FAMOUS MONKEYS PROVIDE SURPRISING RESULTS

New data from macaques confiscated from a Silver Spring researcher a decade ago challenge neuroscience dogma

EXPERIMENTS that are among the most controversial ever performed on research animals have yielded results that challenge neuroscience dogma about how much "rewiring" goes on in the adult brain after nervous-system injury. But even before these findings hit the scientific literature (this week's Science, p. 1857), animal rights activists are calling them nothing more than a politically driven effort to justify scientifically bankrupt research.

At issue once again are the Silver Spring monkeys. These 16 crab-eating macaque monkeys and one rhesus monkey gained fame 10 years ago when Alex Pacheco, then a lab technician and now head of People for the Ethical Treatment of Animals (PETA) , accused his boss, Edward Taub of the Institute for Behavioral Research, of inflicting unnecessary pain on the monkeys and failing to provide them with adequate food and veterinary care. He convinced the local police to confiscate the animals, and since then, PETA and other animal rights groups have been locked in a legal struggle over who should have the ultimate say about the animals' fare.

"There's an incredible irony here," says Robert H. Wurtz, a neuroscientist at the National Eye Institute and current president of the Society for Neuroscience. "The animal rights activists are keeping these monkeys alive. It's the scientists who wanted to put them to sleep a decade ago. Since the animal rights activists have kept them alive, they're now, as it's turning out, incredibly valuable animals."

The macaques' value to science arises indirectly out of experiments conducted in the late 1970's by Taub. He wanted to determine whether the animals could be trained to use an arm even when the nerve leading from the arm to the brain had been severed. Taub also wanted to probe for new nerve connections in the spinal cord that might accompany the behavioural improvements.

When the monkeys were confiscated in 1981, that research was put on hold. Then, in 1987, a group of scientists led by Mortimer Mishkin, a neuroscientist at the National Institute of Mental Health (NIMH), suggested that the monkeys provided a unique opportunity to look at a different question: what happens to portions of the brain deprived of sensory input over a long period of time. The researchers secured permission to go forward with this inquiry even as the custody battles raged, and their results, as explained in this week's paper, proved surprising.

Although Taub had thought the reorganization might take place in the spinal cord, more recent work by Michael Merzenich of the University of California at San Francisco and John H. Kaas of Vanderbilt University suggested there might be changes in the brain as well. Sensory nerve impulses from various parts of the body go to a brain structure called the somatosensory cortex; a particular part of that

structure responds to each portion of the body. If the brain suddenly loses sensory input from some part of the body – the thumb, for example – Merzenich showed that there is a tendency for nerve impulses from a neighbouring part of the body (a finger, say) to encroach on the area dedicated to the thumb.

Merzenich's work showed only a small amount of encroachment might be if the input from an entire limb was cut off.

When they probed the area of the somato-sensory cortex formely dedicated to the arm, the researchers found that now they could find responses to stimulation of nerves as far away as the face. And the reorganization extended over a brain area 10 to 14 millimeters long, an order of magnitude greater than what Merzenich had found.

These results challenge a long-held dogma in brain research. Nobel Prize-winning work by David Hubel and Torsten Wiesel in the early 1960s had shown that, for the visual system, there is a critical period shortly after an animal is born where changes in a sensory system – in this case, input from the eyes – can result in a "rewiring" of the brain connections. Once the animals pass that critical period, the connections are "hardwired," that is, unable to change. According to Marigonka Sur, a neuroscientist at the Massachusetts Institute of Technology, the plasticity newly demonstrated by Mishikin and his colleagues may alter researchers' opinions about when these changes can take place.

Tim P. Pons, Mishikin's colleague at NIMH, says the question to ask now is whether the reorganization starts with the cortex, or whether, as is likely , it is preceded by changes in an intermediate structure between the cortex and the spinal cord. And, he adds, "If we know the mechanism and rules by which this stuff is operating, then there's the possibility that we can harness this type of reorganizational capacity for therapeutic purposes."

Animal rights activists remain sceptical, to say the least. "They have to publish something that wows the scientific community," says physician Neal Barnard, president of the Physicians Committee for Responsible Medicine, a group that has sought to block experiments on the monkeys. Barnard adds: "Had this been done on anything other than celebrity animals, I doubt that *Science* would have published this." But *Science* editor Daniel E. Koshland denies that the decision to publish the Pons paper was motivated by political considerations; the Mishikin paper, he says, went through the ordinary peer review process.

And what of the last two monkeys still available for research, now being kept at the Delta Regional Primate Center new New Orleans? The U.S: Supreme Court has cleared the way for a Louisiana state court to hear arguments about why PETA should be granted custodial rights to them. And Pons and Edward Jones, a neuroanatomist at the University of California at Irvine, have continued to work with the one remaining macaque. After becoming political celebrities, the monkeys may yet become famous for the research these new findings will generate. *Joseph Palca*

MASSIVE CORTICAL REORGANIZATION AFTER SENSORY DEAFFERENTATION IN ADULT MACAQUES

Tim P.Pons, Preston E. Garraghty, Alexander K. Ommaya, Jon H. Kaas, Edward Taub, Mortimer Mishkin

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After limited sensory deafferentations in adult primates, somatosensory cortical reorganize over a distance of 1 to 2 millimeters mediolaterally, that is, in the dime…..along which different body parts are represented. This amount of reorganisation considered to be an upper limit imposed by the size of the projection zone individual thalamocortical axons, which typically also extend a mediolateral dista…..1 to 2 millimeters. However, afterextensive long-term deafferentations in primates, changes in cortical maps were found to be an order of ……. them those previously described. These results show the need for a re……of the upper limit of cortical reorganization in adult primates and the ……..responsible for it.

MERZENICH AND HIS COLLEAGUES demonstrated that primary cortical sensory maps in adult animals, like those in infant animals, are capable of reorganization after various peripheral sensory perturbations. Yet, compared to the massive functional changes that have been found in neonates, in which entire cortical maps may be reorganized, the changes reported in adults have been relatively small, with an upper limit of 1 to 2 mm along the cortical surface. Although the finding of any plasticity in primary sensory maps of adult animals was unexpected, the limited extent of the changes suggested they were confined to the projection ones of single thalamocortical axons. Both the limits of reorganization and the mechanisms responsible must now be reconsidered because of new evidence in adult macaques showing reorganization in the cortex at least an order of magnitude greater than that reported ……..

Tactually elicited neuronal activity recorded in area SI of four cynons monkeys (Macaca f….icularis) that received deafferentations of an upper three unilateral and one bilateral, m… 12 years before the recording sessions procedures were carried out in accord with NIH guidelines on the care and laboratory animals. Electrode p..tions were placed approximately 0,75 … apart across the mediolateral extent … cortical region that had been deprived normal input and less densely in parts cortex containing maps of body parts were unaffected by the deafferentation procedure. We typically recorded activities each 300- üm advance of the electrode penetration. Normally the cortical representation body parts are organized into highly graphic maps. In caca… the upper lim representation in SI is a.. bordered by the representation of the medially and the face laterally. In region of the border of the

face and representations, which is located opp…. Te trip of the intraparietal sulcus, the map contains the representation of the …..

…and lower jaw and the hand map contains the representation of the thumb. The entire upper-limb representation extends lateromedially for 10 to 14mm, from the lateral tip of the intraparietal sulcus, where the trunk representation is normally found. The area of the cortex deprived of its normal input by the deafferentation procedure, which we refer to as the deafferented zone, included the SI maps of the fingers, palm, remaining upper limb, neck and occiput. Our recordings unexpectedly revealed that this entire zone responded to stimulation of the face. In the animal illustrated in Fig. 2, we were able to obtain vigorous neuronal responses to light stimulation of the face in 124 recording sites distributed throughout the deafferented zone. Furthermore, none of the sites we tested was unresponsive.

Virtually identical findings were obtained in the three other animals. All 320 sites tested in the deafferented zone in the four animals were activated by face stimulation. An additional 90 and 51 recording sites located lateral and medial, respectively, to the deafferented zone revealed the expected normal topography of face and trunk. Thus, in all cases, the medial border of the expanded face representation abutted the normal representation of the trunk. There was no apparent elevation of response thresholds at any of the recording sites across the new face map as compared to those across the normal face map; in both, a slight deflection of facial hairs was sufficient to obtain a vigorous neuronal response.
Not all of the face, however, was represented in the reorganized region; rather, stimulation of only a relatively small portion of the face, from the chin to the lower jaw, was found to activate neurons in this zone. At the same time, the pattern of reorganization in this new part of the face map was not random but highly systematic. As in normal face maps, the midline of the face, in this case the chin, was represented caudally in area 3b (that is, near the border of areas 1 and 3b), whereas progressively more lateral parts of the face, in this case the lateral parts of the lower jaw, were represented in progressively more rostral parts of area 3b (that is, toward the border of areas 3b and 3a). Normally, the representation of the chin and lower jaw is located immediately adjacent to the hand representation. Consequently, it appeared although each point on the normal face map along the original border of the hand and face representations had been stretched medially into a line approximately 10 to 14 mm long, the length of the deafferented zone. This resulted in the apparent stretching of the entire chin and lower jaw map (at least in areas 3b and 1) onto a cortical sheet 10 to 14mm long, until the expanded face representation met the normal trunk map. These findings extend the previously proposed upper limit for reorganization in adult primates by an order of magnitude and leave open the possibility that the limit is even greater.

What mechanisms could account for such massive cortical reorganization in mature animals? In earlier studies on the effects of peripheral deafferentations in adult primates, the deafferentations were relatively restricted, involving small parts of the hand or visual field, and the deafferented zone came to represent the sensory surfaces mapped along the zone's lateral and medial edges, with each of these two representations expanding toward the deafferented zone's center. Furthermore, the occupation of the deafferented zone by these new inputs was often incomplete, with small islands of tissue remaining unresponsive to stimulation of any body part. Because of those features and the spatial limit of reorganization, which was generally in the range of 1 go 2 mm, it was reasonable to relate the filling in of the map to the mediolateral arborisation of single thalamocortical axons, which is also in the range of 1 to 2 mm. Because of the spatial extent of such arborisation, neurons at a given cortical site could receive overlapping thalamic projections from two populations of axons, one representing a dominant skin region and the other an adjacent, nondominant skin region; if so, then loss of the former would allow neuronal activation by the later, either immediately or after a delay. Although such a mechanism may suffice for the limited changes described previously, it is insufficient to account for the extensive reorganization reported here.

An alternative possibility is that pre-existing inputs from face representations in cortical areas outside SI came to activate the deafferented zone. Such a possibility seems remote, however, because all connections of these areas with SI are between somatotopically matched representations, a circumstance that should impose the same constraints on reorganization as the smatotopically matched thalamocortical projections. If the reorganization we found took place exclusively at the cortical level, then the only alternative to the immediate or delayed unmasking of pre-existing thalamocortical or corticocortical projections would be the sprouting of new projections across the deafferented zone. Yet there is no evidence to date of even limited sprouting of sensory terminals in the neocortex after peripheral nervous system injury in adult mammals.

These considerations lead us to propose that much of the functional reorganization we observed was a reflection of changes that had taken place subcortically and were then simply relayed to the cortex. Body part maps are represented within a much smaller neural space in the brain stern than in the thalamus, and in the thalamus than in the cortex, reflecting the extensive divergence that occurs along pathways connecting the brainstem, thalamus, and cortex; as a result, reorganization over a relatively small distance at the brain stem or thalamic levels would be reflected as much larger changes at the cortical level. Thus, if projections to or from brain stem nuclei representing the face were to have synapsed onto all or most of the brain stem or thalamic cells that had previously represented the upper limb, then the entire upper limb representation in the cortex would likewise have come to represent the face. Furthermore, axonal sprouting after deafferentation has been reported to occur

in the spinal cord, making it more plausible that such changes could also be taking place at higher subcortical stations.

Our finding of extensive reorganization after peripheral deafferentation raises many additional questions. For example, why was the deafferented zone not occupied by an expanded trunk as well as by an expanded face representation? Did the expanded face representation mediate tactile perception, and could it serve as a substitute for the normal face representation? Was the neural activity in the expanded representation relayed to higher order cortical and subcortical stations? Answers to such questions about mechanism and function could lead to harnessing the immense reorganizational capability of the adult nervous system for therapeutic purposes.