contained both GABA and glycine, and the relative density of immunostaining for each transmitter changed with development, resulting in greater levels of glycine detected in more mature axons.

The simplest explanation for these results is that single presynaptic cells shift from releasing GABA to glycine during development. A developmental change in the response to transmitter may occur not just through a shift in transmitter type; shifts in the relative expression of GABA and glycine receptors could also contribute. The authors partially controlled for this possibility by applying exogenous GABA or glycine to activate non-synaptic receptors on the LSO cell. They found that the response amplitude was stable over time, suggesting that developmental changes in receptor-mediated current did not explain the shift in mPSC shape. However, the specific receptors (GABA and/or glycine) expressed at a single synapse may also complicate the interpretation of the mPSC. The subtypes of receptors do shift during development, in part evidenced by the shortening of the decay time of both GABA- and glycine-mediated events, and an increase in peak amplitude of the glycine-mediated mPSC. Immunostaining for the GABA synthetic enzyme glutamate decarboxylase, and the bicuculline-sensitive current evoked by electrical stimulation of afferent axons, both decrease[2] during development, further evidence for a shift away from GABA-mediated activity.

Furthermore, as any axon in synaptic contact with the recorded cell could release GABA or glycine, a less likely possibility remains that there is a shift in the population of presynaptic axons from those that release more GABA to those that release more glycine. As both GABA and glycine are carried from the cytoplasm into synaptic vesicles by the same inhibitory amino acid transporter[8], if both are synthesized in the same neuron, it is difficult to see how some vesicles could contain only GABA and others only glycine in the same presynaptic axon. Thus, the three mPSC decay shapes reported in the Nabekura *et al.* study could represent three phenotypes of presynaptic axon terminals: GABA, glycine, and GABA + glycine (**Fig. 1**). In addition to axons that will continue to release one of the three combinations, it is also possible that some axons could be at the beginning of their developmental switch (primarily GABA), whereas others could be at the end of it (primarily glycine). The ideal preparation to confirm these results would be one where a single axon could be identified and studied over time.

Why do presumptive MNTB axon terminals in the LSO change from releasing GABA to releasing glycine? It seems odd that a cell might benefit functionally from a shift from one neurotransmitter to another, when both appear to have similar excitatory or inhibitory effects. During development, when both GABA and glycine exert excitatory actions, the slower decay of GABA-mediated events may enhance the duration of postsynaptic depolarization and increase cytoplasmic calcium levels—exactly what a developing neuron may need when it is stabilizing or refining synapses[9,10]. In contrast, a mature functional auditory system must track and orient to high-frequency environmental sounds based on minor amplitude differences between the two ears. Such processing might benefit from rapid glycine-mediated inhibitory events that are essential in the fine-tuning of sound localization. Indeed, we may not have fared so well with the hypothetical rattlesnake if the slower time course of GABA-mediated inhibition during development had not shifted to glycine and its more rapid actions in the LSO. Another possible difference between GABA and glycine function is that only the former will activate the metabotropic $GABA_B$ receptor, which might be involved in presynaptic inhibition during axonal development[1,2].

Nabekura *et al.* provide converging lines of evidence that single neurons and single synaptic vesicles of the CNS shift from GABA to glycine neurotransmission. Similar coexpression of GABA and glycine exists in other regions[11,12], and peripheral neurons can shift their transmitter phenotype from norepinephrine to acetylcholine, a change that may depend on feedback from the postsynaptic target[13]. This leaves open the question regarding what mechanisms drive the projections to the LSO to make their switch in transmitter. Nonetheless, this paper highlights the general theme that inhibitory pathways may need transient excitation, potentially enhanced by the long decay times associated with GABA, to fine-tune developing synapses.

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Adaptation and attentional selection

Geoffrey M Boynton

Attention improves perception, presumably by influencing neural responses. In this issue, an fMRI study shows that paying attention to an object might enhance perception by increasing the selectivity of neuronal subpopulations in higher visual areas.

Over 100 years of psychological research shows that directing attention to an object improves a person's ability to make discriminations about it. In both monkeys and humans, we also know that attention can change the stimulus-driven response to an object in the visual cortex. How does attention modify the neuronal representation of an object so that it leads to better perception? In this issue, Murray and Wojciulik[1] show evidence that attention narrows the orientation selectivity of neurons in the human lateral occipital cortex (LOC), which is believed to be the human homolog of the object-selective area IT in monkeys.

Some neurophysiological studies suggest that attention simply increases neuronal responses to an attended visual stimulus by a multiplicative factor[2,3]. A related possibility is that attention increases the effective strength of an attended stimulus—similar to increasing the object's contrast[4]. Both of

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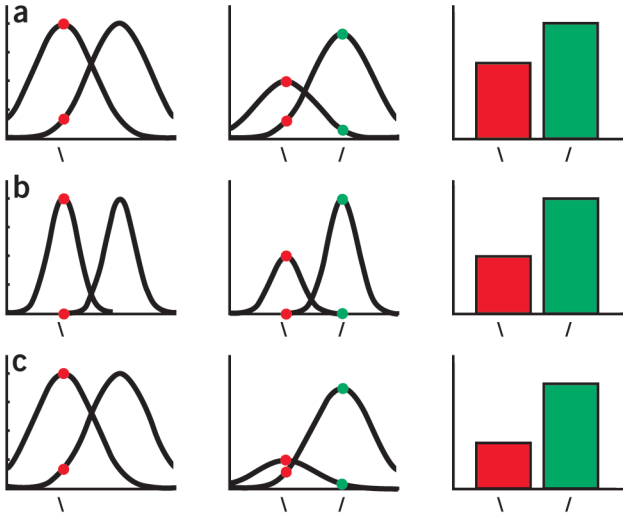

Figure 1 Using fMRI adaptation to study mechanisms of attention. (**a**) Left, consider a population of two neurons with differing orientation selectivity (although this simulation generalizes to a large population of neurons). Red circles show how the left-hand neuron responds more to an adapting stimulus than the right-hand neuron. Middle, if adaptation is proportional to the size of the response, sensitivity is reduced. The circles show the responses to a second stimulus that has the same orientation (red) and a different orientation (green) as the adapting stimulus. If the population-based fMRI response is the sum of the responses of the two neurons, the bar graph (right) shows how, after adaptation, the fMRI response depends on the orientation of a second stimulus. (**b**) If attention narrows orientation selectivity, then the adapting stimulus affects only the sensitivity of the left-hand neuron. The population response is then more affected by the orientation of the second stimulus. (**c**) If attention increases adaptability, the effect of orientation on the population response is much like changing orientation selectivity.

these effects could increase the reliability of the attended object's neuronal representation if the firing rates of neurons simply increase faster than the variability in their firing.

A more sophisticated hypothesis, though one not entirely supported by the neurophysiological literature, is that attention increases the selectivity of neurons that respond to the stimulus by narrowing their selectivity along one or more stimulus dimensions[5–7]. For example, in the inferior temporal (IT) cortex in monkeys, neurons are responsive to objects, and are sensitive to the spatial orientation of the object. Narrowing the range of preferred orientations with attention would make these neurons more sensitive to subtle changes in object orientation, which would lead to better orientation discrimination. A similar mechanism has been shown for perceptual learning in the primary visual cortex (V1) of monkeys after repeated training on an orientation discrimination task[8].

Murray and Wojciulik[1] used a new technique called 'fMRI adaptation'[9] to measure tuning properties of subpopulations of neurons (**Fig. 1a**). Functional MRI responses in higher visual areas such as the LOC decrease with repeated presentation of the same stimulus[10,11], possibly because the underlying neuronal responses adapt[12,13]. With fMRI adaptation, there is a smaller response to the second of a pair of successively presented stimuli if the two stimuli are represented by the same population of neurons. The first stimulus adapts the population, leading to a smaller response to the second stimulus. If the two stimuli differ so that they excite separate populations of neurons, then the fMRI signal, which presumably represents an overall population response, will show less adaptation.

In one condition in the present study[1], subjects ignored successive presentations of two objects that had either the same or different orientation and instead performed a color-discrimination task at the point of fixation. The fMRI response in the LOC to the two objects increased as the difference between their orientations increased. This release in adaptation of the fMRI response with orientation shows that the underlying neuronal population in LOC is sensitive to the orientation of an object, even without attention.

Most importantly, the authors found an even sharper release from adaptation with difference in object orientation when subjects made judgments about, and therefore focused attention on, the orientation of the objects. Murray and Wojciulik conclude that attention to the objects narrowed the orientation tuning of neurons in the LOC (**Fig. 1b**). They also acknowledge an alternate explanation: attention could increase the response, and therefore the adaptation, among a more selective subset of neurons.

Is adaptation a tool for studying attention, or is adaptation itself an attentional mechanism? A release from adaptation in the fMRI response in a given brain area may be caused by stimulus selectivity at an earlier stage of processing. For example, the same object presented in two different orientations should excite two different subpopulations within V1. The selectivity for orientation in the LOC could therefore simply reflect the orientation-selective properties of V1 neurons. However, Murray and Wojciulik found no increase in selectivity in V1 or V2 with attention, for the simple but surprising reason that no orientation-specific adaptation occurred there at all.

Recently, my laboratory looked for short-term adaptation of the fMRI response in early visual areas using simple oriented gratings, and also failed to find orientation-specific adaptation[14]. A strong interpretation of our adaptation results, and of Murray and Wojciulik's, is that human primary visual cortex does not contain orientation-tuned neurons. This is unlikely. Indeed, with a long enough adapting stimulus, fMRI responses in V1 do show orientation-specific tuning[15]. A more likely explanation is that there is an increase in the adaptability of neurons along the hierarchy of visual areas. In our study, we did find significant orientation-specific adaptation effects in higher visual areas (V3 and V4)[14].

It could be that higher visual areas, like the LOC, adapt to unchanging visual stimuli so that the visual system remains primed to increase its response to novel inputs. Thus, adaptation, like attention, could be a mechanism for increasing the brain's sensitivity to changes in a visual stimulus. Adaptation may be weaker in early visual areas so that they can maintain a veridical representation of the world, leaving to higher visual areas the job of representing only what is behaviorally relevant.

Perhaps attention does not change the selectivity of neurons, but rather increases the adaptability of neurons (**Fig. 1c**). Such a simple mechanism would greatly increase the sensitivity of a population of neurons to detect changes in an attended stimulus, with greatest recovery from adaptation in neurons that are most closely tuned to the stimulus attribute that changed.

It makes ecological sense for attention to regulate adaptation. For example, while scanning a new scene, before any particular object has captured attention, the most important task may be simply to detect potentially important stimuli. Then, once attention is directed to an object, adaptation can enhance our ability to determine whether and how that object changes. It also makes sense that adaptability should increase along the hierar-

chy of visual processing. Adapting rapidly and strongly to low-level features such as spatial frequency or orientation too early in the processing stream would filter out important information, as many different objects share common low-level features.

Increased adaptation with attention is easily implemented in the brain. Qualitatively, the results from Murray and Wojciulik[8] might be expected even with a simple multiplicative gain mechanism of attention. This is because the enhancement of a neuronal response should also cause greater adaptation of those neurons that are selective to the adapting stimulus. Murray and Wojciulik acknowledge this, but argue that under reasonable assumptions, their effects are greater than would be expected without additional sharpening of selectivity with attention. But perhaps this simple explanation should not be dismissed, because it demonstrates how a simple gain change with attention can result in more adaptation and thus greater sensitivity to changes in an attended stimulus.

Clearly the mechanisms serving both attention and adaptation are complex. But from the results of Murray and Wojciulik, it does appear that attention leads to a larger effect of orientation on the population response of neurons in area LOC. It remains to be seen whether attention causes a sharpening of the tuning of underlying neurons, an enhancement of the response of a more selective subset of neurons, changes in the adaptability of neurons, or a combination thereof. Future single-unit neurophysiological studies should help to distinguish among these hypotheses.

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How does practice makes perfect?

John Jonides

Studies of nonhuman animals have taught us a great deal about how the brain changes during learning. An imaging study in this issue investigates how behavioral strategies interact with brain activation in humans during learning of a working memory task.

What happens when we learn? One possibility is that we acquire greater skill at applying our initial strategy to the problem at hand, making it more efficient. Another possibility is that we acquire a new, more efficient strategy. In this issue, Olesen, Westerberg and Klingberg[1] investigate the brain mechanisms that accompany learning a simple task. They find a set of brain regions that increase activation with practice and another set of regions that decrease activation. These results may bear on which of the two learning possibilities occurs in this case.

To see how learning might proceed along two different paths, consider a simple example. Suppose you practice the mental arithmetic problem of multiplying two-digit numbers, for example, 23×18. As you work on more of these problems, your time to solve them decreases and your accuracy increases. On the one hand, with practice you may acquire greater skill at applying elementary arithmetic facts to each problem because you can retrieve them from memory faster[2]. Thus, if you continue to use the strategy you learned in school, you might remember more quickly that $3 \times 8 = 24$. On the other hand, practice might lead you to a new and faster strategy to apply to the problem. For example, you might come to realize that the problem can be solved by multiplying 20×18 followed by 3×18, and then adding these two sums. We can often characterize learning as a function of either increased automaticity in the application of one strategy or development of some new strategy.

These alternative accounts can be difficult to distinguish using behavioral data alone. However, brain imaging offers the opportunity to see whether patterns of brain activation change as a function of learning, thereby suggesting the acquisition of new strategies. Olesen and colleagues[1] took advantage of this opportunity. They trained participants in tasks that required working memory, the system used to store small amounts of information for several seconds in the service of more complex tasks such as mental arithmetic. In one task (**Fig. 1**), participants had to memorize a series of spatial locations on a screen so that they could reproduce this series in the correct order. 0A sequence of 4×4 target matrices was presented, each blank except for one cell colored in red. After the last target matrix, participants saw a sequence of blank matrices, and they had to mark one cell in each to reproduce the sequence of locations that had been marked in the target matrices. Participants were trained on this task (and two others) for 18 days, during which they improved both their accuracy and speed. Before, during and after the training, they were scanned using functional MRI to assess the effect of training on brain activations.

Let's examine some predictions before considering the results. On the one hand, if learning results from a change in strategy, then one might expect that the brain regions activated early in training might be different from those activated later in training—assuming that the new strategy and the old strategy involve some different brain regions. For example, in the mental arithmetic example above, the canonical strategy of working with one digit at a time may rely on retrieval of arithmetic facts from memory, whereas the strategy that treats each number as a whole may require more complex calculation. If memory retrieval and calculation are mediated by different mechanisms, this would

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