Dædalus

Winter 2015: What is the Brain Good For?

Dædalus

Journal of the American Academy of Arts & Sciences

Winter 2015

What is the Brain Good For?

Neuroscience: The Study of the Nervous System & Its Functions

Fred H. Gage

> Any man could, if he were so inclined,
> be the sculptor of his own brain.
>
> – Santiago Ramón y Cajal,
> *Advice for a Young Investigator* (1897)

Neuroscience is the scientific study of the nervous system (the brain, spinal cord, and peripheral nervous system) and its functions. The belief that the brain is the organ that controls behavior has ancient roots, dating to early civilizations that connected loss of function to damage to parts of the brain and spinal cord. But the modern era of neuroscience began – and continues to progress – with the development of tools, techniques, and methods used to measure in ever more detail and complexity the structure and function of the nervous system. The modern era of neuroscience can be traced to the 1890s, when the Spanish pathologist Santiago Ramón y Cajal used a method developed by the Italian physician Camillo Golgi to stain nerve tissues to visualize the morphology and structure of the neurons and their connections. The detailed description of the neurons and their connections by Cajal, his students, and their followers led to the "neuron doctrine," which proposed that the neuron is the functional unit of the nervous system.

We now know that the human brain contains approximately one hundred billion neurons and that these neurons have some one hundred trillion connections, forming functional and definable circuits. These neural circuits can be organized into larger

FRED H. GAGE, a Fellow of the American Academy since 2005, is Professor in the Laboratory of Genetics and the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease at the Salk Institute for Biological Studies. He studies the unanticipated plasticity and complexity represented in the brain.

doi:10.1162/DAED_e_00313

networks and anatomical structures that integrate information across and between all sensory modalities – including hearing, seeing, touching, tasting, and smelling – from all parts of the nervous system. These networks process information derived from the internal and external environment, and the consequence of processing this sensory information is *cognition*, a concept that includes learning and memory, perception, sleep, decision-making, emotions, and all forms of higher information processing. In response to a simple or complex sensory experience, an organism responds or behaves. The behavior can be simple, like a motor reflex in response to pain, or more complicated, like playing squash, working a crossword puzzle, or painting. However, behavior is not just what an organism *does* in response to a stimulus or sensory input; it is most often what an organism *chooses* to do from a variety of available options in response to a complex set of environmental conditions. Thus, except for rare responses, like simple reflexes, a behavior is expressed in response to a combination of the immediate sensory stimuli integrated over time with cognition.

Neuroscientists conduct experiments to understand how sensory information is processed to lead to behavior. Because of the obvious complexity of the brain, neuroscientists conduct their studies at different levels of depth. While *neurons* are conceivably the smallest units in which behavior can be clearly described, the neuron is itself made up of unique anatomical features, including a *soma* (cell body), *dendrites* (the antennae branching from the soma that receive signals from other neurons), and *axons* (the processes extending from the soma that send signals to other neurons).

These neuronal components in turn contain subcellular specializations that represent the defining features of the neuron. Key among these specializations is the *synapse*: a structure shared by the dendrite and the axon that represents the junction point for the principal form of communication between two neurons. On the dendritic side of the synapse is a structure called a *spine*, which responds to signals from the axon. On the axonal side is the *bouton*, which has vesicles containing neurotransmitters – the signals to which the spine responds. Each neuron can have multiple dendrites and thousands of spines connected to comparable numbers of boutons, which together form the thousands of synapses that make up the units of communication between individual neurons.

In the soma, specialized proteins and microstructures form the basis for the intracellular communications and physiological features of neurons; for example, specialized enzymes produce the neurotransmitters and vesicles that are used in the bouton to signal the spine. Furthermore, specialized cytoskeletal proteins form long and active extensions that allow the dendrites and axons to act as a supply train for the vesicles and neurotransmitters that are made in the soma and transported to the boutons. Among the most important proteins in the neuron are those that form the ion channels. These are multi-protein structures that span the neuron's membrane and allow neurons to form electrochemical gradients, which are the driving forces of activity in neurons.

These proteins – which are crucial for the functioning of a neuron – are all the products of genes that are the functional unit of the genome, which is located in the nucleus of the neuron. Each neuron's genome contains about twenty thousand genes, but different genes are expressed in different types of neurons, and it is this unique expression pattern of genes in any particular neuron that provides its unique identity.

Even from this brief survey of the different levels of brain connectivity it is clear that it would be impossible to study the total functioning of the brain – from behavior to gene expression – in one experiment. So neuroscientists instead generally choose some limited number of brain-activity levels to probe as they address their own specific questions. The many methods used to study the nervous system differ depending on the level of analysis, but they fall generally into one of two categories: *descriptive*, for generating hypotheses, or *manipulative*, for testing hypotheses.

One type of descriptive study is a case study, in which an experimenter observes the behavior of a person or group of people before, during, or after an event that may demonstrate a role for the nervous system. The circumstances surrounding the event are usually non-repeatable and cannot be precisely reconstructed in a laboratory setting. One could argue that these are not true experiments, but these studies have revealed substantial information about aspects of neural function that was previously unknown. One remarkable example is the case of H.M., a patient whose epilepsy was treated through removal of a portion of his brain called the hippocampus and parts of the temporal lobe on both sides of his brain. As a result of the surgery, which did successfully control his epilepsy, he displayed a unique form of memory loss, and his behavior was examined over a period of forty years from the time of his operation until he died, revealing through careful documentation and experimentation some of the most important concepts about human learning and memory. Another important case study is that of Phineas Gage, a railroad worker involved in an accident in 1848 that resulted in an iron rod passing through his skull. The rod entered the left side of his head, passing just behind his left eye, exiting through the top of his head and completely transecting his frontal lobes. He lived for twelve years following the accident and his behavior was recorded in some detail, informing scientists about the unique function of the frontal lobes and their important role in personality and decision-making. The insights from such case studies have often generated hypotheses to be tested in subsequent manipulative experiments.

Descriptive studies can also consist of the straightforward act of observing properties of the nervous system without manipulations. This type of research is usually the first crucial step in acquiring knowledge about a newly discovered gene, protein, neural subtype, or connection between neurons. Examples can be highlighted at every level of analysis. A novel gene can be sequenced and its expression pattern in the brain can be mapped, or the peptide sequence of a protein can be described and its distribution in the nervous system can be shown in great detail. In addition, a specific neuron can be described in terms of the genes and proteins it expresses, as well as its unique morphological characteristics and electrophysiological properties. On a broader scale, the connections between groups of neurons can be elucidated, describing both their input to their respective dendrites and spines and also their outputs, by way of the axons and boutons. Once the anatomical properties of a network are described, the electrochemical properties of their connections and network can be revealed.

These descriptive studies are excellent for generating hypotheses about the function of the brain at all levels of analysis. Once there is enough basic information to generate a coherent hypothesis about the function of some level of the brain – for example, an anatomical pathway in the brain that is responsible for our ability to recognize a face – we then want to test if the pathway is required for facial recognition. In all areas of biological sciences and at all levels of analysis, testing a hypothesis is achieved through *gain-* and *loss-of-function* experiments. In a loss-of-function experiment, the experimenter silences, blocks, disrupts, or turns off specific components of a proposed pathway in an attempt to determine the required elements for appropriate function. In some cases, the loss-of-function technique may not be precise, so to further track down the requirement for a component in the functional path, a gain-of-function experiment can be conducted to replace each of the components of the pathway that were disrupted in the loss-of-function experiment. Loss-of-function experiments can be conducted at all levels of function: to test the importance of specific genes in cells within the inner ear for specific components of hearing; to test the roles of specific regions of the temporal lobe in learning; or even to test the importance of sleep in the consolidation of memory.

This volume of *Dædalus* dedicated to the brain and nervous system cannot cover all aspects of this very deep and broad field of study; but we are fortunate to have recruited an outstanding group of active scientists to help us examine select subdivisions in the field of neuroscience. These authors and scientists are not only major contributors to their particular areas of focus, but are experienced communicators with track records of explaining and translating complex concepts to intelligent readers and listeners outside of their discipline.

Robert Wurtz, in "Brain Mechanisms for Active Vision," presents a clear and lucid essay on the remarkable mechanisms behind our ability to see the world around us. In "Perceiving," Thomas Albright reveals how we change the sensory experience of vision into a cognitive perception and how this is regulated by other events in the environment. A. J. Hudspeth's essay, "The Energetic Ear," explains the dynamic inner workings of the ear and how sound waves are translated in the brain to allow us to hear. Larry Squire and John Wixted offer a primer on memory entitled "Remembering," based on both critical case studies and the experimental studies that have led to our current understanding. And in their essay "Sleep, Memory & Brain Rhythms," Brendon Watson and György Buzsáki provide a coherent and provocative study of the importance of sleep in our memory and how the rhythmic activity in the circuits of the brain may control the relationship between sleep and memory.

Emilio Bizzi and Robert Ajemian have contributed the essay "A Hard Scientific Quest: Understanding Voluntary Movements," which explains both the basics of how we move through our environment and how movement is regulated by sensory experience. "Feelings: What Are They & How Does the Brain Make Them?" – Joseph LeDoux's addition to the volume – describes the fundamentals of emotional behaviors both from the behavioral perspective and from the neurobiological basis of emotions. Earl Miller and Timothy Buschman, in their essay "Working Memory Capacity: Limits on the Bandwidth of Cognition," discuss cognitive capacity, with a special focus on processing limitations rooted in oscillatory brain rhythms ("brain waves"). Finally, in his essay "Consciousness," Terry Sejnowski tackles the slippery concept of consciousness and helps us understand the difference between being aware and being consciously aware.

Although this volume cannot extend to all sensory and motor systems and their integration, we are hopeful that this sampling of neuroscience will encourage you to read more on these exciting topics, and we hope we will be able to return to *Dædalus* with additional volumes on neuroscience. More specific, we have not here considered what happens when the brain is damaged or aged, or when genetic errors occur. A volume on "The Brain and its Disorders" is currently in the planning stages at the American Academy; in the meantime, we hope this collection provides a foundation for you to learn about the brain and whets your appetite for more.