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Fact or Phrenology?

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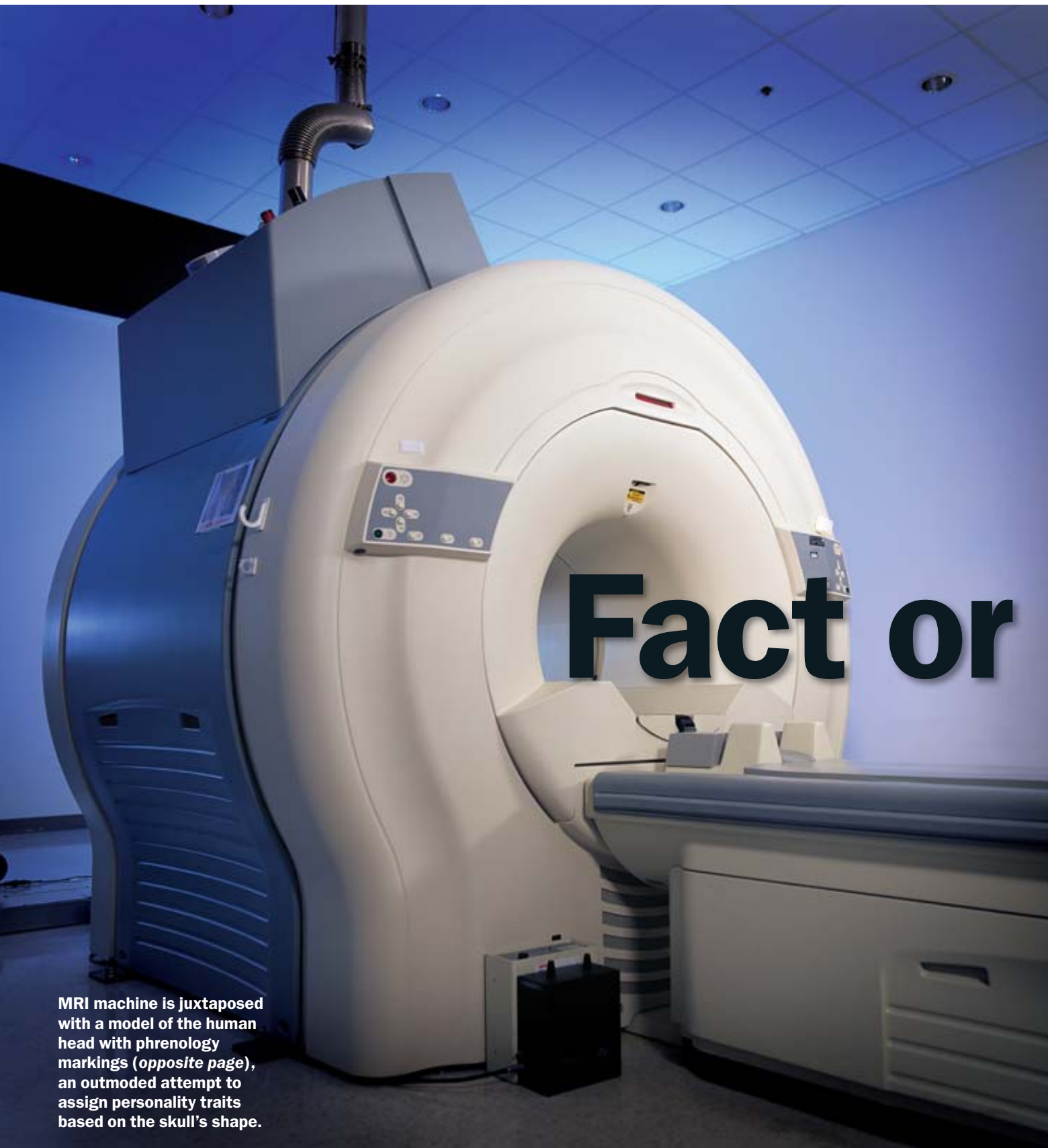
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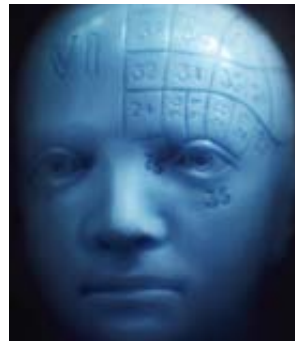


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MRI machine is juxtaposed with a model of the human head with phrenology markings (*opposite page*), an outmoded attempt to assign personality traits based on the skull's shape.



The growing
controversy over
fMRI scans
is forcing us to
confront whether
brain equals mind
By David Dobbs

Phrenology?

unctional magnetic resonance imaging—or fMRI—has made quite a splash since its introduction a decade ago. Operating at spatial dimensions and time-scales far finer than previous brain-scanning techniques, it has sparked great excitement by letting us finally watch the brain at work. Thousands of fMRI studies have explored a wide range of differences in brain activation: adolescents versus adults, schizophrenic and normal minds, the empathetic and the impassive. Researchers have used fMRI to draw bold conclusions about face and word recognition, working memory and false memories, people anticipating pain, mothers recognizing their children, citizens pondering ethical dilemmas—not to mention why many consumers buy Coke even though they really prefer the taste of Pepsi. Psychologists have praised fMRI for finally making their science more quantifiable. And cognitive neuroscientists have cited the scans heavily in the recent, vast expansion in understanding of the brain.

Increasingly, however, arguments are stirring over the reliability of fMRI findings. This debate, at once technical and philosophical, concerns both fMRI's accuracy, because it measures neuronal activity indirectly by detecting associated increases in blood flow, and its legitimacy in linking complex men-

CORBIS (fMRI machine and phrenology head)

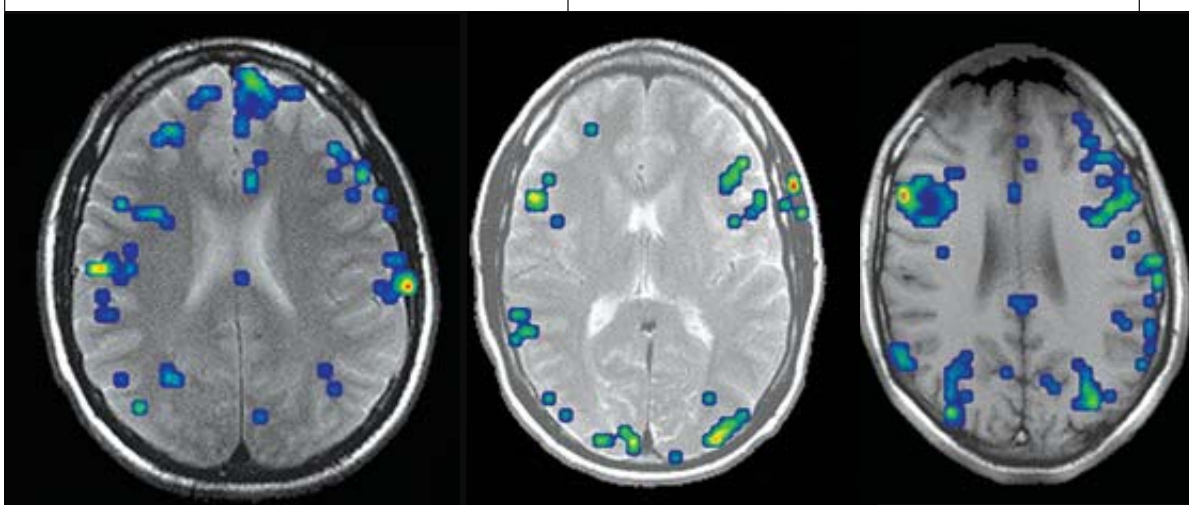
tal functions to particular brain regions. Critics feel that fMRI overlooks the networked or distributed nature of the brain's workings, emphasizing localized activity when it is the communication among regions that is most critical to mental function.

"This is a very gross technique," says critic Steven Faux, who heads the psychology department at Drake University. "It's like a blurry photo—better than no photo but still blurry, with real limitations that are too often overlooked. It's very easy to overextend [the value of] this technology."

Many fMRI practitioners seem bewildered that this powerful new tool has created controversy. "It is a huge surprise to me how big this issue has become," says Marcus E. Raichle, a Washington University neurologist who has re-

The 1970s also brought the first functional imaging technology—scans designed to show not just how the brain is structured but how it functions. Positron emission tomography (PET) measures increases in blood flow associated with neuronal activity, giving a sense of which neurons may be processing information. A subject is injected with radioactive elements that tag molecules such as glucose that are delivered to the brain by blood. The tags emit positrons and reveal the relative rates at which cells consume the glucose, a marker of which cells are active during mental processes. The scans are captivating, but there are a number of drawbacks. Subjects worry about taking in radioactive material; the process requires the better part of an hour for a scan; and the images provide a rather broad temporal resolution of 60 seconds (meaning it

Functional MRI scans of six people who took the same spatial memory test show how varied brain activation patterns can be. Scientists must design fMRI experiments carefully to avoid misleading conclusions.



searched brain scanning for more than two decades.

Vague Precision

Brain imaging began with an early 20th-century method called pneumoencephalography, a dangerous procedure in which the skull's cerebrospinal fluid was replaced with air to show the brain more clearly on x-ray. The angiograph, developed in the 1920s, produced improved results by capturing images of dyes injected into the bloodstream. (Angiography is still used to help diagnose and track blood vessel defects and some tumors.) These early methods showed only static structure rather than function. Computed axial tomography (CAT or CT) scans, developed in the 1970s, exploited x-ray technology and took static pictures, too, but with far greater detail.

takes that long to measure the blood flow to an area) and a spatial resolution of six to nine cubic millimeters—large for a nuanced understanding of what is happening.

In contrast, fMRI can scan a brain cross section in less than two seconds, enabling it to model most of the brain in one to two minutes. It can work at spatial resolutions as fine as two to three cubic millimeters, although in practice it usually collects information in voxels (a term that merges "volume" with "pixel") about two millimeters square and four to five millimeters long, about the size of a grain of rice. FMRI requires no injections, allowing more extensive scanning. In a typical study, a subject lies in a doughnut-shaped machine and is first scanned at rest with his eyes closed to provide a baseline reading. He is then scanned again while performing some mental task: identifying faces, threading a computerized

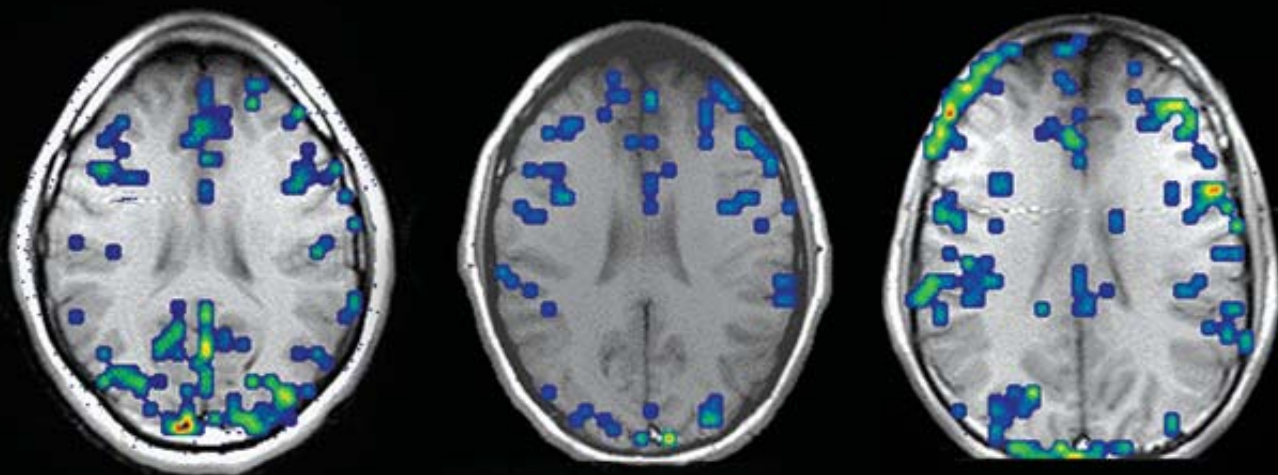
DAVID C. OSMON University of Wisconsin-Milwaukee

(The beautiful graphics fMRI produces imply much more precision than there actually is.)

maze, engaging in a role-playing game. In the most common technique, called BOLD (for blood oxygen level-dependent) fMRI, the machine measures increases in blood flow by spotting a change in magnetism that occurs when a blood surge raises the ratio of fresh, oxygenated hemoglobin to “used,” deoxygenated hemoglobin, which has a significantly different charge. The regions creating surges appear as brighter colors on the images, red changing to yellow as flow rises. Doubts about whether these increases correspond to actual neuronal activity have been answered by several studies tying blood flow di-

small group of neurons drawing little blood, or a thin network of neurons connecting large regions, may perform functions as crucial as a larger group elsewhere but either go undetected or show up as minor activity. Likewise, some neurons might operate more efficiently than others, consuming less blood. All these factors could mean that an fMRI image misrepresents actual neurodynamics.

Processing the scan’s gigabytes of raw data so that they become images introduces other caveats. Researchers must choose among and adjust many different algorithms to extract an accurate



rectly to neuron signaling, including recent animal models that used probes to match the firing of individual neurons to the heightened flow seen in fMRI scans.

Yet the link is decidedly rough. Abigail A. Baird, a Dartmouth College psychologist who uses fMRI to study brain changes during adolescence, puts it succinctly: “Hemodynamic response is a sloppy thing.” For starters, neuronal action takes milliseconds, whereas the blood surge follows by two to six seconds; a detected increase in blood flow therefore might be “feeding” more than one operation. In addition, because each voxel encompasses thousands of neurons, thousands or even millions may have to fire to significantly light up a region; it is as if an entire section of a stadium had to shout to be heard.

Meanwhile it is possible that in some cases a

image, compensating along the way for variations in skull and brain configuration, movement of subjects in the scanner, noise in the data, and so on. This “chain of inferences,” as a recent *Nature Neuroscience* article called it, offers much opportunity for error.

Finally, most fMRI studies use univariate processing, which critics say shortchanges the distributed nature of neurodynamics. The charges rise because univariate (literally “one variable”) algorithms consider the data coming in from each voxel during a scan as one sum, which makes it impossible to know how the activity in a particular voxel accrued (all at once, for instance, or in several pulses) or how it related sequentially with activity in other voxels. Univariate processing *does* see all the parts working—thus the multiple areas lit up in most images—but not in a way that shows how one area follows or

Functional MRI is still young and is being used as a first-survey tool of more complex mapping to come.

responds to another. This situation makes viewing an fMRI image something like listening to a string quartet by hearing (condensed into a single noise after the music has ended) only the total amount of sound each instrument produced during the piece, rather than hearing how the players accompany and respond to one another. Statistical methods known as multivariate analysis can break down each voxel's activity and analyze the interchanges among brain regions, but the complexity of those analyses has so far limited their use.

Obvious and Not So Obvious

For some, these vagaries and limitations make fMRI too rough an instrument for the more ambitious work for which it is being used. "The beautiful graphics fMRI produces imply much more precision than there actually is," says Drake University's Faux. "It's really a very gross, if not vague, physiological measurement that people are using to try to pin down some very complex behaviors. And in too many studies the authors way overinterpret the data. None of that advances the science."

Raichle says this damns an invaluable tool for practitioners' occasional improper use. "We have to remember we're studying the brain," Raichle says, "about which we know very little. Imaging lets us probe it to generate new hypotheses. Some of the probing will look silly in retrospect. But much of it is very productive."

The silly pursuits are not terribly hard to find. Consider, for instance, a study showing that men's amygdalas (which play a key role in generating emotion) light up when they view Ferraris. Others, as Faux says, recklessly overinterpret: a study of Democrats and Republicans watching videos of John Kerry and George W. Bush concluded that heightened activity in the subjects' emotion-sensitive amygdalas when they viewed the opposing candidate "suggest[ed] the volunteers were actively trying to dislike the opposition." Yet other studies suffer from major design failures, as did more than 30 that claimed to find physiological markers of ADHD in children diagnosed with the disorder—but failed to control for the effects of their subjects' Ritalin use.

Such work does not prove any fatal flaw in fMRI, Dartmouth's Baird says, but instead high-

lights the importance of using careful technique, solid study design and judicious interpretation. Baird, who likes to check her fMRI studies against similar research using other methods, likens fMRI interpretation to analyzing skid marks at an accident scene: "Someone who's done it often, who is careful and who collects a lot of other evidence will probably draw useful conclusions. Someone who's inexperienced or who doesn't check the whole scene will probably read them poorly."

Even serious, well-crafted studies can be undermined by subtle design failures. In a widely cited and publicized study of adolescent emotional responsiveness, for instance, Deborah Yurgelun-Todd of Harvard Medical School's McLean Hospital scanned adolescents as they characterized the expressions of fear-struck, middle-aged faces shown in black-and-white photographs. Compared with adults, adolescents viewing the images showed less activity in the frontal lobes, where much analysis and judgment occurs, and more in the amygdala. The adolescents also scored poorly in characterizing the expressions. Yurgelun-Todd told PBS's *Frontline* that the results suggested that "the teenager's brain may be responding with more of a gut reaction than an executive or thinking kind of response." But in a follow-up, Baird ran a similar experiment using color photographs of adolescent faces and found the adolescent subjects responded and scored much like adults. "They were simply more engaged by more contemporary photos in color," Baird says. "They did well if they cared."

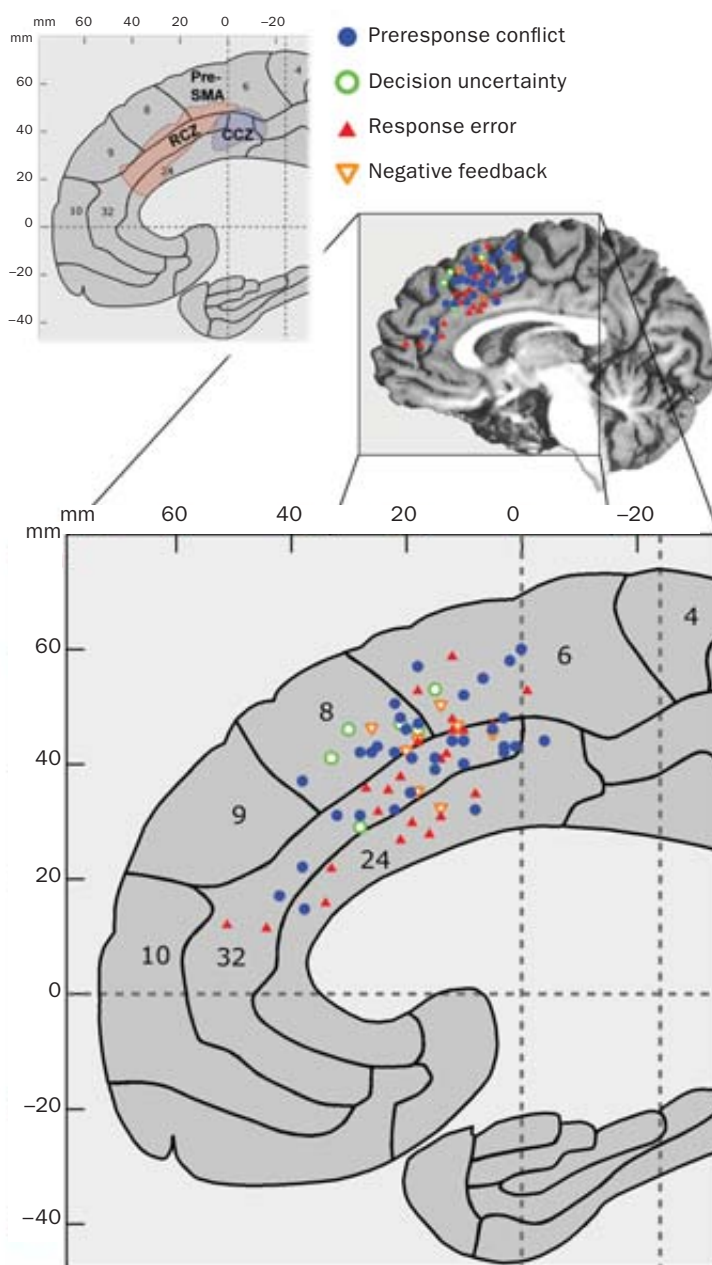
This tale highlights some of fMRI's most vexing nontechnical difficulties: the danger and ease with which a design flaw can corrupt results; the imagery's power to sway professionals, the media and the public despite those flaws; and the way results can reinforce conventional ideas, such as those regarding teen thinking and behavior. This last problem animates some of fMRI's most significant critiques. Some critics, including

(The Author)

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Find the Executive

Many fMRI studies have “pinpointed” the brain’s so-called executive function, believed to organize thoughts and planning, and declared it to be the cause of various mental deficiencies (*noted in key*). Yet an analysis by K. Richard Ridderinkhof of the University of Amsterdam of 38 such studies shows that determination of the executive function’s location (*colored icons, middle and bottom*) varied considerably across the medial frontal cortex (*colored regions, top*), notably in zones of the cingulate cortex (Pre-SMA, RCZ, CCZ). Critics also note that these regions may “light up” on many tests simply because the executive function underlies so many brain activities, providing little insight into the cause of a given deficit. (Numbers on schematics, such as 10 and 32, identify general anatomical zones.)



Faux and psychologist William R. Uttal, professor emeritus at the University of Michigan at Ann Arbor, argue that many of the cognitive functions under study in fMRI work are so abstract and vague that they denote little more than a conceptual nervous system. At the top of Faux’s list is the brain’s so-called executive function. “That’s a real favorite,” he says, “to measure the ‘central executive.’ Now—what is that?”

Many psychiatrists and neurologists agree that executive function is a real faculty, and im-

aging and physical studies indicate it arises from a network of regions in the prefrontal cortex and anterior cingulate cortex (a small location tucked between the two frontal lobes). The executive function organizes thoughts and gives people the ability to plan and carry out their resolutions. But brain experts are suspicious about how often executive function is cited as a factor in fMRI tests; the regions involved light up frequently. Too many researchers may too glibly conclude that executive function is therefore the

culprit, whereas its regions may just be lighting up because executive function underlies so many brain activities that it may pretty much always be “on.”

In part, critics such as Faux and Uttal are protesting the arbitrary nature of terms that are necessarily abstract; they are questioning judgment calls about the reality of an unseen thing. A scan is only a representation of activity. But fMRI proponents counter that everyone seems to accept when physicists and astronomers describe distant cosmological objects that are not seen at all but that are inferred from data. The same goes for the ultimate building blocks of matter. “You can’t see or measure subatomic particles directly,” notes John Darrell Van Horn, who directs operations at the fMRI Data Center at Dartmouth. “But they’re useful, well-supported mod-

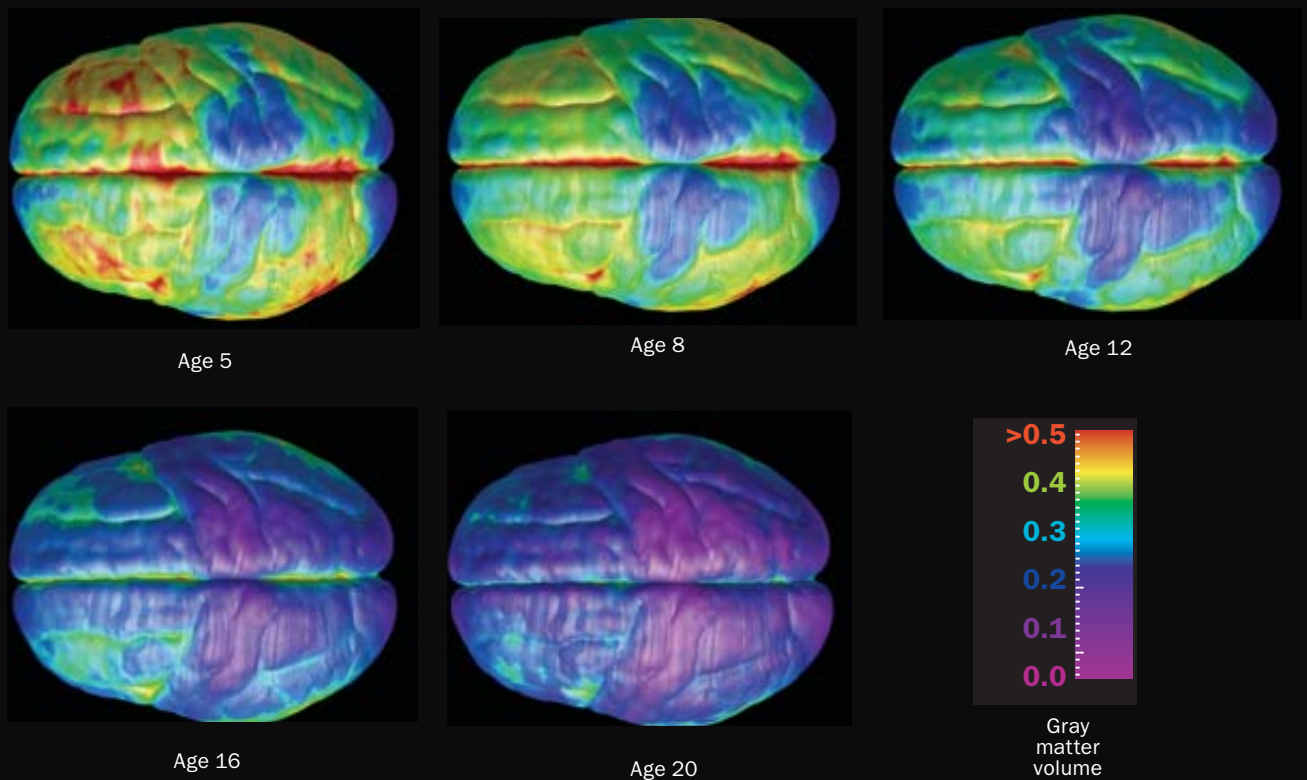
els we can refine based on experiment. I think many of these functions are quite similar.” Yet as Van Horn points out, the central executive concept pushes the limit for many, including him; he considers it more metaphor than model. Further evidence will be needed to resolve these fuzzy nomenclature issues.

A Wider View

It is not happenstance that fMRI controversies concern matters both conceptual and tangible. This duality is inherent in scientists’ attempts to connect the ephemeral mind to the corporeal brain. One basic concern is that fMRI is a new wrinkle on the old temptation to tie specific mental processes to particular brain regions.

Few researchers seriously believe that brain

Gray Areas



Functional MRI can map the brain’s composition with exquisite clarity. This sequence shows how gray matter is gradually replaced or overgrown with white matter between ages 5 and 21. A defense attorney could ostensibly use such information to ask that a teenager convicted of a violent crime not be sentenced as an adult since his cognitive capacity is not as fully developed.

IMAGES COURTESY OF PAUL THOMPSON, KIRALEE HAYASHI AND ARTHUR TOGA University of California, Los Angeles AND NITIN GOGTAY, JAY GIEDD AND JUDITH RAPOPORT National Institute of Mental Health

functions are so compartmentalized. As Raichle says, “No rational person would suggest there’s a single ‘emotion’ spot, for instance.” Yet most fMRI studies have indeed focused on how a given mental process activates certain areas. This has provoked the biting accusation that fMRI studies constitute “the new phrenology,” a modern version of the 19th-century practice of interpreting the bumps on a person’s skull as a map of his or her intelligence and character. Uttal has written an entire book about the subject [see “Further Reading,” below].

which object that person had been viewing. Expanding and refining such multivariate protocols should let fMRI reveal far more about how the brain’s regions work together.

Will such improvements end the controversies about fMRI and other brain imaging? Perhaps in part. More standardized processing protocols and peer review should reduce methodological blunders. And advances will most likely overcome technical concerns; researchers are already working on combining fMRI’s spatial acuity with the tighter temporal resolution of electro-

(Most people are uncomfortable with having their ideas and feelings reduced to pixelated pictures of neurons.)

This charge may be overstated. Most fMRI investigators seek not to localize brain function but to map the parts of the system that act in different combinations for different tasks. Although the very approach may suggest a localization mind-set, it may simply be that fMRI is still young as a technique and is being used as a first-survey tool of more complex mapping to come; it is only natural to plot a simple map of cities before delineating the intricate road systems that link them. Even when compared with those of just three years ago, fMRI studies today more often identify and discuss relations between several active brain regions. Someday fMRI may be able to show the brain’s true nature, which Raichle says is “like an orchestra,” with the different sections playing at various times, volumes and timbres depending on the effect needed, interacting in endless combinations to create an infinite variety of music.

What’s Next?

To hear that music more fully, current fMRI technology must advance. One key is to improve the multivariate algorithms that can track interactions among brain regions. Researchers such as James V. Haxby of Princeton University, David Cox of the Massachusetts Institute of Technology, Mona Spiridon of the University of Geneva in Switzerland and Christian Habeck of Columbia University have successfully used multivariate processing to reveal interactions among brain areas. Cox found that volunteers looking at different objects produced patterns so distinctive that he could quickly learn to examine a series of scans from a subject and correctly guess

encephalography and magnetoencephalography, which measure neuronal activity by detecting, respectively, the minute electrical and magnetic activity that neurons produce. Such innovations, and others not yet foreseen, should someday measure neural activity with more spatial and temporal precision.

Such advances may or may not resolve the philosophical anxiety that brain imaging provokes. The attempt to identify the neural correlates of consciousness rouses the long insistence, first fully articulated by René Descartes, that our minds are more than our brains. We resist the notion of “the mind as meat,” as novelist Jonathan Franzen phrased it when contemplating his father’s Alzheimer’s disease. Most people are uncomfortable with having their ideas and feelings—what seem to be their very character and identity—reduced to pixelated pictures of neurons in action.

As technology makes it easier to bind the two, this metaphysical unease may only grow. Or perhaps we will get over it. As noted University of Iowa neuroscientist Antonio R. Damasio, who calls this resistance “Descartes’ error,” argues, we may eventually tie the complexities of thought and emotion to our neurons without any sense of loss.

(Further Reading)

- ▮ **A Measured Look at Neuronal Oxygen Consumption.** John E. W. Mayhew in *Science*, Vol. 299, pages 1023–1024; February 14, 2003.
- ▮ **The New Phrenology.** William R. Uttal. MIT Press, 2003.
- ▮ **Interpreting the BOLD Signal.** Nikos K. Logothetis and Brian A. Wandell in *Annual Review of Physiology*, Vol. 66, pages 735–769; March 2004.