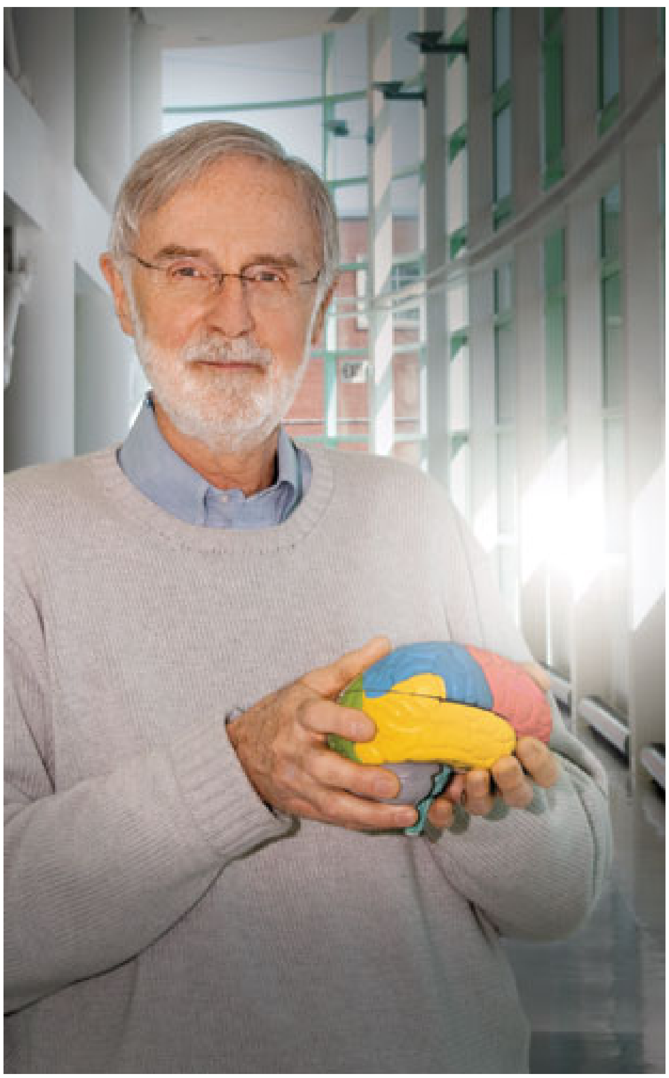
Brains in Action

An inspiring lecturer turned Marcus Raichle's focus from music and history to science. Since then, he has pioneered the use of imaging to study how our brains function.

By Anna Azvolinsky | November 1, 2014



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Marcus Raichle was a University of Washington junior majoring in history and political science when he took his first biology class to fulfill a science requirement. Introduction to zoology as taught by marine biologist Dixy Lee Ray was so transformative that he immediately switched his major to premed, says Raichle, who had to start his science education from scratch. After a year's setback because of a misplaced invite for a medical school interview, Raichle was accepted at the University of Washington School of Medicine . "I felt like a fish out of water, surrounded by people who must have gotten out of the crib and said, 'I want to go to medical school.'"

Raichle became fascinated by neuroscience. "I read our neuroanatomy textbook cover to cover, and I still have it," he says. Raichle was particularly inspired by his teacher and subsequent mentor, Fred Plum, at that time the youngest person to chair a neurology department in the U.S. "He asked us in class what the relationship was between a pain and a tickling sensation, and I happened to know. Even though I was shy and not in the habit of raising my hand, I gave an answer that he appeared pleased with, and from that moment on, I felt like, 'OK, I have arrived.'"

Since graduating from medical school in 1964, Raichle has been pushing the boundaries of what technological advances can teach us about how the brain works. He was among the first researchers who developed and used positron emission tomography (PET) as a noninvasive language, emotion, and cognitive function using brain imaging; and discovered that blood flow and glucose consumption change more than the amount of oxygen used during fluctuations in brain activity—a controversial finding at the time.

measure of brain activity; linked brain regions to

"I think, for better or worse, imaging has become the face of neuroscience."

Here, Raichle discusses the clay brain he made in medical school, how a language barrier almost forced him to fly a cargo airplane, and how not one scientist but a whole mass of talented people from different disciplines developed crucial techniques for brain imaging.

Raichle Realizes

A misplaced application. Raichle had received a rejection letter from UW Medicine and was getting ready to apply to law school when he went to ask the med school's director of admissions why he had been turned down. "He told me, 'Well, you never showed up for your interview!' I was astonished, and we pulled up my application. Instead of typing out 1617 East 47th street, the fraternity house on campus where I was living, I had typed in 1616 East 47th street—the house across the street—that never bothered to bring over the letter." Although the delay cost him a year, Raichle reapplied for admission and was accepted into the class of 1960.

Medical arts. By his third year Raichle decided neurology was his calling. But he envied his peers with prior laboratory experience. During his summers in college and for the first two years of medical school, Raichle had been a lifeguard on the Puget Sound, but after his third year he landed a summer laboratory spot in the orthopedic surgery department, studying the anatomy of the rat spinal cord. The highlight for Raichle was the 7 a.m. lectures on the anatomy of the human brain by leading neuropathologist Ellsworth Alvord. "We each built a model of the brain using colored clay, wires, and metal. It really helped me to visualize the three-dimensional organization of the brain. The thing is about three feet tall and sits outside my office now. This summer experience cemented my desire to do research, even though I didn't publish anything."

Antibiotics and seizures. Wanting to train with Plum, who had moved to New York Hospital–Cornell Medical Center in New York City, Raichle first had to complete two years of residency training, which he did at Johns Hopkins Hospital in Baltimore. "I saw a lot of acutely ill patients with brain problems and became interested in what spinal fluid could tell us about the brain's acute medical history." During his residency, Raichle made measurements of hemoglobin breakdown products in the spinal fluid to assess the risk of future bleeding. By the time he arrived at Cornell in 1966 for the neurology residency, he was primed for research. "It was a time when serious infections and sepsis were devastating, and there was little to treat with except penicillin. Giving people a massive dose of intravenous penicillin was found to treat the deadly bacterial infection, but produced epileptic-like seizures and jerky motions in patients. We had an epidemic of patients with confusion and seizures, and I was running around the New York hospitals with an EEG machine to try to figure out why." Raichle and colleagues created an animal model, showing that intravenous penicillin could elicit encephalopathy and that the antibacterial effect of penicillin was directly linked to the symptoms.

Earning his wings. "My residency was at the height of the Vietnam War in 1969. People like me were allowed to finish our residencies, but there was no question about going into the military. I was sent to the School of Aerospace Medicine. It was a fantastic place that had a clinical service focused on medical problems that could compromise the performance of pilots and other navigators. When they found out that I knew how to measure blood flow in the brain, I was thrust into a laboratory that studied the effects of space flight on the body using rhesus monkeys, and I learned a tremendous amount about working with primates. At the same time, Plum had submitted an abstract on our work for a meeting in London, and as first author it was me, rather than Plum, who was invited to give the talk. As a flight surgeon, I donned my flight suit and wings, and my only option was to fly with an Iranian flight crew on a large transport plane that was going to Tehran via London. They didn't speak any English and didn't know the difference between a pilot and a flight surgeon and kept insisting that I fly the plane. I finally convinced them that that was not a good idea!”

Raichle Recognized

A chance encounter. At the meeting in London, Raichle met Michel Ter-Pogossian, a physicist at Washington University in St. Louis who had pioneered the use of the cyclotron to produce isotopes for medical research. Ter-Pogossian asked Raichle to join his group to study brain activity using short-lived radioisotopes. Raichle joined the faculty in 1971 and has been there ever since. “It was a unique appointment. I was recruited by a physicist to work in a radiology department with a hot-atom chemist, computer scientists, and engineers. I was the only neuroscientist. It was interdisciplinary by any stretch of the imagination even though that term was not around yet.”

The first PET. In 1971, Godfrey Hounsfield announced the invention of the X-ray computed tomography (CT) scanner. A conversation about these developments led two of Raichle’s Washington University colleagues, computer scientist Jerome Cox and nuclear chemist Michael Phelps, to propose the creation of a three-dimensional image of a living organism by administering positron-emitting radionuclides, such as ^{15}O, ^{11}C, ^{13}N, or ^{18}F, attached to biological molecules. “I had a bunch of equipment that would be needed, and they persuaded me that they wanted to take it over and build a model of what was to be the first PET scanner. It was called PETT III for positron emission transaxial tomograph. The first human instrument was called PETT III because there were two prior tabletop versions. I didn’t help design or build it, but my job was to figure out how to use it.” According to Raichle, the first human case study, which was never published, was conducted in 1974 on a stroke patient and established that the technique could be used in humans.

“Instead of using tissue autoradiography, where you inject an isotope, sacrifice the animal, slice up the organ and put it on autoradiography film to see the isotope distribution, we could suddenly do all of it electronically in a living system. Others were also working on PET scanners, including at Massachusetts General Hospital, the Hammersmith Hospital in London, and Memorial Sloan Kettering Cancer Center, but our agenda in St. Louis was to do this quantitatively and to focus on the brain. I think the machines built here were the prototypes of everything else that was to come.”

Brain mapping. “I spent the rest of the 1970s using the instrument that was specifically designed to probe the brain,” says Raichle. He and colleagues first figured out how best to measure blood flow, using 15O as a tracer. To measure oxygen consumption in the brain was more challenging than in other tissues, requiring a triple combination of gas and liquid tracers.

Form equals function. In 1984, Raichle began to work with Michael Posner, a cognitive psychologist interested in how attention functions. In 1988, Raichle, Posner, and colleagues published a seminal paper describing how our brains process single words. The parts of the visual system the team identified ultimately became known as the visual word form area (VWFA), and other elements of how the brain processes words also emerged from the work. The study provided a map of the brain’s cortical regions required for single-word processing, and drew on 17 years’ worth of work and expertise on imaging and interpreting data. Scans from the study are still icons of cognitive psychology. “This publication set the stage for how to do these types of experiment,” Raichle says. “The questions one can ask are much more sophisticated now, but the basic strategy has come from these initial experiments.”

Creating a stir. Raichle also studied brain metabolism. He first showed that blood flow and oxygen consumption were not coupled during changes in brain activity, and then followed this study with one showing that blood flow and the use of glucose by the active brain change more than oxygen consumption. The dogma in the field had been that blood flow and oxygen use were correlated, but Raichle and colleagues proposed that blood flow could operate independently of oxygen consumption in the brain during task-induced changes in activity. “When we published this, there was a lot of controversy about it not being right. It was one of my first introductions to saying something really new in science. A prominent researcher in the field came up to me at a meeting and said that what we published was all wrong and that we needed to put a stop to this, which was very daunting for a still-young investigator.”

Paving the way for fMRI. The discovery that blood flow changes were greater than those of oxygen use during fluctuations in brain activity provided the physiological support for functional magnetic resonance imaging (fMRI). Seiji Ogawa, then at Bell Labs, had known of Linus Pauling's 1937 observation that hemoglobin molecules carrying oxygen are less disruptive of magnetic fields like those found in an MRI scanner than those without attached oxygen. "Ogawa demonstrated, using rodents, that if blood flow increased more than oxygen consumption during increases in brain activity, then the MRI signal would increase locally because there was less deoxyhemoglobin present. Four more papers from the Ogawa group and other research teams then showed that you can map the human brain by changing the oxygenation of hemoglobin, and all four cited our 1988 paper."

More imaging. In 2001, Raichle and colleagues defined the baseline activity of the brain, now known as the default mode of brain function, based again on measures of blood circulation and metabolism. In 2010, Raichle's laboratory measured the distribution of aerobic glycolysis (glucose utilization in excess of that used for oxidative phosphorylation despite sufficient oxygen for complete metabolism of glucose to CO2 and water) in the brain and found it's not uniformly distributed and is not simply a function of the overall metabolic rate of the region. The activity is highest in the prefrontal cortex and lowest in the cerebellum and medial temporal lobes and appears to correlate with the distribution of amyloid plaques, suggesting a potential link between this type of metabolism and the later development of dementia.

Raichle Regales

Musical ties. Despite his busy schedule, Raichle plays the English horn, a relative of the oboe, in the St. Louis Civic Orchestra—rehearsing once a week and performing several concerts in the community throughout the year. Raichle began piano lessons when he was 5 years old and then switched to the oboe, which he has played ever since. "I just get a kick out of playing, and I love the music, so I've kept it up. The civic orchestra is a collection of all sorts of people who love to play music—we have a retired pilot who used to fly planes for NASA, a constitutional lawyer, school teachers."

A team effort. "There have certainly been debates about who invented PET. To me, PET is not just a machine, but an infrastructure and a multidimensional accomplishment. I think we need to take a broad view of it. The machines were being driven by the biology, and the biology was being driven by the understanding of what you wanted to measure."

A new science field. "I think, for better or worse, imaging has become the face of neuroscience." Cognition, memory, and aging are on a lot of people's minds, and images are power, says Raichle. "There are one hundred billion neurons in the brain, and each has about 20,000 connections, [which] is daunting. I think what impresses me about this field is that certain important themes only emerge when you stand back and reflect generally on how the brain functions. But we need both holistic and reductionist viewpoints and less of a 'my way or the highway' approach."

Greatest Hits

- Member of the team that developed PET for use as a noninvasive, safe technique for measuring activity in the brain using radioactive tracers
- Developed methods to measure blood flow, glucose uptake, and oxygen consumption in the brain using PET
- Provided and demonstrated the utility of the first comprehensive strategy for using PET to interpret brain function
- Discovered that, when the brain is active, blood flow and glucose use are more dynamic than is oxygen consumption. This observation overturned the previous dogma that the brain uses oxidative phosphorylation of glucose to provide energy for its activity and provided physiological evidence for the development of fMRI.
- Mapped the regions of the brain needed for language, cognition, emotions, and attention
- Demonstrated the utility of studying the brain in a resting, rather than active, state and described the default network, which led to the idea of a default or baseline brain function state

Tags

PET scanning, oxygen consumption, neuroscience, language processing, imaging, Glucose metabolism, fMRI, default mode, brain metabolism, brain mapping and aerobic glycolysis

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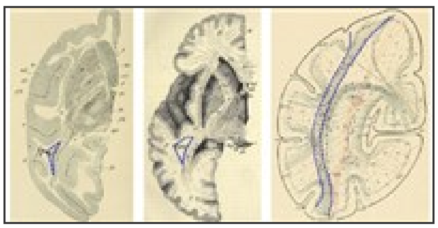

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By Jef Akst

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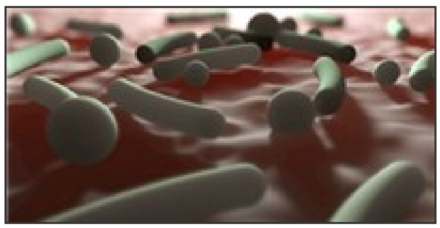

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