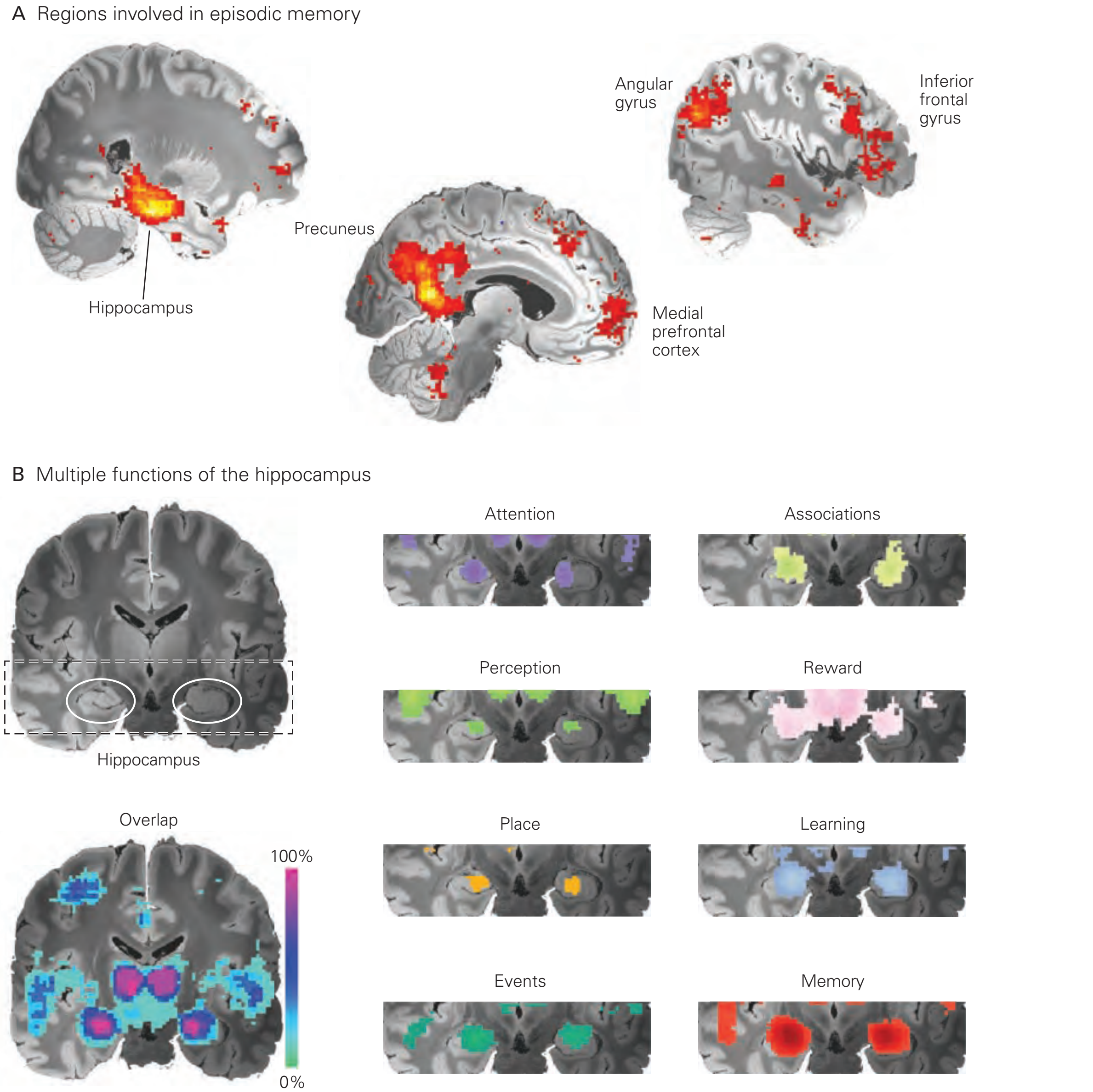

Figure 6–3 Challenges of mapping mind and brain. Any interpretation of data from fMRI must consider the complexity of the relationship between cognitive functions and brain regions. This complexity is illustrated here with a meta-analysis from a database containing more than 14,000 published fMRI studies. (Data retrieved in 2019 from http://neurosynth.org, displayed on brain from Edlow et al. 2019; figure updated and adapted from Shohamy and Turk-Browne 2013 by Tristan Yates.)

A. This map shows that multiple brain regions are engaged by episodic memory—that is, encoding and retrieval of specific events from one's past. Colored voxels indicate a high probability of the term "episodic" in studies that reported activation in these voxels (reverse inference). This example illustrates how a single cognitive function can be associated with multiple brain regions (one-to-many mapping).

B. These maps show that multiple cognitive functions engage the hippocampus (circled in white in each hemisphere). Colored voxels in each inset brain indicate a high probability that these voxels were activated in studies that examined the corresponding term (forward inference). The overlap map shows the percentage of these terms that activated each voxel. This example illustrates how a single brain region can be associated with multiple cognitive functions and behaviors (many-to-one mapping).

Box 6–2 Brain Imaging in the Real World

The ability to image the human brain with noninvasive tools and to measure internal mental processes has led to interest in applying fMRI to a variety of real-world problems, such as clinical diagnosis and treatment, law and justice, artificial intelligence, marketing and economics, and politics.

In the clinical realm, one interesting direction is the use of fMRI to examine patients in a vegetative state. Studies suggest that some such patients exhibit brain activity that reflects mental processing. For example, a patient might appear comatose—unconscious, noncommunicative, and unreactive to external stimuli—yet exhibit neural activity in the motor cortex when asked to think of an action or in category-specific visual regions when asked to imagine specific visual cues. Such findings could influence the prognosis and treatment of patients by clinicians.

Another potential real-world application of fMRI is lie detection. The ability to accurately distinguish truth from lies based on brain activity could have significant value in the courtroom. Some laboratory studies have reported differential brain activity when groups of subjects are instructed to lie repeatedly. To be useful, however, fMRI would need to provide highly reliable evidence about whether an *individual* person is lying about a *specific* event, in a way that is immune from strategies or countermeasures. This is not possible at present, and indeed, fMRI evidence is generally inadmissible in court.

These and other applications of fMRI raise ethical and privacy concerns. For example, authorities could use fMRI data to justify consequential decisions (eg, guilt or innocence), exploiting the public's bias to believe biological explanations, even when the underlying science is not settled. More troubling, humans currently have autonomy over whether we share our internal thoughts and feelings, but devices that sense this information could change that. As a result, an important challenge for neuroscientists when considering practical applications is to accurately convey that fMRI is powerful but has limitations and that our understanding of the human brain is a work in progress.

astrocytes and other glia, neuromodulatory systems, and the vascular system. A better understanding of the relationship between BOLD activity and these processes is essential for knowing when and why measurements of different types align and diverge. Although some experimental conditions lead to an increase in both neuronal activity and BOLD activity, others do not. For example, although the presentation of a visual cue increases both blood flow in the visual cortex and neuronal firing, if this visual cue is highly expected but not presented, blood flow can still increase but without an increase in neuronal activity. This suggests that there are important nuances to the coupling of neural and vascular activity that may have functional significance and that the vascular signals themselves may be more complex than previously appreciated.

As the history of fMRI shows, scientific discoveries in one field can lead to unexpected breakthroughs in other fields. The discovery of MRI in the 1970s (which 20 years later led to fMRI) came from physics and chemistry, and was so profound and far-reaching that it was recognized by the Nobel Prize in Physiology or Medicine in 2003 to Paul Lauterbur and Peter Mansfield. This in turn was made possible by the discovery of nuclear magnetic resonance decades earlier, which resulted in the Nobel Prize in Physics in 1944 to Isidor Rabi and in 1952 to Felix Bloch and Edward Purcell. These discoveries had no initial connection to neuroscience but came to spark a revolution in the study of mind, brain, and behavior.

Highlights

1. Functional brain imaging methods in cognitive neuroscience seek to record activity in the human brain associated with mental processes as they unfold in the human mind, linking biological and behavioral measures. Currently, the dominant technique is fMRI.
2. fMRI is based on two main concepts: the physics of magnetic resonance and the biology of neurovascular coupling. Combined, they allow fMRI to measure the BOLD response to neuronal activity. When human subjects perform cognitive tasks during fMRI, measurements of BOLD activity can be linked to particular mental processes and behaviors over time.
3. The link between BOLD activity and behavior is inferred through a series of preprocessing steps and statistical analyses. These analyses can answer

a range of questions, such as which brain regions are active during specific tasks, what information is coded in the spatial pattern of activity within a region, and how regions interact with each other over time as part of a network.

4. Human brain imaging has led to fundamental insights about the neural mechanisms of behavior across many domains. Some prominent examples are understanding how the human brain processes faces, how memories are stored and retrieved, and how we learn from trial and error. Across these domains, data from fMRI have converged with findings from neuronal recordings in animals and with theoretical predictions from computational models, providing a more complete picture of the relationship between brain and mind.
5. fMRI records brain activity but does not directly modify activity. Therefore, it does not support inferences about whether a brain region is necessary for a behavior, but rather whether the region is involved in that behavior. Most studies support forward inferences about this involvement, whereby activity in the brain can be linked to a mental process because the experiment manipulates that process.
6. fMRI provides an opportunity to study the function of the human brain as it engages in a variety of mental processes, in both health and disease. This technology and analyses of the data it generates are undergoing continual development to improve the temporal and spatial resolution of biological measurements and to clarify the links between these measurements, mental processes, and behavior.

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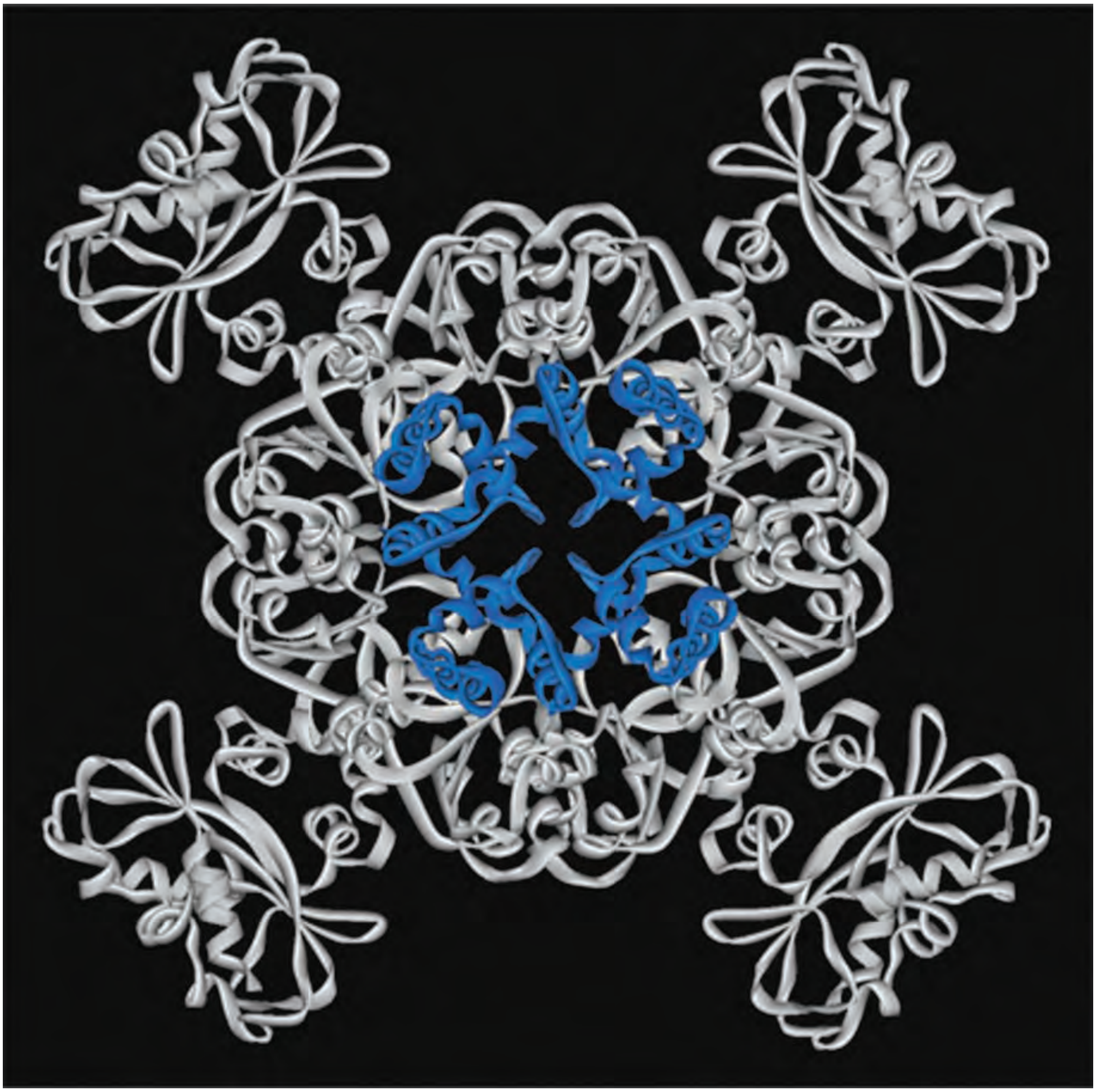
Part II



Preceding Page

Crystal structure of the MthK Ca^{2+}-regulated K^+ channel from the archaeon *Methanobacterium thermoautotrophicum*, a thermophilic microbe. The view is from the extracellular side of the channel in the Ca^{2+}-bound open state. MthK consists of two major functional domains. An integral membrane protein forms an aqueous pore (**blue**), which selects and conducts K^+ ions, and has a gate that switches between open and closed conformations; an intracellular Ca^{2+}-binding gating ring (**gray**) controls the gate. When it binds Ca^{2+}, the resulting conformational change is mechanically transmitted to the pore, causing it to switch to the open state. (Used with permission of Kenton Swartz, based on PDB code 1LNQ, from Jian Y, Lee A, Chen J, et al. 2002. Nature 417:523–526.)

II

Cell and Molecular Biology of Cells of the Nervous System

In all biological systems, from the most primitive to the most advanced, the basic building block is the cell. Cells are often organized into functional modules that are repeated in complex biological systems. The vertebrate brain is the most complex example of a modular system. Complex biological systems have another basic feature: They are architectonic—that is, their anatomy, fine structure, and dynamic properties all reflect a specific physiological function. Thus, the construction of the brain and the cell biology, biophysics, and biochemistry of its component cells reflect its fundamental function, which is to mediate behavior.

The nervous system is made up of glial cells and nerve cells. Earlier views of glia as purely structural elements have been supplanted by our current understanding that there are several types of glial cells, each of which is specialized to regulate one or more particular aspects of neuronal function. Different varieties of glial cells play essential roles in enabling and guiding neural development, insulating axonal processes, controlling the extracellular milieu, supporting synaptic transmission, facilitating learning and memory, and modulating pathological processes within the nervous system. Some glial cells have receptors for neurotransmitters and voltage-gated ion channels that enable them to communicate with one another and with neurons to support neuronal signaling.

In contrast to glial cells, the great diversity of nerve cells—the fundamental units from which the modules of the nervous systems are assembled—are variations on one basic cell plan. Four features of this plan give nerve cells the unique ability to communicate with one another precisely and rapidly over long distances. First, the neuron is polarized, possessing receptive dendrites on one end and communicating axons with presynaptic terminals at the other. This polarization of functional properties restricts the predominant flow of voltage impulses to one direction. Second, the neuron is electrically excitable. Its cell membrane contains specialized proteins—ion channels and receptors—that permit the influx and efflux of specific inorganic ions, thus creating electrical currents that generate the voltage signals across the membrane. Third, the neuron contains proteins and organelles that endow it with specialized secretory properties that allow it to release neurotransmitters at synapses. Fourth, this system for rapid signaling over the long distances between the cell body and its terminals is enabled by a cytoskeletal structure that mediates, on a slower time scale, efficient transport of various proteins, mRNAs, and organelles between the two compartments.

In this part of the book, we shall be concerned with the distinctive cell biological properties that allow neurons and glia to fulfill their various specialized functions. A major emphasis will be on properties of ion channels that endow neurons with the ability to generate and propagate electrical signals in the form of action potentials. We begin the discussion of neurons by considering general properties shared by ion channels—the ability to select and conduct ions, and to gate between open and closed conformations. Neurons use four major classes of channels for signaling: (1) resting channels generate the resting potential and underlie the passive electrical properties of neurons that determine the time course of synaptic potentials, their spread along dendrites, and the threshold for firing an action potential; (2) sensory receptor channels respond to certain sensory stimuli to generate local receptor potentials; (3) ligand-gated channels open in response to neurotransmitters, generating local synaptic potentials; and (4) voltage-gated channels produce the currents that generate self-propagating action potentials. In this part, we focus mainly on resting and voltage-gated channels. In Part III, we consider in more detail ligand-gated channels, and the neurotransmitters and second messengers that control their activity. The channels that are activated by sensory stimuli will be examined in Part IV.

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Part II