New Maps of the Human Brain

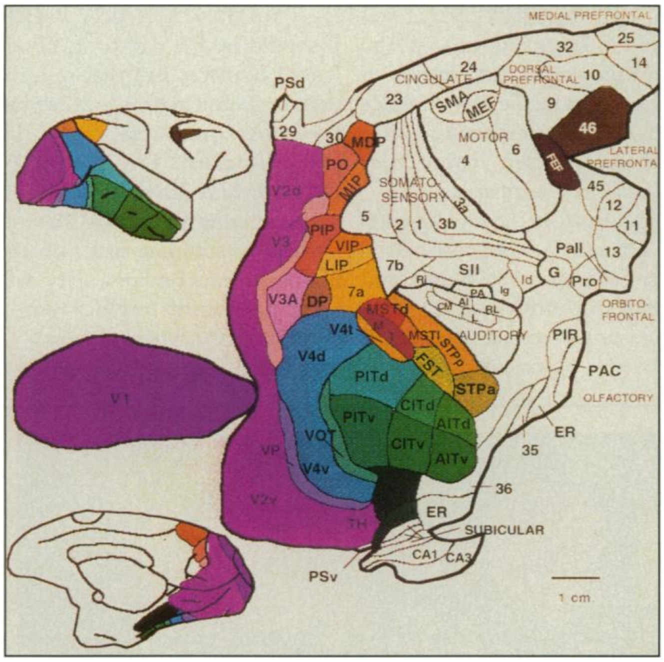
A whole generation of imaging methods are now coming of age—and will soon provide the best look yet at how structure and function match up in the human brain

THREE YEARS AGO, SEMIR ZEKI got a surprise. Zeki, a neurobiologist at University College, London, had organized a brain imaging workshop at the Neurosciences Institute in New York. He envisioned that at the workshop the participants would talk about the big picture—using imaging to understand the workings of the human brain. But it wasn't so. In fact, much of the discussion bogged down in embarrassingly simple problems such as how to hold patients' heads still when they were being scanned by positron emission tomography (PET).

How different the picture was at another workshop devoted to making images of the brain, this one held at Johns Hopkins University.* At that recent gathering, workers in the field displayed their most colorful wares: slides of the human brain at work. Using PET scanning, magnetic resonance imaging (MRI), and other methods, the slides illustrated specific brain regions lighting up as human subjects recognized words or colors, moved their arms, or concentrated on specific tasks. "Images like these would have been impossible a few years ago," says Zeki. "The technology has improved greatly. We're on the threshold of a fantastic takeoff of mapping in humans."

And, indeed, although some skepticism remains, there does seem to be a growing consensus that brain imaging is coming of age. After difficult times in the early 1980s, when the new methods were plagued by uneven application and by technical problems, imaging—particularly PET scanning—seems ready to move out of clinical settings into basic research. Largely on the basis of work in animals, much more precise correlations are being established between brain regions and specific functions. The understanding of complex processes such as language is clearly a long way off, but the mapping of simpler operations, such as vision, has moved forward very quickly.

One of the central themes of the Hopkins workshop was using what has been learned in animals to improve our understanding of the human brain. Much of what is known about brain architecture and circuitry comes from animals, which can be studied with invasive methods unacceptable in humans.



David Van Essen and Daniel Felleman

Monkey map. *The 32 areas in the cerebral cortex of the macaque that have been associated with visual processing.*

Maps of animal brains remain far more sophisticated than those of the human brain—as was shown in a workshop report by David Van Essen of the California Institute of Technology.

Van Essen displayed a computerized data base describing the arrangement of cortical areas associated with vision in the macaque—a database so complex he called it a "subway chart." Van Essen's chart reveals that researchers have identified 32 areas of the macaque's cerebral cortex associated with some aspect of vision and 305 circuits connecting those areas—far more detail than is known about the human visual system.

The current challenge, according to many at the workshop, is to find out how relevant such knowledge is for the human nervous system. "How do we extrapolate what we have learned from the monkey brain to the ten times bigger human brain?" asks Van Essen. And this is not likely to be an easy question to answer. So far, the record of correlating findings between animals and humans has been dismal. One reason is that the human brain is tremendously complex and variable.

But another, and perhaps more critical, drawback has been the limits on the techniques for getting inside the human brain. Traditional methods such as studies of brain lesions are too crude to measure the small-scale workings of the brain. Electrical recordings of neural activity in humans undergoing brain surgery are difficult to trace to specific brain regions. Furthermore, scientists can't do manipulative, ongoing studies in the living human brain, as they can in animals.

And that's where the newly refined mapping methods come in. Of these, the one that got the most discussion at the conference was PET scanning, partly because it is the only technique now capable of giving images of activity across the entire brain. Other methods, such as MRI, show structure but not activity, while others, including electroencephalography and magnetoencephalography measure neural activity in local areas only.

PET works by measuring gamma rays emitted by radioactive tracers attached to substances such as blood or glucose as they move through the target organ. The method has been used for clinical diagnosis since the early 1980s, but has faced obstacles in gaining respect as a research tool. "The trouble with PET in the past is that it's been a look-see method, with people using it as sort of a candid camera," says Dr. Guy McKhann, director of the year-old Zanvyl Krieger Mind/Brain Institute at Hopkins, where the workshop was held. "Then, they'd go back

*"Functional Mapping of the Human Brain," a workshop organized by Zanvyl Krieger Mind/Brain Institute at Johns Hopkins University and held in Baltimore on 29 and 30 June.

and figure out what kind of biological question to ask. That's changing."

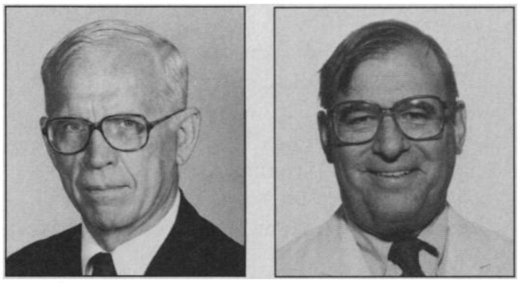
Part of the problem has been that PET doesn't necessarily provide images that correlate directly with brain activity. PET scanning can measure blood flow. But some researchers, including Vernon Mountcastle, university professor of neuroscience at Hopkins, are concerned that blood flow doesn't always represent an increase in neural activity—that it's too crude a measure for the subtle processes neurologists are trying to trace. Mountcastle is also concerned that PET just isn't fast enough—that changes in neural activity happen long before there's any change in blood flow.

Furthermore, the people who jumped on the PET bandwagon in the early '80s weren't always the most rigorous investigators. "I get discouraged when I see bad science with PET," says Marcus Raichle, a pioneer in research with PET and a professor of neurology and radiology at the Washington University Medical Center. "The key issue is to introduce rigor into these experiments, such that people not directly involved will understand that this is a legitimate scientific tool, that this isn't just game playing or picture taking."

And rigor—particularly in data analysis—is precisely the concern of the new group of reseachers who are using PET. Teams from Washington University and the MRC Cyclotron Unit at Hammersmith Hospital in London are among those who have developed new ways to analyze the data they get from PET. They are also attempting to standardize results by labeling parts of the brain with coordinates rather than names—coordinates that will enable them to adjust for the different sizes of human brains and to compare data obtained by different techniques.

These advances in method have already begun to lead to intriguing findings. The best results have been obtained in work on the relatively simple systems, such as those of the visual and motor cortex, where the underlying physiology is already fairly well understood. And this approach is the right one, says Zeki. "The last thing we want to do is concentrate on the grand design (of the brain) to bridge the gap between animal and human studies. Instead, we should concentrate on more trivial problems." His research on vision is an example. He began by tracing visual centers in the macaque, came up with a theory about how different regions of the cerebral cortex participate in vision, then tested that idea in humans by the use of PET scanning.

Yet not all of those working with PET are taking Zeki's advice and starting small. Some groups are making forays into language and perception. In pathbreaking work, a team of researchers from Washington University and Johns Hopkins, including Raichle and Peter Fox of the Mind/Brain Institute, has used PET to watch how the brain processes individual words that are spoken or read; their results suggest that separate regions of the cerebral cortex are involved in processing written and spoken language. They have also traced the response of the brain in anxiety-provoking situations such as the application of a painful electric shock—and found that during the anticipatory anxiety there were significant increases in blood flow in the temporal regions.



Left brain, right brain. *Vernon Mountcastle (left) says maps have a long way to go; Guy McKhann thinks they've come a long way already.*

Although PET scanning came in for the lion's share of attention at the workshop, it is by no means the only method contributing to better understanding of spatial relations in the brain. Several groups reported results gleaned from epileptic patients undergoing surgery. Before surgery, electrodes are implanted to determine where to operate. The electrical recording arrays offer researchers a chance to study basic brain activities and to map speech centers and other functions in alert humans for up to two weeks. A team at Hopkins that includes Barry Gordon and Ronald Lesser has refined the approach by shooting weak electrical currents through the brain to stimulate specific regions and see how they affect the patient's use of language.

One mapping method that is just beginning to emerge relies not on high-tech signals such as positrons or nuclear magnetic resonance but on visible light. Gary Blasdel at Harvard uses light to probe the striated visual cortex of monkeys, the structure in which light coming from each eye is integrated stereoscopically. The striated cortex is at the back of the brain, and it is exposed by removing part of the skull. The beam of light penetrates the outer gelatinous layer of the brain, and the pattern of reflection from the striated cortex underneath gives Blasdel a measure of fine structure— making it possible for him to "see" in real time how local regions participate in vision.

Not all of the research reported at the workshop focused on the methods of imaging themselves. Some concentrated on refining the analysis of data from those methods. One of those doing such work on MRI is Michael Gazzaniga, a Dartmouth neuroscientist. A significant limitation of MRI scans is that it remains difficult to quantify the exact size and scope of a lesion or other structure in the brain. To overcome this limitation, Gazzaniga has developed a method for making two-dimensional computerized images from the MRI sections, which improve spatial resolution.

"Ultimately, people have to get these methods right, because I'm convinced that if you want to understand the human brain, you have to study the human brain," says Gazzaniga. "There are just too many discontinuities between humans and animals."

And indeed, the thrust of the workshop lay in getting things right in human beings. In all probability that task will require combining results from a variety of different methods, including PET scanning, MRI, NMR, and the newer techniques such as the optical work pioneered by Blasdel.

"No single technique here is going to give us what we want to know," says McKhann. "It's going to be the utilization of these various techniques, understanding the limitations of each one of them, that will give us a functional map of the human brain."

McKhann is quite positive about the ground that has already been gained. "I think we are getting ideas about the function of the brain that we just couldn't approach as recently as 5 years ago, and they are giving us totally unsuspected insights," he says. Others are a bit more skeptical about whether the results achieved in mapping can yet be correlated with function.

"I think the whole field is very promising," says Mountcastle, of Hopkins. "But the problem with this technology is it's still a geographic measure. Mapping tells us where the parts are and how they are linked together, but it doesn't tell us how the works. It tells us the where, not the how."

Even the most optimistic mappers admit that they've got a long way to go before they obtain a complete picture of how brain regions brain work together when a human being uses language or experiences deep emotion. But the optimists argue that in the 3 years since Semir Zeki's surprise, they've learned far more than they ever could have learned from animals alone. "None of this was possible until recently in humans," says McKhann. "Now, we're saying that with the new technology, we can start to study the processes that are distinctly human, like language." ■ ANN GIBBONS