serves as the superlens that transfers the image of a lithographically written pattern to a nearby layer of photoresist. But coaxing evanescent waves to grow requires two stringent criteria to be satisfied. First, the surface of the film must be extremely smooth; otherwise, surface imperfections scatter the incident light and wash out the finer details carried by the evanescent waves. Second, the thickness of the silver film must be optimized: If it is too thick, material losses dominate over the evanescent wave refocusing, and none of the information carried by the evanescent waves is recovered in the image. The film produced by Fang *et al.* meets both criteria, with an optimal thickness of ~35 nm and a surface roughness of less than 1 nm (*6*).

The demonstration of superlensing requires a subwavelength object. In the experiments of Fang *et al.*, such an object is formed by the light that passes through thin slits (with a width of 40 nm) that have been patterned into an otherwise opaque chromium mask. Because the slits are narrow relative to the wavelength (365 nm), the light is strongly diffracted, with most subwavelength features being contained in the evanescent waves. As a result, the image blurs rapidly as a function of distance away from the mask. The reduction in image quality is noticeable over a distance of tens of nanometers, as can be seen in the second figure.

Fang *et al.* use the light that passes through the chromium mask and the lens to expose a layer of photoresist, where the optical image is converted into a topographic map of peaks and valleys that can be scanned with an atomic force microscope. As an example, the authors patterned the word "NANO" into the mask (see the second figure, top panel). In the absence of the silver superlens, the lines that form the letters are diffuse (bottom panel), with a measured line width of more than 300 nm. With the silver superlens, the evanescent waves are recovered, and markedly better resolution is obtained (middle panel), with an observed line width of less than 90 nm.

The results of Fang *et al.* (*5*) confirm that the predicted phenomenon of evanescent wave refocusing is indeed possible at visible wavelengths. This important advance not only resolves a controversial aspect of negative-index materials, but also opens the door to a variety of possible applications, including higher resolution optical imaging and nanolithography. Optical elements can now be designed to access and exploit the near-field of light.

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NEUROSCIENCE

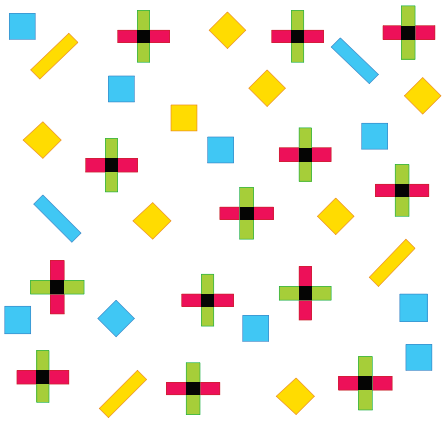
Watching Single Cells Pay Attention

Jeremy M. Wolfe

As visual organisms, we spend much of our time engaged in visual search behavior. We seek to make the current object of our desire into the current object of our visual attention and motor action. You want a sip of coffee. There is the mug. Then you wonder, where is the "%" sign on the keyboard? Next, the ring of the phone redirects your attention to that object. Most searches such as these go by so quickly and effortlessly that we don't notice the search aspect at all. We do notice when the task becomes more difficult: Where is that corkscrew in the kitchen gadget drawer? Ah, there it is, in full view, but somehow not noticed until after a prolonged period of searching. Insights into how area V4 of the visual cortex might participate in these sophisticated search tasks are revealed by Bichot *et al.* (*1*) on page 529 of this issue.

So, how do we carry out these search tasks? Behavioral and physiological experiments conducted over more than a quarter century have emphasized one of two types of mechanism: parallel processing, in which all (or many) objects are analyzed at once (*2*, *3*); and serial processing, in which one (or very few) of the available objects are selected for specialized analysis (*4*, *5*).

You may be able to get a qualitative appreciation for these modes of processing by searching for one of the objects in the figure. Find the blue diamond. You will probably notice that all of the blue items seem to make themselves available to you at the same time. If you now search for the yellow square, the blue items recede into the background, while the yellow ones take center stage. Obviously, the stimulus has not changed. Your search goal has changed your analysis of that stimulus. If you are asked to search for the plus sign with red-vertical and green-horizontal elements, all the red and green plus signs may seem to become salient. But at the same time, you may be aware that some scrutiny of single items is needed before you find the plus sign having red linked to vertical. (If it felt instantaneous, go find the *other* plus sign with a red-vertical element. There are two.) The color and orientation features seem to be present almost immediately, but the binding of a color to an orientation seems to require something more.



Finding a needle in a haystack. Your analysis and experience of this display will change depending on whether you are looking for a blue diamond or for a plus sign with a red-vertical element. Bichot *et al.* reveal how different aspects of attention modulate the response of neurons in area V4 of the visual cortex as monkeys perform similar tasks (*1*).

Here, then, are two rather different types of processing that might be seen to fall into the general category of "attention." First, it seems possible to attend to a distributed set of items based on features like color. And second, it seems possible to select individual items for fixation or to select an item for further analysis even if it is not fixated. In most, if not all, search tasks, these processes interact to produce an effective visual search (*6*, *7*). Parallel information about features will guide your serial selection of individual objects—as you pick your favorite bits out of a fruit salad, for example.

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In their new study, Bichot *et al*. (*1*) demonstrate that both sorts of processing occur in area V4 of the visual cortex during a single search task. They recorded neuronal responses from area V4 in the brain of alert macaque monkeys who were searching through displays of colored shapes similar to those shown in the figure. In the first experiment, at the start of a trial, the monkey would be shown a stimulus that cued him to the target color (for example, red) or shape (for example, star). To find this target, the monkey typically made a succession of eye movements that changed the position of the visual stimuli on the retina. During a trial, Bichot *et al*. recorded from a V4 neuron that was sensitive to stimulation in one specific region of the retina (its "receptive field"). Beyond being sensitive to one location in space, a V4 neuron might also have a preferred color and/or shape. Thus, as the monkey moved his eyes around, he presented different stimuli to the receptive field of the neuron under study. If the neuron preferred red stimuli, then, by definition, that neuron responded more vigorously whenever the monkey saw red. Of more interest, on trials when the target color was red, the neuron produced a still larger response. This happened even when the monkey was not about to make a quick eye movement to the target. The red item had not yet become the specific object of attention, but the response of the neuron still received a boost because red was the desired color. Moreover, neurons that preferred the target feature synchronized their activity, perhaps giving them a better chance of activating subsequent postsynaptic neurons.

So much for the parallel enhancement of all items on the basis of a feature like color. What about the selection of specific items? Imagine the situation in which the monkey is searching for a red item, and a red item lies in the receptive field of the studied neuron. We know from previous work (*8*) that covert attention shifts to an object before it is fixated by the eyes. So Bichot *et al*. went back over their data and sorted the responses into two categories: responses from just before the monkey made an eye movement toward the red item and responses from just before he made an eye movement somewhere else. They found that the neuron responded more strongly just before the eyes fixated on the red item. Thus, it seems that the act of attentional selection that precedes serial fixation also enhanced the response of the neuron. What we have here is attractive evidence at the level of single cells indicating that parallel feature processes are guiding serial selection of plausible targets for further scrutiny.

Understanding how monkeys (and presumably other primates, such as ourselves) perform search tasks is of more than academic interest. Visual search is a task each of us performs a thousand times a day, from searching for a coffee cup to looking for a face in a crowd. However, some searches are more important than others. As a society, we have created many artificial but critically important search tasks, such as airport baggage screening and routine mammography. Many of these tasks are complicated and currently performed imperfectly. We eagerly await development of new ways to improve human performance on such tasks or the invention of machines that could take over or assist with them. Understanding how biological systems do so well at performing a range of search tasks should help us to improve the outcome of those artificial search tasks on which we, quite literally, stake our lives.

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CELL BIOLOGY

A Fishing Buddy for Hypothesis Generators

Roger Brent and Larry Lok

In the last half of the 20th century, the dominant experimental modality in biology was hypothesis-directed research. Of course, biology has a proud tradition of important insights arising from undirected poking around and following hunches. However, until genomic biology made undirected fishing for information more respectable (*1*), the most common response to requests for money for such projects was dismissal with the term "fishing expedition." The study by Sachs *et al*. (*2*) on page 523 of this issue suggests it may be time to reexamine this prejudice.

In their study, Sachs, Nolan, Lauffenburger, and their co-workers outline what may be a powerful new way to fish. They combine measurements of different signal transduction proteins in large numbers of individual human $CD4^+$ T lymphocytes and computational frameworks called Bayesian networks with experimental perturbations that are close to hypothesis-free. These investigators not only regenerated known causal relationships among the signaling proteins but also predicted new connections that they verified by targeted testing. For example, they predicted interpathway cross-talk between the Erk1 and Akt kinases. Their approach suggests a way that "fishing expeditions" and investigator reasoning might supplement one another, generating testable assertions about chains of causation and action in biological systems.

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Consider how biologists identify candidate gene products and suggest how these might act in chains of cause and effect. With "genomic" methods, two grounds for identification correspond to logical fallacies: "guilt by association" (for example, these two proteins touch one another, and might cooperate in the same cellular process) and "post hoc ergo propter hoc" (for example, this gene regulator is expressed before this transcript appears and therefore might regulate production of that transcript) (*3*). In contemporary biology, such observations are supplemented by additional information including DNA sequences, which can suggest direction of action from the biochemical function of the encoded proteins and similarities to known pathways in other organisms. Such inferences are complemented by experimental methods that more rigorously establish flows of action and consequence. These approaches go back to the work of Ephrussi and Beadle in the 1930s. These experimenters isolated fruit flies with mutations in genes for eye color. They then showed that an eye disk containing the *cinnabar* (*cn*) gene product but lacking the *vermillion* (*vm*) gene product produced a wild-type eye when transplanted into flies that lacked *cinnabar* but contained *vermillion*; they also showed that the converse was not true (*4*, *5*) (see the top figure). This phenomenon, called "epistasis," established both that *cn* and *vm* act in an eye-color "pathway" and that the wild-type *vm* gene product must act first in order for the wild-type *cn* gene product to exert its effect.