

- Sapolsky RM. 2004. Mothering style and methylation. *Nat Neurosci* 7:791–792.
- Savic I, Berglund H, Gulyas B, Roland P. 2001. Smelling of odorous sex hormone-like compounds causes sex-differentiated hypothalamic activations in humans. *Neuron* 31:661–668.
- Savic I, Berglund H, Lindstrom P. 2005. Brain response to putative pheromones in homosexual men. *Proc Natl Acad Sci U S A* 102:7356–7361.
- Savic I, Lindstrom P. 2008. PET and MRI show differences in cerebral asymmetry and functional connectivity between homo- and heterosexual subjects. *Proc Natl Acad Sci U S A* 105:9403–9408.
- Sekido R, Lovell-Badge R. 2009. Sex determination and *SRY*: down to a wink and a nudge? *Trends Genet* 25:19–29.
- Shah NM, Pisapia DJ, Maniatis S, Mendelsohn MM, Nemes A, Axel R. 2004. Visualizing sexual dimorphism in the brain. *Neuron* 43:313–319.
- Stockinger P, Kvitsiani D, Rotkopf S, Tirian L, Dickson BJ. 2005. Neural circuitry that governs *Drosophila* male courtship behavior. *Cell* 121:795–807.
- Stowers L, Holy TE, Meister M, Dulac C, Koentges G. 2002. Loss of sex discrimination and male-male aggression in mice deficient for TRP2. *Science* 295:1493–1500.
- Unger EK, Burke KJ Jr, Yang CF, Bender KJ, Fuller PM, Shah NM. 2015. Medial amygdalar aromatase neurons regulate aggression in both sexes. *Cell Rep* 10:453–462.
- Weaver IC, Cervoni N, Champagne FA, et al. 2004. Epigenetic programming by maternal behavior. *Nat Neurosci* 7:847–854.
- Wei YC, Wang SR, Jiao ZL, et al. 2018. Medial preoptic area in mice is capable of mediating sexually dimorphic behaviors regardless of gender. *Nat Commun* 9:279.
- Wierman ME. 2007. Sex steroid effects at target tissues: mechanisms of action. *Adv Physiol Educ* 31:26–33.
- Wu MV, Manoli DS, Fraser EJ, et al. 2009. Estrogen masculinizes neural pathways and sex-specific behaviors. *Cell* 139:61–72.
- Wu Z, Autry AE, Bergan JF, Watabe-Uchida M, Dulac CG. 2014. Galanin neurons in the medial preoptic area govern parental behaviour. *Nature* 509:325–330.
- Xu X, Coats JK, Yang CF, et al. 2012. Modular genetic control of sexually dimorphic behaviors. *Cell* 148:596–607.
- Yang CF, Chiang MC, Gray DC, et al. 2013. Sexually dimorphic neurons in the ventromedial hypothalamus govern mating in both sexes and aggression in males. *Cell* 153:896–909.
- Yang T, Yang CF, Chizari MD, et al. 2017. Social control of hypothalamus-mediated male aggression. *Neuron* 95:955–970.
- Zhang J, Webb DM. 2003. Evolutionary deterioration of the vomeronasal pheromone transduction pathway in catarrhine primates. *Proc Natl Acad Sci U S A* 100:8337–8341.
- Zhang TY, Meaney MJ. 2010. Epigenetics and the environmental regulation of the genome and its function. *Annu Rev Psychol* 61:439–466.

Part VIII



Preceding Page

Tingarri Men and Initiates at Marabindinya. In this painting by the Aboriginal Australian artist, Anatjari Tjampitjinpa, Tingarri instructors are depicted as concentric circles and their young initiates are shown as horseshoe shapes along the boundaries. The background of the painting depicts the sandhill country of the central Australian desert. Such symbolic representations recall the neural representations of episodic memories, consisting of events taking place in space and time, encoded in the firing of grid cells and place cells in the entorhinal cortex and hippocampus, respectively. (© Estate of the artist licensed by Aboriginal Artists Agency Ltd.)

VIII

Learning, Memory, Language and Cognition

MOTOR AND SENSORY FUNCTIONS take up less than one-half of the cerebral cortex in humans. The rest of the cortex is occupied by the association areas, which coordinate events arising in the motor and sensory centers. Three association areas—the prefrontal, parietal-temporal-occipital, and limbic—are involved in cognitive behavior: speaking, thinking, feeling, perceiving, planning skilled movements, learning, memory, decision-making, and consciousness.

Most of the early evidence relating cognitive functions to the association areas came from clinical studies of brain-damaged patients. Thus, the study of language in patients with aphasia yielded important information about how human mental processes are distributed in the two hemispheres of the brain and how they develop. More refined analyses have come from human imaging studies using functional magnetic resonance imaging (fMRI) and other methods.

Deeper insights into the neural circuitry and cellular mechanisms giving rise to cognitive processes have come from electrophysiological recordings and genetic-based manipulations, including cell type-specific gene deletions and cell type-specific optogenetic excitation or inhibition in experimental animals, particularly in rodents. Such studies can evaluate the relative contribution of specific genes, neurons, and synaptic connections to specific types of behavior.

So far in this book, we have considered neural mechanisms associated with basic functions of the brain, including primary sensory perception, movement, and homeostatic control. In this part and the next, we begin to consider the more complex, higher-order brain functions mentioned earlier, the realm of cognitive neural science. The aim of this merger of neurophysiology, anatomy, developmental biology, cell and molecular biology, theory, and cognitive psychology is to ultimately provide an understanding of the neural mechanisms of the mind.

Until the latter part of the 20th century, the study of higher mental function was approached through behavioral observations gleaned from brain-damaged patients and animals with experimental lesions. In the first part of the 20th century, to avoid untestable

concepts and hypotheses, psychology became rigidly concerned with behaviors defined strictly in terms of observable stimuli and responses. Orthodox behaviorists thought it unproductive to deal with consciousness, feeling, attention, or even motivation. By concentrating only on observable actions, behaviorists asked: What can an organism do, and how does it do it? Indeed, careful quantitative analysis of stimuli and responses has contributed greatly to our understanding of the acquisition and use of “implicit” knowledge of perceptual and motor skills. However, humans and other higher animals also have “explicit” knowledge of facts and events. They have knowledge of space, rules, and relations—what Edward Tolman termed *cognitive maps*. Animals can choose a newly available route to a goal without ever learning the sensory-response association, and humans can reason deliberately from what they know to imagine something unknown. Indeed, that is what makes neural science possible—in fact, all of science and the humanities.

Thus, we also need to ask: What does the animal know about the world, and how does it come to know it? How is that knowledge represented in the brain? Does explicit knowledge differ from implicit knowledge? And how can such knowledge be communicated to others and enable us to make rational decisions based on past experience? Much, perhaps most, knowledge is unconscious a great deal of the time. We need to know the nature of the unconscious processes, the systems that mediate them, and their influence on the nature of conscious mental activity. Finally, we need to know about the highest realms of conscious knowledge, the knowledge of oneself as an individual, a thinking and feeling human being.

The modern effort to understand the neural mechanisms of higher mental functions began at the end of the 19th century when Pierre Broca and Carl Wernicke discovered regions of the cerebral cortex responsible for the production and comprehension of language. Throughout the 20th century, studies of patients with brain damage resulting from accidents, war, and disease led to an expansion of knowledge of the roles of specific brain areas responsible for cognitive functions, including attention, intention (planning), reasoning, and learning and memory. However, it was only in the past 20 to 30 years, based in part on new technological approaches, that our understanding of cognitive processes advanced from anatomical localization to an understanding of how neural activity in specific brain regions underlies such processes.

In Part VIII, we explore such questions of cognitive brain science. Chapter 52 introduces basic mechanisms of human learning and memory, focusing on the use of fMRI and behavioral studies to elucidate the role of different brain regions in implicit and explicit memory. In Chapter 53, we discuss the cellular and molecular mechanisms responsible for implicit memory storage, focusing on studies in invertebrates and vertebrates that have elucidated the role of synaptic plasticity in implicit memory storage. In Chapter 54, we

expand on the theme of synaptic plasticity, this time for the storage of explicit memory by the hippocampus and related brain regions. We further consider how the synaptic connectivity between the entorhinal cortex and hippocampus enables us to perceive and remember our spatial location in a given environment. Next, in Chapter 55, we focus on the neural mechanisms underlying language, a uniquely human function that enables us to communicate our store of knowledge to others, including brain circuits necessary for speaking and perceiving the spoken word. Finally, in Chapter 56, we examine how the brain enables us to use our knowledge to make rational decisions. Viewed through the lens of decision-making, the distinction between the apparently separate processes of knowledge and know-how can be seen as a unified function, one that provides a basis for understanding how consciousness may emerge from brain activity. Achieving a full understanding of the neural mechanisms that enable us to maintain a rich set of memories of our past experiences over a lifetime, to communicate those memories to others, and to use them to make informed, conscious decisions is perhaps one of the most daunting challenges in all of science.

Part Editors: Eric R. Kandel and Steven A. Siegelbaum

Part VIII

- Chapter 52 Learning and Memory
- Chapter 53 Cellular Mechanisms of Implicit Memory Storage and the Biological Basis of Individuality
- Chapter 54 The Hippocampus and the Neural Basis of Explicit Memory Storage
- Chapter 55 Language
- Chapter 56 Decision-Making and Consciousness

This page intentionally left blank

Learning and Memory

Short-Term and Long-Term Memory Involve Different Neural Systems

Short-Term Memory Maintains Transient Representations of Information Relevant to Immediate Goals

Information Stored in Short-Term Memory Is Selectively Transferred to Long-Term Memory

The Medial Temporal Lobe Is Critical for Episodic Long-Term Memory

Episodic Memory Processing Involves Encoding, Storage, Retrieval, and Consolidation

Episodic Memory Involves Interactions Between the Medial Temporal Lobe and Association Cortices

Episodic Memory Contributes to Imagination and Goal-Directed Behavior

The Hippocampus Supports Episodic Memory by Building Relational Associations

Implicit Memory Supports a Range of Behaviors in Humans and Animals

Different Forms of Implicit Memory Involve Different Neural Circuits

Implicit Memory Can Be Associative or Nonassociative

Operant Conditioning Involves Associating a Specific Behavior With a Reinforcing Event

Associative Learning Is Constrained by the Biology of the Organism

Errors and Imperfections in Memory Shed Light on Normal Memory Processes

Highlights

IN HIS MASTERFUL NOVEL *One Hundred Years of Solitude*, Gabriel Garcia Márquez describes a strange plague that invades a tiny village and robs people of their memories. The villagers first lose personal recollections, then the names and functions of common objects. To combat the plague, one man places written labels on every object in his home. But he soon realizes the futility of this strategy, because the plague eventually destroys even his knowledge of words and letters.

This fictional incident reminds us of how important learning and memory are in everyday life. Learning refers to a change in behavior that results from acquiring knowledge about the world, and memory refers to the processes by which that knowledge is encoded, stored, and later retrieved. Marquez's story challenges us to imagine life without the ability to learn and remember. We would forget people and places we once knew, and no longer be able to use and understand language or execute motor skills we had once learned; we would not recall the happiest or saddest moments of our lives and would even lose our sense of personal identity. Learning and memory are essential to the full functioning and independent survival of people and animals.

In 1861, Pierre Paul Broca discovered that damage to the posterior portion of the left frontal lobe (Broca's area) produces a specific deficit in language. Soon thereafter, it became clear that other mental functions, such as perception and voluntary movement, are also mediated by discrete parts of the brain (Chapter 1). This naturally led to the question: Are there discrete neural systems concerned with memory? If so, is there a "memory center," or is memory processing widely distributed throughout the brain?

Contrary to the prevalent view that cognitive functions are localized in the brain, many students of learning doubted that memory is localized. In fact, until the middle of the 20th century, many psychologists doubted that memory is a discrete function, independent of perception, language, or movement. One reason for the persistent doubt is that memory storage involves many different parts of the brain. We now appreciate, however, that these regions are not all equally important. There are several fundamentally different types of memory, and certain regions of the brain are much more important for encoding some types of memory than for others.

During the past several decades, researchers have made significant progress in the analysis and understanding of learning and memory. In this chapter, we focus on studies of normal human memory behavior, its perturbations following brain lesions due to injury or surgery, and measurements of brain activity during learning and memory recall using functional magnetic resonance imaging (fMRI) and extracellular electrophysiological recordings. These studies have yielded three major insights.

First, there are several forms of learning and memory. Each form of learning and memory has distinctive cognitive and computational properties and is supported by different brain systems. Second, memory involves encoding, storage, retrieval, and consolidation. Finally, imperfections and errors in remembering can provide clues about the nature and function of learning and memory and the fundamental role that memory plays in guiding behavior and planning for the future.

Memory can be classified along two dimensions: (1) the time course of storage and (2) the nature of the information stored. In this chapter, we consider the time course of storage. In the next two chapters, we focus on the cellular, molecular, and circuit-based mechanisms of different forms of learning and memory, based largely on studies of animal models.

Short-Term and Long-Term Memory Involve Different Neural Systems

Short-Term Memory Maintains Transient Representations of Information Relevant to Immediate Goals

When we reflect on the nature of memory, we usually think of the long-term memory that William James referred to as “memory proper” or “secondary memory.” That is, we think of memory as “the knowledge of a

former state of mind after it has already once dropped from consciousness.” This knowledge depends on the formation of a memory trace that is durable, in which the representation persists even when its content has been out of conscious awareness for a long period.

Not all forms of memory, however, constitute “former states of mind.” In fact, the ability to store information depends on a form of short-term memory, called working memory, which maintains current, albeit transient, representations of goal-relevant knowledge. In humans, working memory consists of at least two subsystems—one for verbal information and another for visuospatial information. The functioning of these two subsystems is coordinated by a third system called the *executive control processes*. Executive control processes are thought to allocate attentional resources to the verbal and visuospatial subsystems and to monitor, manipulate, and update stored representations.

We use the verbal subsystem when we attempt to keep speech-based (phonological) information in conscious awareness, as when we mentally rehearse a password before entering it. The verbal subsystem consists of two interactive components: a store that represents phonological knowledge and a rehearsal mechanism that keeps these representations active while we need them. Phonological storage depends on posterior parietal cortices, and rehearsal partially depends on articulatory processes in Broca’s area.

The visuospatial subsystem of working memory retains mental images of visual objects and of the location of objects in space. The rehearsal of spatial and object information is thought to involve modulation of this information in the parietal, inferior temporal, and occipital cortices by the frontal and premotor cortices.

Single-cell recordings in nonhuman primates indicate that, over a period of seconds, some prefrontal neurons maintain spatial representations, others maintain object representations, and still others represent the integration of spatial and object knowledge. Although neurons concerned with working memory of objects tend to lie in the ventrolateral prefrontal cortex and those concerned with spatial knowledge tend to lie in the dorsolateral prefrontal cortex, all three classes of neurons are found in both prefrontal subregions (Figure 52–1).

Thus, working memory involves activation of representations of information stored in specialized cortical regions that vary based on the content of the information, as well as activation of general control mechanisms in prefrontal cortex. Prefrontal control signals in working memory are further dependent on interaction with the striatum and ascending dopaminergic inputs from the midbrain.