nuclei in the brain stem contain neurons that synthesize and release the modulatory neurotransmitter norepinephrine (the locus coeruleus) and serotonin (the dorsal raphe nucleus). Such neurons set the general arousal level of an animal through their widespread connections with forebrain structures. A group of cholinergic modulatory neurons, the basal nucleus of Meynert, is involved in arousal or attention (Chapter 40). This nucleus is located beneath the basal ganglia in the basal forebrain portion of the telencephalon. The axons of its neurons project to essentially all portions of the neocortex.

If a predator finds potential prey, a variety of cortical and subcortical systems determine whether the prey is edible. Once food is recognized, other cortical and subcortical systems initiate a comprehensive voluntary motor program to bring the animal into contact with the prey, capture it and place it in the mouth, and chew and swallow.

Finally, the physiological satisfaction the animal experiences in eating reinforces the behaviors that led to the successful predation. A group of dopaminergic neurons in the midbrain are important for monitoring reinforcements and rewards. The power of the dopaminergic modulatory systems has been demonstrated by experiments in which electrodes were implanted into the reward regions of rats and the animals were freely allowed to press a lever to electrically stimulate their brains. They preferred this self-stimulation to obtaining food or water, engaging in sexual behavior, or any other naturally rewarding activity. The role of the dopaminergic modulatory system in learning through reinforcement of exploratory behavior is described in Chapter 38.

How the brain's modulatory systems, concerned with reward, attention and motivation, interact with the sensory and motor systems is one of the most interesting questions in neuroscience, one that is also fundamental to our understanding of learning and memory storage (Chapter 40).

The Peripheral Nervous System Is Anatomically Distinct From the Central Nervous System

The peripheral nervous system supplies the central nervous system with a continuous stream of information about both the external environment and the internal environment of the body. It has somatic and autonomic divisions (Figure 4–16).

The *somatic division* includes the sensory neurons that receive information from the skin, muscles, and

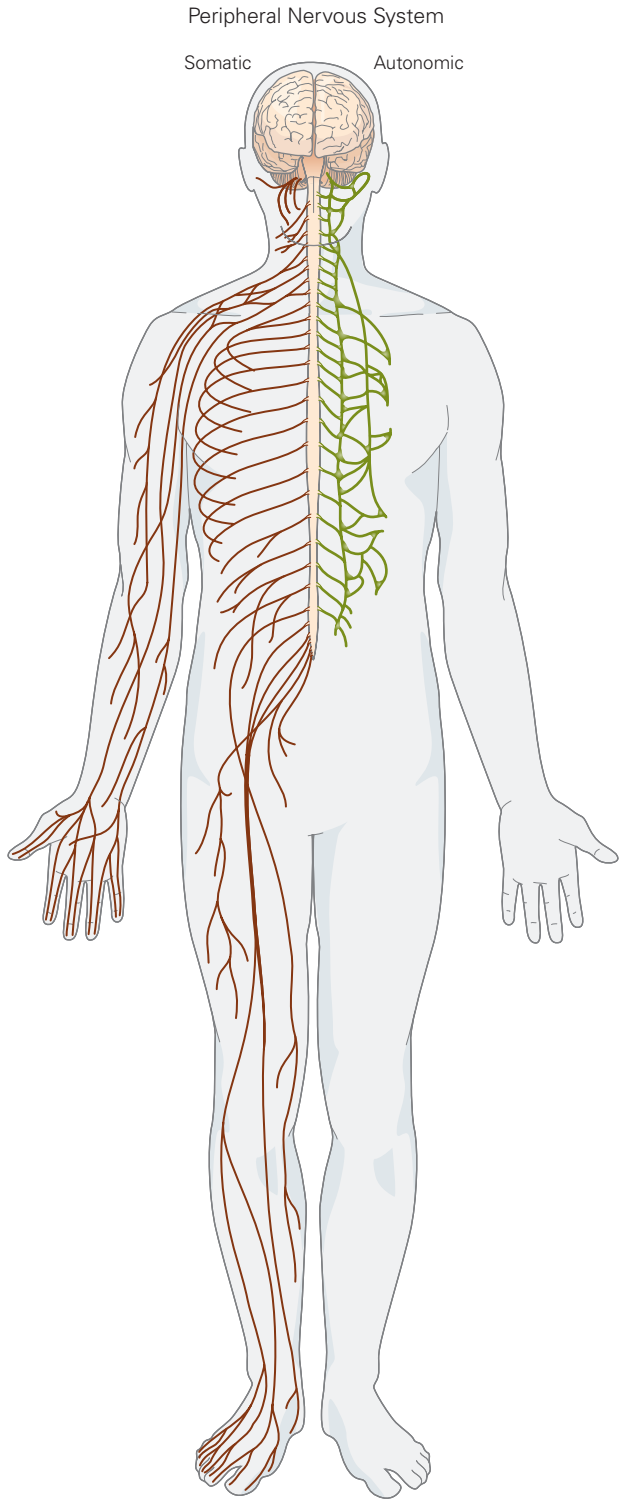

Figure 4–16 The peripheral nervous system has somatic and autonomic divisions. The somatic division carries information from the skin to the brain and from the brain to muscles. The autonomic division regulates involuntary functions, including activity of the heart and smooth muscles in the gut and glands.

joints. The cell bodies of these sensory neurons lie in the dorsal root ganglia and cranial ganglia. Receptors associated with these cells provide information about muscle and limb position and about touch and pressure at the body surface. In Part IV (Perception), we shall see how remarkably specialized these receptors are in transducing one or another type of physical energy (eg, deep pressure or heat) into the electrical signals used by the nervous system. In Part V (Movement), we shall see that sensory receptors in the muscles and joints are crucial to shaping coherent movement of the body.

The *autonomic division* of the peripheral nervous system mediates visceral sensation as well as motor control of the viscera, vascular system, and exocrine glands. It consists of the sympathetic, parasympathetic, and enteric systems. The sympathetic system participates in the body's response to stress, whereas the parasympathetic system acts to conserve body resources and restore homeostasis. The enteric nervous system, with neuronal cell bodies located in or adjacent to the viscera, controls the function of smooth muscle and secretions of the gut. The functional organization of the autonomic nervous system is described in Chapter 41 and its role in emotion and motivation in Chapter 42.

Memory Is a Complex Behavior Mediated by Structures Distinct From Those That Carry Out Sensation or Movement

Research over the past 50 years has provided a sophisticated view of memory systems in the brain. We now know that different forms of memory (eg, fear memory versus skill memory) are mediated by different brain regions. Here we contrast the organization of the system responsible for coding and storing our experiences of other individuals, places, facts, and episodes, a process called explicit memory.

We know that a structure called the hippocampus (or more properly the hippocampal formation, since it is several cortical regions) is a key component of a medial temporal lobe memory system that encodes and stores memories of our lives (Figure 4–17). This understanding is based largely on the analysis of the

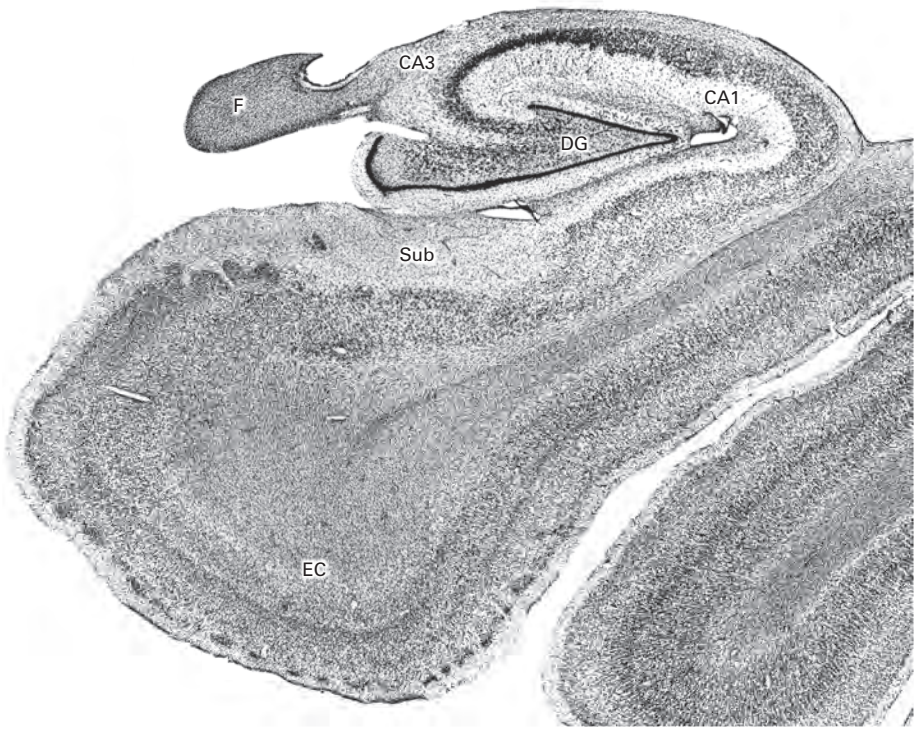

Figure 4–17 Coronal section of the human hippocampal formation stained by the Nissl methods to demonstrate cell bodies. The main cytoarchitectonic fields are shown in this section of the human hippocampal formation. (Abbreviations: **CA3** and **CA1**, subdivisions of the hippocampus; **DG**, dentate gyrus; **EC**, entorhinal cortex; **F**, fimbria; **Sub**, subiculum.)

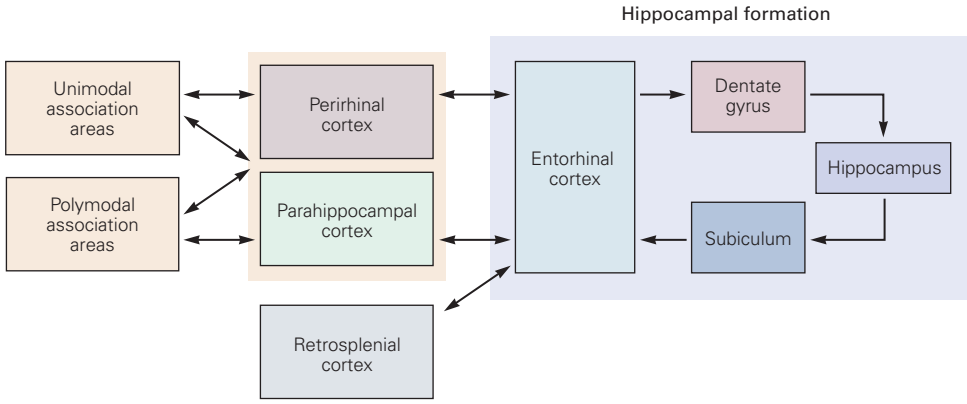

Figure 4–18 Hierarchical organization of connections to the hippocampal formation. The hippocampal formation receives highly processed sensory information, primarily through the entorhinal cortex, from multimodal association regions such as the perirhinal, parahippocampal, and retrosplenial cortices.

famous patient Henry Molaison (referred to as HM by the scientists who studied him during his life), who in the early 1950s had bilateral temporal lobe surgery to reduce his life-threatening epilepsy. In contrast to the six-layered neocortex, the hippocampus, along with olfactory cortex (piriform cortex), is a three-layered cortical structure referred to as archicortex, one of the phylogenetically older areas of cortex.

The reason we briefly describe the hippocampal formation in this chapter is to emphasize that not all brain circuits are alike. In fact, whether one talks about the olfactory bulb, where the sense of smell begins to be processed, or the cerebellum, where fine motor movements are refined, the general principle is that the structure of a circuit is specific to the function that it mediates. And the hippocampal circuit is as different from the circuits that mediate sensory perception or motor movement as one could imagine. Hippocampal circuitry of the brain will be dealt with in much more detail in later chapters. Chapter 5 introduces the idea that the hippocampus encodes information about an animal's spatial location in its environment and that the encoding of explicit memory (including spatial memory) requires plastic changes in synaptic function. Chapters 52 and 54 explore human memory function and the cellular and molecular bases of explicit memory and spatial representation, respectively.

The Hippocampal System Is Interconnected With the Highest-Level Polysensory Cortical Regions

Sensory systems are hierarchical and process progressively more complex stimuli at higher levels, particularly of the neocortex. Moreover, from the highest levels of each modality, circuits connect with polysensory cortical regions located at various places around the cortex, where information from many sensory modalities converges onto single neurons. The hippocampal system receives most of its input, the raw material with which it makes memories, from a few specific polysensory regions. These include the perirhinal and parahippocampal cortices, located in the medial temporal lobe, as well as the retrosplenial cortex, located in the caudal portion of the cingulate gyrus. These polysensory regions converge on the entry structure to the hippocampal system, the entorhinal cortex (Figure 4–18). The polysensory information that enters the entorhinal cortex can be thought of as providing summaries of immediate experience.

The Hippocampal Formation Comprises Several Different but Highly Integrated Circuits

The hippocampal formation is made up of a number of distinct cortical regions that are simpler in organization than the neocortex—at least they have fewer layers. The regions include the dentate gyrus, hippocampus, subiculum, and entorhinal cortex. Each of these regions is made up of subregions containing many neuronal cell types. The simplest subregion of the hippocampal formation is the dentate gyrus, which has a single principal neuron called the granule cell. The subregions of the hippocampus termed CA1, CA2, and CA3, consist of a single layer of pyramidal cells whose dendrites extend above and below the cell body layer and receive inputs from several regions. The subiculum (divided into subiculum, presubiculum and parasubiculum) is another region made up largely of pyramidal cells. Finally, the most complex part of the hippocampal formation is the entorhinal cortex, which has multiple layers but still has an organization distinctly different from the neocortex. For example, it lacks a layer IV and has a much more prominent layer II.

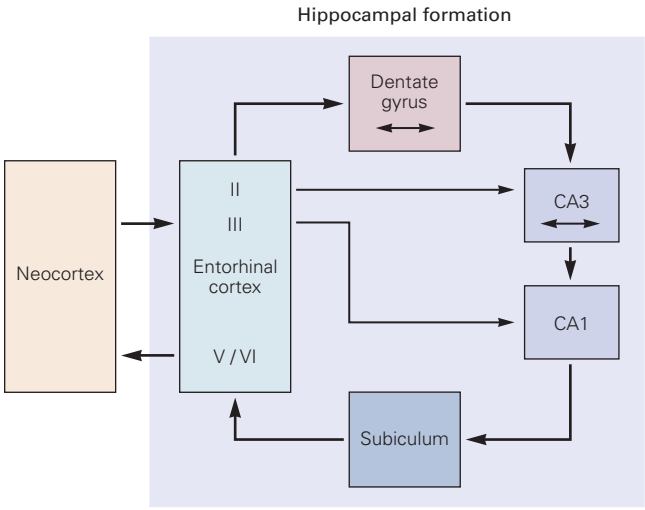

Figure 4–19 Simplified diagram on internal connections within the hippocampal formation. The circuit begins from cells in layer II of the entorhinal cortex to the dentate gyrus, which then projects to the CA3 region of the hippocampus. The CA3 portion of the hippocampus projects to CA1, and CA1 then projects to the subiculum. The hippocampal circuit is closed when the subiculum projects to the deep layers of the entorhinal cortex. Not shown are the feedback pathways from entorhinal cortex to the same multimodal areas from which it receives sensory information.

The Hippocampal Formation Is Made Up Mainly of Unidirectional Connections

Here we describe the fundamental circuitry of the hippocampal formation. The circuitry is described in more detail in Chapter 54. The simplified version of the hippocampal circuit shown in Figure 4–19 emphasizes its stepwise serial processing of multimodal sensory information, with each hippocampal region contributing to the formation of explicit memories. This serial processing implies that damage to any one of the components of this system would lead to memory impairment. And, in fact, another famous patient, known by the initials R.B., did suffer profound memory impairment due to loss of cells in the CA1 region after an ischemic episode.

As it turns out, while the hippocampal formation is essential for the initial formation of memories of our lives, these memories are ultimately stored elsewhere in the brain. In patients such as HM, in whom the entorhinal cortex and much of the rest of the hippocampal system was removed, memories prior to the surgery were largely intact. Thus, to achieve creation and long-term storage of the memories of our lives, the hippocampus and entorhinal cortex must communicate with circuits in the cerebral cortex. Where and precisely how that happens remain a mystery.

Highlights

1. Individual neurons are not able to carry out behavior. They must be incorporated into circuits that comprise different types of neurons that are interconnected by excitatory, inhibitory, and modulatory connections.
2. Sensory and motor information is processed in the brain in a variety of discrete brain regions that are active simultaneously.
3. A functional pathway is formed by the serial connection of identifiable brain regions, and each brain region's circuits process more complex or specific information than the preceding brain region.
4. The sensations of touch and pain are mediated by pathways that run between different circuits in the spinal cord, brain stem, thalamus, and neocortex.
5. All sensory and motor systems follow the pattern of hierarchical and reciprocal processing of information, whereas the hippocampal memory system is organized largely for serial processing of very complex, polysensory information. A general principle is that circuits in the brain have an organizational structure that is suited for the functions that they are carrying out.
6. Contrary to an intuitive analysis of our personal experience, perceptions are not precise copies of the world around us. Sensation is an abstraction, not a replication, of reality. The brain's circuits construct an internal representation of external physical events after first analyzing various features of those events. When we hold an object in the hand, the shape, movement, and texture of the object are simultaneously analyzed in different brain regions according to the brain's own rules, and the results are integrated in a conscious experience.
7. How sensation is integrated in a conscious experience—the *binding problem*—and how conscious experience emerges from the brain's analysis of incoming sensory information are two of the most intriguing questions in cognitive neuroscience (Chapter 56). An even more complex issue is how these conscious impressions are encoded into memories that are stored for decades.

David G. Amaral

Selected Reading

Brodal A. 1981. *Neurological Anatomy in Relation to Clinical Medicine,* 3rd ed. New York: Oxford Univ. Press.

Carpenter MB. 1991. *Core Text of Neuroanatomy,* 4th ed. Baltimore: Williams and Wilkins.

England MA, Wakely J. 1991. *Color Atlas of the Brain and Spinal Cord: An Introduction to Normal Neuroanatomy.* St. Louis: Mosby Year Book.

Martin JH. 2012. *Neuroanatomy: Text and Atlas,* 4th ed. New York: McGraw Hill.

Nieuwenhuys R, Voogd J, van Huijzen Chr. 1988. *The Human Central Nervous System: A Synopsis and Atlas,* 3rd rev. ed. Berlin: Springer-Verlag.

Peters A, Jones EG (eds). 1984. *Cerebral Cortex.* Vol. 1, *Cellular Components of the Cerebral Cortex*. New York: Plenum.

Peters A, Palay S, Webster H de F. 1991. *The Fine Structure of the Nervous System,* 3rd ed. New York: Oxford Univ. Press.

References

Brodmann K. 1909. *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues.* Leipzig: Barth.

Felleman DJ, Van Essen DC. 1991. Distributed hierarchical processing in the primate cerebral cortex. Cereb Cortex 1: 1–47.

Heimer L. 1994. *The Human Brain and Spinal Cord: Functional Neuroanatomy and Dissection Guide*, 2nd ed. New York: Springer.

Jones EG. 1988. The nervous tissue. In: *Cell and Tissue Biology: A Textbook of Histology*, 6th ed., pp. 305–341. Baltimore: Urban & Schwarzenberg.

Jones EG. 1986. Connectivity of the primate sensory-motor cortex. In: EG Jones, A Peters (eds), Cerebral Cortex, Vol. 5, Chapter 4: Sensory-Motor Areas and Aspects of Cortical Connectivity, pp. 113–183. New York/London: Plenum.

Kaas JH. 2006. Evolution of the neocortex. Curr Biol 16: R910–914.

Kaas JH, Qi HX, Burish MJ, Gharbawie OA, Onifer SM, Massey JM. 2008. Cortical and subcortical plasticity in the brains of humans, primates, and rats after damage to sensory afferents in the dorsal columns of the spinal cord. Exp Neurol 209:407–416.

McKenzie AL, Nagarajan SS, Roberts TP, Merzenich MM, Byl NN. 2003. Somatosensory representation of the digits and clinical performance in patients with focal hand dystonia. Am J Phys Med Rehabil 82:737–749.

Penfield W, Boldrey E. 1937. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain 60:389–443.

Penfield W, Rasmussen T. 1950. *The Cerebral Cortex of Man: A Clinical Study of Localization of Function*. New York: Macmillan.

Ramón y Cajal S. 1995. *Histology of the Nervous System of Man and Vertebrates*. 2 vols. N Swanson, LW Swanson (transl). New York: Oxford Univ. Press.

Rockland KS, Ichinohe N. 2004. Some thoughts on cortical minicolumns. Exp Brain Res 158:265–277.

Zola-Morgan S, Squire LR, Amaral DG. 1986. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J Neurosci 6:2950–2967.

5

The Computational Bases of Neural Circuits That Mediate Behavior

The previous chapter focused on the neuroanatomy of the brain and the connections between different brain regions. An understanding of how these connections mediate behavior requires insight into how the information represented by the activity of different populations of neurons is communicated and processed. Much of this understanding has come from recordings of the minute electrical signals generated by individual neurons.

Although much has been learned by recording from just one or a few neurons at a time, advances in miniaturization and electronics technology now make it possible to record action potentials simultaneously from many hundreds of individual neurons across multiple brain areas, often in the context of a sensory, motor, or cognitive task (Box 5–1). Such advances, together with computational approaches for managing and making sense of large data sets, promise to revolutionize our understanding of neural function.

At the same time, modern genetic approaches based on mRNA sequencing from individual neurons are revealing the numerous types of cells that contribute to population activity. Genetic-based approaches also allow defined types of neurons to be activated or silenced during an experiment, supporting tests of causality (Box 5–2).

High-throughput anatomical methods, at the scales of both light and electron microscopy, are providing information about circuit wiring at an unprecedented level of detail and completeness. The complexity of neural circuits and the large data sets collected from them has motivated the development and application of statistical, computational, and theoretical methods for extracting, analyzing, modeling, and interpreting results. These methods are used to study a broad range of issues: experimental design, the extraction of signals from raw data, the analysis of large complex data sets, the construction and analysis of models simulating the data, and, finally and most importantly, building some form of understanding from the results.

Signal extraction is often done on the basis of a Bayesian approach, inferring the most likely signal

Box 5–1 Optical Neuroimaging

Optical imaging methods are a rapidly advancing field of technology for large-scale monitoring of neural circuit dynamics. Most of these approaches use fluorescent sensors—synthetic dyes or genetically engineered and encoded proteins—that signal changes in neural activity via changes in the magnitude or the wavelength of their emitted light following excitation. Various florescence imaging approaches have been developed, depending on the source of fluorescence excitation, including single-photon, multiphoton, and super-resolution fluorescent microscopic imaging.

The most commonly used fluorescence indicators signal changes in intracellular calcium levels as a proxy for the electrical activity of neurons. While the temporal resolution of fluorescence calcium imaging is generally lower than that of electrophysiology, fluorescent imaging with genetically encoded calcium indicators enables simultaneous monitoring of many thousands of individually identified neurons in the behaving animal over several days to weeks and months.

In addition to calcium imaging, synthetic and genetically encoded fluorescent indicators of electrical activity (eg, genetically encoded voltage indicators [GEVIs]), neurotransmitter concentration reporters (eg, glutamate-sensing fluorescent reporter [GluSnFR]), activity states of intracellular signaling molecules, and gene expression provide rapidly expanding and versatile techniques for monitoring neural activity on multiple spatial and temporal scales.

present in a noisy recording. Data analysis often consists of reducing the dimensionality of a large data set, not simply to make it more compact but to identify the essential components from which it is built.

Models of neural systems range from detailed simulations of the morphology and electrophysiology of individual neurons to more abstract models of large populations of neurons. Whatever the level of detail, the aim of models is to reveal how the measured features of a neuron or network of neurons contribute to the function of the neuron or neural circuit.

In addition, at the highest levels of functionality, such as identifying images, playing games, or performing tasks at human levels, ideas from machine learning are increasingly impacting neuroscience research.

In this chapter, we introduce ideas, techniques, and approaches that are used to characterize and interpret the activity of neural populations and circuits, with examples drawn from a number of areas of brain research. Many of these topics are covered in greater detail later in the book.

Neural Firing Patterns Provide a Code for Information

Sensory Information Is Encoded by Neural Activity

Animals and humans continually accumulate information about the world through their senses, make decisions on the basis of that information, and, when necessary, take action. In order for sensory information to be processed for decision making and action, it must be transformed into electrical signals that produce patterns of neural activity in the brain. Studying such neural representations and their relationship to external sensory cues, known collectively as neural coding, is a major area of neuroscience research. The process through which features of a stimulus are represented by neural activity is called encoding.

The structure of a neural representation plays an important role in how information is further processed by the nervous system. For example, visual information is initially encoded in the retina by photoreceptor responses to the color and light intensity over a small region of the visual field. This information is then transformed in the brain within the primary visual cortex to encode a visual scene on the basis of the edges and shapes that define the scene as well as on where these features are located. Further transformations occur in higher-order visual areas that extract complex shapes and further structure from the scene, including the identification of objects and even individual faces. In other brain areas, auditory encoding reflects the frequency spectrum of sounds, and touch is encoded in maps that represent the surface of the body. The sequence of action potentials fired by a neuron in response to a sensory stimulus represents how that stimulus changes over time. Research on neural coding aims to understand both the stimulus features that drive a neuron to respond and the temporal structure of the response and its relationship to changes in the external world.

Box 5–2 Optogenetic and Chemogenetic Manipulation of Neuronal Activity

Functional analysis of neural circuits relies on the ability to accurately manipulate identified circuit elements to elucidate their roles in physiology and behavior. Genetically encoded neural perturbation tools have been developed for remotely controlling neuron function using light (optogenetics) or small molecules (chemogenetics) that activate engineered receptors.

Genetically encoded foreign proteins can be expressed in molecularly, genetically, or spatially specified subsets of neurons using viruses or transgenic animals for subsequent selective perturbations of these cell populations. Optogenetic approaches involve the expression of light-sensitive proteins and subsequent light delivery to the resulting photosensitized neurons. Depending on the type of optogenetic actuator, light activation will then enhance neural activity (eg, light-gated ion channels like channelrhodopsin) or suppress it (eg, light-gated ion pumps like halorhodopsin and archaerhodopsin) by depolarizing or hyperpolarizing the cell's membrane, respectively.

Alternatively, selected neuronal populations can be remotely activated or silenced using chemogenetic actuators, which are genetically engineered receptors that are targeted to defined neuronal populations using genetic methods; they can be activated via small-molecule synthetic ligands that selectively interact with these receptors upon delivery (eg, DREADDs [designer receptors exclusively activated by designer drugs]).

These optogenetic and chemogenetic tools offer precise spatiotemporal control over neuronal activity to probe the causal relationship between neuronal cell types, circuit physiology, and behavior.

Information Can Be Decoded From Neural Activity

Sensory neurons encode information by firing action potentials in response to sensory features. Other brain areas, such as those that lead to decisions or generate motor actions, must correctly interpret the meaning of action potential sequences that they receive from sensory areas in order to respond appropriately. The process by which information is extracted from neural activity is called decoding.

The decoding of neural signals can be done experimentally and in clinical contexts by neuroscientists. Such decoding can infer what an animal or a human is seeing or hearing from recordings of visual or auditory neurons, for example. In practice, only certain features of the stimulus are likely to be inferred, but the results can nevertheless be impressive. A large number of decoding procedures have been developed, ranging from simple weighted sums of neuronal firing rates to sophisticated statistical methods.

Decoding methods are central to the development of neuroprosthetics for people with various nervous system impairments that result in extensive paralysis (Chapter 39). To accomplish this, neurons are recorded in the parietal or motor cortices through implanted electrodes, and online decoding procedures are used to interpret the movement intentions that are represented by the recorded neural activity. The inferred intentions are then used to control a computer cursor or drive a robotic limb.

Decoding recorded neural activity also gives us a remarkable view of what is going on in a neural circuit, which in turn provides insight into memory storage and retrieval, planning and decision making, and other cognitive functions. The following section illustrates these insights using a particularly interesting neural representation, the encoding of spatial location in the rodent hippocampus.

Hippocampal Spatial Cognitive Maps Can Be Decoded to Infer Location

One of the most complex cognitive challenges an animal faces is identifying and remembering its location in an environment relative to the location of other salient objects. For example, seed-caching birds can remember the location of hundreds of different places where they have stored food over a period of several months. The neural circuitry involved in formation of explicit memory—the memory of people, places, things, and events—was briefly introduced in the previous chapter. This form of memory requires the hippocampus, entorhinal cortex, and related structures in the temporal lobe. In 1971, John O'Keefe discovered physiological evidence of a neural representation of the spatial environment in the hippocampus. In 2014, he was awarded the Nobel Prize in Physiology or Medicine, together with May-Britt Moser and Edvard Moser, for their discoveries concerning the neuronal representation of space.

O'Keefe discovered that individual cells in the rat hippocampus, termed place cells, fire only when the animal traverses a particular area of the environment, termed the cell's place field (Figure 5–1). Subsequent research uncovered place cell–like activity in

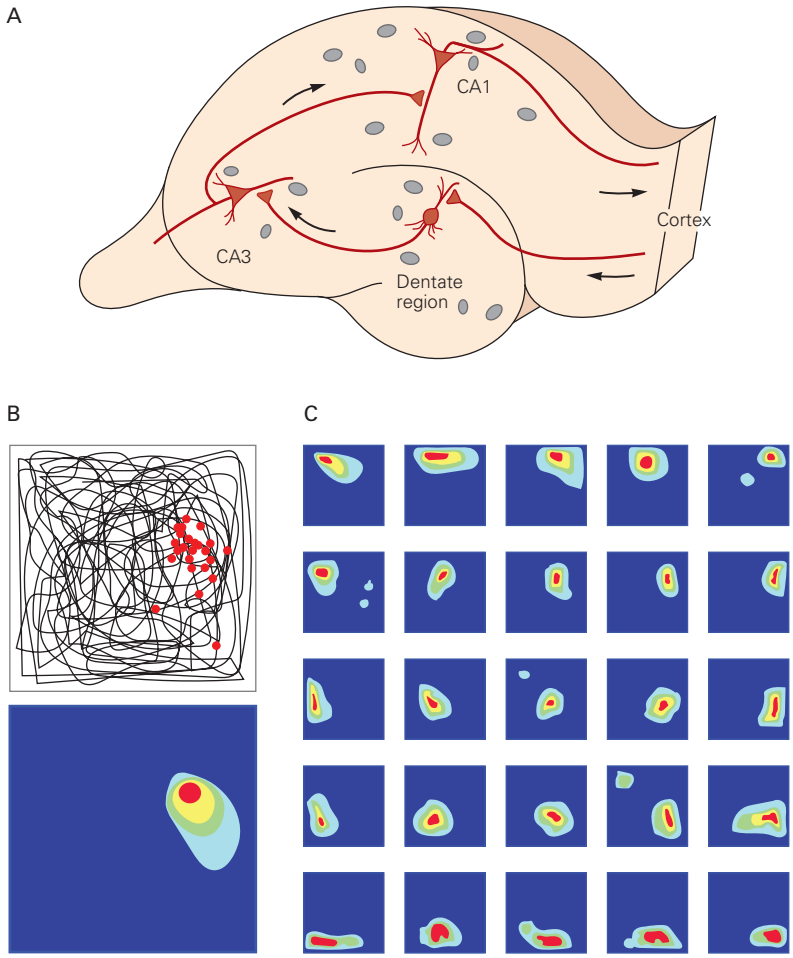

Figure 5–1 Hippocampal place cells and place cell maps.

A. Input–output transformations occur in the trisynaptic circuitry of the mammalian hippocampus, proceeding from the dentate gyrus input region, to the CA3 area, and to the CA1 output region, with principal excitatory neurons (**red**) in each region as primary processing units. Activity of principal cells is modulated by local circuit GABAergic interneurons (**gray**).

B. Place cell firing in the hippocampus. The path taken by a rat is shown in **black** as it traverses a square arena. Electrodes were implanted within the hippocampus to record from individual cells. **Above**: A single place cell increases firing (each action potential represented by a red dot) at discrete locations in the environment. **Below**: A color-coded heat map of firing frequency of the schematic place cell. Lower wavelength colors (**yellow** and **red**) represent higher firing rates on a background of no activity (**dark blue**).

C. Color-coded heat maps showing the firing of 25 different place cells recorded simultaneously in the hippocampal CA1 region as the rat explores a square box.

the hippocampus of several other mammalian species, including bats, monkeys, and humans. Distinct sets of place cells are activated by distinct locations in a given environment. Consequently, although individual place cells represent relatively small spatial areas, the full diverse population of place cells in the hippocampus tiles the entire environment, and any given location is encoded by a unique ensemble of cells. The hippocampal place coding network provides an example of a cognitive map, initially postulated by the psychologist Edward Tolman, that enables an animal to successfully remember and then navigate its environment. The role of the hippocampus in memory formation and the mechanisms by which the hippocampal spatial map is encoded are explored in detail in Chapters 52 and 54.

The electrophysiological methods available to O'Keefe in 1971 were limited to recording one place cell at a time, but subsequent advances allowed investigators to record dozens, and more recently hundreds, of place cells simultaneously. Critically, while single place cells encode only specific parts of the environment and are prone to occasional noisy firing outside of their place fields, entire populations of place cells provide more complete spatial coverage and the