, particularly in the context of hypotheses that suggest that area CA3 is particularly useful for behaviors requiring the retrieval of prior associations, and, as such, would be expected to have a substantial influence on the representation of downstream areas. It was previously suggested that this may be due to the mismatch of information arriving from the MEC (about distal cues) and from CA3 (about local cues) ([Neunuebel et al., 2013](#)).

Another possibility is that the current understanding of how information is carried in the neural representations of area CA1 and the entorhinal cortices remains immature and merits further study. Given a more nuanced model of neural coding in these areas, it may be possible to better observe the influences of CA3 pattern completion on the firing patterns in CA1 or in the entorhinal cortices. The analysis used by the authors ([Neunuebel and Knierim, 2014](#); [Neunuebel et al., 2013](#)) quantified how well the firing of the cells tracked the spatial positions of local or global cues. This analysis should be expected to be particularly sensitive to simple mappings between the locations of the cues and the firing patterns of the cells. Area CA3 may be well characterized by such simple mappings. The LEC, however, has been suggested to carry detailed information about the sensory environment ([Deshmukh and Knierim, 2011](#); [Howard and Eichenbaum, 2013](#); [Neunuebel et al., 2013](#)). The coding of information in the LEC may be highly conjunctive, complicating the job of physiologists seeking to quantify the coherence between the neural representation

and a particular set of cues. Thus, while this analysis may be particularly well suited to accounting for variance in the firing patterns of CA3 cells, it may be poorly suited to accounting for variance in the firing patterns of LEC cells. Additional research into the nature of neural coding in LEC will build our understanding of the transformations that result from reciprocal interactions between the LEC and the hippocampus.

The new report of [Neunuebel and Knierim \(2014\)](#) sets the stage for new work testing other predictions arising out of the same framework that hypothesized that area CA3 could perform pattern completion. That framework predicts, for example, that area CA3 adaptively switches between pattern completion and pattern separation based on environmental demands ([Marr, 1971](#); [McNaughton and Morris, 1987](#)). In the present study, the representation of CA3 remained stable despite large changes in the DG representation—in effect, ignoring the pattern separation that had been performed by the DG. In other circumstances, however, the hypothesis predicts that the pattern-separated input

from the DG would activate a similarly pattern-separated representation in CA3, thereby forming the basis of a new neural representation. Future studies will test this prediction and offer insights into the environmental and physiological determinants of whether, for a given context, CA3 performs pattern completion or separation.

In summary, the findings of [Neunuebel and Knierim \(2014\)](#), together with previous observations of the same group ([Deshmukh and Knierim, 2011](#); [Neunuebel et al., 2013](#)), provide convincing evidence for locally generated pattern separation in the DG and pattern completion in area CA3. These results provide strong support for long-standing hypotheses attributing each hippocampal subregion with distinct roles in neural information processing and set the stage for exciting new research in systems neuroscience.

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