

at various positions in the apical dendritic tree of CA1 pyramids (Cash and Yuste, 1999). In addition to such pairs of inputs, high-frequency synaptic stimulation trains were also investigated. The results suggest that linear summation of excitatory postsynaptic potentials at the soma—as reported by Cash and Yuste—could be compatible with strong nonlinear summation when several inputs are activated simultaneously in a single dendritic branch in the presence of active membrane conductances. In the authors' simulations and data analysis, nonlinear summation was most evident in the dendritic membrane potential recorded at the site of stimulation but could also be detected in the somatic membrane potential. An experimental verification of these predictions using similar methods as in Cash and Yuste (1999) should therefore be possible. An alternative but technically more difficult approach would be to directly stimulate two distinct presynaptic inputs and record from the postsynaptic target neuron as in Tamas et al. (2002). Poirazi et al. go on to show that summation of inputs distributed across more distant branches in their model follows a much more linear characteristic.

These results set the stage for the reductionist approach exposed in the second article (Poirazi et al., 2003b). The authors postulate that individual inputs sum linearly within a dendritic branch before being transformed by a sigmoidal transfer function $s(\cdot)$ similar in shape to nonlinear branch summation described above. The outputs of each branch are then combined to determine the firing rate according to

$$f = g\left(\sum_{i=1}^m \alpha_i s(n_i)\right).$$

In this equation, the index i runs over each dendritic branch, n_i is the total input to the branch, and α_i measures its coupling to the somatic membrane potential. Finally, the output nonlinearity g converts the intermediate sum, a measure of somatic depolarization, into firing rate. This description is formally identical to a two-layered neural network. The fact that two-layered neural networks can fit the input/output relation of a pyramidal cell would not in itself constitute a surprise: although simple in appearance, they are powerful objects known to approximate arbitrary functions with high accuracy (Bishop, 1995). The interesting observation made by Poirazi et al. is rather that the coefficients of such a model can be constrained by and mapped onto biophysically measurable quantities, such as the number of branches in the dendritic tree and their somatic coupling. This suggests a systematic procedure to reduce multicompartmental models to more tractable ones for analyzing the computations performed by neurons. The authors proceed to establish the superiority of this model against several challengers by using an elegant and efficient method. To test the various models under consideration, they select synaptic input patterns designed to optimally challenge their predictive power. A similar strategy is often used in more conventional statistical tests.

The work of Poirazi et al. suggests that the dendritic branches of neurons could act as localized nonlinear summing subunits and brings us closer to understanding how single neurons—the fundamental building

blocks of the nervous system—could process information. It also leaves open several questions. As noted by the authors themselves, it will be interesting to know if their results generalize beyond mean firing rate averaged over 250 ms, the neuronal output variable predicted in their simulations. It is likely that in many cases processing of sensory information occurs on a faster timescale. An extension of their results would allow us to address such situations as well. Another challenge is to investigate whether such reductions can be obtained directly from experimental data. Pyramidal cells might not be the neuron type most easily amenable to testing, since it is currently difficult to selectively stimulate single synaptic inputs at different positions in their dendritic tree and to simultaneously monitor dendritic integration. The method should however be applicable to other neurons where computational dendritic subunits are thought to exist and where integration of synaptic inputs across the cell could be nonlinear (Egelhaaf et al., 2002). In this context, the authors' method should provide a useful complement to traditional compartmental modeling methods in understanding dendritic integration and the relative role played by various dendritic branches and conductances in this process. Finally, one would like to relate the properties of the synaptic weights, α_i , to aspects of computing performed by single neurons and, ideally, compare their values among neurons performing different computations on identical inputs.

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Sequence Learning: What's the Hippocampus to Do?

The medial temporal lobe is crucial for some forms of memory, but its role in implicit learning has remained

in question. A brain imaging study by Schendan et al., in this issue of *Neuron*, provides direct evidence of medial temporal lobe activation during implicit learning of motor sequences.

The existence of multiple memory systems is now firmly established. Under the most well-known framework, conscious memories for facts and events are supported by a *declarative memory* system that relies upon the hippocampus and other medial temporal lobe (MTL) structures, whereas other forms of learning are supported by *nondeclarative or procedural memory* mechanisms that rely upon widespread cortical and subcortical structures (e.g., Cohen and Eichenbaum, 1993). A fundamental question remains, however, regarding the operation of these memory systems: What aspect of a learning task determines whether the MTL will be engaged? One view is that MTL engagement is determined by the degree to which learning involves awareness and explicit intention to learn. Under this view, the MTL is engaged when a task requires that subjects learn material explicitly (i.e., with conscious intention to learn). An alternative view is that MTL engagement is determined by the type of representations that are necessary to learn the task. Under this view, the MTL is engaged when the task requires the flexible representation of novel relationships between distinct stimulus features.

The report by Schendan et al. (2003) in the present issue provides clear evidence in favor of the representational account of MTL function and against the conscious awareness view. They examined subjects performing a sequential reaction time (SRT) task, which has long been used in cognitive psychology to examine dissociations between learning and awareness (e.g., Willingham, 1998). In this task, subjects respond to the location of a simple visual target on a screen; unbeknownst to the subject, on some trials the locations of the targets follow a specific sequence, whereas on other trials the locations are random. The Schendan et al. study used a specific kind of sequence known as a second-order conditional (SOC) sequence, in which all first-order transitions between locations were equally likely. Thus, to the extent that subjects perform better on sequence versus random trials, they must have learned about higher-order sequential regularities (relating at least three positions). Subjects learned one sequence under implicit learning conditions in which they were not informed about the underlying sequence; they then learned another sequence under explicit learning conditions in which they were informed about the sequence. Comparison of fMRI signal during sequence versus random trials showed activation in MTL during both implicit and explicit sequence learning, as predicted by the representational theory. Importantly, MTL activation was present even in subjects for whom there was no evidence of awareness of the sequence. Activation in the caudate nucleus and dorsolateral prefrontal cortex was also observed in both implicit and explicit sequence learning, whereas activation in the putamen was observed only during implicit learning.

These results comport with recent animal work showing that the MTL is necessary for representing sequences of events. Although early work focused on the

role of the MTL in spatial tasks, subsequent work has shown that the MTL is engaged more generally on tasks requiring association of discontinuous stimuli and their contexts across time and/or space (e.g., Eichenbaum, 2000). The anatomy and connectivity of the hippocampus are well-suited to such a role in associative learning. Of particular relevance, the CA3 region of the hippocampus has recurrent connections that allow the representation of sequences of items in time. Biologically plausible modeling has shown that the CA3 region is capable of sequence disambiguation (Levy, 1996) and associating stimuli across time gaps (Rodriguez and Levy, 2001). Recent lesion results are consistent with such a role for the hippocampus. For example, Fortin, Agster, and Eichenbaum (2002) found that rats with lesions to the hippocampus were impaired at selecting an odor based on its position in a sequence of odors but were unimpaired at recognizing whether a particular odor had previously appeared (regardless of its sequence position). Similarly, Gilbert, Kesner, and Lee (2001) found that lesions to CA1 impaired the ability to distinguish the temporal order of stimuli, particularly when they occurred nearby in time. These results highlight the importance of representational constraints on the engagement of MTL in learning.

Why had previous studies of sequence learning failed to find MTL activation? The reason is likely related to the use of an SOC sequence by Schendan et al., in contrast to the simpler sequences used in previous studies. Because all first-order transitions occur equally often in an SOC sequence, sequence learning in this case must rely upon representations that code one transition in the context of the previous transition. This is just the kind of situation in which one might expect the contextual coding mechanisms of the hippocampus to be engaged. However, further work is necessary to directly compare different types of sequences, in order to determine the relation between stimulus structure and memory system engagement.

Several open questions remain regarding the relation of MTL activity to learning and awareness. First is the perennially thorny issue of establishing a true lack of awareness. It has been argued forcefully (e.g., Shanks and St. John, 1994) that assessments of awareness must be sufficiently sensitive to the relevant knowledge and particularly must be sensitive to any conscious knowledge relevant to the task (such as "correlated hypotheses"). The study by Schendan et al. included a number of sensitive assessments of sequence awareness and compared fMRI signal between subjects who were aware of the sequence and those showing no awareness according to these tests. Both groups showed reliable activation of the MTL, and there was no correlation between awareness and MTL activity, consistent with the notion that this activation is related to stimulus structure rather than conscious awareness. However, it remains possible that an even more sensitive measure of awareness might have uncovered a difference between implicit and explicit learning in this region.

A second question regards the relation of the Schendan et al. findings to those using other tasks that rely upon nondeclarative memory, noting that motor sequence learning has long been thought to involve this memory system. In particular, recent studies have found

increasing activity in the striatum associated with learning, using tasks such as mirror-reading (Poldrack and Gabrieli, 2001) and classification learning (Poldrack et al., 2001). These studies have also found learning to be associated with increased *deactivation* of the MTL. In contrast, Schendan et al. found activation of the MTL and decreasing activation of the caudate/putamen with learning. This discrepancy is consistent with the notion that the requirement for higher-order sequence learning results in engagement of declarative (relational) memory mechanisms. However, further work is necessary to determine the boundary conditions of MTL engagement. Of particular interest is how the nature of the task determines interactions between memory systems; recent work (e.g., Poldrack et al., 2001) has demonstrated a negative relationship between MTL and basal ganglia activity during classification learning, whereas Schendan et al. (2003) failed to find any evidence of such an interaction.

Third, questions remain regarding how MTL activation during sequence learning relates to what is actually learned in the task. Recent work has demonstrated that the representation underlying sequence learning appears to encode relative spatial locations rather than specific effector movements (Willingham et al., 2000). Since spatial relations are inherently relational, it could be the case that MTL activation during sequence learning reflects its role in spatial processing. It will be of great interest to determine whether similar MTL activity occurs in tasks where the response is defined by some stimulus feature other than spatial location (such as color).

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