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Encoding New Episodes and Making Them Stick

Minireview

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How do we encode, store, and retrieve new episodic memories, and what are the computations performed by the hippocampus during this process? One system that has been used to model the brain basis of episodic memory in humans is the study of spatial navigation by path integration in rodents. Here I discuss three exciting new findings focused on encoding or replay of spatial sequences in the rat hippocampus. These findings not only provide important new insight into the computations associated with encoding and consolidation of spatial trajectories, but may also have implications for understanding key aspects of human episodic memory.

One of my most vivid New York City memories involves my visit to see The Gates exhibit in Central Park by Cristo and Jeanne Claude. It was a beautiful, sunny, but cold winter's day, and the park was filled with more people than I had ever seen gathered there at one time. I walked from the southeast entrance of the park, by the pond, and then up toward the Central Park Zoo, the whole time admiring the beauty of the brightly colored gates in the late afternoon sun, as well as enjoying the surprisingly good mood of the hundreds of other visitors I was sharing the path with. Despite the fact that this event took place more than a year ago, I still retain a detailed memory of this event. The issue at the heart of this minireview is understanding how the brain allow us to form, retain, and recall these vivid episodic memories. Years of detailed and systematic studies on human amnesic patients have shown that the ability to form and retain episodic memories is dependent on the integrity of the hippocampus and related medial temporal lobe structures (Squire et al., 2004; Squire and Zola-Morgan, 1991). There is also strong evidence supporting the idea that the hippocampus is involved in the strengthening or "consolidation" of episodic memories for a variable time period after they have been encoded (Bayley et al., 2005; Squire and Zola-Morgan, 1991). Data from both rats (Buzsáki, 1998; Wilson and Mcnaughton, 1994) and humans (Maquet et al., 2000) suggest that sleep may play an important role in this gradual consolidation process.

One model system that has been used to understand the computations performed by the hippocampus during episodic encoding and consolidation is the study of spatial navigation by path integration in rats. Both episodic memory and spatial navigation share key overlapping features, including a reliance on temporally sequenced information—both are self-referenced and both require a spatiotemporal context (Buzsáki, 2005).

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Several recent studies shed new light on the neural computations done by hippocampal cells during spatial navigation in rats. The first study, by Dragoi and Buzsáki (2006) (this issue of *Neuron*), provides new evidence that the dynamics of internally coordinated cell assemblies in the hippocampus play a much more important role in the representation of spatial trajectories than previously appreciated. Two other recent studies provide surprising new insights into the replay of spatial information in hippocampal cells that is thought to play a role in memory consolidation (Foster and Wilson, 2006; O'Neill et al., 2006). I will first briefly describe the main results from these three studies and then discuss their implication for the encoding and consolidation of episodic memories.

Interactions between Cell Assemblies and the Encoding of Past, Present, and Future Locations

To explore the encoding of spatial trajectories, Dragoi and Buzsáki (2006) analyzed the patterns of correlated spatial activity in areas CA3 and CA1 as rats ran on an elevated linear maze. Consistent with previous studies (Huxter et al., 2003; Skaggs et al., 1996), the authors show that the distance between adjacent place field peaks of pairs of neurons is represented by the precise temporal relations of spikes at a compressed or "theta" time scale on the order of milliseconds. This distance versus theta-scale time lag correlation is referred to as "sequence compression," and its correlation coefficient is referred to as the "sequence compression index." By plotting the sequence compression for the whole population of place cell pairs over several theta cycles (Dragoi et al., 2003), one can show that the compressed spike timing provides information about past, present, and future spatial locations within the time period of a theta cycle. An important implication of sequence compression is that it brings the representation of sequential events into the range of spike timing-dependent plasticity (Bi and Poo, 1998; Markram et al., 1997), thus providing a potential synaptic mechanism whereby past, present, and future sequences may be linked together, even though the actual sequences are taking place over a much longer time scale.

Dragoi and Buzsáki next asked whether sequence compression can be explained by "phase precession" of independent neurons driven by a common theta pacemaker (pacemaker model) or whether, by contrast, it is the result of temporal coordination between specific hippocampal cell assemblies (assembly model). To contrast these two hypotheses, they compared the sequence compression index for pairs of cells that fire in a correlated way across laps (i.e., cells thought to be part of assemblies) and pairs of cells that did not show a strong correlated activity across laps. The common pacemaker model suggests that no difference should be seen in the compression indices of these two populations of cells. However, they found that, consistent with the assembly hypothesis, pairs of cells with highly correlated activity exhibited higher sequence compression indices than pairs of cells with poorly correlated activity. Also consistent with an assembly hypothesis was

the finding that the sequence compression index was significantly higher during the rising part of the place field (i.e., where the rat enters a place field) than during the falling part of the field (when the rat exits a place field). Because the theta oscillation remains the same over the entire field, these findings suggests that forces other than a common theta drive (i.e., associations within cell assemblies) may be acting differentially in the two parts of the field. These findings support the view that sequential segments of the track are represented by the activity of unique sets of cell assemblies bound together by dynamic interactions.

Dragoi and Buzsáki also showed that CA3 cell assemblies predicted the current location of the rat's head about one-half of a theta cycle earlier than CA1 cell assemblies. Based on all these findings, the authors suggest a model whereby environmental inputs arising from the entorhinal cortex trigger an internal sequence/spatial trajectory readout in area CA3, which signals the location of the rat's head in the next half of a theta cycle. The predicted (CA3) and perceived (EC) spatial locations are then replayed sequentially by the CA3 and CA1 assemblies at the compressed time scale that occurs in the range of spike timing-dependent plasticity mechanisms (Bi and Poo, 1998; Markram et al., 1997). In this way, they propose that overlaping past, present, and future locations are combined into single episodes across successive theta cycles. Importantly, this scenario allows for associations between both adjacent as well as nonadjacent (i.e., higher order) items in the sequence. This feature could be used for flexible associative recall, which is a hallmark of episodic memory in humans.

Consolidating Your Memories during Sleep?...

Why Wait?

We next turn to the question of how information about spatial trajectory may be consolidated in memory. The standard memory replay hypothesis states that patterns of brain activity that occurred during waking states are replayed during sleep and that this replay may be critical for the process of memory consolidation (Louie and Wilson, 2001; Nadasdy et al., 1999; Wilson and Mcnaughton, 1994). Two recent studies provide surprising new twists on this standard memory replay model.

O'Neill et al. (2006) examined hippocampal place cell activity during different kinds of sharp wave ripple events. These events, first described by Buzsáki (1986), consist of irregularly occurring sharp waves caused by the synchronous firing of CA3 and CA1 pyramidal cells. The strong excitatory input from the CA3 region triggers short oscillatory "ripples" in the CA1 region. While the memory replay hypothesis suggests that sleep is required for the replay of waking exploration patterns in the hippocampus, O'Neill and colleagues tested the idea, first suggested by Buzsáki (1989), that it is not sleep per se but sharp waves ripple (SWR) events that are critical for reactivation to occur. While SWR events occur prominently during sleep, O'Neill and colleagues focused on a category of SWR observed during waking exploration (eSWR). By examining the activity of place cells during the eSWR events, they first showed that activity during eSWR remained location dependent in that firing was stronger inside the place field than outside. Because the firing increase during eSPW was even stronger than the baseline firing increase inside compared to outside the place field, this suggested a supralinear summation of eSWR and place selective activity.

They then compared the average cross-correlograms of cell pairs with similar place fields or significantly correlated activity during eSWR and theta oscillation. They found that the cell pairs with similar or correlated firing during exploration showed stronger coactivation during both eSWR and subsequent sleep SWRs. These findings suggest that similar patterns of increased correlated activity occur during both eSWR and during sleep that follows exploration and that this is specific since similar increases were not observed if sleep is not preceded by exploration. They suggest that this increase in correlated activity during eSWR may facilitate the initial associations between cells with similar place fields. These strengthened cell ensembles may then participate in the encoding of ongoing spatial trajectories during theta states as described by Dragoi and Buzsáki (2006).

Consistent with O'Neill and colleagues, Foster and Wilson (2006) recorded in rats as they ran on a linear maze and also found that sequential replay of spatial sequences can occur in waking periods when the animal has stopped moving and ripple events are present in the hippocampal EEG. They then looked at the precise sequence of firing activity of cells during these ripple events. The big surprise was that while they found evidence for trajectory replay, the replay occurred in the backward or reverse order from the sequence of locations that the rat had just traversed. Thus, place fields that had been active closest to the stopping location fired first, followed by place cells with firing fields at increasingly greater distances from the stopping location. While this phenomenon has never before been reported in vivo, reverse replay was predicted in an early theoretical model of memory formation (Buzsáki, 1989). They note that the correlation distribution of all events across the new session was significantly different from that of the distribution of events across all four familiar session, suggesting that the phenomenon is more readily expressed in new environments. They also show that reverse replay requires immediately preceding experience, because it was not observed before the animal started running on the maze. What role could reverse replay serve? Foster and Wilson suggest that reverse replay occurring in waking states may allow the immediately preceding events to be evaluated in precise temporal relation to anchoring events (like reward) and this may be critical for new learning. In this way, the reverse replay may be involved in the early learning process, while forward replay during sleep may be involved in learning/consolidation of more mature memory traces.

What Does This Tell Us about Episodic Memory?

These findings provide a novel and detailed set of predictions for how new episodes may be (1) encoded through the sequential activation of CA3 and CA1 assemblies (Dragoi and Buzsáki, 2006) and (2) strengthened first during periods of waking SPW events (Foster and Wilson, 2006; O'Neill et al., 2006) and also during sleep. While the sophisticated analysis tools that have been developed and applied to the study of spatial navigation in rats make it a particularly powerful animal model system, an important question is, can this model be improved? For example, while the sequential nature

of spatial navigation parallels closely the sequential nature inherent in episodic memories, there are also important differences between these two systems. For example, while the rat model focuses on processing spatial information, episodic memory can involve all forms of sensory information. Thus, it will be important to extend the study of spatial encoding and replay to other sensory modalities (see for example Wood et al., 1999). Another critical feature missing from this current rat model is controlled behavioral assessment. In many studies, hippocampal activity is recorded as animals simply run up and down a linear track for food reward. While it is assumed that spatial information is encoded or consolidated during these sessions, spatial memory is never tested directly, and therefore the status of the memory cannot be confirmed. While it remains difficult to study spatial recall in linear track environments where rats are making repetitive movements, several groups have made strides toward this goal by recording hippocampal activity in the context of various behavioral tasks where memory can be directly assessed (Ferbinteanu and Shapiro, 2003; Frank et al., 2000; Shapiro and Ferbinteanu, 2006; Wood et al., 1999). Combining sophisticated analyses of place cell activity of the kind reviewed here with the application of controlled mnemonic tasks will be a powerful way to understand the causal relationship between hippocampal activity and memory encoding, consolidation, or retrieval. This kind of approach will bring us closer to tapping the full potential of the rat model of episodic memory.

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