Biomedicine in the Age of Imaging

Sensitive imaging techniques, enhanced by the power of the computer, are opening up entirely new areas of research–and also posing novel risks for researchers and clinicians

This year's Science Innovation section, timed to coincide with the Science Innovation meeting in Boston on 6–10 August, takes up one of the fastest moving areas in scientific technique: biomedical imaging. Powered by computers and aided by fundamental advances in physics, chemistry, and biology, an array of new techniques is making it possible to observe phenomena that until recently could only be inferred, such as the beating of the human heart and the normal function of the human brain. Along with those new openings come additional dangers and responsibilities for researchers, as Robert Crease tells us in his main story. In a series of sidebars accompanying that story, Joseph Alper highlights four of the imaging methods that are now changing the face of biomedical science.

John Mazziotta's talk was moving along smoothly when he threw in a surprise. Mazziotta, professor of neurology, radiology, and pharmacology at the University of California, Los Angeles, and director of its Brain Mapping Division, was speaking to a symposium on brain research at the American Psychological Society (APS) meeting in Chicago a few weeks ago. The subject was brain imaging technologies in behavioral research, and most of his slides were what you would expect from the subject matter: an assortment of dramatic images of the human brain made using the various cutting-edge technologies available today.

Suddenly Mazziotta shifted gears, projecting an image of the Eiffel Tower by Georges Seurat. What was an image by the famed pointillist doing among magnetic resonance imaging (MRI) and positron emission tomography (PET) scans? "I use this slide to illustrate the current state of brain and behavioral research thanks to the various imaging technologies," Mazziotta explained. "Individual investigators have each been working on their own dots, developing their own techniques to optimize the precision, accuracy, and reliability of each. But we're just at the stage where we can begin to step back from the canvas and look at the emerging big picture that is the integrated sum of all methods. And what we're beginning to see is something much greater than what we've been able to see before—more than the individual sum of each of the parts."

BRIDGEMAN/ART RESOURCES

Points of reference. At least one expert thinks this image, by Georges Seurat, speaks volumes about the state of the art in biomedical imaging.

Though Mazziotta's powerful message referred specifically to the brain and behavior, neuroscience is hardly the only field where imaging technologies are changing the way science is done. From images of atoms and molecules to sky maps made by contemporary astronomers, imaging technologies are becoming part of the fabric of science in ways that could not have been imagined a decade ago. And although the inroads made by imaging technologies are occurring throughout science, they are most pronounced in biomedical research, where radiology departments have been rebaptized as departments of "Medical Imaging," where entire issues of journals are devoted to imaging technologies, and where a preeminent publication—*The New England Journal of Medicine*—now carries a regular feature on medical imaging.

These developments indicate, many observers believe, that a new age of imaging in biomedicine is under way, an era that will lead to sharp changes in the role of images in science. While in the past images have been exploited primarily for teaching purposes and to express scientific conclusions, a host of new technologies is transforming images into a routine research and clinical tool. For the first time, large amounts of data on the heart, brain, and other organs are being reconstructed and transformed into the visual medium in a way that makes it possible to explore those organs—as well as structures on a smaller scale—without invading the body.

And that possibility heralds some profound transformations for science and for scientists. Among them, three are the most fundamental:

- *Changing the role of the computer*. The new age of imaging is being driven by computers in conjunction with extremely sensitive measuring devices. Initially, computers were essentially accessories to scientific instrumentation; that is no longer true. Now much of the scientific research itself is actually done in the computer, through the selection, manipulation, and processing of data. Imaging technologies are at the forefront of this development. Many of the recent advances in imaging—such as Ultrafast computerized tomographic (CT) scanning, which makes it possible to freeze the fast-moving human heart—are the result of combining enhanced computing power with breakthroughs in physics.
- *Opening up new fields of study*. The new imaging technologies have the power to reveal biological phenomena that were previously hidden from view. The human brain, for instance, is one of the most heavily veiled of all biological structures. And, as a result, most previous investigations of the biological basis of conscious behavior were forced to rely on inference. Now, by intriguing combinations of techniques such as MRI, PET, and electroencephalography (EEG) scientists are able to witness the biological activity underlying consciousness.
- *Creating new responsibilities for researchers*. The seductive power of images not only opens up new areas for research and clinical practice, it also poses new risks for researchers. Images seem to offer a "transparent" view of a biological structure or process: a crystal clear perception of what's "really" going on inside the body. As such, they call out for action: medication or surgery. The availability of fetal monitoring, for example, may have contributed to keeping the rate of Caesarean sections high without significantly improving neonatal health. Countering these dangers means an increased awareness that images are constructs that include just as much "noise" and require just as much care as any other technique.

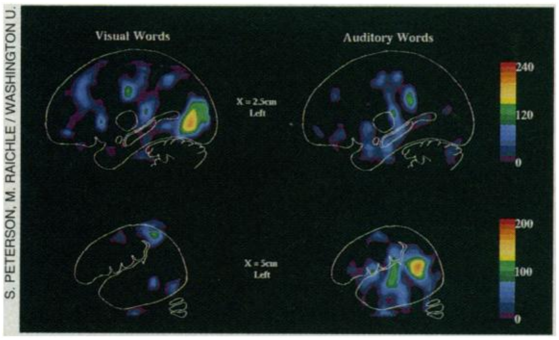
Stalking the elusive heart

The experience of researchers trying to capture images of the elusive human heart reveals how computers have become full partners in the process of obtaining crucial biomedical images—by squeezing the maximum amount of information out of every possible photon or magnetic field measurement. The wave of innovation that is now cresting began forming in the late 1950s and early 1960s, when researchers learned to do CT scans, which offered an increase of several orders of magnitude over conventional x-ray methods. That advance soon exploded into clinical use: There are now some 10,000 CT scanners in use in U.S. hospitals. And the initial version of CT scanning was just the beginning of using computers to improve imaging methods. In the past decade, the process has been carried forward to the point where researchers are on the verge of cracking vital problems in both basic and clinical research.

Few of those problems promise as great an immediate clinical gain as those involving the human heart. Thus far, the heart has proven resistant to conventional imaging techniques thanks to its motion—the constant work of contraction and expansion that, after all, keeps us alive. The temporal resolution ("shutter speed") of conventional imaging techniques such as CT are at best several seconds, and even functional MRI, which is much faster (see sidebar on page 556), has a temporal resolution of at best about a second. At that speed, heart images are still blurred. Recently, however, a computer enhanced offshoot of CT known as Ultrafast CT (also called Electron Beam Tomography) has speeded things up enough so that imaging the human heart in action has become possible.

What limits the speed of conventional CT is the need to move either the patient or the x-ray source to catch the subject from all angles. Ultrafast CT eliminates this need by using computers to steer an intense electron beam around a tungsten ring. The collision between the electron beam and the tungsten ring produces x-rays that traverse the patient from many angles almost simultaneously, without moving either the imaging instrument or the patient. In fact, capturing enough data for an image takes only 50 milliseconds—fast enough to stop the heart in its tracks.

"The ability to focus and control an electron beam of this intensity is a recent breakthrough in electron beam physics," says Douglas Boyd of Imatron, the South San Francisco company that manufactures the device. While the advances in physics were essential, says Boyd, "none of this would be feasible without computers, and the faster the computers get, the better the images. In the field of CT scanning in particular, the resolution and speed of the images has tracked the speed of computers used." Imatron's first commercial machines appeared 6 years ago; today some 50 are in use throughout the country.

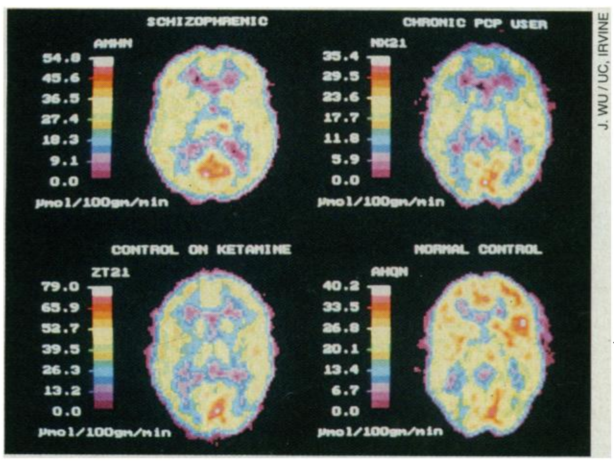


S. PETERSON, M. RAICHLE / WASHINGTON U

Any way you slice it. Positron emission tomography (PET) images of two different sagittal brain slices showing how the brain responds when a word is presented either visually (images at left) or aurally (images at right).

As big an advance as it is to image the working human heart, for clinicians an even more significant step would be to have enough spatial resolution, or sharpness of the image, to tell what is going on within specific coronary arteries. The payoff from that additional resolution would be tremendous, since coronary artery disease is the major cause of death in this country (it is three times more deadly than cancer), as well as the most frequent cause of hospital visits. Unlike catching the heart at work, noninvasively imaging the interior of the arteries is still on the horizon of possibility—but it may be drawing near thanks to yet another clever application of computing.

The conventional way of obtaining images of the interior of an artery is to thread a meter-long catheter from an incision in the thigh's femoral artery through the descending aorta into the heart and inject a contrast agent for a CT scan. This method is accurate but also highly intrusive, and is associated with risks that are far from trivial: complications from strokes and heart attacks ranging from 1% to 3% and a death rate of 1 in 1000. As a result, clinicians are naturally reluctant to prewtients, even those at high risk of coronary artery disease. Their reluctance would vanish, however, if there were a way to exploit a contrast agent that could be injected straight into a vein.



J. WU / UC, IRVINE

PET theories. PET scanning is the most widely utilized of the currently available brain-imaging methods. Here PET scans distinguish among the brains of a schizophrenic, a user of phencyclidine (PCP), and two normal controls (one after injection with an anesthetic).

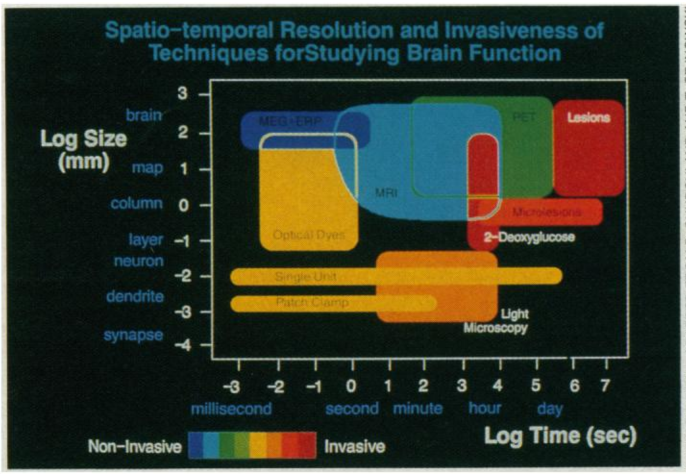
That's the goal of Erik Ritman, professor of physiology and medicine at the Mayo Clinic, whose technique is to enhance the Imatron still further by a computer software program. "The Imatron scanner has two canned modes," Ritman says. "In one it gives you a thin slice [of tissue] but takes about 45 seconds, or several breathholds, to do the heart, which isn't going to work in a clinical setting. In the other it takes about 8 seconds and one breathhold to do the heart, but the slice is 8 millimeters thick and doesn't give you the resolution you need for arteries."

That poses a technical problem for Ritman: "We have to learn how to make thin slices out of thick slices." In solving this problem, his main tool is the computer. The solution is "moving the patient while the scanning is in progress—producing blurred images of overlapped slices—and using the computer to deblur the images. Basically, it boils down to developing the right deconvolution software—'discombobulation software,' I call it. If it works, you could do a heart image with enough clarity to see coronary arteries in a single breath."

If Ritman's work pays off, the gain could be to keep the advantages of current methods of imaging the arteries (detecting arterial disease up to 10 years before symptoms appear) while doing away with the intrusive side effects. "The beauty of this technique for the Imatron scanner," Ritman says, "is that if successful it would be implementable and make coronary artery examinations possible, in a commercially available machine, immediately all over the country." And the key, as in so many other recent imaging advances, will be creative use of that indispensable imaging device: the computer.

Seeing the brain at work

The heart is elusive because its motion is so quick it blurrs images made with conventional imaging devices. The brain is elusive for a completely different reason: It is protected better than almost any other living tissue. As Gordon Bowers, president of the APS, put it at the same conference where Mazziotta unveiled his Seurat, the brain is "difficult to study because it is so bloody inaccessible." Evolution, Bowers added, "has encased the brain in a rock-hard vault of bone, wrapped it in layers of tough membrane, and cushioned it in a viscous bath of cerebral



Three-way trade. Brain imaging methods involve tradeoffs among temporal resolution ("shutter speed"), spatial resolution ("focus"), and invasiveness. All three are indicated here: temporal resolution on the vertical axis, spatial on the horizontal axis, invasiveness in the color scheme.

J. W. BELLIVEAU, ADAPTED FROM P. CHURCHLAND AND T. SEJNOWSKI

spinal fluid. These protective shields pose particularly difficult challenges for scientists who would like to observe human brain activity directly." As a result, he says, "few of us have seen a live, functioning human brain. Only neurosurgeons are allowed to look at live human brains, and their primary aim is medical: to repair an aneurism or excise a tumor."

How can those natural barriers be penetrated so that scientists can grasp the connection between brain and behavior? Only a few decades ago, one of the principal methods of studying that connection was indirect: examining individuals with damaged brains (usually war casualties or industrial accident victims) to see how their lesions affected day-to-day performance. In retrospect it is clear that those observations could only crudely sketch the relations between brain structures and behavior. Yet until recently, there wasn't much hope of going beyond them, since the thought of watching different parts of a normal brain in action was little more than science fiction. Several contemporary imaging technologies, however, offer to make that fiction reality.

At the APS meeting, Bower chose to devote his presidential symposium to those imaging technologies—and the possibilities they open up for visualizing what goes on in the brain during behaviors ranging from perception, memory, and language use to thought and emotional reactions. From the wealth of techniques now available, the symposium zeroed in on the advantages and disadvantages of three of the most useful methods for brain scientists: PET, magnetoencephalography (MEG), and functional MRI. A leader in the use of each method (two in the case of PET) was chosen to explain what his technique has to offer in opening up the functioning brain for inspection.

Given the expense of the imaging technologies involved, and the current funding climate, it was inevitable that competition would be in the air, and that the researchers would act partly as promoters for their methods. PET scan researcher Steven Peterson, director of the division of neuropsychology in the department of neurology and neurological surgery at Washington University in St. Louis, addressed the competitive spirit humorously by including among his slides one that said: "My imaging technology is better than yours."

In spite of the evident humor, Peterson was quite serious about the virtues of his imaging method, virtues that include great flexibility. PET scans, he explained, detect the spatial distribution of positron-emitting radioisotopes, and "anything you can stick a positron emitter on," he said, "you can take a picture of." That includes a very large group of chemical substances, whose course through the brain can be readily traced. Peterson's group sticks its positron emitter onto water molecules, which are carried in the blood stream. Changes in the demand for information processing—such as those caused by giving a subject a different task to do—produce changes in neuronal activity in localized regions of the brain. Through mechanisms that aren't fully understood, those changes alter blood flow. The result: PET maps the brain at work.

PET technology is the most widely utilized of the three, and Peterson accompanied his talk with impressive slides illustrating parts of the brain lit up when subjects perform various linguistic tasks. He was followed by Joseph Wu, in the psychiatry department of the University of California (UC) Medical School, Irvine, and director of UC Irvine's brain imaging center, who sticks his positron emitters on glucose to take pictures of glucose metabolism. Wu described applications of PET to imaging the brains of patients with psychiatric disorders such as schizophrenia, autism, anxiety, and major depression.

Next up was Lloyd Kaufmann, a psychologist and neuropsychologist at New York University, who argued the advantages of MEG, which maps magnetic field patterns given off by ionic currents within neurons. The principal strength of MEG over the other two methods is its higher shutter speed. While PET's best resolution with the techniques used by the St. Louis group is 20 seconds and MRI's a single second, MEG enables researchers to witness the brain in action in real time, with a temporal resolution in the range of tens of milliseconds. "We're finding that speech areas are lighting up 100 milliseconds after the visual areas. You can't see that difference in any measure of blood flow."

The promoter of the third method, functional MRI, was Walter Schneider of the University of Pittsburgh, who began by confessing he once suffered from "PET envy," which he described as "the desire to have a brain-imaging machine in one's home town." The reason for his Freudian condition, he explained, was that PET requires short-lived isotopes that must be made at multimillion-dollar cyclotron facilities—of which there are only about 10 in the country. Hence he could not have easy access to a PET scanner. Yet Schneider suffers PET envy no more, he confessed, since there are 3800 conventional MRI machines in North America capable of being used to create brain images by the clever new twist known as functional MRI. Using conventional MRI machines for functional MRI, researchers can image blood flow without either expensive machines or radioactive tracers in the blood.

Functional MRI is a method that is only now spreading through academic research centers. Indeed, Schneider told the packed plenary that he first learned about functional MRI only a year and a half ago. But, he added, he had his first publication using the method a mere 6 months later, showing how quickly brain scientists can "retool" to do functional MRI brain mapping. With that approach, they can do much of the blood-flow mapping that can be done on larger PET machines. Reflecting the strut-your-stuff atmosphere at the symposium was one of Schneider's slides, which read: "You, too, can have this kind of data."

In spite of the humorous air of competition, all the speakers admitted that each technique has its own strengths and weaknesses, and no one of them can be expected completely to supplant the others. These days, the prudent brain researcher consults all the major methods. "It's like the images made by astronomers at different parts of the electromagnetic spectrum," says Kaufmann. "An astronomer would be an idiot to scorn evidence from any one method, because they each show you a different facet of what you are trying to understand." And in this case researchers would be doubly foolish to scorn any available evidence, since what they are trying to understand—the brain—is an organ that has long been shrouded from the eyes of science.

The seductive—and dangerous—image

Researchers today are awash in floods of data collected by a host of new and powerful techniques. They desperately need ways of putting this data in context, making it intelligible, grasping its essentials and discarding what is trivial. One obvious solution is to rely on images, whose spatial dimensions, shadings, and color codings can easily express large amounts of data. This point was made again and again at the APS conference, perhaps most vividly by a speaker who showed a slide of the famous map of the Paris subway system and invited the audience to contemplate how confused they would be if the map were not color-coded.

Yet in spite of their attractions, or perhaps because of them, images create dangers for both clinicians and researchers—dangers intimately entwined with the benefits that imaging technologies confer. One such benefit is the illusion of familiarity. Unlike a table or a chart or graph, an image often seems to be "transparent," giving us the depicted object directly rather than through the mediation of fallible instruments that incorporate certain types of information and leave out other—perhaps equally important —kinds of data. An image can delude us into thinking we know an object in a way a graph never can.

That knowledge, in turn, encourages us to act. "Maps invite action," writes Stephen Hall in his recent book, *Mapping the Next Millennium*. The same is true of images. By making us feel a certain familiarity with the object, yet at the same time putting the object at an impersonal distance, images make it easier to consider scientific and therapeutic interventions: the surgeon's knife, the investigator's probe, the radiation beam.

"Remember what happened with fetal monitoring?" asks David Benaron, whose research specialties put him very near the question: He's a neonatologist at the Stanford University School of Medicine and an engineer at Stanford's Hansen Free-Electron Laboratory working on optical imaging (see sidebar on page 560). Benaron himself provides an answer. "Fetal monitors became standard equipment too quickly—they were everywhere before people knew what they did and how they worked." Fetal monitors, he says, "gave you too much information, and it was too easy to think that something was malfunctioning when it wasn't. I've been called in numerous times when the infant looked great but the fetal monitor strip looked terrible, and the doctor was sure that something was wrong."

The "oversupply" of information available in the fetal monitoring strip, adds Benaron, coupled "with the tremendous fear of doing harm to the infant...as well as the fear of litigation" contributes to a "tendency to get the baby out and take no chances." As a result, he says, one-quarter of all births in the United States are now performed by Caesarean section. "Now, there's no way that 25% of births have to be C-section! And there's been no concomitant decline in infant mortality. That's the kind of danger that, I'm afraid, may occur in the clinical situation with imaging technologies."

Since Benaron is in the business of developing new—and even more revealing—image-based methods of monitoring, he feels that it is his responsibility to warn others of the possible risks of "information oversupply." To inform his colleagues, he is helping organize conferences and workshops on the appropriate use of optical imaging, the next one scheduled for the January 1994 meeting of the Society for Photo-optical Instrumentation Engineering in Los Angeles.

The overaggressive obstetrician is far from the only potential danger posed by new imaging technologies. Researchers are now able to use computer-generated images to make quantitative comparisons of the brains of different individuals, and to group those data in order to compare different groups. Imagine the social and political controversies that would arise if those techniques were applied to analyzing differences among racial or cultural groups.

No doubt there will be many other unintended consequences of the burgeoning application of imaging technology in the biomedical sciences. For example, an imaging technology is almost always an interdisciplinary effort, involving an entire team of researchers with different skills. A single brain experiment might require computer programmers, biochemists, anatomists, psychologists, technicians, and psychiatrists. If enough experiments on that scale were done, the use of imaging technologies could bring about an expansion in the size of biomedical research groups, following hard on the heels of what has already happened in physics.

Biomedical scientists may applaud such developments or be apprehensive about them. Yet whatever dangers the use of imaging technology may pose, the advantages of images are so appealing that in the years immediately ahead, the age of imaging is sure to take even firmer hold in biomedical research.

–**Robert P. Crease**

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