

structural and view-based information allows us to move beyond the narrow confines of the viewpoint debate and into a richer theoretical future.

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How does the hippocampus contribute to memory?

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Recently, Wirth *et al.* reported that hippocampal neurons signal the acquisition of new associations by altering the selectivity of their responses to crucial stimuli. The course of these changes was gradual, with some neurons recruited before, others at the time of, and yet others shortly after learning. These observations suggest the hippocampus might contribute to memory by identifying consistencies across experiences that constitute important new associations.

A recent paper by Wirth, Suzuki *et al.* [1] has reported that hippocampal neurons signal the acquisition of new associations by altering the selectivity of their responses. Since the 1980s, it has been clear that medial temporal lobe structures, including the hippocampus and surrounding cortical areas mediate declarative memory [2]. Damage to the medial temporal lobe generally affects

two major components of declarative memory, our capacity to recollect personal events (episodic memory) and our ability to accumulate factual knowledge (semantic memory). Recent research has begun to ask whether the hippocampus is involved in only one component of declarative memory. In particular, a selective role for the hippocampus in episodic memory was suggested by the description of case studies in which the hippocampus was selectively damaged [3]. These amnesic patients had a disproportionate deficit in memory for recent events compared with relatively successful acquisition of general knowledge in mainstream schooling. Additional recent evidence from detailed neuropsychological studies on amnesia [4] and from functional brain imaging [5] have emphasized selective hippocampal function in the capacity to recollect specific experiences, the hallmark of episodic memory. These findings tell us that the hippocampus performs some information processing function central to the recollection of specific personal events. At the same

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time, although at least some aspects of new knowledge can be acquired in patients with hippocampal damage, the applicability of this memory in new situations may be quite limited [6]. Is it possible that the hippocampus plays some key role in episodic memory that also contributes to the organization of semantic memory?

What kind of information does the hippocampus process?

If we could reveal the basic information processing functions that the hippocampus performs, we might understand how the hippocampus contributes to episodic and semantic memory. Recent functional imaging studies have highlighted a special role for the hippocampus in the processing of stimulus conjunctions. For example, in one early PET study, Henke and colleagues [7] reported that the hippocampus is activated during the encoding of associations between pictures of dwellings and people who might live in them, but was not activated when subjects made independent perceptual judgments about dwellings or people. Subsequent PET and fMRI studies have observed differential hippocampal activation during the encoding or retrieval of stimulus-stimulus associations, as contrasted with less activation during processing of the same items individually, for picture-word [8] and word-word [9] associations, for personal plus temporal details of autobiographical memories [10], and for words and the visualized context in which the words were elaborated [11], and hippocampal activation for face-name pairs is maximal during new learning [12].

Hippocampal representation of new associations at the level of single neurons

In their recent paper, Wirth *et al.* [1] explored hippocampal processing of associations at the level of single neurons. While the activity of single cells was monitored, monkeys quickly learned a set of novel associations between visual scenes and specific eye movements. Three main findings were described. First, over 60% of hippocampal neurons responded to the presentation of visual scenes, or during a delay period following scene presentation before the behavioural response; and a substantial subset of those cells responded to selectively to particular scenes. Many of the cells showed selective responses from the outset of training, or fired associated with presentations of previously trained reference stimuli. Second, over a third of the cells with selective visual responses changed their patterns of firing during learning by either an increase or a decrease in stimulus selectivity, and the altered cellular response persisted for the remainder of the recording session. Third, the changes in responsiveness occurred at different times relative to learning for individual cells. Some cells changed simultaneously with learning, but many changed either a few trials preceding or a few trials following learning of the associated eye movement.

That hippocampal cells respond to visual stimuli has been reported previously in monkeys [13,14] and humans [15]. Here the proportion of visually responsive cells was exceptionally high, perhaps because of the richness of the scenes used as learning stimuli. Furthermore, the

observation of hippocampal cellular responses to stimulus associations is consistent with previous descriptions of hippocampal neurons responsive to conjunctions of conditioned and unconditioned stimuli in rabbits [16], associations of stimuli and behavioural responses in monkeys [17], and associations of stimuli and the location where they were presented in monkeys [18,19] and rats [20–22]. Also, hippocampal ‘place cells’, neurons that fire when a rat is in a particular location in its environment, have been characterized as representing the association of stimuli perceived from a specific location and with behavioural actions at the location [23]. The present findings add to the growing body of evidence that the hippocampus represents a broad range of stimulus associations.

The finding that hippocampal neurons reflect learning by alterations in the selectivity of stimulus-driven responses and by maintaining selective firing during memory delays is consistent with other characterizations of learning related alterations in neuronal firing patterns in the hippocampus [14] as well as in a variety of neocortical areas [24]. The present findings suggest that the nature of the ‘code’ for learned stimulus representation is not qualitatively different from that in cortical areas with which it communicates.

The present findings also closely tie hippocampal neuronal activity to the formation of new representations that support learning. Previous studies have shown that hippocampal neurons acquire new firing patterns during learning. During classical eyelid conditioning in rabbits, hippocampal neurons showed large firing rate changes to both the conditioned and unconditioned stimuli just before the first appearance of conditioned behavioural responses [16]. In a set of tasks where monkeys learned to associate novel visual scenes with different kinds of manual responses, hippocampal neurons began to fire differentially to the discriminative stimuli just preceding, during, or shortly after acquisition of differential behavioural responses [14]. Wirth *et al.* used elegant analyses to determine the onset of learned neural responses relative to learning, providing strong evidence of the gradual evolution of a hippocampal network representation accrued over several trials during learning.

What is the significance of a gradual accumulation of associative representations?

This observation converges with views from the cognitive science of list learning by humans [25]. Several studies suggest that, under the conditions of distributed practice, learning is accomplished by accumulating consistent associations across multiple experiences with the same core information. According to differing accounts of this process, learning occurs most efficiently when each trial reminds the student of previous specific encounters with the same information, or when each trial re-starts a rehearsal cycle, or when each trial involves variation in the local context in which the information is encoded and thereby increases the number of links that can be used in subsequent retrieval. These accounts are not mutually exclusive; so all the suggested processes could contribute to the efficiency of multi-trial learning.

Importantly, each of these accounts assumes that every single trial plays a unique role, consistent with the notion that episodic memories are integrated to compose a lasting memory for the core material. From this perspective, the Wirth *et al.* findings suggest that the hippocampus might contribute to episodic memory by encoding information from each specific trial and to semantic memory by abstracting the common information that reflects the core association to be learned [23]. During the course of repetitions, some individual cells acquire the key association before the hippocampal network can support behavioural performance, whereas others add to the core association sufficiently to mediate behavioural learning, and later other cells corroborate or add new links to the core information. Thus, each episodic coding by the hippocampus is added to others to compose a final stage of semantic knowledge destined for consolidation in the cerebral cortex.

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Bubbles in the brain?

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How does the brain learn to control motor actions? 'Bubbles' of activity might exist in the cortex, as implied by a simplified model of the cortical sheet. New results show how these bubbles could enable motor actions to be especially efficient, and that they can be used with little difficulty in decoding them.

The way the brain learns to control motor responses, especially in cases when there is no external stimulus to

guide the response, is clearly of interest in helping to understand underlying neural mechanisms. One of the sub-questions arising from this is how a short-term memory is kept of previous brain activity, either resulting from external stimuli or internal brain activity itself. One way to preserve information over suitably long periods of time, is by 'bubbles' of activity created by external input in suitably connected sheets of neurons – such possible localized bubbles were originally explored in a model of neural connectivity for one-dimensional 'lines' of nerve cells [1]. They were shown to possess a number of desirable

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