seeking behavior, is important in the neural plasticity underlying the behavioral learning[9]. Dopamine is a transmitter in large neurons in substantia nigra pars compacta that respond to reward or to salient cues predicting reward. It is important in learning to associate cues with predicted reward[10]. Both regions studied in this report are rich in dopamine. After dopamine in the caudate nucleus is disturbed, monkeys have difficulty making saccades toward the contralateral side of the body; thus, dopamine is important in the caudate nucleus for executing and probably for learning this behavior. However, whether dopamine is needed for the learning of the associations seen here in the prefrontal cortex is not yet known.

Because of the timing differences in the activity of these two brain regions, it is unlikely that either of them simply drives the other in learning or activity. Thus, the new findings require a rethinking of how these brain regions might interact. The missing time makes it appealing to think these two regions complement rather than drive one another. If that were the case, we could imagine that in disorders characterized by failure to control habitual activity, such as drug abuse, in which stimuli become uncontrollably compelling, the normal balance in strength or timing between the basal ganglia and the cortex may be disrupted. If the caudate nucleus becomes overexcitable, activation of stimulus-elicited habitual behavior might no longer be controllable by the prefrontal cortex, which would normally trigger the behavior. Thus, the behavior would occur without needing activation from the prefrontal cortex. In any case, these straightforward latency measurements suggest complexity in processing predictive stimuli that had not been guessed previously.

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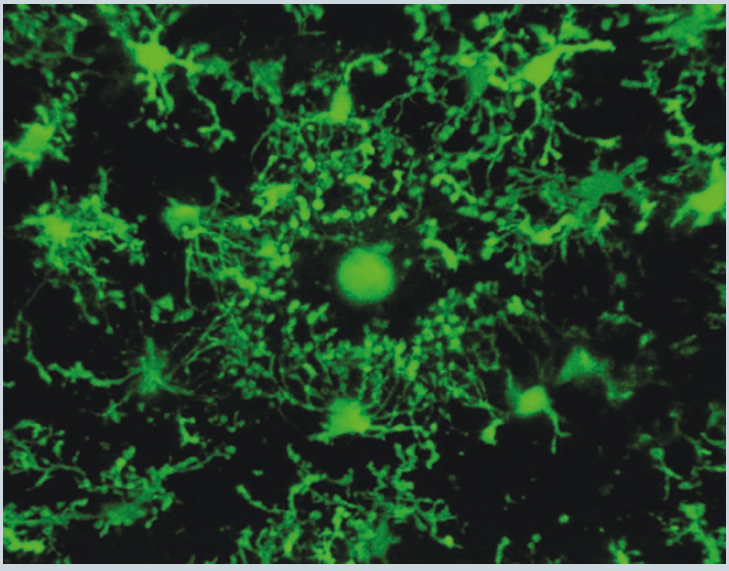
Brain's guard cells show their agility

Microglia, the principal immune cells of the brain, are thought to be the nervous system's roaming cleanup crew. When activated by injury or insult (including lesions, stroke, neurodegenerative disorders and tumors), microglia surround dead cells and clear cellular debris from the area. However, most of this work was done *in vitro* using brain slices, and as the slicing procedure inherently induces some injury, it remained unclear how microglia behave *in vivo.*

In a technical *tour de force*, two recent reports by Fritjof Helmchen and colleagues (published online in Science on 14 April) and Wen-Biao Gan (pp 752-758, this issue) describe the imaging of microglia in intact mouse cortex. Both groups took advantage of transgenic mice in which all the microglia were fluorescently labeled and used transcranial two-photon microcsopy to image the behavior of these cells through the thinned skull. Microglial processes were highly dynamic in the intact brain. Although the somata of microglial cells remained morphologically stable over hours, higher-order branches showed rapid extension and retraction over intervals of seconds to minutes. This high resting mobility may enable the microglia to act as vigilant sentries, constantly screening the surrounding parenchyma.



The microglia also responded rapidly to focal brain injury in both studies. Time-lapse imaging showed that after a small laser ablation, microglia near the site of injury responded within the first minute to extend their processes toward the damaged site. Gan and colleagues report that within 30 minutes after the laser-induced injury, the processes of nearby cells reached the damaged site and appeared to fuse together, forming a spherical containment around it and establishing a potential barrier between the healthy and injured tissue, as shown in the photo. Microglia responded similarly to mechanical injury.

What signals mediate this rapid microglial response? In culture, ATP signaling induces microglial migration. Gan and colleagues extend this work to the *in vivo* situation, and show that extracellular ATP and activation of P2Y receptors on microglia are necessary for the rapid microglial response toward the injury site. Simply inserting an electrode containing ATP allowed the authors to mimic—in time, range and kinetics—the rapid response of microglial processes observed following laser ablation. Furthermore, ATP-induced ATP release was essential for this response; when the authors applied apyrase (which degrades endogenous ATP in the extracellular space), and then released non-hydrolyzable ATP from a microelectrode, they observed no such rapid microglial response. Applying connexin channel inhibitors before laser ablation also inhibited the microglial response toward the laser ablation site. Interestingly, baseline motility of microglial processes in the intact brain seems to be modulated by the same ATP signaling mechanisms that mediate injury-induced responses, because apyrase and connexin channel inhibitors also significantly slowed microglial baseline dynamics.

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