BRAIN MAPPING

Researchers Get a Sharper Image of the Human Brain

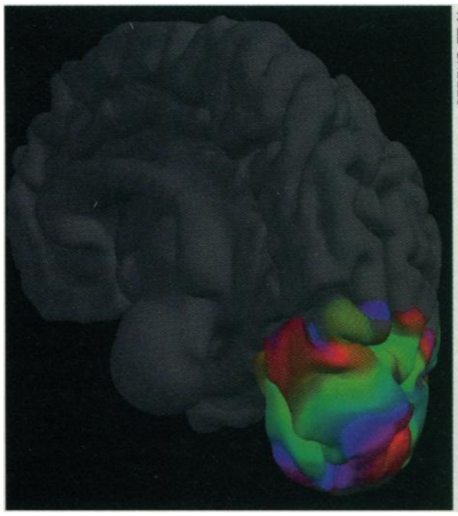
To the neuroscientist, the human brain is anything but crystal clear. Although neuroscientists are anxious to see it in action, they can't use the invasive methods that are available for other species. As a result, although researchers have been able to produce detailed maps of brain areas that perform particular functions in primates such as the macaque monkey, they haven't been able to duplicate that knowledge for the human brain.

Now, aided by a set of new brain imaging techniques, Martin Sereno and Anders Dale of the University of California, San Diego, with Roger Tootell's group at the Massachusetts General Hospital Nuclear Magnetic Resonance Center in Charlestown have, for the first time, mapped with a precision similar to that achieved in monkeys the areas of the human brain that process visual images (see p. 889). "I consider this to be a very important study," says neuroscientist David Van Essen of Washington University in St. Louis, a leader in mapping the monkey's visual cortex. "It gives us significant new information about the organization of visual areas in the human cortex."

That new information supports what some researchers have suspected for a while—that the human visual areas identified so far seem to follow the same basic organization as those of monkeys, although they differ in size and position. By clearly defining the borders of these areas, this study has opened the way for researchers to ask whether those areas whose lineage can be traced back to monkeys have, during the course of evolution, taken on new and distinctly human functions, such as those necessary for language, or whether such functions are instead handled in areas unique to human brains. The techniques, which so far have been applied only to the visual cortex, are also likely to prove useful for identifying and mapping brain areas that process other types of sensory information, such as hearing or touch.

Until now, most human brain-mapping work has used a noninvasive technique called positron emission tomography (PET), which detects the changes in blood flow that accompany increased activity in specific brain regions. By making PET images of a person's brain while that person performs a mental task, PET can locate the brain areas involved in the task. PET has helped researchers identify visual areas that respond to color or motion and those that participate in recognizing written words.

Those revelations constituted a major advance, but they were a far cry from the detailed visual maps available for animal brains. A PET study that localizes a certain visual function, such as word recognition, to a particular fold in the cerebral cortex is a bit like a spy-satellite photo that reveals a missile base on a hill. Without a detailed map that shows that hill's location relative to national borders, you still don't know who owns the missile base.



SERENO ET AL.

Lighting up. The colored areas show the human visual cortex responding to visual images. Red marks the center and also the periphery of the visual field.

Neurobiologists needed better maps that precisely locate the borders of the human visual areas. Such maps had been made of monkey brains by painstaking experiments in which researchers inserted electrodes into the monkeys' brains and recorded the activity of neurons at many locations while images were flashed before the monkeys' eyes. This, along with studies of brain structure and neural connections, enabled researchers to find more than 30 visual areas in the monkey brain, each of which analyzes information corresponding to particular features, such as shape, color, or movement, then passes the information to other areas. In many areas, each neuron responds to signals coming only from a specific part of the retina, resulting in a "retinotopic map," in which each position in the visual area represents a position in the visual world. With the detail provided by retinotopic maps, researchers were able to define the borders of the visual areas.

Sereno and his colleagues set out to make comparable maps of the human brain, but they realized that several technical hurdles had to be overcome. The first was finding a way to take snapshots of brain activity detailed enough to construct a retinotopic map. For that task they turned to a brain imaging method developed in the early 1990s, called functional magnetic resonance imaging (fMRI), that not only has better spatial resolution than PET, but is also much faster, enabling researchers to take thousands of images in less than 10 minutes.

That speed, coupled with a clever trick called "phase encoding," developed by Stephen Engel, a postdoc with neuroscientist Brian Wandell at Stanford University, enabled the Sereno team to get enough data to map a person's visual areas in a matter of minutes. Phase encoding involves sweeping an image across the subject's field of view, in cycles lasting a minute, and tracking the response with fMRI images of the subject's brain. Areas with retinotopic maps stand out, Sereno says, because "at each spot you see activities that are going up and down every minute. The phase of that oscillating activity then tells you what visual field location is represented at that spot."

But getting the images was only half the challenge. The team next faced a complicated version of the old mapmaker's problem: how to accurately project a map of a rounded object—such as Earth or a brain—onto a flat surface. Without a way to flatten the cortex, says Washington University's Van Essen, "we would be hopelessly tangled trying to wind our way through [the data]." But flattening a convoluted brain surface is a very difficult problem. Van Essen and other monkey researchers developed manual methods that Van Essen calls "tedious and not terribly accurate" and too cumbersome to apply to the much more convoluted human brain. In the past few years, however, several groups have devised computer algorithms that can flatten human as well as monkey brains. Sereno's group used one developed by Sereno and Dale, who is now at the University of Oslo in Norway.

This new bag of tricks has so far enabled the Sereno group to map five visual areas in the human brain that process information that has been received and passed along by the primary visual cortex. Based on the positions and other characteristics of these areas, the team concluded that they are counterparts of visual areas found in monkeys. Others who have seen the data agree. "It looks just like the monkey brain," says Leslie Ungerleider, who does brain mapping in monkeys and humans at the National Institute of Mental Health. Ungerleider says that is what she expected, but that "it was done in such a convincing and elegant way that ... it just blows you away."

In unpublished work, a team led by Edgar DeYoe of the Medical College of Wisconsin in Milwaukee and George Carman of the Salk Institute has used similar methods to map human visual areas. And DeYoe says "we get pretty much the same topography and mapping" as Sereno's group.

Despite the striking similarity between the human and monkey visual areas, the studies also revealed salient differences. The human areas are shifted in position along the brain's surface and are larger than their monkey-brain counterparts. Specifically, the centers of the human areas are expanded, with more neurons devoted to processing images at the center of a person's gaze. That suggests humans place a premium on getting detailed information from whatever they are looking at, a trait, Sereno notes, that "would be quite helpful for things like reading."

The methods pioneered by the Sereno and DeYoe groups may help answer a hot question: Do functions that are uniquely human, such as the recognition of written words, take place in areas unique to human brains or in areas present in monkey brains that have taken on new functions in humans? Sereno thinks his data suggest an answer for at least one case. His team's study places the human version of a visual area called V4, known in monkeys to discern form and color, very close to an area that PET studies have linked to word recognition. "That [word recognition] area could in part be V4," says Sereno. But Richard Frackowiak of Hammersmith Hospital in London, who has done PET studies of word recognition, draws the opposite conclusion from Sereno's data—namely, that the word recognition area is separate from V4 and uniquely human. That ambiguity, says Van Essen, may arise from "comparing analyses with different techniques and different individuals."

Washington University neuroscientist Steven Petersen, who does brain mapping with PET, says that the final resolution of ambiguous cases such as this may come from new experiments that first use fMRI to "map out the regions [in an individual subject], then bring the person back and have them do a bunch of word-recognition and color-discrimination tasks" to place those functions directly on that person's individual map. For this and other questions, adds Van Essen, "we now have the tools right at hand for a much more refined set of analyses." And with those tools, researchers will find that their window into the brain has achieved a new level of clarity.

–Marcia Barinaga

MEASUREMENT STANDARDS

Keeping the Kilo From Gaining Weight

The French are known for their finesse in many areas of life, and British physicists are finding that the reputation holds in the arcane realm of weights and measures as well. For years, a specialist named Georges Girard labored unrecognized at the heart of the international metric system at the Bureau International des Poids et Mesures (BIPM) near Paris, keeping the standard kilogram from picking up contaminants—and hence weight. His tools: nothing more than a chamois cloth, a bottle of cleaning fluid, and that old je ne sais quoi. Now Girard has retired, and Martin Seah and Peter Cumpson at the U.K.'s National Physical Laboratory in Teddington near London are hoping that a regimen of ozone and ultraviolet light can match his deftness in keeping the standard kilogram, well—standard.

The curators of the kilogram, a platinum-iridium cylinder kept at the BIPM, say they are eager to test the British scheme. For the moment, they are still trying to keep the kilogram clean by hand-polishing it. But as the keepers of the only standard of measurement still based on an object rather than on a fundamental physical quantity—time, for example, is set by a specific frequency of radiation—they are eager to find ways to maintain the standard that rely more on science and less on one man's skillful fingers.

Thought to have been made in the early 1880s by a Paris instrument-maker, the 4-centimeter-high, 4-centimeter-wide cylinder is the prototype for reference kilograms in national laboratories throughout the world. These standard kilograms—exact copies of the French original—ultimately tie all mass-measuring systems back to the BIPM standard. But over the last decade or so, improved balances have shown that the reference kilogram and its duplicates vary in weight. "We have been measuring the differences between these apparently similar artifacts, and we see they are drifting apart," says Terry Quinn, director of the BIPM. The weight of a freshly minted copy of the standard mass, says Cumpson, "increases by tens of micrograms in the first few weeks after manufacture."

The explanation for this unwanted weight gain, say Seah and Cumpson, is contaminants accumulating on the metal surface. Through spectroscopic analysis of the surface of replica kilograms, they have found that the platinum-iridium alloy picks up hydrocarbons from air pollution and other sources,

BIPM

That special touch. Georges Girard uses a chamois cloth to polish contamination from the surface of a standard kilogram replica.

along with mercury vapor from laboratory instruments. Every so often, explains Cumpson, an instrument breaks, releasing "a very subtle presence of mercury—well below health and safety levels—but enough to adsorb onto the surface of the reference kilogram."

Girard was able to keep the hydrocarbon buildup in check by rubbing the surface with a chamois cloth dipped in a mixture of ultrapure ethanol and ether; a hand-directed steam jet then removed any residue. The cleaned mass "returned to [within] a few micrograms of where it was originally," says Cumpson. "He used just the right degree of abrasion to remove the carbonaceous contamination without removing metal."

Cumpson believes that Girard's technique probably didn't remove the mercury, which worked its way into the grain structure of the metal. Still, it was better than any other standards laboratory could manage, even though a videotape of Girard at work polishing the kilogram was circulated among them. Scientists from the U.S. National Institute of Standards and Technology and the Physikalisch-Technische Bundesanstalt, the German standards institute, even flew to Paris to watch him up close and personal, but to no avail. "It's almost impossible to get the right degree of pressure," says Cumpson.

Now, with Girard's retirement 2 years ago, the BIPM faces the same dilemma. But Cumpson and Seah think they've come up with an answer: Expose the kilogram to ozone and ultraviolet light to oxidize the hydrocarbon contaminants, freeing them to diffuse away into thin air. "The technique looks very promising," says Cumpson. "There's no contact with the mass at all, and the concentrations we use are low," so there's little risk of oxidizing and damaging the kilogram itself.

BIPM Director Quinn is intrigued. "We shall be working with them to assess what they've found," he says. He also hopes to try out the cleaning technique on some of the laboratory's own platinum-iridium test objects. But the laboratory isn't rushing into anything. "We may not know exactly how the old process works," he says, "but we don't want to change until we know how to do it better."

–Sally Croft

Sally Croft is a science writer in Bristol, U.K.