

Hidden depths in the hippocampal circuitry

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Abstract: Danielson et al. (2016) use calcium imaging in mice performing a treadmill task to reveal differences in space-coding dynamics between deep and superficial sublayers of hippocampal CA1, suggesting how the hippocampus might encode both stable and dynamic information simultaneously.

Main text

Navigating around an environment and remembering events that happened at particular places within it are critical cognitive abilities that rely on the mammalian hippocampus. Pyramidal cells (PCs) in the hippocampal CA1 region are most prominently known for their place coding activity – single pyramidal neurons, known as place cells, fire in restricted areas of the environment, called their place fields (O'Keefe and Dostrovsky, 1971). Overall, a group of place cells provide an allocentric representation of space which support an animal's ability to accurately navigate and recall spatially-based memories (Moser et al., 2008). These cells use visual features and landmarks, self-generated motion information, and a wide range of non-metric information (*e.g.* color, texture, odor) to maintain an updated representation of the external environment. Place coding has also been shown to change in response to the behavior of the animal: for example, the stability of place fields increases with the increased need for attention during goal related tasks, and the subsequent place maps incorporate information related to the goal (Dupret et al., 2010).

An ongoing puzzle for spatial encoding, the 'stability-plasticity dilemma' (Carpenter and Grossberg, 1988) is: how can the hippocampus simultaneously

learn new information about environments while also preserving established representations of space? A possible answer is that there are discrete populations of cells in hippocampal CA1 dedicated to learning new vs. preserving old information. However, PCs in CA1 have previously been conceptualized as a homogeneous coding population, whereby individual pyramidal neurons contribute relatively equally to all processes (Treves and Rolls, 1994).

Are CA1 pyramidal cells truly a homogeneous population?

Scientists have started to challenge the notion of PC homogeneity because, in fact, CA1 PCs have highly variable molecular, morphological and electrophysiological properties, as well as distinct connectivity (Cembrowski et al., 2016; Nielsen et al., 2010). These differences are not randomly distributed throughout the structure but align to its principal axes: dorso-ventral, proximo-distal, and most importantly for a study by Danielson et al. in this issue of *Neuron* (Danielson et al., 2016), superficial-deep (radial). The study uses a new, high density imaging method to investigate whether the subdivisions of the CA1 pyramidal cell layer along the deep-superficial axis could contribute differentially to processing.

The difference in PCs between superficial CA1 (which is, paradoxically, deeper in the brain, closer to *stratum radiatum* and to the hippocampal fissure; Fig. 1) and deep CA1 (closer to *stratum oriens*) is well established anatomically – for example, cells in each of the sublayers are born at different times and carry different genetic and neurochemical markers (Cembrowski et al., 2016; Nielsen et al., 2010). However, does this segregation extend functionally, to activity and the relation of activity to behavior? Direct evidence for this idea comes from an electrophysiology study showing that there are functional differences in PCs across the radial axis which emerge during periods of theta oscillation associated with exploration and REM sleep (Mizuseki et al., 2011), consistent with the finding that place coding is modulated by the attentional state of the animal. However, the few studies focusing on the radial axis have only been conducted *in vitro* or acutely *in vivo*, and thus do not provide insight into sublayer-specific

contributions to the dynamics of learning, which can take several days to develop.

New data exploring sublayer dynamics in behavior

Danielson and colleagues provide evidence that these native differences in connectivity and electrophysiological properties between deep and superficial CA1 sublayers map to sublayer-specific place coding dynamics in the behaving animal. The study used two-photon Ca^{2+} imaging of head-fixed mice running on a treadmill for food reward, in order to observe large populations of CA1 neurons in the two sublayers simultaneously. The activity of recorded neurons was tracked in both a random foraging task and a spatial learning paradigm.

Consistent with existing literature, the authors found sublayer-specific differences in both activity and stability during standard foraging (no spatial memory component). While deep CA1 pyramidal cells were a more active place-coding population than the superficial cells (shown by higher firing frequency, larger spike amplitude and longer duration of Ca^{2+} transients), the superficial population displayed less change (or 'remapping') and were more stable across multiple contexts (see also Mizuseki et al., 2011).

Deep CA1 PCs were not only more active during foraging tasks; the deep population also displayed significantly higher spatial stability when the task required goal-oriented learning, in addition to a strong modulation by goal location. Interestingly, this reward-related activity was predictive of performance outcome in a spatial learning paradigm. Superficial PCs were not at all affected by task-related demand or altered attention state elicited by the spatial learning paradigm, reflected by chance level stability and no goal modulation.

These results are important because they provide, for the first time, evidence for distinct information processing within in the hippocampus within a single cell layer of the hippocampus. One mechanism through which the hippocampus could simultaneously convey distinct sets of information (*e.g.* that the part of the environment had changed while another part had stayed the same) is through

partial remapping, whereby some hippocampal cells are unperturbed by contextual change while others remap (see Anderson et al., 2006 for a previous example of this, coupled to behavior). The PC coding dynamics observed by the authors extend the partial remapping idea across the radial axis, suggesting that the more stable superficial CA1 PCs provide a consistently accurate map of the environment, while PCs in the deeper layers are more plastic and communicate information that is largely shaped by learning and salient environmental features.

What causes the different properties in these different sublayers? One possible explanation is that the different CA1 pyramidal cells have different intrinsic properties such as ion channel distribution, receptor distribution or morphology. For example, morphological differences between neurons in the neocortex (Chagnac-Amitai et al., 1990) and hippocampal CA3 region (Bilkey and Schwartzkroin, 1990) can differentially affect firing rate and bursting patterns, and in turn induce variable firing patterns during various local field potential brain states. Consistent differences in firing rate and firing pattern during theta oscillation have been found between deep and superficial layers of hippocampal CA1 (Mizuseki et al., 2011), supporting this idea.

An alternative possibility is that the connectivity within the hippocampus, and especially between sublayers, is dissimilar, creating a differential excitatory and inhibitory input balance. Deep CA1 is known to preferentially receive inputs from the less spatially stable CA2 region (Kay et al., 2016), contributing to a less stable spatial representation than superficial layers, but could also be more strongly driven by the entorhinal cortex.

Better organization, for what?

One of the important findings of this study was that there is a sublayer-specific response to attention state and task demand. When looking at population dynamics of neurons under a multiple day goal-directed learning paradigm, the authors found that only deep CA1 pyramidal cells were significantly modulated by the presence of a goal (a rewarded zone on the treadmill), and in fact their place maps were stabilized by this. Presence of a goal means that the animal

receives reward here, so one potential cause of the functional difference between the sublayers is differential response (perhaps due to differential receptor density) to reward-related neuromodulatory inputs such as acetylcholine or dopamine.

The study of Danielson and colleagues highlights the complexity of network dynamics: they show that there is a behavioral and functional divide in the superficial-deep axis of the hippocampal CA1 area, but also reinforce that dynamics of spatial and goal-oriented learning must be influenced by interplay between intrinsic cell properties and circuit connectivity, as well as neuromodulation. This work allows the field to challenge the idea that CA1 pyramidal cells are not clearly organized, and introduces a mechanism for simultaneous coding of distinct processes in the same structure by refined populations. It could also be a step towards solving the 'stability plasticity dilemma' of how the hippocampus can remain plastic for learning while also having to hold stable spatial representations: if the superficial CA1 pyramidal cells could be relied upon to faithfully represent space, their deep CA1 counterparts would be free to remain plastic and adjust their responses based on the changing inputs.

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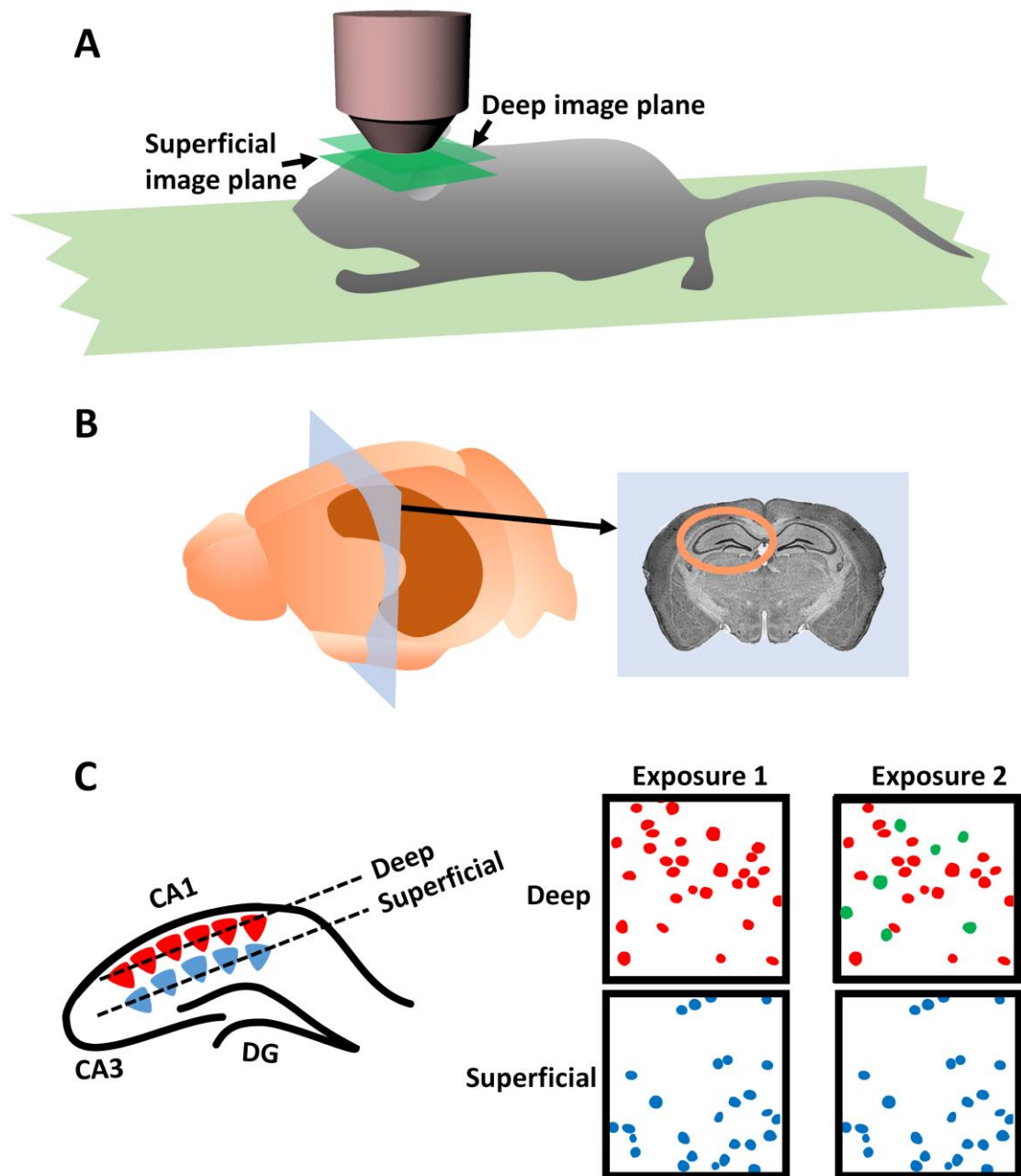


Figure 1. Differential stability of place cells in deep and superficial layers of the hippocampal CA1 subfield. (A) A mouse transfected with a viral calcium imaging protein (GcAMP6f) in dorsal hippocampus ran on a treadmill while its CA1 neurons were imaged in two planes, deep and superficial, by an overhead two-photon microscope. (B) Schematic of the mouse brain and hippocampus. The coronal section on the right represents the plane indicated in blue on the left; the region of the dorsal hippocampus is circled. (C) Imaging of deep and superficial CA1 neurons. Left – schematic of the dorsal hippocampus showing the pyramidal neurons in CA1, and the imaging planes. Right – schematic of active neurons as

imaged in the two planes. The red and blue blobs depict active neurons in deep and superficial planes, respectively while the left and right panels depict successive recording sessions. The pattern of the active deep neurons changed, with some new cells becoming active (green), some remaining unchanged (red) and some ceasing to fire (not shown). The superficial pattern was stable, with the same neurons active in both sessions.