

One way to check the validity of the PET technique is to compare PET scans with the known facts of how neuronal activity changes during various types of normal human activity. For example, if PET scans and other functional brain imaging techniques are providing a reliable picture of the activities of the human brain, we should fully expect that activities such as looking, listening, and touching would be seen on PET scans as activity in the appropriate sensory areas of the human brain. And, indeed, that is just what we observe. However, such a simple demonstration, although necessary, is not sufficient for our goals. We must be able to explore brain organization in much greater detail if PET and other functional imaging techniques are to contribute to our understanding of brain function. That is why we and others have turned frequently to the visual system as an initial proving ground for these techniques.

One of the best understood of the brain's cognitive activities is the passive processing of visual stimuli, which creates the experiences of visual objects that flood in when we open our eyes, even when we make no effort to actively process the visual input. Our extensive knowledge of the brain pathways activated during passive visual perception makes a good standard against which we can compare PET images. Thus, the study of passive visual perception is a base upon which we can build our understanding of more active cognitive processes, such as reading, recognizing a familiar face, or recalling something we have seen previously—that is, actually creating a mental image in the absence of any sensory stimulation.

The other way to reassure ourselves of the PET technique's validity is to fully understand *why* it should work, as an indicator of blood flow in the brain. Therefore, we turn first to the phenomenon (blood flow) and then to the technique (PET) before moving on to studies of passive visual stimulation.

BLOOD FLOW AND BRAIN ACTIVITY

The idea that local blood flow within the brain is it timely related to brain function is surprisingly old. As is frequently the case in science, this idea was initially the result of serendipitous observations. It was first expressed in the late nineteenth century by the Italian physiologist Angelo Mosso

from Posner and Raichle (1997)

while he was studying pulsations of the living human brain that keep pace with the heartbeat.

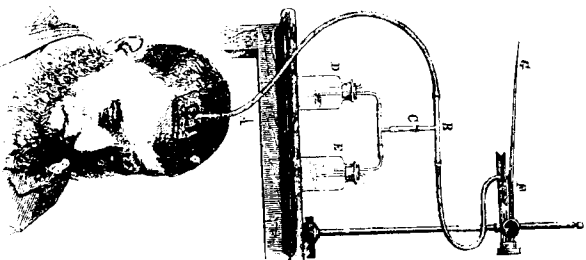
The brain pulsations that fascinated Mosso and others before him can be observed by parents in their newborn children. In the fontanelles, soft areas of the head where the bones of the skull are incompletely developed, the surface can be seen gently pulsating in time with the beating of the heart and the flow of the breath. Although he had no way to prove it at the time, Mosso believed that these pulsations reflected blood flow to the brain. He observed similar pulsations in two adults who had suffered head injuries that had left them with permanent defects in the skull over the frontal lobes of the brain.

While working with one of his subjects, a peasant named Bertino, Mosso observed a sudden increase in the magnitude of pulsations over the frontal lobes. The pulsations grew larger just when the ringing of local church bells and the chiming of a clock signaled 12 o'clock noon, the time for a required prayer. Suspecting that the bells and the clock chimes reminded Bertino of his obligation to say the Ave Maria, Mosso asked if this was true, and immediately observed a second increase in brain pulsations. In both instances the changes in brain pulsations occurred independently of any change in heart rate or blood pressure as measured in Bertino's forearm.

Intrigued by these observations and what they might imply about the relationship between a person's mental state and blood flow in the brain, Mosso then asked Bertino to perform a simple calculation, multiplying 8 by 12. Mosso immediately noted an increase in pulsations and, presumably, in blood flow as his subject began the calculation and a second rise just as he responded with an answer. This was the first study of a human subject to suggest that measurement of blood flow in the brain might be an important way of assessing brain function during mental activity.

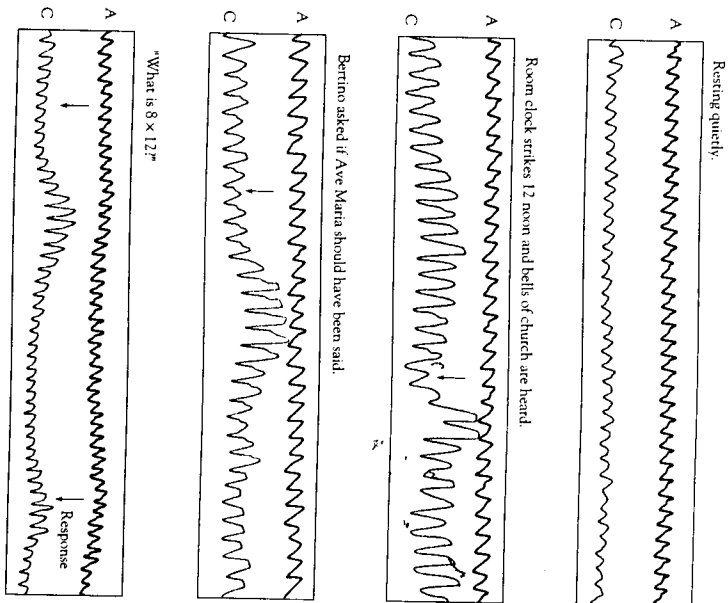
The relationship between brain function and blood flow was further characterized in 1890 by Charles Roy and Charles Sherrington, then working in the pathology laboratory at Cambridge University in England. Based upon experiments conducted with laboratory animals, they suggested that there exists an "automatic mechanism" that regulates the blood supply to accord with local variations in brain activity. The observations of Roy and Sherrington were closer to the truth than many before and since, and their brilliant deductions have dominated neurology ever since.

One of the most extraordinary examples of the relationship posited by Roy and Sherrington was observed in a patient of the neurosurgery clinic at the Peter Bent Brigham Hospital in Boston. The observations were made



The apparatus used by Mosso to record brain pulsations.

Mosso's recordings, taken of the forearm (A) and the brain (C), show stronger brain pulsations after the events marked by the arrows have stimulated brain activity.



between 1926 and 1928 and published in 1928 in the famous neurological journal *Brain* by the patient's physician Dr. John Fulton.

Fulton's patient had suffered a gradual loss of vision due to a collection of congenitally abnormal blood vessels serving his visual cortex. The blood flow through these abnormal vessels was turbulent, unlike the smooth, silent blood flow in normal vessels, and created a brief rushing sound with each heartbeat—like air rushing from a bicycle pump. This sound was audible to the patient, and his physicians were also able to hear it when they listened with their stethoscopes through a defect in the skull. The sound increased whenever the patient opened his eyes and, especially, when he read a news-

paper. Indeed, the correlation between the sound of the blood flow through these vessels and the patient's visual activities was remarkable, as detailed in the box on the next page.

Thus, well before the advent of modern brain imaging techniques, we had direct evidence that the blood flow in a specific sensory system (visual system) changed during mental activity (reading). However, the full importance of this work was not appreciated until accurate techniques were developed for measuring brain blood flow and metabolism in laboratory animals and human beings. These new techniques were created through the efforts of Seymour Kety and Louis Sokoloff, and their colleagues, working after the Second World War first at the University of Pennsylvania and later at the newly formed National Institutes of Health in the United States. In addition to greatly stimulating scientific interest in the subject, their work gave us both the theoretical basis for accurate techniques and a wealth of new information on the relationship of brain blood flow and metabolism to brain function. The techniques they developed included the autoradiography techniques described briefly in Chapter 1, which became the basis for measurements of brain blood flow and metabolism with PET.

A shortcoming of the early methods developed by Kety and Sokoloff was that they could not be used in humans to measure the blood flow or metabolism in limited regions (their autoradiography techniques, which could provide very regional data, could only be applied to animals because the subject had to be sacrificed at the end of the experiment in order to read the results). However, stimulated by the work of Kety and Sokoloff, methods for measuring regional blood flow in human beings were developed by David Ingvar, Nels Lassen, and their colleagues and students in Scandinavia.

Although the techniques of Ingvar and Lassen lacked both the safety (they required the administration of isotopes directly into the carotid arteries in the neck leading to the brain) and the precision of later imaging techniques, they were the first to provide us with direct confirmation in human beings of the remarkable observations and insights of Mosso, Roy and Sherrington, and Fulton. The close relationship between brain function and changes in local blood flow in the human brain was no longer in doubt. A potential window to the workings of the human brain had been identified.

Thus, the stage was set for the introduction of PET and other more precise and safe techniques for measuring blood flow, which could be used in combination with measures of cognitive operations developed in cognitive science. Together these approaches ushered in a new era of brain-behavior studies, especially of normal human beings.

