Visualizing the Mind

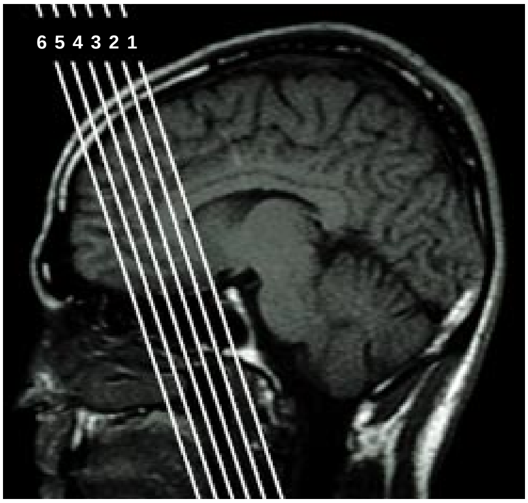
Strategies of cognitive science and techniques of modern brain imaging open a window to the neural systems responsible for thought

by Marcus E. Raichle

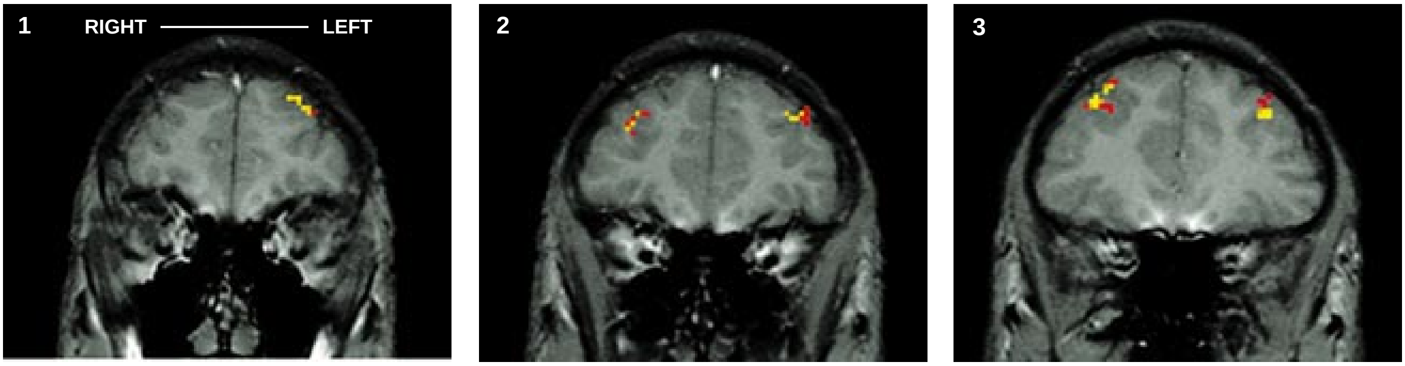
What causes the pity we might feel for the melancholy Dane in *Hamlet* or the chill during a perusal of the *Raven?* Our brains have absorbed from our senses a printed sequence of letters and then converted them into vivid mental experiences and potent emotions. The "black box" description of the brain, however, fails to pinpoint the specific neural processes responsible for such mental actions. While philosophers have for centuries pondered this relation between mind and brain, investigators have only recently been able to explore the connection analytically—to peer inside the black box. The ability stems from developments in imaging technology that the past few years have seen, most notably positron-emission tomography and magnetic resonance imaging. Coupled with powerful computers, these techniques can now capture in real time images of the physiology associated with thought processes. They show how specific regions of the brain "light up" when activities such as reading are performed and how neurons and their elaborate cast of supporting cells organize and coordinate their tasks. The mapping of thought can also act as a tool for neurosurgery and elucidate the neural differences of people crippled by devastating mental illnesses, including depression and schizophrenia.

I hasten to point out that the underlying assumptions of current brain mapping are distinct from those held by early phrenologists. They posited that single areas of the brain, often identified by bumps on the skull, uniquely represented specific thought processes and emotions. In contrast, modern thinking posits that networks of neurons residing in strictly localized areas perform thought processes. So just as specific members of a large orchestra perform together in a precise fashion to produce a symphony, a group of localized brain areas performing elementary operations work together to exhibit an observable human behavior. The foundation for such analyses is that complex behaviors can be broken down into a set of constituent mental operations. In order to read, for example, one must recognize that a string of letters is a word; then recognize the meaning of words, phrases or sentences; and finally create mental images.

The challenge, of course, is to determine those parts of the brain that are active and those that are dormant during the performance of tasks. In the past, cognitive neuroscientists have relied on studies of laboratory animals and patients with localized brain injuries to gain insight into the brain's functions. Imaging techniques, however, permit us to visualize safely the anatomy and the function of the normal human brain.



ACTIVE NEURAL AREAS from a subject remembering a sequence of letters are mapped by magnetic resonance imaging. The images below represent six slices through the frontal cortex. The slices are identified by numbers in the corners that correspond to those in the scan at the left. Red, orange and yellow represent areas of increasing activity. Jonathan D. Cohen and his colleagues at the University of Pittsburgh and Carnegie Mellon University formed the images.



MARCUS E. RAICHLE is professor of neurology, radiology and neurobiology as well as a senior fellow of the McDonnell Center for Studies of Higher Brain Function at the Washington University School of Medicine in St. Louis. He received his B.S. and M.D. degrees from the University of Washington in Seattle. He began researching brain metabolism and circulation when he was a neurology resident at the New York Hospital–Cornell Medical Center. His current focus is the use of positron-emission tomography and magnetic resonance imaging to study human cognition and emotion.

The modern era of medical imaging began in the early 1970s, when the world was introduced to a remarkable technique called x-ray computed tomography, now known as x-ray CT, or just CT. South African physicist Allan M. Cormack and British engineer Sir Godfrey Hounsfield independently developed its principles. Hounsfield constructed the first CT instrument in England. Both investigators received the Nobel Prize in 1979 for their contributions.

Computed tomography takes advantage of the fact that different tissues absorb varying amounts of x-ray energy. The denser the tissue, the more it absorbs. A highly focused beam of x-rays traversing through the body will exit at a reduced level depending on the tissues and organs through which it passed. A beam of x-rays passed through the body at many different angles through a plane collects sufficient information to reconstruct a picture of the body section. Crucial in the development of x-ray CT was the emergence of clever computing and mathematical techniques to process the vast amount of information necessary to create images themselves. Without the availability of sophisticated computers, the task would have been impossible to accomplish.

X-ray CT had two consequences. First, it changed forever the practice of medicine because it was much superior to standard x-rays. For the first time, investigators could safely and effectively view living human tissue such as the brain with no discomfort to the patient. Standard x-rays revealed only bone and some surrounding soft tissue. Second, it immediately stimulated scientists and engineers to consider alternative ways of creating images of the body's interior using similar mathematical and computer strategies for image reconstruction.

One of the first such groups to be intrigued by the possibilities opened by computed tomography consisted of experts in tissue autoradiography, a method used for many years in animal studies to investigate organ metabolism and blood flow. In tissue autoradiography, a radioactively labeled compound is injected into a vein. After the compound has accumulated in the organ (such as the brain) under interest, the animal is sacrificed and the organ removed for study. The organ is carefully sectioned, and the individual slices are laid on a piece of film sensitive to radioactivity. Much as the film in a camera records a scene as you originally viewed it, this x-ray film records the distribution of radioactively labeled compound in each slice of tissue.

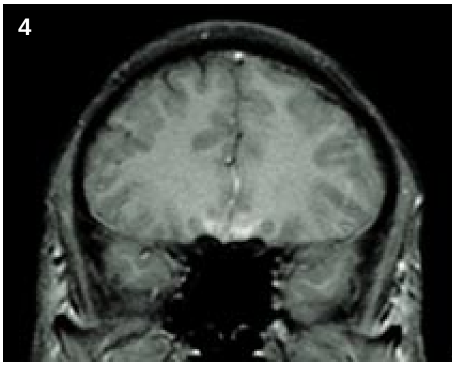
Once the x-ray film is developed, scientists have a picture of the distribution of radioactivity within the organ and hence can deduce the organ's specific functions. The type of information is determined by the radioactive compound injected. A radioactively labeled form of glucose, for example, measures brain metabolism because glucose is the primary source of energy for neurons. Louis Sokoloff of the National Institute of Mental Health introduced this now widely used autoradiographic method in 1977.

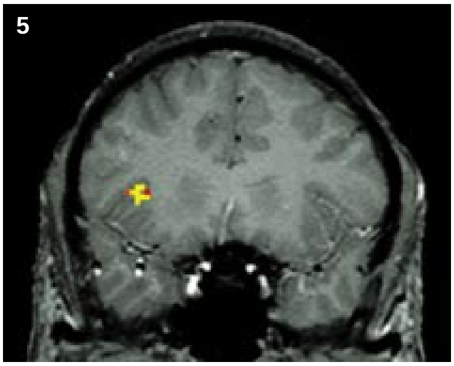
Investigators adept with tissue autoradiography became fascinated when CT was introduced. They suddenly realized that if they could reconstruct the anatomy of an organ by passing an x-ray beam through it, they could also reconstruct the distribution of a previously administered radioisotope. One had simply to measure the emission of radioactivity from the body section. With this realization was born the idea of autoradiography of living human subjects.

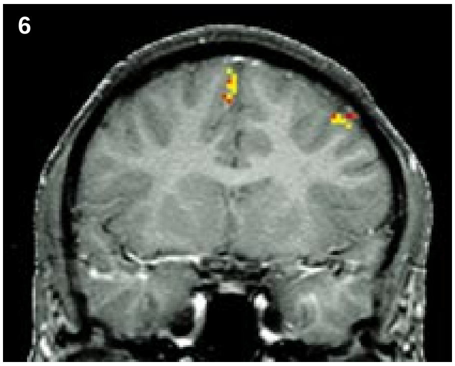
A crucial element in the evolution of human autoradiography was the choice of radioisotope. Workers in the field selected a class of radioisotopes that emit positrons, which resemble electrons except that they carry a positive charge. A positron would almost immediately combine with a nearby electron. They would annihilate each other, emitting two gamma rays in the process. Because each gamma ray travels in nearly opposite directions, devices around the sample would detect the gamma rays and locate their origin. The crucial role of positrons in human autoradiography gave rise to the name positron-emission tomography, or PET [see "Positron-Emission Tomography," by Michel M. Ter-Pogossian, Marcus E. Raichle and Burton E. Sobel; SCIENTIFIC AMERICAN, October 1980].

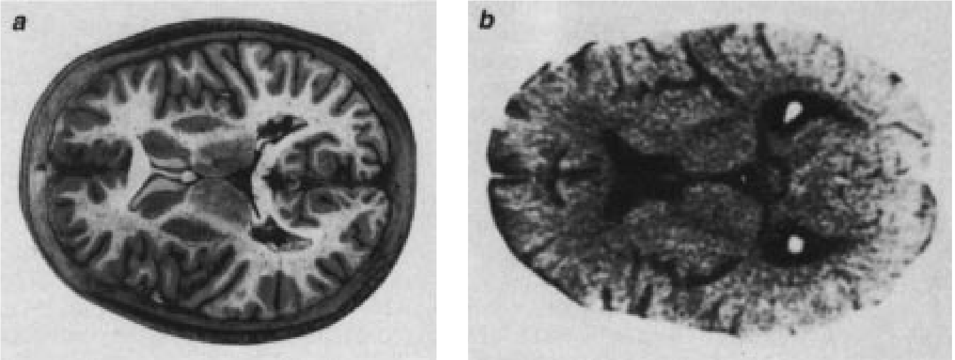
Throughout the late 1970s and early 1980s, researchers rapidly developed PET to measure various activities in the brain, such as glucose metabolism, oxygen consumption, blood flow and interactions with drugs. Of these variables, blood flow has proved the most reliable indicator of moment-to-moment brain function.

The idea that local blood flow is intimately related to brain function is a surprisingly old one. English physiologists Charles S. Roy and Charles S. Sherrington formally presented the idea in a publication in 1890. They suggested that an "automatic mechanism" regulated the blood supply to the brain. The amount of blood depended on local variations in activity. Although subsequent experiments have amply confirmed the existence of such an automatic mechanism, no one as yet is entirely certain about its exact nature. It obviously remains a challenging area for research.





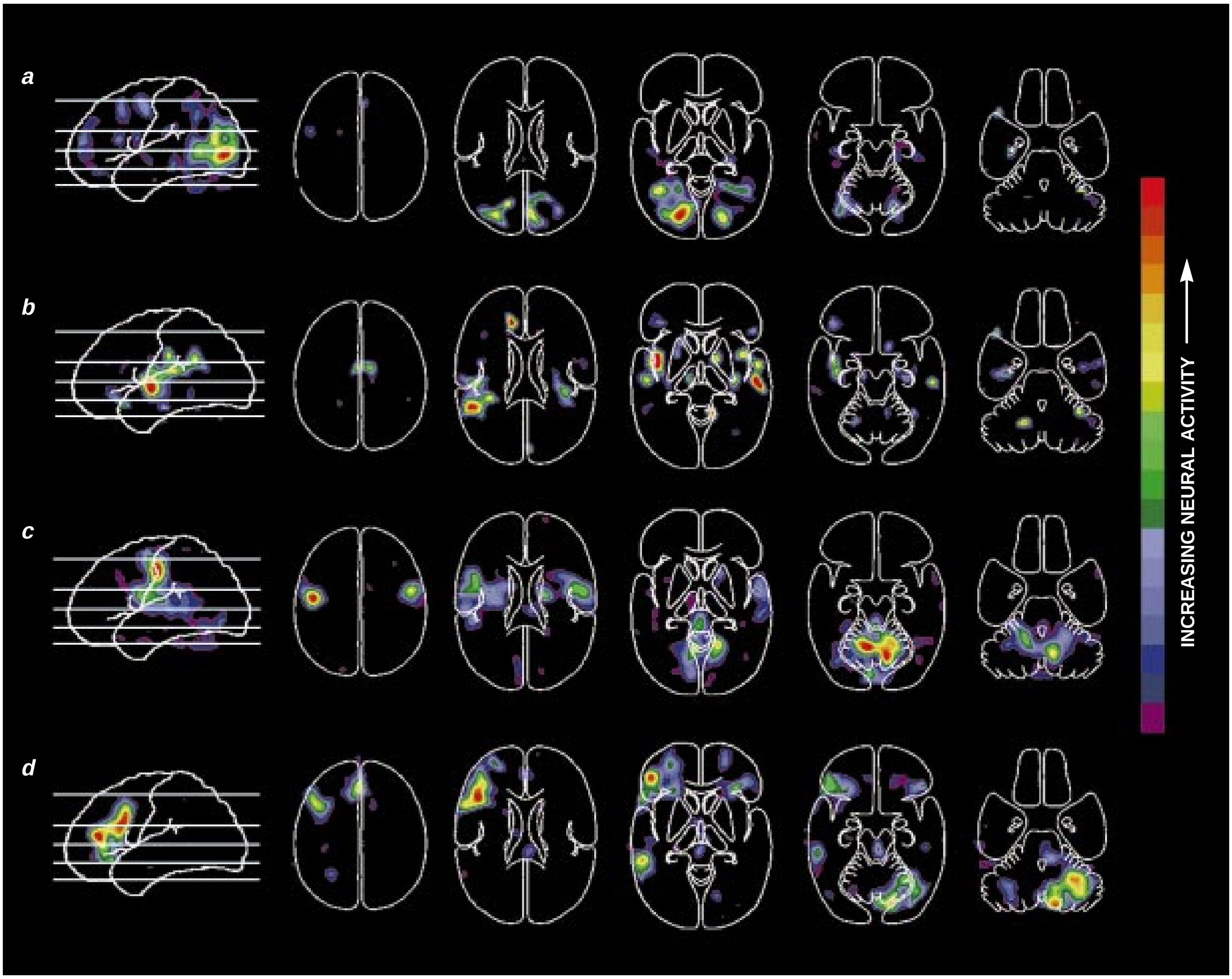




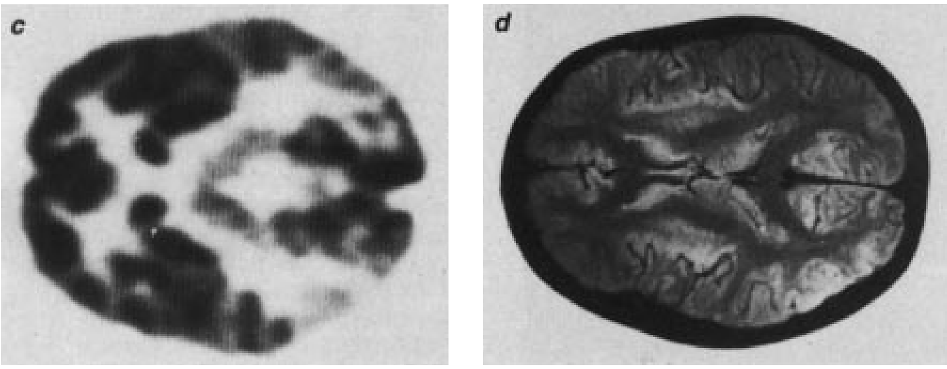
BRAIN SECTION (*a*) is compared with corresponding images of the slice taken by x-ray computed tomography (CT) (*b*), positron-emission tomography (PET) (*c*) and magnetic resonance imaging (MRI) (*d*). CT depicts the features of the brain section, whereas PET shows the amount of neuronal work (the darker the area, the greater the activity). Properly set up, MRI can do both tasks. Here it images structure.

PET measures blood flow in the normal human brain by adapting an autoradiographic technique for laboratory animals developed in the late 1940s by Seymour S. Kety of the National Institute of Mental Health and his colleagues. PET relies on radioactively labeled water—specifically, hydrogen combined with oxygen 15, a radioactive isotope of oxygen. The labeled water emits copious numbers of positrons as it decays (hydrogen isotopes cannot be used, because none emit positrons). The labeled water is administered into a vein in the arm. In just over a minute the radioactive water accumulates in the brain, forming an image of blood flow.

The radioactivity of the water produces no deleterious effects. Oxygen 15 has a half-life of only two minutes; an



PET SCANS show active neural areas. In the far left column the left side of the brain is presented; the next columns show five horizontal layers (the right side faces to the right, with the front to the top). Each row corresponds to the difference between a specific task and the control state of gazing at a dot on a television monitor. When subjects passively view nouns (*a*), the primary visual cortex lights up. When nouns are heard (*b*), the temporal lobes take command. Spoken nouns minus viewed or heard nouns (*c*) reveal motor areas used for speech. Generating verbs (*d*) requires additional neural zones, including those in the left frontal and temporal lobes corresponding roughly to Broca's and Wernicke's areas.



entire sample decays almost completely in about 10 minutes (five half-lives) into a nonradioactive form. The rapid decay substantially reduces the exposure of subjects to the potentially harmful effects of radiation. Moreover, only low doses of the radioactive label are necessary.

The fast decay and small amounts permit many measurements of blood flow to be made in a single experiment. In this way, PET can take multiple pictures of the brain at work. Each picture serves as a snapshot capturing the momentary activity within the brain. Typical PET systems can locate changes in activity with an accuracy of a few millimeters.

A distinct strategy for the functional mapping of neuronal activity by PET has emerged during the past 10 years. This approach extends an idea first introduced to psychology in 1868 by Dutch physiologist Franciscus C. Donders. Donders proposed a general method to measure thought processes based on a simple logic. He subtracted the time needed to respond to a light (with, say, the press of a key) from the time needed to respond to a particular color of light. He found that discriminating color required about 50 milliseconds. In this way, Donders isolated and measured a mental process for the first time.

The current PET strategy is designed to accomplish a similar subtraction but in terms of the brain areas implementing the mental process. In particular, images of blood flow taken before a task is begun are compared with those obtained when the brain is engaged in that task. Investigators refer to these two periods as the control state and the task state. Workers carefully choose each state so as to isolate as best as possible a limited number of mental operations. Subtracting blood-flow measurements made in the control state from each task state indicates those parts of the brain active during a particular task.

To achieve reliable data, workers take the average of responses across many individual subjects or of many experimental trials in the same person. Averaging enables researchers to detect changes in blood flow associated with mental activity that would otherwise be easily confused with spurious shifts resulting from noise.

One of the first assignments in which PET blood-flow mapping has proved useful is in the study of language. The manner in which language skills are acquired and organized in the human brain has been the subject of intense investigation for more than a century. Work began in earnest in 1861, when French physician Pierre Paul Broca described a patient whose damaged left frontal lobe destroyed the ability to speak. (To this day, patients who have frontal lobe damage and have trouble speaking are often referred to as having Broca's aphasia.) Broca's studies of language localization were complemented by Carl Wernicke, a German neurologist. In 1874 Wernicke told of people who had difficulty comprehending language. They harbored damage to the left temporal lobe, a region now usually referred to as Wernicke's area. From these beginnings has emerged a concept of language organization in the human brain: information flows from visual and auditory reception to areas in the left temporal lobe for comprehension and then on to frontal areas for speech production [see "Specializations of the Human Brain," by Norman Geschwind; SCIENTIFIC AMERICAN, September 1979].

All this information was gleaned from brain-damaged patients. Can investigators derive insight about language organization from a healthy brain? In 1988 my colleagues Steven E. Petersen, Michael I. Posner, Peter T. Fox and Mark A. Mintun and I at the Washington University Medical Center began a series of studies to answer just this question. The initial study was based on a PET analysis of a seemingly simple job: speaking an appropriate verb when presented with a common English noun. For example, a subject might see or hear the word "hammer," to which an appropriate response might be "hit."

We chose this assignment because it could be broken down into many components. Each component could separately be analyzed through a careful selection of tasks. The most readily apparent elements include visual and auditory word perception, the organization and execution of word output (speech), and the processes by which the brain retrieves the meanings of words. (Of course, each of these operations can be divided further into several additional subcomponents.)

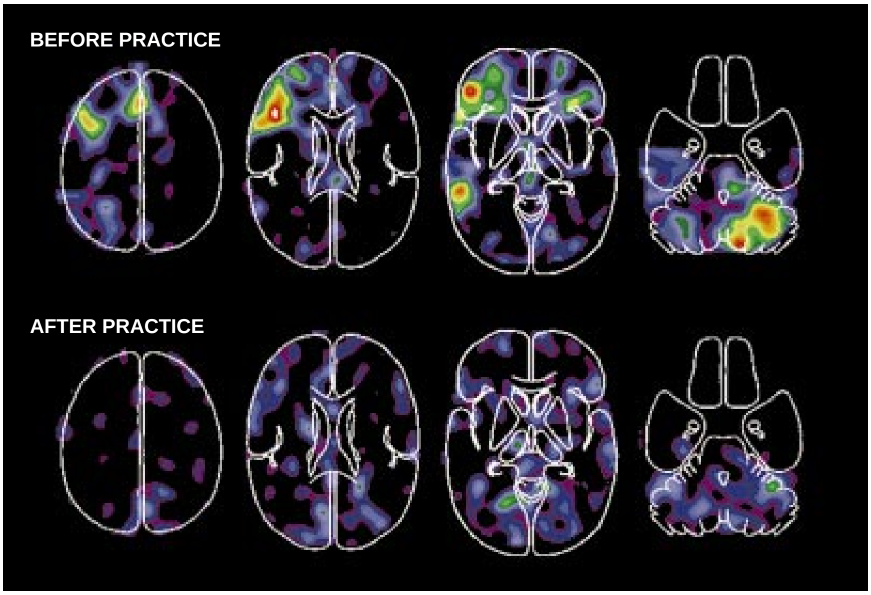
To identify the areas of the brain used in a particular operation, we composed four levels of information processing. Such a hierarchy has become standard among laboratories doing this type of research [*see bottom illustration on opposite page*]. In the first level, subjects were asked to fix their gaze on a pair of small crosshairs—the arrangement looks like a small plus sign—in the middle of a television monitor. At the same time, a PET scan measured blood flow in the brain, providing a snapshot of mental activity.

In the second level, subjects continued to maintain their gaze on the crosshairs as blood flow was measured, but during this scan they were exposed to common English nouns. The nouns either appeared below the crosshairs on the television monitor or were spoken through earphones (separate scans were performed for visual and auditory presentations). In the third level, subjects were asked to recite the word they viewed or heard. Finally, in the fourth level, the subjects said out loud a verb appropriate for the noun.

Subtracting the first level from the second isolated those brain areas concerned with visual and auditory word perception. Deducting the second level from the third pinpointed those parts of the brain concerned with speech production. Subtracting level three from level four located those regions concerned with selecting the appropriate verb to a presented noun.

The final subtraction (speaking nouns minus generating verbs) was of particular interest, because it provided a portrait of pure mental activity (perception and speech—or input and output—having been subtracted away). This image permitted us to view what occurs in our brains as we interpret the meaning of words and, in turn, express meaning through their use. It renders visible conscious function because much of our thinking is carried out by concepts and ideas represented by words.

The results of this study clearly demonstrate how brain imaging can relate



LEARNING-INDUCED CHANGES in neural activity are revealed by PET imaging. The top row shows the brain of a subject who must quickly generate verbs appropriate to visually presented nouns. The bottom row shows the result of 15 minutes of practice; the regions activated are similar to those used in simply reading out loud.

mental operations of a behavioral task to specific networks of brain areas orchestrated to perform each operation. As anticipated by cognitive scientists and neuroscientists, the apparently simple task of generating a verb for a presented noun is not accomplished by a single part of the brain but rather by many areas organized into networks. Perception of visually presented words occurs in a network of areas in the back of the brain, where many components of the brain's visual system reside. Perception of aurally presented words occurs in an entirely separate network of areas—in our temporal lobes.

Speech production (that is, simply repeating out loud the presented nouns) predictably involves motor areas of the brain. Regions thought to be Broca's and Wernicke's areas do not appear to be engaged routinely in this type of speech production, an activity that would be viewed by many as quite automatic for most fluent speakers in their native language. This finding suggests what we might have suspected: we occasionally speak without consciously thinking about the consequences.

Regions of the left frontal and temporal lobes (those corresponding in general to the respective locations of Broca's and Wernicke's areas) only become active when two tasks are added: consciously assessing word meaning and choosing an appropriate response. Moreover, two other areas come into play under these circumstances, forming a network of four brain regions. Interestingly, two areas used in the routine repetition of words were turned off. This shutdown suggests that the demands of generating a verb to a presented noun does not simply build on the task of just saying the noun. Rather the act of speaking a verb to a presented noun differs from speaking the noun, as far as the brain is concerned.

This finding caused us to pause and consider what would happen if we allowed subjects a few minutes of practice on their task of generating verbs. Although subjects initially discover that forming verbs rapidly is difficult (nouns are presented every 1.5 seconds), they become relaxed and proficient after 15 minutes of practice. An examination of the brain after training reveals that practice completely changes the neural circuits recruited [*see top illustration on this page*]. The circuits responsible for noun repetition now generate the verbs. Thus, practice not only makes perfect (something we have always known) but also changes the way our brain organizes itself (something we may not have fully appreciated).

As cognitive neuroscientists demonstrated the utility of PET technology, a newer method swiftly emerged that could compete with PET's abilities. Magnetic resonance imaging, or MRI, has now become a fairly common tool for diagnosing tissue damage. Recent developments have vastly increased the speed with which MRI can form images, thus making it suitable for research in cognitive neuroscience.

MRI derives from a potent laboratory technique known as nuclear magnetic resonance (NMR), which was designed to explore detailed chemical features of molecules. It garnered a Nobel Prize for its developers, Felix Bloch of Stanford University and Edward M. Purcell of

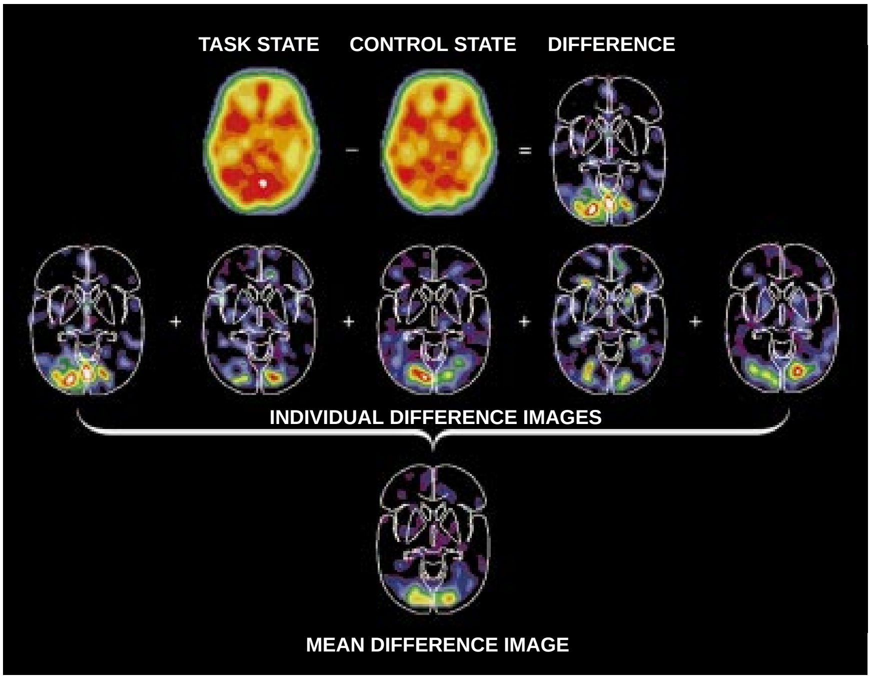


IMAGE SUBTRACTION AND AVERAGING serve as the foundation of functional brain imaging. Researchers subtract the PET blood-flow pattern of a control state from that of a task state to produce a difference image (*top row*). Data from different subjects are averaged (*bottom two rows*) to eliminate statistical fluctuations.

Harvard University, in 1952. The method depends on the fact that many atoms behave as little compass needles in the presence of a magnetic field. By skillfully manipulating the magnetic field, scientists can align the atoms. Applying radio-wave pulses to the sample under these conditions perturbs the atoms in a precise manner. As a result, they emit detectable radio signals unique to the number and state of the particular atoms in the sample. Careful adjustments of the magnetic field and the radio-wave pulses yield particular information about the sample under study.

NMR moved from the laboratory to the clinic when Paul C. Lauterbur of the University of Illinois found that NMR can form images by detecting protons. Protons are useful because they are abundant in the human body and, by acting as little compass needles, respond sensitively to magnetic fields. Their application resulted in excellent images of the anatomy of organs that far surpassed in detail those produced by x-ray CT [see "NMR Imaging in Medicine," by Ian L. Pykett; SCIENTIFIC AMERICAN, May 1982]. Because the term "nuclear" made the procedure sound dangerous, NMR soon became known as magnetic resonance imaging.

The current excitement over MRI for brain imaging stems from the technique's ability to detect a signal inaccessible to PET scans. Specifically, it can detect an increase in oxygen that occurs in an area of heightened neuronal activity. The basis for this capacity comes from the way neurons make use of oxygen. PET scans had revealed that functionally induced increases in blood flow accompanied alterations in the amount of glucose the brain consumed but not in the amount of oxygen it used. In effect, the normal human brain during spurts of neuronal activity resorts to anaerobic metabolism. Few had suspected that the brain might rely on tactics similar to those used by sprinter's muscles. In fact, this form of metabolism occurs despite the presence of abundant oxygen in the normal brain. Why the brain acts this way is a mystery worthy of intense scientific scrutiny.

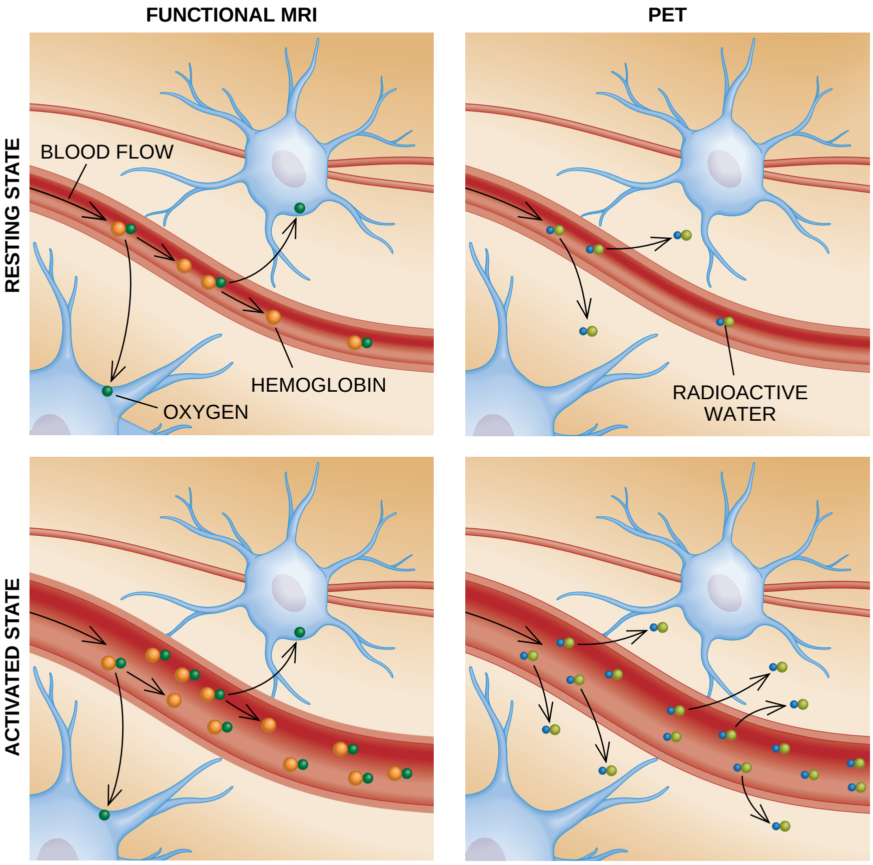
Additional blood to the brain without a concomitant increase in oxygen consumption leads to a heightened concentration of oxygen in the small veins draining the active neural centers. The reason is that supply has increased, but the demand has not. Therefore, the extra oxygen delivered to the active part of brain simply returns to the general circulation by way of the draining veins.

Why does oxygen play a crucial role in MRI studies of the brain? The answer lies in a discovery made by Nobel laureate Linus C. Pauling in 1935. He found that the amount of oxygen carried by hemoglobin (the molecule that transports oxygen and gives blood its red color) affects the magnetic properties of the hemoglobin. In 1990 Seiji Ogawa and his colleagues at AT&T Bell Laboratories demonstrated that MRI could detect these small magnetic fluctuations. Several research groups immediately realized the importance of this observation. By the middle of 1991 investigators showed that MRI can detect the functionally induced changes in blood oxygenation in the human brain. The ability of MRI machines to detect functionally induced changes in blood oxygenation leads many to refer to the technique as functional MRI, or fMRI.

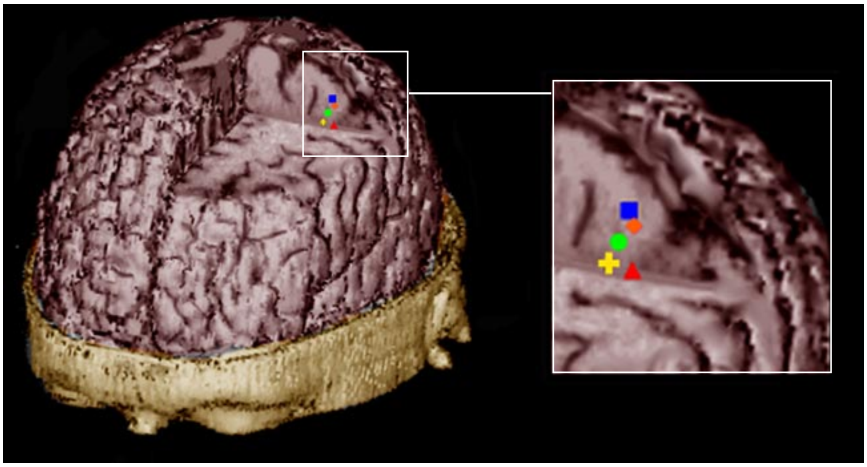
Functional MRI has several advantages over x-ray CT and other imaging techniques. First, the signal comes directly from functionally induced changes in the brain tissue (that is, the change in venous oxygen concentration). Nothing, radioactive or otherwise, needs to be injected to obtain a signal. Second, MRI provides both anatomical and functional information in each subject, hence permitting an accurate structural identification of the active regions. Third, the spatial resolution is quite good, distinguishing parts as small as one to two millimeters (better than PET's resolution). Fourth, when properly equipped (that is, given so-called echoplanar capability), MRI can monitor the rate of change in the blood-flow-induced oxygen signal in real time [*see illustration below*].

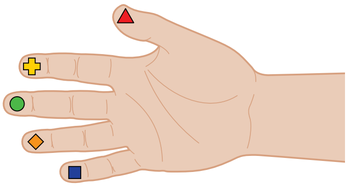
Finally, MRI has little, if any, known biological risk. Some workers have raised concerns about the intensity of the magnetic field to which the tissues are exposed. So far most studies have found the effects to be benign. The largest drawback is the claustrophobia some subjects may suffer. In most instrument designs the entire body must be inserted into a relatively narrow tube.

Several intriguing results with functional MRI were reported this past year. Robert G. Shulman and his colleagues at Yale University have confirmed PET findings about language organization in the brain. Using conventional, hospital-based MRI, Walter Schneider and Jonathan D. Cohen and their colleagues



BLOOD FLOW to the brain provides the signals detected by functional MRI and PET. When resting neurons (*top*) become active (*bottom*), blood flow to them increases. MRI (*left*) detects changes in oxygen levels, which rise in the nearby blood vessels because active neurons consume no more oxygen than when they are at rest. PET (*right*) relies on the increased delivery of injected radioactive water, which diffuses out of the vessels to reach all parts of the brain.





MAGNETOENCEPHALOGRAPHY, or MEG, captures neural activity too brief to be detected by PET or MRI. Above, MEG has located the areas in the normal adult somatosensory cortex associated with the digits of the right hand (*colored symbols*). The symbols on the MRI image of the brain correspond to those on the fingers.

at the University of Pittsburgh have corroborated work in monkeys that indicated the primate visual cortex is organized into topographic maps that reflect the spatial organization of the world as we see it. Other groups are actively trying to visualize other forms of mental activity, such as the way we create mental images and memories.

The ability of MRI systems to monitor the oxygen signal in real time has suggested to some the possibility of measuring the time it takes for different brain areas to exchange information. Conceptually, one might think of a network of brain areas as a group of individuals in the midst of a conference call. The temporal information sought would be equivalent to knowing who was speaking when and, possibly, who was in charge. Such information would be critical in understanding how specific brain areas coordinate as a network to produce behavior.

The stumbling block, however, is the speed of neuronal activity compared with the rate of change of oxygenation levels. Signals from one part of the brain can travel to another in 0.01 second or less. Unfortunately, changes in blood flow and blood oxygenation are much slower, occurring hundreds of milliseconds to several seconds later. MRI would not be able to keep up with the "conversations" between brain areas. The only methods that respond quickly enough are electrical recording techniques. Such approaches include electroencephalography (EEG), which detects brain electrical activity from the scalp, and magnetoencephalography (MEG), which measures the magnetic fields generated by electrical activity within the brain.

Why don't researchers just use EEG or MEG for the whole job of mapping brain function? The limitations are spatial resolution and sensitivity. Even though great strides in resolution have been made, especially with MEG [*see illustration above*], accurate localization of the source of brain activity remains difficult with electrical recording devices. Furthermore, the resolution becomes poorer the deeper into the brain we attempt to image.

Neither MRI nor PET suffers from this difficulty. They both can sample all parts of the brain with equal spatial resolution and sensitivity. As a result, a collaboration seems to be in the making between PET and MRI and electrical recording. PET and MRI, working in a combination yet to be determined, can define the anatomy of the circuits underlying a behavior of interest; electrical recording techniques can reveal the course of temporal events in these spatially defined circuits.

Regardless of the particular mix of technologies that will ultimately be used to image human brain function, the field demands extraordinary resources. Expensive equipment dominates this work. MRI, PET and MEG equipment costs from $2 million to $4 million and is expensive to maintain. Furthermore, success requires close collaboration within multidisciplinary teams of scientists and engineers working daily with these tools. Institutions fortunate enough to have the necessary technical and human resources need to make them available to scientists at institutions less fortunate. Although some radiology departments have such equipment, the devices are usually committed mostly for patient care.

In addition to the images of brain activity, the experiments provide a vast amount of information. Such an accumulation not only yields answers to the questions posed at the time of the experiment but also provides invaluable information for future research, as those of us in the field have repeatedly discovered to our amazement and delight. Recent efforts to create neuroscience databases could organize and quickly disseminate such a repository of information.

Wise use of these powerful new tools and the data they produce can aid our understanding and care of people who have problems ranging from developmental learning disorders to language disabilities arising from, say, stroke. Researchers have begun to use functional brain imaging to learn about the mood disturbances that afflict patients with such mental illnesses as depression. The technology could guide neurosurgeons in the excision of brain tumors, enabling them to judge how the removal of tissue will hamper the patient. Centers across the world are investigating such other mental activities as attention, memory, perception, motor control and emotion. Clearly, we are headed toward a much richer grasp of the relation between the human mind and the brain.

FURTHER READING

Intrinsic Signal Changes Accompanying Sensory Stimulation: Functional Brain Mapping with Magnetic Resonance Imaging. S. Ogawa, D. W. Tank, R. Menon, J. M. Ellermann, S.-G. Kim, H. Merkle and K. Ugurbil in *Proceedings of the National Academy of Sciences,* Vol. 89, No. 13, pages 5951–5955; July 1, 1992.

Somatosensory Cortical Plasticity in Adult Humans Revealed by Magnetoencephalography. A. Mogilner et al. in *Proceedings of the National Academy of Sciences,* Vol. 90, No. 8, pages 3593–3597; April 15, 1993.

Images of Mind. M. I. Posner and M. E. Raichle. W. H. Freeman and Company, 1994.

Practice-Related Changes in Human Functional Anatomy during Nonmotor Learning. M. E. Raichle, J. A. Fiez, T. O. Videen, A.-M. K. MacLeod, J. V. Pardo, P. T. Fox and S. E. Petersen in *Cerebral Cortex,* Vol. 4, No. 1, pages 8–26; January/February 1994.

Materials received from the Scientific American Archive Online may only be displayed and printed for your personal, non-commercial use following "fair use" guidelines. Without prior written permission from Scientific American, Inc., materials may not otherwise be reproduced, transmitted or distributed in any form or by any means (including but not limited to, email or other electronic means), via the Internet, or through any other type of technology-currently available or that may be developed in the future.