

# MAPPING THE HUMAN MIND

**Using PET scans to probe the human mind, researchers have been uncovering new ways to understand intelligence as well as differences in the way men and women think. Are these true breakthroughs or junk science?**

**A** RECENT SPATE OF PET BRAIN IMAGING studies have landed front-page headlines and newsmagazine cover stories. The research being heralded is not uncovering new advances in the diagnosis of Alzheimer's or Parkinson's diseases. Nor is it furthering the understanding of schizophrenia, head injuries or brain seizures, the traditional bastions of PET brain research. Rather, the studies that are making big news claim to have mapped the mysterious workings of the "normal" human mind: how we feel emotions, verbalize our thoughts, store our memories and exhibit intelligence—and how, as men and women, our brains work in profoundly different ways.

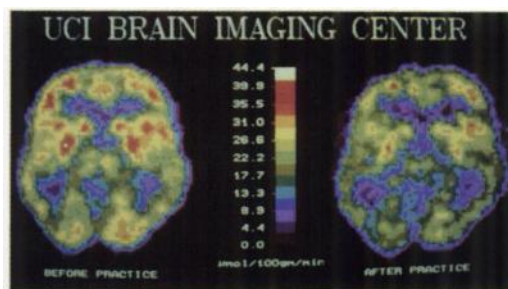
The latest research findings have peaked the public's interest and made for interesting topics of discussion at scientific conferences. Of the more intriguing findings: Our brains become more efficient and generate less activity as we learn complex tasks; when thinking of nothing, men activate different areas in their brains than women; men and women use different thought processes to solve the same mathematical equations. Some researchers, neuroscientists and nuclear physicians alike, are now questioning whether these findings are as dramatic as they seem. "I'm worried that some of the results have been overinterpreted," said Georg Deutsch, PhD, associate professor of radiology and neurology at the University of Alabama and co-author of *Left Brain, Right Brain* (WH Freeman, 1994). "If the data are used to make generalities about why learning disorders occur or the basis for differences between genders, it can be very dangerous."

## The Battle of the Sexes

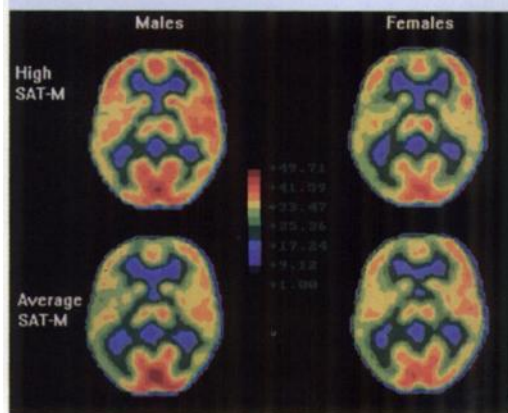
Just by seeing a little girl reach for a doll while a little boy grabs for a toy truck, it should be fairly obvious that men and women are inherently different. Although researchers have long observed differences in the verbal and spatial abilities of men and women, they only recently have been able to get a glimpse at how men's and women's brains function. To compare male and female brains at work, researchers at the University of Pennsylvania School of Medicine in Philadelphia used PET scans to examine the brains of 61 healthy adults who were in a relaxed resting state and told to "think of nothing." Fluorine-18-fluorodeoxyglucose (FDG) and arterial samples acquired over 90 minutes revealed that women and men whose brains were

idle had virtually the same amount of total metabolic activity. They found, however, two significant differences within the brain regions: Men had a higher metabolism than women in the temporal-limbic regions of the brain and lower activity in the cingulate gyrus, according to Ruben C. Gur, PhD, head of the school's Brain Behavior Laboratory and leader of the study published in *Science*. The cingulate gyrus is more highly evolved and is thought to be responsible for the switch to symbolic expression, said Gur. He speculates that these findings give weight to the hypothesis that men are more prone to express emotion through physical aggression, whereas women tend to vocalize their feelings.

In other research, Gur wanted to see if men and women varied in their ability to distinguish emotions such as happiness and anger. When he flashed photos of emotional states in front of the volunteers,



Does the intelligent brain work harder, or is it more efficient? PET images show both may be true. The research above shows a sharp drop in glucose metabolic activity in the brain (red areas) of a volunteer attempting to learn a computer game (left) and after 1-2 months of daily practice (right). The research below shows male students with high SAT scores have more intense activity in the temporal lobes (red areas), whereas men with average scores—as well as all women—have no increase.



## Brain Scans in the Courtroom

During the past few years, PET and SPECT scans have been making their way into courts of law from murder cases to product liability suits to toxic exposures during environmental accidents. This growing trend has many nuclear medicine researchers concerned that these scans are being used to diagnose specific brain abnormalities before these patterns are grounded in scientific studies. For instance, PET and SPECT scans have been used more and more in criminal cases by defense lawyers often during sentencing hearings in an effort to try to prevent their clients from receiving the death penalty. "There are no scientific data at this time to indicate that abnormalities in blood flow or glucose metabolism can identify or predict personality traits such as incompetence, impaired judgement or homicidal tendencies," said Helen S. Mayberg, MD, an associate professor of neurology, psychiatry and radiology and a senior scientist in the PET division of the Research Imaging Center, University of Texas Health Science Center, San Antonio who serves as a consultant to both prosecutors and defense attorneys in criminal and civil cases.

Mayberg believes that, in most cases, functional brain imaging scans do not yet meet the admissibility requirements necessary in a court of law. To date, brain scans performed for legal purposes have involved cases of suspected seizures and minor head trauma in criminal defendants or neurotoxic exposures in plaintiffs for which measures of reliability (sensitivity and specificity rates) have not been established. "Judges not only often want to know if the technique itself is reliable and generally accepted in the medical community but also if the application of a test for a specific purpose is widely accepted," said Mayberg.

Despite the rigidity of the legal admissibility standards, PET and SPECT scans have made star appearances at some of the most well-known trials. In several breast implant cases against Dow Corning, rheumatologists have claimed that the implants cause neurotoxic effects and have ordered SPECT scans on women with vague neurological symptoms. Many of these scans have been interpreted by nuclear physicians as abnormal, and women are being given horrifying diagnoses of brain damage which are then presented to the court. "I've reviewed a number of these so-called 'abnormal' scans and have found many to have been overinterpreted or to have overlooked other possible causes for abnormalities," said Mayberg. Functional brain scans have also been used in the Exxon Valdez case to support the claim of residents who live near the oil spill site that they suffer from multiple chemical sensitivity, another condition that the scans cannot reliably diagnose, according to Alan Waxman, MD, director of nuclear medicine at Cedars-Sinai Medical Center in Los Angeles.

Although against the use of functional brain scans for many situations, Mayberg, Waxman and other nuclear physicians believe that the scans may be useful for limited forensic purposes. "If someone has a seizure and commits a crime, the legal system should take this into account," said Abass Alavi, MD, head of the division of nuclear medicine at the University of Pennsylvania School of Medicine and chairman of the SNM Brain Imaging Council. "Seizure patterns have been well documented in the medical literature." But, he cautions, normal variations in brain scans also need to be considered. In a study published this month (*J Nucl Med* 1995;36:1141), Alavi and colleagues found a significant variability in the patterns of brain metabolic activity among healthy people. Alavi advises nuclear physicians who are called upon to perform scans in court cases to be aware of such variations in brain scans before rendering a definitive opinion about a finding on a scan. "Nuclear physicians should not interpret abnormalities lightly because any chart can be subpoenaed in a future court case," he said. "During a trial, their diagnosis may be taken for evidence as absolute proof."

he found that both sexes performed equally well, but the PET scans showed that women's brains were less activated than men's. "This could mean that women are instinctively better at identifying emotions, thus their brains are more efficient," said Gur. Researchers have also used PET to see how men and women process their own emotions. A new study from the National Institute of Mental Health found that women, who were asked to recall sad memories, showed limbic system activation eight times greater than that in the men. According to the study's researchers, this fits into the theory that women experience a more profound sadness than men and may be related to why women are twice as likely to suffer from depression.

### The New IQ Test

Ever since French psychologist Alfred Binet devised the first intelligence test, scientists have been trying to develop fool-proof ways to measure intelligence. The use of PET scans to measure an individual's IQ may be unrealistic, but researchers have been taking images of thinking brains to gain clues to the nature of intelligence. For the past several years, neuropsychologist Richard J. Haier, PhD, has been injecting volunteers with FDG and instructing them to engage in various mental tasks to measure glucose metabolic rates in their brains with PET. His initial findings indicated that intelligent brains solve complex problems by conserving energy rather than by guzzling glucose. In one noteworthy study, Haier documented sharp drops in overall brain activity for eight men after one to two months of daily practice playing Tetris, a computer game that required them to rotate and move various shaped floating blocks to create solid rows of blocks. He also found that the glucose metabolic rate is higher among those who are mildly retarded. "The reason for the increased activity in a retarded person's brain may be due to a lack of pruning of the neural synaptic connections during infancy," Haier said. "This over-firing of neurons could make the brain much less efficient."

Glucose efficiency shows only part of the bigger picture of intelligence. In a recent study, Haier discovered that a harder working brain may actually signal a superior mathematical ability in males, although not in females. He gave a group of male and female college students who had high SAT math scores a mathematical reasoning test and then took a series of PET scans. He found the high-SAT men had large increases in glucose use throughout their brains as the equations grew more difficult. On the other hand, men with average SAT scores and women with both high and average SAT scores

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helpers. Residents donated so much blood that blood banks announced that they had more donations than they could use or even process. Also, relief organizations such as the Red Cross and Feed the Children responded overwhelmingly. One business owner found and donated "boots" for the rescue dogs whose paws were cut and bleeding from the glass and sharp edges in the building as they searched for living survivors. On the Sunday after the bombing, a local TV station announced that certain supplies were needed and set up a collection point on their grounds. Within 30 minutes, there was a line of cars nearly one mile long bringing needed items.

For the first time in history, I suspect, there was continuous 24-hour TV and radio coverage of an event without a single commercial or advertisement for more than six days in our city. There was not a single case of someone looting the business establishments with bombed-out doors and windows, although the police were busy at the bomb site itself. In fact, there were virtually no reported crimes in Oklahoma City until the weekend after the bombing.

At the public memorial service, more than 10,000 people stood

uncomplainingly in line for hours to gain admittance, and they applauded the loudest for the exhausted rescue workers who took a few hours off to attend. The presence of President and Mrs. Clinton and Reverend Graham was an appreciated response to the events. The healing in the heartland had begun.

*Tuesday, May 23, 1995:* The remainder of the Alfred P. Murrah federal office building was brought down in 6.5 seconds. Some residents wanted it left as a reminder, but most felt it should be removed. I believe the correct decision was made. I sense a further relief and a progression of the healing process in myself and others. The last three bodies will be recovered in a few days, and the site will be cleared in about two weeks. I hope that a memorial will be constructed soon at the bombing site, where years from now one can visit for a quiet moment of remembrance and reflection on the meaning of this event for our country and ourselves. I hope mostly, however, that this site will be the only such memorial ever needed.

*E. William Allen, MD*

*Dr. Allen is the director of nuclear medicine service at the University of Oklahoma Health Sciences Center.*

### ***Brain Mapping*** (Continued from page 12N)

experienced no increases in activity. "There was increased activity in the temporal lobes of the high-SAT men, but we don't know why this isn't true for women," Haier said. "Women must be using a different part of the brain not yet identified."

#### **Real Science or Not?**

The contradictions that seem to be arising in these studies have alarmed some neuroscientists. If an educated brain works more efficiently, why do men with mathematical abilities have more of an increase in their glucose metabolic rate when performing a complex equation? If sad women have more activated anterior limbic systems, why do clinically depressed people have unresponsive, almost lethargic, limbic systems? "The activity could be on a bell curve," explains Haier, "where the brain activity of people at both extremes is similar." He does, however, concede that this is only speculation and that the brain efficiency versus brain capacity contradictions are, as yet, unexplainable.

Even without these discrepancies, researchers have begun questioning the scientific processes that are being used in these studies. Although PET has the capacity to make quantitative measurements, researchers often do not obtain these measurements in their studies because repeat blood sampling would be required throughout the imaging. They also rely on one human brain from a 60-year-old woman as the standard for determining where brain regions lie. "Human brain shapes are different and the methods of analyses often used in these studies homogenize the normal variations in structures to exaggerate the differences in regions that are activated," said Floyd E. Bloom, MD, editor-in-chief of the journal *Science*.

A third problem with functional brain imaging studies: Researchers use a subtraction paradigm to determine the brain areas being more activated as a result of performing a task. To hone in on the areas stimulated by a complicated task, researchers

### **The New Brain Imaging Technique**

Until now, most human brain mapping research has used PET scans to detect changes in blood flow that accompany increased activity in specific brain regions. Over the past several months, however, many of the mapping studies earning prominent spots in scientific journals have used functional magnetic resonance imaging (fMRI). Case in point: Researchers from Yale University grabbed front page headlines when they used fMRI to find that men and women use different parts of their brains to figure out rhymes.

This new brain imaging method, developed in the early 1990s, has some advantages over PET: "Functional MRI has a very fast time resolution, requiring only 40 seconds for each image whereas with <sup>15</sup>O for blood flow studies, it requires 3 to 4 minutes; with FDG for glucose metabolism studies, it takes about 30 minutes for each image," said Ruben C. Gur, PhD, head of the University of Pennsylvania School of Medicine's Brain Behavior Laboratory. The MRI technique also does not expose patients to radiation, so researchers can perform experiments more readily on children. Moreover, hospitals are more likely to have an MRI scanner than a PET scanner, which requires a cyclotron and is generally more expensive.

There is no indication that fMRIs will eventually replace PET. "A major drawback to fMRI is that it is not yet quantitative," said Georg Deutsch, PhD, associate professor of radiology and neurology at the University of Alabama. Results are based on qualitative comparisons, that is, whether one testing condition produced more or less activity than another condition. "This can't tell you the extent of the increase or decrease," said Deutsch. Although fMRI may eventually become quantitative, it will still be limited in that it can only measure blood flow. PET, on the other hand, can image glucose metabolism and be even more specific by mapping the functioning of neurotransmitter-defined pathways.

divide the task into several parts and take multiple images. They then subtract the images of simpler tasks from the most complicated to isolate a "pure mental act" and obtain an image of how a specific task or emotion activates the brain. This subtraction method works fairly well in simple situations—such as using a finger tapping task as a motor control for a task involving decisions made by finger taps. The multiple subtractions become unreliable, however, when used in an attempt to isolate high level mental functions such as how the brain interprets the meaning of words as opposed to speech sounds. According to Deutsch, this is because the subtractions are based on untested assumptions of how complex mental operations break down into simpler steps.

"There's no question that many of the images that appear in scientific journals are highly manipulated data," said Deutsch. "They may capitalize on chance differences that fit the investigator's hypotheses." This means that subtle differences, say, between the way men's and women's brains are activated during emotional tasks can lead to exaggerated conclusions.

These subtracted and manipulated images do not mean that the findings are false, but they should be considered when the study's authors write about the possible implications of their findings in journals. Instead, researchers sometimes take liberties when explaining how their results could be applied in the clinical world. "These studies are very preliminary," said Henry N. Wagner, Jr., MD, professor of medicine, radiology and environmental sciences at The Johns Hopkins Medical Institutions in Baltimore. "Blood flow and glucose metabolism studies can only show the general area of where the brain is activated and tell researchers where to look further. The media and some of the researchers themselves are taking giant leaps by saying the results can explain how the brain functions. They are taking complicated multifactorial systems and oversimplifying them."

On the flip side, some neuroscientists claim the new brain imaging research—whether exaggerated or not—is actually old hat. "I have yet to see any findings that are truly surprising or deviate much from what has been shown over the past 100 years by neuropsychology," said Deutsch. For instance last December, a highly publicized study from Yale University, which used functional MRI to assess the brain activity of men and women performing rhyming tasks, found that men use only one region in the left side of the brain, whereas women use a much wider area on both sides. "Sex differences in the lateralization of the human brain have been documented in clinical studies of female stroke patients who lose less

of their language ability than male patients," he said, "although it is nice to have it demonstrated in a functional scan."

The major problem with brain imaging studies is that there is so much data generated in each experiment that it is often difficult for researchers to sort out the true patterns from the artifacts. "Researchers thus tend to disregard data that do not fit with scientific theory and to keep the findings that do," Deutsch said. The dilemma? Scientific findings are supposed to lead to new theories not be molded to fit existing ones.

### What to Do with the Findings

Although functional brain imaging is still in its earliest stages, the accuracy and specificity of PET brain measurements are constantly improving: There may come a point when PET scans are reliable enough to assess a person's intelligence, job performance and emotional states. Brain scans have already become widespread in courtrooms for criminal and product liability cases (see page 12N). Who's to say that the scans won't become a litmus test to measure the spatial abilities of would-be pilots, or to weed out learning-disabled children from regular classes or even to alter our beliefs that men and women are capable of performing the same jobs equally well?

"I'm always wary of using science for a political agenda, especially if the agenda outpaces the science," said Wagner. "Researchers who extrapolate from simple measurements of blood flow to explain complicated phenomenon are inviting the danger that their preliminary observations will become statements of fact to advance someone else's ideas." Some recently published pop-science books are already claiming that male brains are not as easily distracted by superfluous information and that women may be less able to separate emotion from reason.

Gur, however, points out that suppressing human curiosity to find out how the brain works is also dangerous. He recounted an incident where his wife, psychiatrist Raquel Gur, MD, gave a talk to medical students about sex differences in brains. A group of women asked her to stop publicizing the work saying that they were afraid women would lose the professional gains they have made over the last 20 years if researchers asserted that the sexes are not the same. "I would hope that as we understand sex differences better, we can understand each other better as men and women," he said. One can only hope that a new understanding of the brain does not advance old stereotypes.

*Deborah Kotz*

## NEWS BRIEF

The Nuclear Regulatory Commission (NRC) has a new leader at the helm: As of July 1, Shirley Jackson, PhD, will serve as chairman. The U.S. Senate confirmed Jackson in April, and she was sworn in as a commissioner of the NRC on May 3 before being named chairman by President Clinton.

Before coming to the NRC, Jackson was

a physics professor at Rutgers University and served as a theoretical physicist at AT&T Bell Laboratories. She was also a member of the board of directors of Public Service Electric and Gas Company, and a member of the Institute of Nuclear Power Operations Advisory Council.

With three vacant commissioner posts due to the recent departure of Commissioner E. Gail DePlanque, the NRC is still left without a quorum. Clinton nominated Dan M.

Berkovitz last January for a commissioner post, but his nomination has stalled in the Senate Environment and Public Works Committee. Eight of the committee's nine Republicans wrote a letter to Clinton last month urging him to withdraw the nomination because they think Berkovitz "would impose burdensome regulations" on the industry with no public benefit. As for the other openings, no nominations have been forthcoming as of presstime.