

MAY 19, 2005

Brain May Be Less Plastic Than Hoped

The visual cortex of the adult primate brain displays less flexibility in response to retinal injury than previously thought, according to a new study published in the May 19, 2005, issue of the journal *Nature*. This may have implications for other regions of the brain, and the approach the investigators used may be a key to developing successful neurological interventions for stroke patients in the future.

Stelios M. Smirnakis, a Howard Hughes Medical Institute physician-postdoctoral fellow in Nikos K. Logothetis' group at the Max Planck Institute for Biological Cybernetics, used functional magnetic resonance imaging (fMRI) to monitor cortical activity for seven and one-half months after injury to the retina of adult monkeys. They found limited reorganization in the primary visual cortex.

"It's a powerful way to stimulate and study reorganization that may turn out to be beneficial in the future."

— Stelios M. Smirnakis

Their results contradict previous thinking. In a "News and Views" commentary published in the same issue of *Nature*, Martin I. Sereno, a neuroscientist at the University of California, San Diego, says the latest data indicate that adult brains may be less plastic than scientists had hoped.

In children, the brain's ability to compensate for injuries is well known. Children with severe epilepsy who lose an entire hemisphere during surgery can regain motor control on the affected side of their body and go on to develop normal language skills. But in adults, the case for brain plasticity has been less clear.

A series of studies in the 1980s and 1990s seemed to show that, in adult animals, neurons "filled in" blank spots in the motor and visual cortex after these areas fell silent from lack of sensory input due to injury. This led to speculation that adult brains could compensate for permanent damage to the eyes, ears, skin, or even to itself. In the case of damage to the retina, Smirnakis said, "the predominant-but by no means universal-view was that

significant reorganization occurred as early as it does in the primary visual cortex.”

But the latest imaging research from his team shows that, in monkeys, this is not the case. “We asked: Can visually driven activity in the region of the primary visual cortex that corresponds to the retinal injury recover to pre-lesional levels in the months following the lesion?” said Smirnakis. “The answer is, in that time interval the primary visual cortex did not achieve anything like normal responsiveness.”

To arrive at this conclusion, Smirnakis and his group first photocoagulated the retinas of four monkeys with a laser, creating small blind spots on the same sides of the field of vision. The retina sends signals that the brain interprets as light, color, or objects. Each section of the retina corresponds to a specific location in the primary visual cortex. Without any visual signal to interpret, the cortical area corresponding to each monkey's blind spot fell silent, generating no activity.

The team measured the size and shape of each of these cortical quiet spots. They placed the lightly anesthetized monkeys into a fMRI machine, which measures blood flow, and hence, brain activity. With the monkey's eyes held open, the team focused various grid and circle patterns on the animal's retina, centered on the fovea—a small depression in the retina where vision is most acute—and covering the blind spot. They made baseline measurements of the cortical quiet zone two to three hours after the laser surgery and compared them to new readings taken every few weeks for up to seven and a half months.

“If the visual cortex of the monkeys did reorganize, it would happen as they were behaving normally in their cages in between scans,” said Smirnakis. “And then, when we brought them back to the scanner, the region of their cortex corresponding to the blind spot would have shrunk.” Instead, though, the silent region remained the same size each time. The neurons surrounding it did not reach out to fill it in.

Because fMRI data is subject to interpretation, the researchers checked their results with a second method. They placed tiny electrodes on the cortex and measured electrical activity in the visual cortex; mapping virtually the same cortical quiet zones. The results confirmed the fMRI readings.

Smirnakis said it is possible that the visual cortex could reorganize before or after the two- hour to seven-month time frame of his study. Other research has suggested that the visual cortex adapts somewhat immediately after injury. “And it is possible that, years after injury, the visual cortex could begin to reorganize,” he said.

“Since there is similar organization across the neocortex of the brain, we could speculate that functional new connections mediating reorganization may also be difficult to form elsewhere,” Smirnakis added. “Reorganization in these areas might then depend more on the modification of existing patterns of connectivity, be it subcortical, feedback, or other broad

area-to-area connections. Of course, that is highly speculative. It is also conceivable—although in our opinion less likely—that in neocortical areas other than the primary visual cortex, new functional connections may have an easier time forming, and axonal sprouting may occur over longer distances.”

The study also establishes fMRI as a valid method to measure reorganization in the monkey brain, Smirnakis added. Similar studies could one day show scientists how to help the brain to recover from injuries. “In humans, studying brain reorganization is difficult. Cortical injuries are not happening in a controlled fashion, and resulting data consequently are difficult to interpret,” he said. “But in the macaque, you can design lesions and test pharmaceuticals to sort out what kind of reorganization the brain is capable of after, say, a stroke. It’s a powerful way to stimulate and study reorganization that may turn out to be beneficial in the future.”