topography of the synaptic vesicle to VGCC cluster relationship. As of yet, the coupling distance between vesicles and the calcium source must be functionally determined. A major breakthrough in ultrastructural analysis could combine the resolution of vesicle placement through tomography of synapses fixed by high-pressure freezing (Imig et al., 2014) with immunogold labeling techniques. This could address the open question of whether VGCC perimeter size itself determines the number of vesicles that can be coupled within close proximity; i.e., does a larger VGCC cluster lead to more readily releasable vesicles (Figure 1)? At hippocampal synapses, Holderith et al. (2012) found that both the number of docked vesicles and VGCC cluster size correlated with AZ size. Additionally, in the calyx, the readily releasable pool of vesicles was determined to increase approximately 2.5- to 3-fold with age (P7–P14; Taschenberger and von Gersdorff, 2000). These could be hints that the available perimeter affects the number of release-ready vesicles. Nevertheless, structural information of the synaptic vesicle-VGCC relationship will provide insight into neurotransmitter release mechanisms. Hopefully, with the rapid development of high-resolution imaging techniques, determining the physical distance between docked synaptic vesicles and calcium channels within a synapse is on the horizon.

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CA2: It's About Time—and Episodes

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In this issue of Neuron, Mankin et al. (2015) show that CA2, an oft-neglected hippocampal subregion, has place representations that change from one episode to the next, even as the spatial environment does not. This finding may help explain how time is encoded in episodic memories.

We form memories of what happens to us by organizing all components of each episode in space and time. Much of this process takes place in the hippocampus, and it has been long known that lesions of this structure impair episodic memory in humans and other animals. The hippocampal code for space is expressed by place cells, neurons that activate as the subject traverses a specific spatial location. Place cells provide the brain with useful information for self-localization and navigation, but can also be seen as scaffolding for episodic memories: items found at one place, or occurrences taking place there, may be represented in the hippocampus by modulations in the activity of place cells tied to that location, in a phenomenon known as rate remapping (Leutgeb et al., 2005).

Thus, the hippocampus has the daunting task of combining sensory information of all modalities with a spatial metric, probably supported by self-motion signals. It accomplishes this feat with a very complex wiring pattern, involving the interplay of multiple substructures. In the traditional view, metric information and sensory inputs flow into the hippocampus, respectively, from the medial (where the eminently spatial responses of grid cells are measured) and the lateral entorhinal cortex. Within the hippocampus,

a trisynaptic circuit forms with the sequential involvement of the dentate gyrus (DG), the cornu ammonis (CA) 3, and CA1. The serial character of the connectivity is complemented by bypass connections reaching CA3 and CA1 from the entorhinal cortex. DG, CA3, and CA1 differ in their anatomical connectivity and physiological characteristics, allowing for a division of labor. The very large number of cells and the very sparse representations in DG seem optimal for pattern separation—that is, the ability to distinguish similar but distinct items. CA3 has high levels of recurrent connectivity, which make it a candidate for working as an auto-associative neural network. CA3 may thus help in pattern completion, for example when we need to recognize the same environment, even as some cues have been removed or changed. CA1 combines information from DG, CA3, and the entorhinal cortex to provide a coherent output to the rest of the brain.

This picture may explain a good deal about hippocampal function in the spatial domain but leaves out the time dimension. While neurons that signal elapsed time within a task have been reported in the hippocampus and entorhinal cortex (MacDonald et al., 2011), in CA3 and CA1 the place cell representation of an environment remains by-and-large unchanged from one visit to that place to the next. Although this activity pattern may optimally denote the constancy of an environment, it is not as useful if memories of different episodes occurring in the same place, possibly with different valence and meaning, are to be formed.

A possible candidate for the role of distinguishing between different episodes that occurred in the same place is the hippocampal subfield CA2 (Jones and McHugh, 2011). CA2 has been long neglected as a transition area between CA3 and CA1. Recent data, however, have pointed out several unique features of this substructure in terms of gene expression and in terms of connectivity patterns and neuronal physiology. CA2 has been implicated in social memory (Hitti and Siegelbaum, 2014), an ability that requires keeping track of time in addition to space.

In this issue, Mankin et al. provide one of the very first reports about place cell activity in CA2 from rats. They used painstaking anatomical analyses in order to locate their recording electrodes in this small hippocampal subfield, as well as neighboring CA3 and CA1. At first glance, the place cells' behavior seems quite similar to what has been observed in CA3 and CA1. Basic physiological measures and the amount of spatial information that may be extracted from neuronal firing are quite similar. This is not too surprising, as, after all, all subfields receive the same mix of entorhinal inputs, albeit in different proportions and with different intervening processing.

As the authors exposed the rats repeatedly to the same environment over the course of several days, however, striking differences started to emerge. CA3 and CA1 showed similar place cell activity during repeated exposure to the same environment but can differentiate between a circular and a square enclosure placed at the same location. In striking contrast, enhanced representational drift was observed in CA2 over time, even as the environment stayed exactly the same, but no distinctive correlates of the one or the other enclosure was observed.

Thus, across repeated exploration sessions, we see different types of representational changes. CA1 and CA3 cells keep the location of their firing fields, so that the same physical location is signaled by a constant group of neurons, but remodulate their firing rate in response to large environmental changes, such as the walls changing shape (Leutgeb et al., 2005). This is the so-called 'rate remapping' phenomenon. CA2 instead changes the place representation from one session to the next, with the similarity between the firing maps for the same environment falling down to asymptotic levels after 24 hr. Not only are firing rates remodulated, but also completely new firing fields emerge as the animal is exposed to the same environment again. This is akin to "global remapping" (Leutgeb et al., 2005), a complete reshuffling in place field position, which is observed as the animal visits an environment that is classified by the hippocampus as a different physical location.

These findings raise two important questions. First, how do these "drifting" representations of the same environment come about? Second, what are such unstable encodings good for? An enticing suggestion about mechanisms comes from the following hint: CA2 receives very little input from CA3 and is dominated by entorhinal inputs, feeding it with information about current position and sensory signals (Chevaleyre and Siegelbaum, 2010). CA3 is thought to be a key structure for memory consolidation: during sleep and inactive period, the hippocampus reactivates neural activity patterns that are related to the preceding experience. This "memory replay" is important for the stabilization of newly formed memories, and its disruption has been found to affect both memory performance and the consistency of place cell representation over time. Memory replay is likely to originate in CA3, most importantly in sharp wave events, rapid spontaneous bursts of activity that are generated in CA3 and propagated to CA1 and then to the rest of the cortex (Battaglia et al., 2011). Thus, CA2 may be partially excluded from the replay/consolidation circuitry, which may explain why the representation drifts from one recording session to the next when there is an intervening consolidation period. Notably, the stability of CA2 place fields is on par with CA1 and CA3 within a session— that is, before consolidation plays a role.

Somewhat counterintuitively, these "non-consolidating," "forgetful" representations may play an important role for the encoding of episodic memories: the hippocampus is thought to provide an index coding (Frankland and Bontempi, 2005) that links, and points to, representations in multiple cortical areas covering all aspects of a given experience. According to the systems consolidation theory, this "glue code" is what keeps an episodic memory coherent, at least immediately after its formation, and its replay may help generate cortical representations that are independent of the hippocampus. But, if hippocampal representations are strictly related to space (and the objects that populate space), as those in CA1 and CA3 appear to be, there is no way for the index code to distinguish between episodes that occur at the same place but at different moments in time. CA2, as shown by Mankin et al., produces different representations as a function of time, a "unique identifier" of sorts for a given episode (in computer science parlance, a "hash code"; Figure 1). Interestingly, the time code from CA2 only reflects

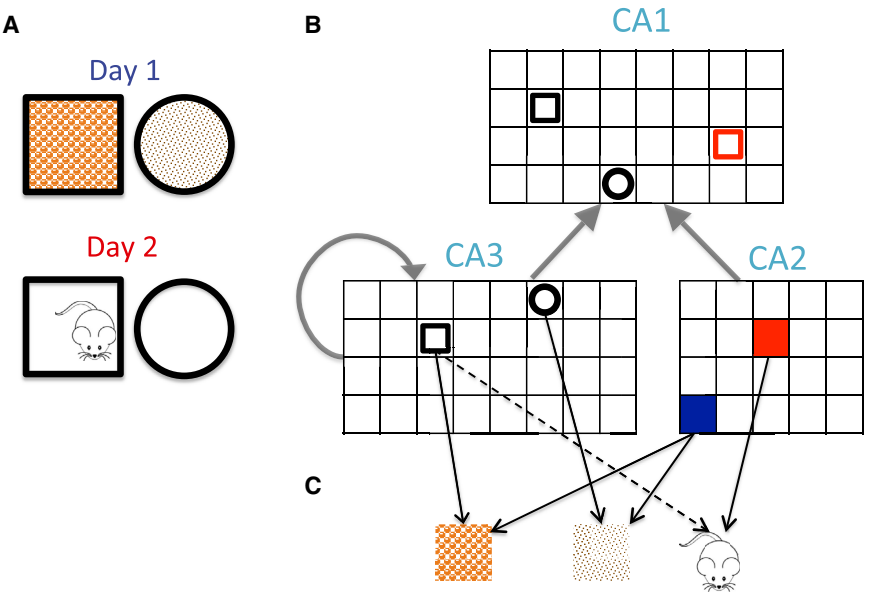

Figure 1. Differential Memory Tagging by CA Subregions

(A) Hypothetical episodic experiences. On day 1, a rat explores a square shaped environment, and is rewarded with fruit loops. Immediately after, he is placed in the same environment, but the walls are changed to form a circular enclosure. In this configuration, the rat is rewarded with chocolate sprinkles. The next day, the rat is placed in the square configuration, and encounters another rat there.

(B) Activation of place cells from CA sub-regions. CA3 cells rate remap in response to large changes in the environment. Thus some cells will fire most strongly in the circular configuration, and some in the square configuration (marked with black circle and square). The activity of these cells is not different between day 1 and day 2. Mankin et al. show that different CA2 cells represent the same space in experiences separated by several hours (the blue cell activates on day 1, whereas the red cell activates on day 2, both in both environment configurations). CA1 cells receive inputs from both CA3 and CA2, and thus may form representations that are both feature and time tagged. These cells, however, are active on multiple days, similarly to CA3 (black shapes) and thus it is likely that only a few significant episodes are consolidated uniquely and stored for long periods of time (red square).

(C) Encoded experiences. According to memory indexing theory, hippocampal cells become associated with the sensory experiences that occur when those cells are active. CA3 cells, which exhibit different firing rates for the different environment shapes, would become associated with the different foods, and would help the rat predict which food to expect in which shape. The new CA2 representation formed on day 2 could differentiate the encounter with an intruder rat from all previous experiences in the same environment. CA1 may consolidate that specific encounter, while CA2 forgets.

temporal ordering for about one day. Beyond that period, it is not possible to use the CA2 codes to infer the time elapsed between two episodes.

This idea for time identifiers resembles a role that has been advocated for the cells generated by adult neurogenesis in DG. The slow integration into the DG network and increased excitability of newly born granule cells was suggested to increase the similarity of the representations of events occurring close in time and make the neural correlates of events happening at a larger time distance more different (Aimone et al., 2010). The results about CA2 from Mankin et al. suggest an alternative mechanism for a very similar function.

Besides the theoretical implications, the findings of Mankin et al. help delineate the behavioral functions of different CA subfields and open new lines for investigation. For example, the forgetful representation of CA2 cells suggests a substrate for temporary memories such as "Where did I park my car this morning?" Memories of common events would rather interfere with future behavior if they were stored for long periods. CA2 has been shown to be important for increased socialization with a novel rat (Hitti and Siegelbaum, 2014). The current finding suggests that CA2 cells may indicate to the rat that it has interacted with the familiar rat recently—and thus can focus on other behaviors. CA3 cells, by contrast, are required for rapid learning in a new environment (Lee and Kesner, 2002) and produce coherent representations, which lump small changes together (Colgin et al., 2010).

Unlike CA3, CA1 cells display learning during repeated exposures to the same, unaltered environment (Lee et al., 2004). Indeed, CA1 is in a position to combine the spatial code from CA3 and entorhinal cortex and the time code from CA2 to create a spatio-temporally organized index code, ideally suited for supporting episodic memory (Figure 1).

The ability to locate the memory of events in space and time is critical to animal survival and can be studied, with clever behavioral paradigms, even in animals such as birds and rats (Clayton et al., 2003). While much work is still required to understand the role of CA2 in memory, the results of Mankin et al. highlight the degree of complexity and specialization of the hippocampal circuitry for supporting episodic memory, with multiple subfields, each with different circuit and dynamic properties, contributing to different aspects of this multifaceted function.

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