a Action potentials converted into postsynaptic currents

Layer 1   Layer 2

b

Neuron 300   Random firing

Neuron 300   Synchronous firing

Neuron 1   Neuron 1

1 s   1 s

Layer 1   Layer 10

Ivelisse Robles

Figure 1 Making a sparsely connected multi-layer feedforward network using a single cortical neuron and a computer. (**a**) Each action potential (AP) from the red trains in the simulated 'input' layer 1 is transformed, by the computer, to a transient postsynaptic current (PSC). The summed PSCs are injected intracellularly to a real neuron. The resultant AP train represents the firing of one neuron in layer 2. Another set of trains is randomly chosen from layer 1 (green traces); the new output train represents a second neuron in layer 2. The set of AP trains representing layer 2 are, in turn, used to construct the activities of layer-3 neurons, and so forth. (**b**) Fast and robust synchrony develops in deep layers.

axon[11,12]) are ignored. This could be partially circumvented by impaling the cortical neuron with two or even three electrodes in soma and dendrites[13,14]. Two dendritic electrodes could be used to mimic multiple inputs into the neuron while the somatic electrode could be used to monitor the resultant firing as above. How would these multiple dendritic inputs be represented through the feedforward network?

Clearly, the most demanding assignment for the novel method presented here is to mimic real cortical networks that are dominated by recurrent connections. In this case, the firing of the neuron should be updated in real time in response to the activity arising from the feedback connections. One may push the method to start doing this by simultaneously recording from several synaptically connected neurons (preferably from different cortical layers) and/or by using the dynamic-clamp method to effectively connect the neurons to each other (electrically, via the respective intracellular electrodes). A small recurrent network created in this way can then serve as a building block for larger networks using the iterative method described above. Theoretical studies[15] of the behavior of such networks—with balanced excitatory and inhibitory activity—predict chaotic dynamics and linear responses to input rates; this could then be examined directly.

So we should celebrate this innovative marriage between real neurons and the computer. It enables one to construct semi-realistic cortical networks of different size and architecture. The computer traces down how action potentials are transmitted and processed through cortical networks with thousands of neurons; the neurons, in turn, help us to understand how signal processing in cortical networks depends on the synaptic and membrane properties of single neurons. This fruitful collaboration between the neuron and the computer will shed light on how cortical circuits encode (rate-wise, temporal-wise or otherwise) the world around us.

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A signature of salience in the *Drosophila* brain

Mark A Frye & Michael H Dickinson

Electrophysiological recordings coupled with genetic manipulations in fruit flies reveal activity patterns in the brain associated with the conspicuousness of visual objects, providing an elusive physiological link between gene products and behavior.

Some of the most complex animal behavior is so commonplace that it escapes our attention. For example, seeking, detecting,

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approaching and landing on a piece of fallen fruit is a seemingly simple task for a fruit fly, yet it requires that the animal track a fragmented odor plume through a changing and varied landscape. Eventually, the fly must orient toward some conspicuous visual feature that might represent the source of the attractive odor. Does this behavior reflect a confluence of sensori-motor reflexes, or do higher centers of the brain decide that a smelly blob is sufficiently conspicuous to warrant further investigation? More generally, how do brains distinguish environmental features worthy of selective attention?

In this issue, van Swinderen and Greenspan[1] identify neural activity that may be associated with perception in the

central brain of *Drosophila*. They report that a change in gross neural activity within a specific brain region correlates with the conspicuousness (or 'salience') of visual objects displayed on an electronic screen surrounding the fly. This electrophysiological correlate of object salience can be modulated by different sensory systems mediating object tracking during flight, and it seems to emerge in part from regions of the brain associated with learning and memory. These results represent the first physiological correlate of perception in flies—and will likely catalyze the discovery of molecular and systems level determinants of how brains encode the context and relevance of sensory cues.

The cascade of neural processes that enables fruit flies to distinguish and attend to a desirable object set within a complex sensory landscape begins with the detection and discrimination of visual objects and odor sources within primary sensory centers and ends with the fusion of sensory signals within higher-order centers to form a cohesive 'percept'. This percept is then somehow transformed into motor output to bias an animal's behavior (**Fig. 1**). The hierarchical structure, robustness and experimental tractability of first-order sensory structures, particularly in insects, has attracted the attention of researchers studying general physiological mechanisms for detecting and encoding environmental stimuli[2,3]. Likewise, robust and relatively straightforward input–output relationships in *Drosophila* make sensorimotor reflexes amenable to examining the synaptic and cellular physiology of motor coordination[4]. However, a percept is an abstraction of sensory signals—an emergent property of staggeringly complex parallel and recursive neuronal networks in the brain. There is at best an enigmatic relationship between sensory input and behavioral output. Thus, finding a physiological basis of perception—even in model systems of comparatively few neurons—presents a challenging experimental hurdle.

Over the past several decades, behavioral analyses using psychophysical techniques in flies have been applied to examine the implicit relationships among sensorimotor integration, selective attention and memory[5]. To analyze explicit physiological processes, van Swinderen and Greenspan exploit a behavioral reflex in which *Drosophila* are attracted to a visual landmark composed of a high-contrast vertical edge[6,7]. The authors teth-

ered a fly within a wrap-around arena of light-emitting diodes and recorded multi-unit local field potentials within the central brain while a vertical stripe rotated continuously around the animal once every 3 seconds. The gross electrical potential slowly increased and decreased in register with the rotating stripe—a response not unexpected in the primary visual ganglion, the site of the reference electrode. However, as the stripe moved around the fly, the authors noticed a pronounced elevation of power density between 20 and 30 Hz, which was at least coarsely localized to the medial protocerebrum (**Fig. 1**). The activity within this bandwidth was strongest when the stripe was positioned in front of the fly and slowly decayed over repeated stimulus cycles, unlike the slow fluctuations that were phase-locked to stripe motion. These results led the authors to suspect that the 20–30 Hz response in the central brain is not part of the primary motion detection pathway, but rather is somehow associated with higher-order processes. This conclusion is supported by the finding that the 20–30 Hz activity is enhanced by visual cues thought to increase the salience of the object, such as changes in its shape or speed. Additionally, under 'virtual reality' conditions in which stripe motion is electronically coupled to the fly's attempt to steer, 20–30 Hz power increases when the fly begins to fixate the stripe frontally—a behavior analogous to object tracking in free flight.

It is perhaps not so surprising that visual features modify the salience of a visual object, but what about other sensory modalities? The fusion of information from different sensory systems is critical in many behaviors requiring object recognition. For example, visual feedback is crucial to *Drosophila*'s ability to localize an odor source in free flight[7]. Classical conditioning experiments in flight simulators have shown that odor can strongly modify an animal's response to a visual object. By repeatedly activating a stream of banana vapor as the rotating stripe passed the fly's frontal field of view, van Swinderen and Greenspan show that such conditioning results in an elevation of the 20–30 Hz response to the moving stripe.

Visual ganglia do not appear to receive input from olfactory centers. Therefore, it is unlikely that olfactory cues directly alter figure/ground discrimination or other visual detection processes in flies. However, once an object has been distinguished based on luminance, contrast, shape or relative motion, olfactory and visual signals may converge in higher-order centers of the brain to enhance the perceptual image of the object.

What exactly is the cellular basis of the 20–30 Hz response? Field potentials represent the ensemble activity of hundreds or thousands of individual neurons. Thus, this recording technique can neither distinguish the activity of individual cells, nor examine the information carried by subthreshold graded potentials. Notwithstanding these shortcomings, the sheer complexity of brains and the importance of distributed processing guarantees that intracellular 'circuit busting' techniques are not alone sufficient for elucidating the neuronal mechanisms of context-dependent and highly adaptive cognitive processes. Neuroimaging techniques have been widely used in humans to localize cognitive processes to specific brain regions[8]. Recent advances in multi-unit extracellular array electrodes and associated analysis methods permit simultaneous recordings of many
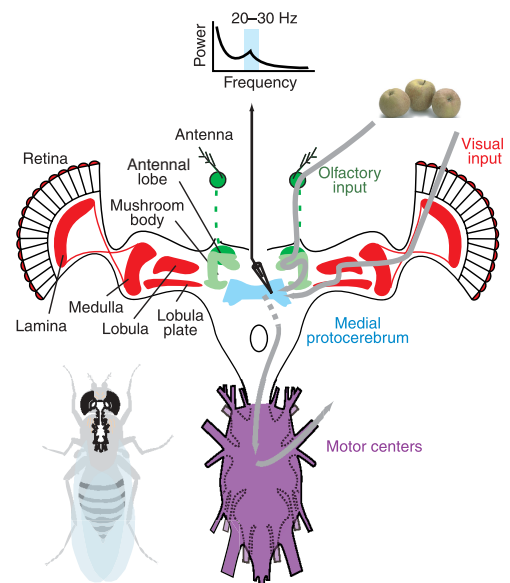
Figure 1 Schematic representation of the 20–30 Hz response in *Drosophila*. Encoding and processing of environmental stimuli (gray arrows) occur through a hierarchy of brain centers. Multisensory convergence results in a peak in evoked field potentials (top) associated with the salience of visual objects. Higher-order integrated feedback is ultimately coupled with premotor networks that guide or bias an animal's behavior (dorsal view; not to scale).

cells within one or more region of the brain. The preliminary results of van Swinderen and Greenspan suggest that 20–30 Hz activity is phase-locked across regions of the central brain, thus showing spatiotemporal synchrony or coherence—a hallmark of early perception in vertebrates[9]. Increases in power within the 20–30 Hz bandwidth may reflect changes in the recruitment, firing rate and synchrony of a subpopulation of cells within the medial protocerebrum or an adjacent region. Future experiments using micro-arrays of extracellular electrodes combined, when possible, with intracellular recordings, should be able to test these various hypotheses.

Although *Drosophila* will never win high marks as an electrophysiological model, it does permit extraordinarily precise manipulations of gene expression in both time and space. In particular, by clever implementation of the GAL4/UAS expression system of yeast[10], it is possible to express a gene of interest (including ones not found in the fly's genome) ectopically within specific regions of the nervous system. For example, the gene for tetanus toxin or an allele of *shibire* can be introduced to block synaptic transmission. Such techniques have been used to

examine mechanisms of sensory discrimination[11], sensorimotor integration[12] and learning and memory[13]. Until now, however, physiological links between gene products and behavior have been elusive—especially at the systems level.

By systematically targeting reversible temperature-sensitive mutations in membrane conductance and synapse function to specific regions of the brain, van Swinderen and Greenspan spatially localized the origins of the 20–30 Hz response—at least in part—to synaptic output from the mushroom bodies. Biochemical, physiological and behavioral evidence implicates these structures in odor-mediated learning in flies[14]. It remains to be shown how visual feedback is integrated with mushroom body output. Postsynaptic targets of mushroom body efferents such as those within the lateral horn are probably involved[15].

The discovery of structure–function relationships mediating higher-order brain processes such as perception, attention and learning will be accelerated by integrating molecular-genetic, physiological and behavioral approaches. Toward these ends, the experimental power of coupling spatially localized and reversible genetic manipulations with robust physio-

logical recording preparations in behaving flies is difficult to overstate. Armed with a physiological assay for object salience, the next challenge is to find out how this signal is used to structure fly motor behaviors such as foraging or courtship. Given the remarkable complexity even within one of nature's smaller brains, this challenge is not an easy one. As Donald Hebb noted, "the brain…may not be able to do simple things in a simple way."

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Aging, spatial behavior and the cognitive map

Emma R Wood & Paul A Dudchenko

Hippocampal neurons are thought to form a cognitive map of the environment based on multiple cues. A new study shows that young animals switch between cues more easily than aged animals and also perform better on a spatial learning task.

In the Scottish highlands, hikers risk being caught in a sudden mist that obliterates all visible landmarks. People in this situation have two options: attempt to retrace their steps by estimating how far and in which direction they have traveled, or wait until the mist lifts and the landmarks return. The neural basis of these spatial abilities in humans is not clear. In rodents, however, both types of navigation may rely on hip-

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pocampal neurons called 'place cells'[1], which encode spatial information defined by self-motion cues[2,3] or by visual landmarks[4–6]. One influential theory is that together, the population of place cells provides a 'cognitive map' of an animal's environment[7].

In this issue, Rosenzweig *et al.*[8] compare these hippocampal cognitive maps and spatial behavior in young adult and aged rodents. They find that the ability of both young adult and aged rats to find a reward in the environment is correlated with the ability of place cells in the hippocampus to switch between two different cognitive maps, one based on self-motion cues that are irrelevant to solving the task, and another based on relevant landmark cues. Intriguingly, they observe that old rats are impaired relative to young adult rats, both

in switching from the irrelevant to the relevant map and in finding the reward (**Fig. 1**).

Since the discovery of hippocampal place cells[1] in the early 1970s, researchers have sought to understand which aspects of the environment control their spatial activity. Early studies demonstrated that the location in which a place cell fires—its 'place field'—is controlled by visual landmarks in the environment[4–6]. Thus, if one rotates the landmarks in an environment by 90° while the rat is elsewhere, then when the rat returns, its place fields will also rotate by 90° to agree with the landmarks. Visual landmarks are not the whole story, however. Place cells are also controlled by path integration—deriving the direction and distance traveled from self-motion information, including motor proprioception, the vestibular system and perhaps optic flow[2,3].