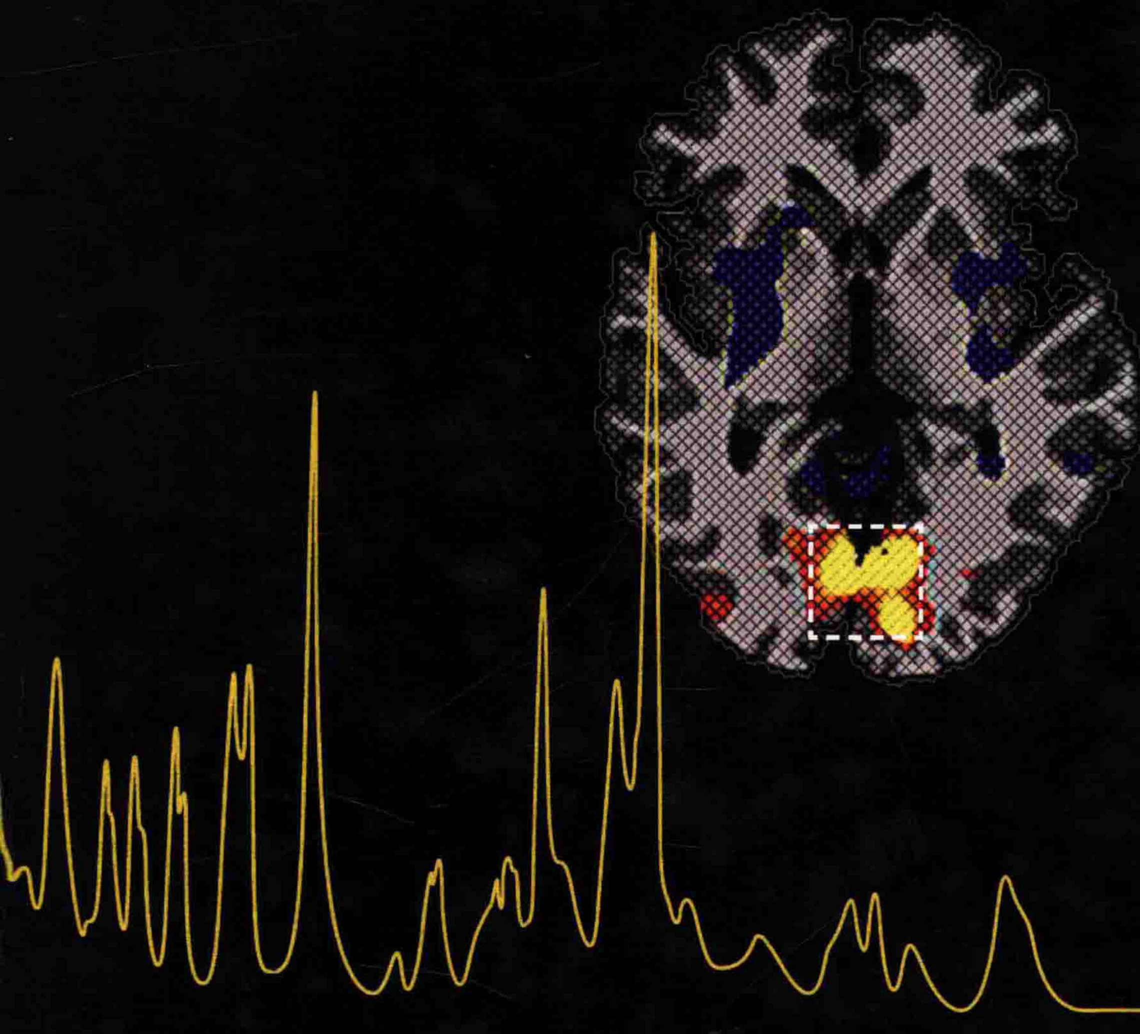
BRAIN IMAGING

What It Can (and Cannot) Tell Us About Consciousness

ROBERT G. SHULMAN



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Introduction

The progress of noninvasive nuclear magnetic resonance (NMR) methods over the past 30 years has been a stunning story of our growing ability to look into the complexities of brain chemistry and physics. As someone who has seen magnetic resonance progress from a crude tool that could measure water in the 1950s and simple biomolecules in the 1960s to the powerful lens it offers today for the study of *in vivo* brain activities and metabolism, I can testify to the astonishing progress that we have made. In this time, NMR methods have become tools for diagnosis in clinical medicine, for following metabolism *in vivo*, and for measuring changes in brain activity during stimulation. This multidirectional expansion of our ability to analyze physical and chemical activities within living beings has moved scientific inquiry to the inner workings of the living human—to study the force of muscle, the chemistry of liver, the malfunctions of diseases—and, recently, to that most fascinating of all activities, the function of the human brain. In contrast to the muscle, liver, heart, and kidney, all of which can be excised from the body and maintained in a living state on the bench top, the brain must be studied in the living person. The possibilities of noninvasive studies of brain activity *in vivo* have created a wave of excitement in neuroscience, and rightfully so.

NMR, the method of choice for *in vivo* studies, has been central in my entire career. The early homemade electronic equipment, interfaced with permanent magnets whose steel faces we hand-polished with sandpaper, has been replaced by superconducting magnets and by spectrometers of unimagined sensitivity, controlled by computers of equally undreamt-of ability. Improvements in equipment for data acquisition were much needed because the NMR signal is very weak compared to thermal noise. However, the very weakness of the signal has been responsible for the value of the method. The radio waves that readily penetrate matter such as air, buildings, or tissue are very weak compared to other electromagnetic waves like visible light, ultraviolet, and x-rays, and therefore they do not disturb the atoms and molecules surrounding the nuclei that are being detected.

THREE FORMS OF NMR

NMR is a form of spectroscopy in which the nuclei in a material, placed in a magnetic field, exchange energy with radiofrequency electromagnetic waves. Invented by physicists as a method for studying nuclear properties, it soon became of wide value in chemistry, condensed-matter physics, geology, and biochemistry, and more recently it has become a fundamental method for studying the properties of tissue *in vivo*. How we can (and might) frame our experiments utilizing noninvasive NMR studies of humans and animals *in vivo*, particularly of their otherwise inaccessible brains, is the subject of this book. The applications of NMR to noninvasive studies of humans and animals *in vivo* are served by a rich variety of methods. The first NMR method recognized to be valuable in human studies was magnetic resonance imaging (MRI), which provided a three-dimensional image of H_2O molecules *in vivo*. Within a decade of its demonstration in principle in test tubes by Paul Lauterbur,[1] international meetings were organized by neurologists, cardiologists, neuroscientists, and the rag-tail group of NMR specialists and computer scientists who had been developing MRI methods and interpretations. MRI was extended in the early 1990s to functional MRI (fMRI), which located changes in brain activity in response to stimulations of the person.[2,3] These experiments were based upon Seiji Ogawa's proposal[4] that changes in the degree of oxygenation of hemoglobin could be detected in MRI maps. Since these signals came from coupled changes in cerebral blood flow and oxygen consumption, they contained information about metabolic responses to stimulation. fMRI responses of the human visual cortex to sensory stimuli reproducing and extending previous invasive animal studies, mainly of cats and nonhuman primates, and noninvasive human studies by positron emission tomography (PET)[5] created a widespread excitement about the possible uses of fMRI for the study of more complex responses of the human brain. The quantitative understanding of fundamental metabolic pathways reached by these *in vivo* experiments has built upon and gone far beyond the knowledge that could be found in the biochemistry textbooks from studies of extracts. *In vivo* metabolism was studied directly by magnetic resonance spectroscopy (MRS), which followed the flow of labeled ^{13}C compound through metabolic pools.[6]

BRAIN ENERGY AND WORK

My interest in cerebral metabolism were formed by early MRS studies of glucose metabolism in yeast and muscle in the 1970s at Bell Telephone Laboratories, where, with an enthusiastic group of young colleagues (Seiji Ogawa, Kamil Ugurbil, Gil

Navon, Tetsue Yamane, Jan den Hollander, and others), we established methods for following glucose metabolism in the primary energy-producing pathways. It took 20 years until larger magnets, better computers, improved spectroscopic techniques, and the advances made by several young collaborators at Yale, particularly Douglas Rothman and Kevin Behar, produced well-resolved, high-quality spectra of metabolites in the human brain. Once such spectra were available, the metabolic pathways of the brain, more complex than yeast or skeletal muscle but built upon the same basic reactions of glucose oxidation, provided information about the specifically cerebral activities of neuronal firing. By the early 1990s, brain spectra measuring the flow of the ^{13}C label from glucose to glutamate could be directly interpreted to give the flux into the Krebs cycle and the cerebral metabolic rate of glucose oxidation.

More improvements in spectral acquisition measured the flow from glutamate to glutamine, a flux that provided the rate of neuronal firing. Most neuronal firing in the human brain releases the neurotransmitter glutamate, which is recognized by the postsynaptic neuron. The glutamate is then picked up by nearby glial cells, which convert it to glutamine and eventually recycle it to the presynaptic neurons. The flux of neurotransmitter glutamate to glutamine, obtained from these spectra, determined the rates of neuronal firing. Each experiment measured both the rate of energy production by the oxidation of glucose and the rate of work done by neurotransmitter cycling.[7] Energy and work in the brain provided an understanding similar to that obtained by studying the same parameters in cardiac and skeletal muscle: namely, how the brain consumes nutrients, how brain activity affects the rates of energy consumed and fuel delivery, and how increased energy demands are handled during stimulation. The metabolic ^{13}C measurements, in conjunction with PET measurements and the existing lore of neurophysiology, moved brain studies into thermodynamics, and the brain became an organ whose work made chemical and physical sense. It provided opportunities for physical scientists to build a bottom-up understanding of brain functions from measurements of the energy consumed and the work of neuronal firing.

The following chapters describe how neurophysiology, attending to the chemical and physical brain properties described by imaging experiments, provides reliable physical understanding of mechanisms that support tentative proposals about relations between brain energetics and human behavior.

BUILDING UPON BEHAVIORISM

By confining attention to brain processes that are necessary for the person to perform observed behaviors, and by not studying mental processes postulated to relate brain activities to the observed behavior, my approach has some similarities with the once-popular school of psychology called Behaviorism. While there are similarities in our dependence upon observable behavior, our methods differ significantly from this older psychology as well as from the more recent cognitive psychology. J. B. Watson's definitive summary[8] showed the reliable role of behavior in science. Watson started with the clear statement, "Behavior can be observed like the phenomena of all other natural sciences." When controlled experiments established the connection between stimulus and response, then, Watson continued, the behaviorist's psychological questions have been answered. Not being able to observe in these investigations any mental processes, like "consciousness, sensation, perception, imagery or will," behaviorists, Watson writes, "reached the conclusion that all such terms can be dropped out of the description of man's activity." He continued: "the neurologists and physical chemists have problems to solve about the neuronal connections and in determining the physical and chemical work done in the reaction." However, he adds, those are not the concern of psychology, which he felt could be best pursued as the study of behavior. Watson does not conclude that mental processes do not exist, or that the brain played no role in supporting them—quite the contrary: he assumed they did but did not think that psychology had the tools to study them. That was close to a century ago. In the 1970s cognitive psychology started to fill the gap between stimulus and response by proposing both the nature of these mental processes and the brain mechanism for dealing with them from the perspective of computers, information theory, and linguistics. I share Watson's enthusiasm about the reliable explanatory powers of observable behavior and, as a Pragmatist, share his skepticism about the value of assuming mental processes. As a modern representative of the "neurologists" and physical chemists to whom he defers, I believe that physical scientists should study mechanisms of brain activity supporting a person's behavior rather than invoking mental processes responsible for that behavior. Freed from the need to answer questions that have been the responsibility of psychology, I have turned to neurophysiological studies of brain energy and work for insights into the neuronal support for behavioral activities.

THE NEED FOR PHILOSOPHY

Scientific directions exploring how brain experiments can be related to behavior and mental activity are intricately interdependent with philosophical issues that influence the choice of questions addressed and the methods used for their study. A scientist involved in neuroimaging studies can choose between many well-developed philosophical positions on issues of mind. Because mental activities have been so thoroughly integrated into social sciences, religion, and our culture, an individual cannot avoid taking a position on brain contributions to mental processes, so that the choice is not whether or not we follow a philosophical position but rather whether we do so knowingly or unthinkingly.

In a recent Tanner Lecture at Yale, Rebecca Goldstein, a novelist and philosopher, addressed the apparent differences between writing fiction, generally recognized as a creative personal activity, and the commitment to a philosophy, often pictured as an impersonal, rational, logical choice. The reality, she claimed, was quite different in that there was no subject more personal, more dependent upon individual preferences, lifestyles, and goals than philosophy. She illustrated this opinion zestfully and left me convinced of the subjective nature of the choice we make in finding that one philosophy, rather than another, offers a better description of the world and of the values we hold. The following chapters of this book reveal the basic validity of Goldstein's description. As an experimental biophysicist evaluating noninvasive brain studies, my scientific values had been created by the traditional empirical-inductive scientific methods of hypothesis and observation. It is my philosophical choice to stand by this method and to avoid other philosophical frames for conducting my work. I find certain schools of philosophy and psychology sympathetic to my views of how to think about the brain and its relation to behavior.

The following chapters are written for scientists who are seeking to reflect upon how they compose and interpret neuroimaging experiments studying aspects of behavior. They might appeal to neuroscientists, cognitive scientists, psychologists, philosophers of mind, philosophers of science, and general readers interested in contemporary brain research. Furthermore, since this book touches upon the reliability and limitations of functional imaging methods that are being claimed to offer scientifically objective answers to issues in psychology, economics, linguistics, political sciences, and bioethics, and in the law courts, the book's questioning of what are sometimes considered to be "obvious" truths about the brain should have general implications for a readership beyond these directly interested groups.

CHAPTERS TO COME

Chapter 1 follows up on the questions posed in this introduction about whether mental processes can be explained by neural activities. My concerns about some approaches to localize everyday activities within regions of the brain are examined in terms of the underlying epistemology. The limitations of these efforts are discussed from the viewpoint of a philosophy of Pragmatism, which proposes that words like "working memory" and "consciousness" are abstract concepts that are used to describe the everyday world, but their values for empirically based scientific investigation are yet to be established. For Pragmatism, the meaning of such concepts is determined by the actions they lead to and therefore depends upon their context where their contributions can be assessed.

Regarding neuroscience as a biophysical field, in which physical understanding is sought of biological phenomena, Chapter 2 shows that generalizations in neuroscience are but one example of how untested assumptions proposed to explain human functions are moving physical science away from its empirical-inductive method.

Chapter 3 has selected features from the history of philosophy relevant to neuroimaging, intending to make them accessible to a non-philosopher. Some histories of the qualities of mental processes, assumed and interpreted since Descartes and Galileo, continue to influence contemporary neuroscience. The chapter reviews epistemological assertions about the nature of living processes that were recognized by the great nineteenth-century physiologists who first systematically applied physical science to bodily functions. It is intended to contextualize the assumptions that undergird a scientist's approach to research by reflections on issues that affect scientific choices. This chapter emphasizes the value for neuroscience of philosophical Pragmatism, which, because it denies the value of many traditional philosophical conceptualizations, has been called "less a philosophy than a method of doing without philosophy."[9]

Chapter 4 describes the degree of subjectivity and objectivity in scientific examples and begins to address the general interdisciplinary question of relating subjective phenomena, like human awareness, to objective understanding obtained by physics or chemistry. Niels Bohr faced questions raised about the meaning of the term "electron" by the uncertainty principle. In his *Theory of Complementarity* the description of an electron is complete when we specify how it was measured both as a wave and as a particle, which are subjectively chosen experiments, without integrating these measurements into an "electron" with simultaneous values of velocity and position that can be "objectively" communicated.[10] I propose a neuroscientific analogue in which the fullest available understanding of mental processes is found by simultaneously accepting and correlating experimental observations of human behavior and neurophysiological measurements without trying to unify them into a brain performance of a mental process. Just as the phenomena of an "electron" has lost its usefulness at the quantum level, so too (I propose) have descriptions of mental processes, like "mind," "memory," and "attention," lost their usefulness as explanations at the neuronal level. Long-established concepts like "electron" or "mind," which have been so useful in their respective domains that they have seemed to be innately understood, can no longer be meaningfully discussed in quantum physics or neuroscience, respectively. As Bohr observed, "It is wrong to think that the task of physics is to find out how nature is. Physics concerns what we can say about nature."[11] This scientific approach has been systematized by the philosophy of Mechanisms, recently formalized by Carl Craver,[12] which proposes that an understanding can be created by the many mechanisms found at the different levels that participate in the phenomenon without trying to integrate them.

Chapter 5 reviews neurophysiological measurements and shows how modern neuroimaging methods have become the working tools of brain science by their ability to localize the metabolism of brain energetics and neural firing. This chapter traces the development of these neurophysiological methods for measuring blood flow and the energetics of metabolism, culminating in reproducible, localized, energetic responses to sensory stimulations of animals and humans. The proposals by Cognitive Neuroscience to extend these findings of brain localization to complex mental processes involving subjective, personal responses are analyzed in two typical experimental programs—*willed action* and *working memory*—showing how interpretations continue to be based on hopes of defining these terms in face of experimental disappointments.

Chapter 6 describes our present understanding as to how brain energy consumption is almost completely dedicated to the work of neural firing, as revealed by noninvasive fMRI, MRS, and PET experiments. This leads to an explanation of the metabolic processes responsible for producing the imaging signals. The incremental energies measured during fMRI differencing experiments and the high baseline energy consumption from PET and MRS experiments provide a unified bottom-up understanding of brain activities that allows us to move upward to the higher level of observable behaviors, as discussed in the following chapters.

Earlier chapters have been anticipating the detailed results discussed in Chapter 7 that relate the state of consciousness to physical measurements of brain activity. The approach in this chapter follows the distinction between the *state of* consciousness, which enables the person to respond, and the *acts of* consciousness, discussed in the next chapter, which are the person's specific response to stimuli. Instead of defining consciousness as a mental process, a person is defined to be in the state of consciousness by his ability to respond to simple stimuli. A high level of brain energy production and consumption, evenly distributed throughout the cortex, is shown to be necessary for a person to be in the state of consciousness. A severe reduction of the total energy consumption causes the loss of consciousness during deep anesthesia, slow-wave sleep, or coma.

The acts of consciousness are defined in Chapter 8 as a person knowing that something is of a certain nature and not otherwise. An fMRI BOLD comparison is an example of the acts of consciousness. In a task where the subject is aware of the difference between upside-down and right-side-up faces, or is conscious of either the horizontal or vertical lines in a test of binocular awareness, an fMRI difference signal is clearly observed. These acts of consciousness, together with the total brain energy support of the state of consciousness, create a model of brain function in which individually measured brain activities support identifiable aspects of the person's behavior. These results support a model of brain function in which the person's interests determine brain activity rather than the model of Cognitive Neuroscience in which intrinsic brain properties create human behavior. They show connections between reliable bottom-up brain studies and observable behavior without making psychological assumptions about mental activities.

The epilogue, Chapter 9, reviews autobiographical events that illustrate my intermingled activities in science and the humanities. Acknowledging the powers of science, this story emphasizes the similarities of the two fields rather than focusing on their palpable differences of subject matter and the differing degrees of reliability. Both disciplines are considered to have been built by humans in their effort to understand the world and have relied on the creation and testing of hypotheses as viewed from the perspective of Pragmatism.

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1

Mind and Matter

Recent advances in imaging have encouraged neuroscientists to investigate a wide range of previously unanswerable questions about brain function. Scientists from the many disciplines of neuroscience—psychology, computer science, linguistics, neurochemistry, and cognition—are designing imaging experiments intended to explore their views of brain activities. Because the images measure glucose and oxygen consumption and the rate of blood flow that supplies these nutrients, the experiments track the traditional physiological parameters of brain energy consumption and metabolism. However, the experimental possibility of measuring changes in brain properties during behavior such as the response to cognitive tasks, sensory stimulation, and the remembrance of events and instructions has encouraged studies of mental processes via these techniques. Views of mental processes are diverse, and I will propose that introducing them as goals of physiological study raises questions about reliability that generally are considered settled matters in physical chemistry. For example, if I want to talk about my forgetfulness with my wife, as in, "My memory is failing! I forgot that I was supposed to play poker last night," our shared sense of the concept of "memory" is very useful for our communication. However, modern imaging experiments raise the question as to whether experiments designed to measure rates of glucose consumption that occur during what the investigator defines as a "memory" task are going to produce results that are as reliable as biochemical experiments that measure glucose incorporation into glycogen. Questions about the meaningfulness of the different kinds of experiments allowed by imaging chemical reactions in the body can be illustrated by comparing two recent applications of these methods.

Note: Chapter 1 was previously published (in essentially the same form) in *Frontiers in Neuroenergetics.*

PHYSICAL STUDIES OF DIABETES

Studies of type 2 diabetes and the brain responses during a memory task both measure chemical reactions of glucose (a common source of human energy), but these different explorations interpret this information very differently. Type 2 diabetes has been around and its properties have been observed for thousands of years. The great Indian physician Sushruta (fl. sixth century BCE) identified the disease[1] and characterized it by ants being attracted to the urine of patients. Now, after 2,000 years of study, we identify the disease by the patient's high blood glucose and by his slow return to normal blood sugar levels after a glucose infusion. We know of the damages wrought by the high glucose, and recent studies using MRS have shown how its immediate cause is downregulation of the insulin control of glucose flow into muscle glycogen.[2] These metabolic results are one step in the growing understanding of this disease. Our scientific understanding uncovers layers of observables—from the sweet smell that once identified the disease to the present biochemical mechanisms contributing to the high blood glucose level. There is in this typical research history not a single step but an unveiling of mechanisms that with time have moved the field of enquiry to the molecular level. Because of these new methods employed in the chemical research—better lenses, really—we now understand the biochemical conditions that cause the disease, and this understanding allows us to control its symptoms. It is now becoming possible to explain this disease at a molecular or cellular level because its defining properties were, from the very beginning of its history, observable and measurable. The story of our unfolding analysis, understanding, and control of type 2 diabetes based on study of its observable properties is one of the triumphs of the scientific method.

METHODS FOR BRAIN STUDIES

The road to understanding brain anatomy and activity has, like our path to understanding diabetes, been much traveled, with advances made possible by methodological and technological advances. Long before the nineteenth-century insights by physiologists, and the subsequent elaboration of neurons, axons, and synapses, we have records from the beginning of the sixteenth century, when, for a brief period, autopsies were allowed in Florence. Leonardo, whose continuing interests in brain anatomy had been interrupted by a temporary ban on the study of cadavers, returned to study the brain's ventricles. Studies of peripheral nerve connections to the ventricles since Galen's time had been