Copyrighted Material

# PRINCIPLES OF NEURAL SCIENCE

# Sixth Edition

Eric R. Kandel John D. Koester Sarah H. Mack Steven A. Siegelbaum

**Copyrighted Material** 

Mc Graw Hill

# PRINCIPLES OF NEURAL SCIENCE

Sixth Edition

Edited by

ERIC R. KANDEL JOHN D. KOESTER SARAH H. MACK STEVEN A. SIEGELBAUM



New York Chicago San Francisco Athens London Madrid Mexico City Milan New Delhi Singapore Sydney Toronto Copyright © 2021 by McGraw Hill. All rights reserved. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without the prior written permission of the publisher.

ISBN: 978-1-25-964224-1 MHID: 1-25-964224-0

The material in this eBook also appears in the print version of this title: ISBN: 978-1-25-964223-4, MHID: 1-25-964223-2.

eBook conversion by codeMantra Version 1.0

All trademarks are trademarks of their respective owners. Rather than put a trademark symbol after every occurrence of a trademarked name, we use names in an editorial fashion only, and to the benefit of the trademark owner, with no intention of infringement of the trademark. Where such designations appear in this book, they have been printed with initial caps.

McGraw-Hill Education eBooks are available at special quantity discounts to use as premiums and sales promotions or for use in corporate training programs. To contact a representative, please visit the Contact Us page at www.mhprofessional.com.

### TERMS OF USE

This is a copyrighted work and McGraw-Hill Education and its licensors reserve all rights in and to the work. Use of this work is subject to these terms. Except as permitted under the Copyright Act of 1976 and the right to store and retrieve one copy of the work, you may not decompile, disassemble, reverse engineer, reproduce, modify, create derivative works based upon, transmit, distribute, disseminate, sell, publish or sublicense the work or any part of it without McGraw-Hill Education's prior consent. You may use the work for your own noncommercial and personal use; any other use of the work is strictly prohibited. Your right to use the work may be terminated if you fail to comply with these terms.

THE WORK IS PROVIDED "AS IS." McGRAW-HILL EDUCATION AND ITS LICENSORS MAKE NO GUARANTEES OR WARRANTIES AS TO THE ACCURACY, ADEQUACY OR COMPLETENESS OF OR RESULTS TO BE OBTAINED FROM USING THE WORK, INCLUDING ANY INFORMATION THAT CAN BE ACCESSED THROUGH THE WORK VIA HYPER-LINK OR OTHERWISE, AND EXPRESSLY DISCLAIM ANY WARRANTY, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. McGraw-Hill Education and its licensors do not warrant or guarantee that the functions contained in the work will meet your requirements or that its operation will be uninterrupted or error free. Neither McGraw-Hill Education nor its licensors shall be liable to you or anyone else for any inaccuracy, error or omission, regardless of cause, in the work or for any damages resulting therefrom. McGraw-Hill Education has no responsibility for the content of any information accessed through the work. Under no circumstances shall McGraw-Hill Education and/or its licensors be liable for any indirect, incidental, special, punitive, consequential or similar damages that result from the use of or inability to use the work, even if any of them has been advised of the possibility of such damages. This limitation of liability shall apply to any claim or cause whatsoever whether such claim or cause arises in contract, tort or otherwise.



Sarah H. Mack 1962–2020 WE DEDICATE THIS SIXTH EDITION OF *Principles of Neural Science* to our dear friends and colleagues, Thomas M. Jessell and Sarah H. Mack.

Sarah Mack, who contributed to and directed the art program of *Principles of Neural Science* during her more than 30-year tenure, passed away on October 2, 2020. She worked courageously and tirelessly to ensure that all the artwork for this edition met her high standards and could be completed while she still had the strength to continue.

After graduating from Williams College with honors in English literature in 1984, Sarah worked for five years in the field of social work, while taking

courses at Columbia in studio art and computer graphics. She first contributed to the art program for the third edition of the book when she joined the Kandel lab as a graphic artist in 1989. Five years later, as the fourth edition went into the planning stage, Sarah, together with Jane Dodd as art editor, completely redesigned the art program, developing and converting hundreds of figures and introducing color. This monumental task required countless aesthetic decisions to develop a stylistic consistency for the various figure elements throughout the book. The result was a set of remarkably clear, didactic, and artistically pleasing diagrams and images. Sarah maintained and extended this high level of excellence as art editor of the fifth and sixth editions of the book. She has thus left an enduring mark on the thousands of students who over the years, as well as in years to come, have been introduced to neuroscience through her work.

Sarah was a most remarkable and gifted artist, who developed a deep understanding and appreciation of neuroscience during the many years she contributed to the book. In addition to her artistic contributions to the figures, she also edited the associated text and legends for maximum clarity. Because her contributions extended far beyond the preparation of the figures, Sarah was made co-editor of the current edition of the book. Sarah also had an amazing ability to juggle huge numbers of negotiations with dozens of authors simultaneously, all the while gently, but firmly, steering them to a final set of elegantly instructive images. She did this with such a spirit of generosity that her interactions with the authors, even those she never met in person, developed into warm friendships.

Over the past three editions, Sarah was the driving force that formed the basis for the aesthetic unifying vision running throughout the chapters of *Principles*. She will be greatly missed by us all.



Thomas M. Jessell 1951–2019

Tom Jessell was an extraordinary neuroscientist who made a series of pioneering contributions to our understanding of spinal cord development, the sensory-motor circuit, and the control of movement. Tom had a deep encyclopedic knowledge and understanding of all that came within his sphere of interest. Equally at home discussing a long-forgotten scientific discovery, quoting Shakespeare by heart, or enthusing about 20th-century British or Italian Renaissance art, Tom was a brilliant polymath.

Tom's interest in neuroscience began with his undergraduate studies of synaptic pharmacology at the University

of London, from which he graduated in 1973. He then joined Leslie Iversen's laboratory at the Medical Research Council in Cambridge to pursue his PhD, where he investigated the mechanism by which the newly discovered neuropeptide substance P controls pain sensation. Tom made the pivotal observation that opioids inhibit transmission of pain sensation in the spinal cord by reducing substance P release. After receiving his doctoral degree in 1977, he continued to explore the role of substance P in pain processing as a postdoctoral fellow with Masanori Otsuka in Tokyo, solidifying his lifelong interest in spinal sensory mechanisms while managing to learn rudimentary Japanese. Tom then realized that deeper insights into spinal cord function might best be obtained through an understanding of neural development, prompting him to pursue research on the formation of a classic synapse, the neuromuscular junction, in Gerry Fischbach's laboratory at Harvard.

Tom then joined the faculty of Harvard's Department of Neurobiology as an Assistant Professor in 1981, where he explored the mechanisms of sensory synaptic transmission and the development of the somatosensory input to the spinal cord. In 1985 Tom was recruited to the position of Associate Professor and investigator of the Howard Hughes Medical Institute in the Center for Neurobiology and Behavior (now the Department of Neuroscience) and Department of Biochemistry and Molecular Biophysics at Columbia University's College of Physicians and Surgeons. Over the next 33 years, Tom, together with a remarkable group of students and collaborators, applied a multidisciplinary cellular, biochemical, genetic, and electrophysiological approach to identify and define spinal cord microcircuits that control sensory and motor behavior. His studies revealed the molecular and cellular mechanisms by which spinal neurons acquire their identity and by which spinal circuits are assembled and operate. He defined key concepts and principles of neural development and motor control, and his discoveries generated unprecedented insight into the neural principles that coordinate movement, paving the way for therapies for motor neuron disease.

Eric Kandel and Jimmy Schwartz, the initial editors of *Principles* of *Neural Science*, recruited Tom as co-editor as they began to plan the third edition of the book. Tom's role was to expand the treatment of developmental and molecular neural science. This proved to be a prescient choice as Tom's breadth of knowledge, clarity of thought, and precise, elegant style of writing helped shape and define the text for the next three editions. As co-authors of chapters in *Principles* during Tom's tenure, we can attest to the rigor of language and prose that he encouraged his authors to adopt.

In the last years of his life, Tom bravely faced a devasting neurodegenerative disease that prevented him from actively participating in the editing of the current edition. Nonetheless Tom's vision remains in the overall design of *Principles* and its philosophical approach to providing a molecular understanding of the neural bases of behavior and neurological disease. Tom's towering influence on this and future editions of *Principles*, and on the field of neuroscience in general, will no doubt endure for decades to come.

### Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

# Contents in Brief

Contents xiii Preface xli Acknowledgments xliii Contributors xlv

### Part I

### **Overall Perspective**

- 1 The Brain and Behavior 7
- 2 Genes and Behavior 26
- 3 Nerve Cells, Neural Circuitry, and Behavior 56
- 4 The Neuroanatomical Bases by Which Neural Circuits Mediate Behavior 73
- 5 The Computational Bases of Neural Circuits That Mediate Behavior 97
- 6 Imaging and Behavior 111

### Part II

### Cell and Molecular Biology of Cells of the Nervous System

- 7 The Cells of the Nervous System 133
- 8 Ion Channels 165
- 9 Membrane Potential and the Passive Electrical Properties of the Neuron 190
- 10 Propagated Signaling: The Action Potential 211

### Part III

### Synaptic Transmission

11 Overview of Synaptic Transmission 241

- 12 Directly Gated Transmission: The Nerve-Muscle Synapse 254
- 13 Synaptic Integration in the Central Nervous System 273
- Modulation of Synaptic Transmission and Neuronal Excitability: Second Messengers 301
- 15 Transmitter Release 324
- 16 Neurotransmitters 358

### Part IV

### Perception

- 17 Sensory Coding 385
- 18 Receptors of the Somatosensory System 408
- 19 Touch 435
- 20 Pain 470
- 21 The Constructive Nature of Visual Processing 496
- 22 Low-Level Visual Processing: The Retina 521
- 23 Intermediate-Level Visual Processing and Visual Primitives 545
- 24 High-Level Visual Processing: From Vision to Cognition 564
- 25 Visual Processing for Attention and Action 582
- 26 Auditory Processing by the Cochlea 598
- 27 The Vestibular System 629
- 28 Auditory Processing by the Central Nervous System 651
- 29 Smell and Taste: The Chemical Senses 682

### Part V Movement

- 30 Principles of Sensorimotor Control 713
- 31 The Motor Unit and Muscle Action 737
- 32 Sensory-Motor Integration in the Spinal Cord 761
- 33 Locomotion 783
- 34 Voluntary Movement: Motor Cortices 815
- 35 The Control of Gaze 860
- 36 Posture 883
- 37 The Cerebellum 908
- 38 The Basal Ganglia 932
- 39 Brain–Machine Interfaces 953

### Part VI

# The Biology of Emotion, Motivation, and Homeostasis

- 40 The Brain Stem 981
- 41 The Hypothalamus: Autonomic, Hormonal, and Behavioral Control of Survival 1010
- 42 Emotion 1045
- 43 Motivation, Reward, and Addictive States 1065
- 44 Sleep and Wakefulness 1080

### Part VII

# Development and the Emergence of Behavior

- 45 Patterning the Nervous System 1107
- 46 Differentiation and Survival of Nerve Cells 1130
- 47 The Growth and Guidance of Axons 1156
- 48 Formation and Elimination of Synapses 1181

- 49 Experience and the Refinement of Synaptic Connections 1210
- 50 Repairing the Damaged Brain 1236
- 51 Sexual Differentiation of the Nervous System 1260

### **Part VIII**

# Learning, Memory, Language and Cognition

- 52 Learning and Memory 1291
- 53 Cellular Mechanisms of Implicit Memory Storage and the Biological Basis of Individuality 1312
- 54 The Hippocampus and the Neural Basis of Explicit Memory Storage 1339
- 55 Language 1370
- 56 Decision-Making and Consciousness 1392

### Part IX

### Diseases of the Nervous System

- 57 Diseases of the Peripheral Nerve and Motor Unit 1421
- 58 Seizures and Epilepsy 1447
- 59 Disorders of Conscious and Unconscious Mental Processes 1473
- 60 Disorders of Thought and Volition in Schizophrenia 1488
- 61 Disorders of Mood and Anxiety 1501
- 62 Disorders Affecting Social Cognition: Autism Spectrum Disorder 1523
- 63 Genetic Mechanisms in Neurodegenerative Diseases of the Nervous System 1544
- 64 The Aging Brain 1561
- Index 1583

# Contents

Preface xli Acknowledgments xliii Contributors xlv

### Part I

**Overall Perspective** 

### 1 The Brain and Behavior.....7

Eric R. Kandel, Michael N. Shadlen

Two Opposing Views Have Been Advanced on the Relationship Between Brain and Behavior 8

The Brain Has Distinct Functional Regions 10

The First Strong Evidence for Localization of Cognitive Abilities Came From Studies of Language Disorders 16

Mental Processes Are the Product of Interactions Between Elementary Processing Units in the Brain 21

Highlights 23

Selected Reading 23

References 24

#### 

Matthew W. State, Cornelia I. Bargmann, T. Conrad Gilliam

An Understanding of Molecular Genetics and Heritability Is Essential to the Study of Human Behavior 27

The Understanding of the Structure and Function of the Genome Is Evolving 27

Genes Are Arranged on Chromosomes 30

The Relationship Between Genotype and Phenotype Is Often Complex 31

Genes Are Conserved Through Evolution 32

Genetic Regulation of Behavior Can Be Studied in Animal Models 34

A Transcriptional Oscillator Regulates Circadian Rhythm in Flies, Mice, and Humans 34

Natural Variation in a Protein Kinase Regulates Activity in Flies and Honeybees 42

Neuropeptide Receptors Regulate the Social Behaviors of Several Species 44

### Studies of Human Genetic Syndromes Have Provided Initial Insights Into the Underpinnings of Social Behavior 46

Brain Disorders in Humans Result From Interactions Between Genes and the Environment 46

Rare Neurodevelopmental Syndromes Provide Insights Into the Biology of Social Behavior, Perception, and Cognition 46

### Psychiatric Disorders Involve Multigenic Traits 48

Advances in Autism Spectrum Disorder Genetics Highlight the Role of Rare and De Novo Mutations in Neurodevelopmental Disorders 48

Identification of Genes for Schizophrenia Highlights the Interplay of Rare and Common Risk Variants 49

Perspectives on the Genetic Bases of Neuropsychiatric Disorders 51

Highlights 51

Glossary 52

Selected Reading 53

References 53

### **3** Nerve Cells, Neural Circuitry,

and Behavior ......56

Michael N. Shadlen, Eric R. Kandel

### The Nervous System Has Two Classes of Cells 57

Nerve Cells Are the Signaling Units of the Nervous System 57

Glial Cells Support Nerve Cells 61

Each Nerve Cell Is Part of a Circuit That Mediates Specific Behaviors 62

Signaling Is Organized in the Same Way in All Nerve Cells 64 The Input Component Produces Graded Local Signals 65

The Trigger Zone Makes the Decision to Generate an Action Potential 67

The Conductive Component Propagates an All-or-None Action Potential 67

The Output Component Releases Neurotransmitter 68

The Transformation of the Neural Signal From Sensory to Motor Is Illustrated by the Stretch-Reflex Pathway 68

#### Nerve Cells Differ Most at the Molecular Level 69

The Reflex Circuit Is a Starting Point for Understanding the Neural Architecture of Behavior 70

Neural Circuits Can Be Modified by Experience 71

Highlights 71

Selected Reading 72

References 72

### 4 The Neuroanatomical Bases by Which Neural Circuits Mediate Behavior....73

David G. Amaral

Local Circuits Carry Out Specific Neural Computations That Are Coordinated to Mediate Complex Behaviors 74

# Sensory Information Circuits Are Illustrated in the Somatosensory System 74

Somatosensory Information From the Trunk and Limbs Is Conveyed to the Spinal Cord 76

The Primary Sensory Neurons of the Trunk and Limbs Are Clustered in the Dorsal Root Ganglia 79

The Terminals of Central Axons of Dorsal Root Ganglion Neurons in the Spinal Cord Produce a Map of the Body Surface 81

Each Somatic Submodality Is Processed in a Distinct Subsystem From the Periphery to the Brain 81

### The Thalamus Is an Essential Link Between Sensory Receptors and the Cerebral Cortex 82

Sensory Information Processing Culminates in the Cerebral Cortex 84

Voluntary Movement Is Mediated by Direct Connections Between the Cortex and Spinal Cord 89

Modulatory Systems in the Brain Influence Motivation, Emotion, and Memory 89

The Peripheral Nervous System Is Anatomically Distinct From the Central Nervous System 92

Memory Is a Complex Behavior Mediated by Structures Distinct From Those That Carry Out Sensation or Movement 93 The Hippocampal System Is Interconnected With the Highest-Level Polysensory Cortical Regions 94

The Hippocampal Formation Comprises Several Different but Highly Integrated Circuits 94

The Hippocampal Formation Is Made Up Mainly of Unidirectional Connections 95

Highlights 95

Selected Reading 96

References 96

### 5 The Computational Bases of Neural Circuits That Mediate Behavior.....97

Larry F. Abbott, Attila Losonczy, Nathaniel B. Sawtell

### Neural Firing Patterns Provide a Code for Information 98

Sensory Information Is Encoded by Neural Activity 98

Information Can Be Decoded From Neural Activity 99

Hippocampal Spatial Cognitive Maps Can Be Decoded to Infer Location 99

### Neural Circuit Motifs Provide a Basic Logic for Information Processing 102

Visual Processing and Object Recognition Depend on a Hierarchy of Feed-Forward Representations 103

Diverse Neuronal Representations in the Cerebellum Provide a Basis for Learning 104

Recurrent Circuitry Underlies Sustained Activity and Integration 105

### Learning and Memory Depend on Synaptic Plasticity 107

Dominant Patterns of Synaptic Input Can be Identified by Hebbian Plasticity 107

Synaptic Plasticity in the Cerebellum Plays a Key Role in Motor Learning 108

Highlights 110

Selected Reading 110

References 110

### 6 Imaging and Behavior ..... 111

Daphna Shohamy, Nick Turk-Browne

# Functional MRI Experiments Measure Neurovascular Activity 112

fMRI Depends on the Physics of Magnetic Resonance 112

fMRI Depends on the Biology of Neurovascular Coupling 115

### Functional MRI Data Can Be Analyzed in Several Ways 115

fMRI Data First Need to Be Prepared for Analysis by Following Preprocessing Steps 115

fMRI Can Be Used to Localize Cognitive Functions to Specific Brain Regions 118

fMRI Can Be Used to Decode What Information Is Represented in the Brain 118

fMRI Can Be Used to Measure Correlated Activity Across Brain Networks 119

### Functional MRI Studies Have Led to Fundamental Insights 120

fMRI Studies in Humans Have Inspired Neurophysiological Studies in Animals 120

fMRI Studies Have Challenged Theories From Cognitive Psychology and Systems Neuroscience 121

fMRI Studies Have Tested Predictions From Animal Studies and Computational Models 122

Functional MRI Studies Require Careful Interpretation 122

Future Progress Depends on Technological and Conceptual Advances 123

Highlights 125

Suggested Reading 126

References 126

### Part II

Cell and Molecular Biology of Cells of the Nervous System

### 7 The Cells of the Nervous System.... 133

Beth Stevens, Franck Polleux, Ben A. Barres

Neurons and Glia Share Many Structural and Molecular Characteristics 134

The Cytoskeleton Determines Cell Shape 139

Protein Particles and Organelles Are Actively Transported Along the Axon and Dendrites 142

Fast Axonal Transport Carries Membranous Organelles 143

Slow Axonal Transport Carries Cytosolic Proteins and Elements of the Cytoskeleton 146

### Proteins Are Made in Neurons as in Other Secretory Cells 147

Secretory and Membrane Proteins Are Synthesized and Modified in the Endoplasmic Reticulum 147

Secretory Proteins Are Modified in the Golgi Complex 149

Surface Membrane and Extracellular Substances Are Recycled in the Cell 150

### Glial Cells Play Diverse Roles in Neural Function 151

Glia Form the Insulating Sheaths for Axons 151

Astrocytes Support Synaptic Signaling 154

Microglia Have Diverse Functions in Health and Disease 159

### Choroid Plexus and Ependymal Cells Produce Cerebrospinal Fluid 160

Highlights 162

Selected Reading 163

References 163

### 8 Ion Channels ..... 165

John D. Koester, Bruce P. Bean

Ion Channels Are Proteins That Span the Cell Membrane 166

Ion Channels in All Cells Share Several Functional Characteristics 169

Currents Through Single Ion Channels Can Be Recorded 169

The Flux of Ions Through a Channel Differs From Diffusion in Free Solution 171

The Opening and Closing of a Channel Involve Conformational Changes 172

The Structure of Ion Channels Is Inferred From Biophysical, Biochemical, and Molecular Biological Studies 174

Ion Channels Can Be Grouped Into Gene Families 177

X-Ray Crystallographic Analysis of Potassium Channel Structure Provides Insight Into Mechanisms of Channel Permeability and Selectivity 180

X-Ray Crystallographic Analysis of Voltage-Gated Potassium Channel Structures Provides Insight into Mechanisms of Channel Gating 182

The Structural Basis of the Selective Permeability of Chloride Channels Reveals a Close Relation Between Channels and Transporters 185

### Highlights 187

Selected Reading 188

References 188

9	Membrane Potential and the
	Passive Electrical Properties of
	the Neuron 190

John D. Koester, Steven A. Siegelbaum

### The Resting Membrane Potential Results From the Separation of Charge Across the Cell Membrane 191

### The Resting Membrane Potential Is Determined by Nongated and Gated Ion Channels 191

Open Channels in Glial Cells Are Permeable to Potassium Only 193

Open Channels in Resting Nerve Cells Are Permeable to Three Ion Species 194

The Electrochemical Gradients of Sodium, Potassium, and Calcium Are Established by Active Transport of the Ions 195

Chloride Ions Are Also Actively Transported 198

The Balance of Ion Fluxes in the Resting Membrane Is Abolished During the Action Potential 198

The Contributions of Different Ions to the Resting Membrane Potential Can Be Quantified by the Goldman Equation 199

The Functional Properties of the Neuron Can Be Represented as an Electrical Equivalent Circuit 199

The Passive Electrical Properties of the Neuron Affect Electrical Signaling 201

Membrane Capacitance Slows the Time Course of Electrical Signals 203

Membrane and Cytoplasmic Resistance Affect the Efficiency of Signal Conduction 204

Large Axons Are More Easily Excited Than Small Axons 206

Passive Membrane Properties and Axon Diameter Affect the Velocity of Action Potential Propagation 207

#### Highlights 208

#### Selected Reading 209

References 210

#### 

Bruce P. Bean, John D. Koester

The Action Potential Is Generated by the Flow of Ions Through Voltage-Gated Channels 212

Sodium and Potassium Currents Through Voltage-Gated Channels Are Recorded With the Voltage Clamp 212 Voltage-Gated Sodium and Potassium Conductances Are Calculated From Their Currents 217

The Action Potential Can Be Reconstructed From the Properties of Sodium and Potassium Channels 219

The Mechanisms of Voltage Gating Have Been Inferred From Electrophysiological Measurements 220

Voltage-Gated Sodium Channels Select for Sodium on the Basis of Size, Charge, and Energy of Hydration of the Ion 222

Individual Neurons Have a Rich Variety of Voltage-Gated Channels That Expand Their Signaling Capabilities 224

The Diversity of Voltage-Gated Channel Types Is Generated by Several Genetic Mechanisms 225

Voltage-Gated Sodium Channels 225

Voltage-Gated Calcium Channels 227

Voltage-Gated Potassium Channels 227

Voltage-Gated Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels 228

Gating of Ion Channels Can Be Controlled by Cytoplasmic Calcium 228

Excitability Properties Vary Between Types of Neurons 229

Excitability Properties Vary Between Regions of the Neuron 231

Neuronal Excitability Is Plastic 233

Highlights 233

Selected Reading 234

References 234

### Part III

### Synaptic Transmission

### **11** Overview of Synaptic

Steven A. Siegelbaum, Gerald D. Fischbach

Synapses Are Predominantly Electrical or Chemical 241

Electrical Synapses Provide Rapid Signal Transmission 242

Cells at an Electrical Synapse Are Connected by Gap-Junction Channels 244

Electrical Transmission Allows Rapid and Synchronous Firing of Interconnected Cells 247 Gap Junctions Have a Role in Glial Function and Disease 248

#### Chemical Synapses Can Amplify Signals 248

The Action of a Neurotransmitter Depends on the Properties of the Postsynaptic Receptor 249

Activation of Postsynaptic Receptors Gates Ion Channels Either Directly or Indirectly 250

Electrical and Chemical Synapses Can Coexist and Interact 251

Highlights 252

Selected Reading 252

References 253

### 12 Directly Gated Transmission: The Nerve-Muscle Synapse ......254

Gerald D. Fischbach, Steven A. Siegelbaum

### The Neuromuscular Junction Has Specialized Presynaptic and Postsynaptic Structures 255

The Postsynaptic Potential Results From a Local Change in Membrane Permeability 255

The Neurotransmitter Acetylcholine Is Released in Discrete Packets 260

#### Individual Acetylcholine Receptor-Channels Conduct All-or-None Currents 260

The Ion Channel at the End-Plate Is Permeable to Both Sodium and Potassium Ions 260

Four Factors Determine the End-Plate Current 262

### The Acetylcholine Receptor-Channels Have Distinct Properties That Distinguish Them From the Voltage-Gated Channels That Generate the Muscle Action Potential 262

Transmitter Binding Produces a Series of State Changes in the Acetylcholine Receptor-Channel 263

The Low-Resolution Structure of the Acetylcholine Receptor Is Revealed by Molecular and Biophysical Studies 264

The High-Resolution Structure of the Acetylcholine Receptor-Channel Is Revealed by X-Ray Crystal Studies 267

#### Highlights 268

Postscript: The End-Plate Current Can Be Calculated From an Equivalent Circuit 269

Selected Reading 272

References 272

### 

Rafael Yuste, Steven A. Siegelbaum

Central Neurons Receive Excitatory and Inhibitory Inputs 274

Excitatory and Inhibitory Synapses Have Distinctive Ultrastructures and Target Different Neuronal Regions 274

Excitatory Synaptic Transmission Is Mediated by Ionotropic Glutamate Receptor-Channels Permeable to Cations 277

The Ionotropic Glutamate Receptors Are Encoded by a Large Gene Family 278

Glutamate Receptors Are Constructed From a Set of Structural Modules 279

NMDA and AMPA Receptors Are Organized by a Network of Proteins at the Postsynaptic Density 281

NMDA Receptors Have Unique Biophysical and Pharmacological Properties 283

The Properties of the NMDA Receptor Underlie Long-Term Synaptic Plasticity 284

NMDA Receptors Contribute to Neuropsychiatric Disease 284

Fast Inhibitory Synaptic Actions Are Mediated by Ionotropic GABA and Glycine Receptor-Channels Permeable to Chloride 287

Ionotropic Glutamate, GABA, and Glycine Receptors Are Transmembrane Proteins Encoded by Two Distinct Gene Families 287

Chloride Currents Through GABA<sub>A</sub> and Glycine Receptor-Channels Normally Inhibit the Postsynaptic Cell 288

Some Synaptic Actions in the Central Nervous System Depend on Other Types of Ionotropic Receptors 291

Excitatory and Inhibitory Synaptic Actions Are Integrated by Neurons Into a Single Output 291

Synaptic Inputs Are Integrated at the Axon Initial Segment 292

Subclasses of GABAergic Neurons Target Distinct Regions of Their Postsynaptic Target Neurons to Produce Inhibitory Actions With Different Functions 293

Dendrites Are Electrically Excitable Structures That Can Amplify Synaptic Input 295

#### Highlights 298

Selected Reading 299

References 299

#### 

### Steven A. Siegelbaum, David E. Clapham, Eve Marder

### The Cyclic AMP Pathway Is the Best Understood Second-Messenger Signaling Cascade Initiated by G Protein–Coupled Receptors 303

### The Second-Messenger Pathways Initiated by G Protein–Coupled Receptors Share a Common Molecular Logic 305

A Family of G Proteins Activates Distinct Second-Messenger Pathways 305

Hydrolysis of Phospholipids by Phospholipase C Produces Two Important Second Messengers, IP<sub>2</sub> and Diacylglycerol 305

### Receptor Tyrosine Kinases Compose the Second Major Family of Metabotropic Receptors 308

### Several Classes of Metabolites Can Serve as Transcellular Messengers 309

Hydrolysis of Phospholipids by Phospholipase A<sub>2</sub> Liberates Arachidonic Acid to Produce Other Second Messengers 310

Endocannabinoids Are Transcellular Messengers That Inhibit Presynaptic Transmitter Release 310

The Gaseous Second Messenger Nitric Oxide Is a Transcellular Signal That Stimulates Cyclic GMP Synthesis 310

### The Physiological Actions of Metabotropic Receptors Differ From Those of Ionotropic Receptors 312

Second-Messenger Cascades Can Increase or Decrease the Opening of Many Types of Ion Channels 312

G Proteins Can Modulate Ion Channels Directly 315

Cyclic AMP–Dependent Protein Phosphorylation Can Close Potassium Channels 317

# Second Messengers Can Endow Synaptic Transmission with Long-Lasting Consequences 317

### Modulators Can Influence Circuit Function by Altering Intrinsic Excitability or Synaptic Strength 317

Multiple Neuromodulators Can Converge Onto the Same Neuron and Ion Channels 320

Why So Many Modulators? 320

### Highlights 321

Selected Reading 322

References 322

#### 

Steven A. Siegelbaum, Thomas C. Südhof, Richard W. Tsien

# Transmitter Release Is Regulated by Depolarization of the Presynaptic Terminal 324

### Release Is Triggered by Calcium Influx 327

The Relation Between Presynaptic Calcium Concentration and Release 329

Several Classes of Calcium Channels Mediate Transmitter Release 329

### Transmitter Is Released in Quantal Units 332

### Transmitter Is Stored and Released by Synaptic Vesicles 333

Synaptic Vesicles Discharge Transmitter by Exocytosis and Are Recycled by Endocytosis 337

Capacitance Measurements Provide Insight Into the Kinetics of Exocytosis and Endocytosis 338

Exocytosis Involves the Formation of a Temporary Fusion Pore 338

The Synaptic Vesicle Cycle Involves Several Steps 341

### Exocytosis of Synaptic Vesicles Relies on a Highly Conserved Protein Machinery 343

The Synapsins Are Important for Vesicle Restraint and Mobilization 345

SNARE Proteins Catalyze Fusion of Vesicles With the Plasma Membrane 345

Calcium Binding to Synaptotagmin Triggers Transmitter Release 347

The Fusion Machinery Is Embedded in a Conserved Protein Scaffold at the Active Zone 347

### Modulation of Transmitter Release Underlies Synaptic Plasticity 350

Activity-Dependent Changes in Intracellular Free Calcium Can Produce Long-Lasting Changes in Release 351

Axo-axonic Synapses on Presynaptic Terminals Regulate Transmitter Release 351

### Highlights 354

Selected Reading 356

References 356

#### 

Jonathan A. Javitch, David Sulzer

A Chemical Messenger Must Meet Four Criteria to Be Considered a Neurotransmitter 358

### Only a Few Small-Molecule Substances Act as Transmitters 360

Acetylcholine 360

Biogenic Amine Transmitters 361

Amino Acid Transmitters 364

ATP and Adenosine 364

Small-Molecule Transmitters Are Actively Taken Up Into Vesicles 364

Many Neuroactive Peptides Serve as Transmitters 367

Peptides and Small-Molecule Transmitters Differ in Several Ways 370

Peptides and Small-Molecule Transmitters Can Be Co-released 370

Removal of Transmitter From the Synaptic Cleft Terminates Synaptic Transmission 371

Highlights 376

Selected Reading 377

References 378

### Part IV

Perception

### **17** Sensory Coding ...... 385

Esther P. Gardner, Daniel Gardner

Psychophysics Relates Sensations to the Physical Properties of Stimuli 387

Psychophysics Quantifies the Perception of Stimulus Properties 387

Stimuli Are Represented in the Nervous System by the Firing Patterns of Neurons 388

Sensory Receptors Respond to Specific Classes of Stimulus Energy 390

Multiple Subclasses of Sensory Receptors Are Found in Each Sense Organ 393

Receptor Population Codes Transmit Sensory Information to the Brain 395

Sequences of Action Potentials Signal the Temporal Dynamics of Stimuli 396

The Receptive Fields of Sensory Neurons Provide Spatial Information About Stimulus Location 397

### Central Nervous System Circuits Refine Sensory Information 398

The Receptor Surface Is Represented Topographically in the Early Stages of Each Sensory System 400

Sensory Information Is Processed in Parallel Pathways in the Cerebral Cortex 402

Feedback Pathways From the Brain Regulate Sensory Coding Mechanisms 403

Top-Down Learning Mechanisms Influence Sensory Processing 404

#### Highlights 405

Selected Reading 406

References 406

#### 

Esther P. Gardner

Dorsal Root Ganglion Neurons Are the Primary Sensory Receptor Cells of the Somatosensory System 409

Peripheral Somatosensory Nerve Fibers Conduct Action Potentials at Different Rates 410

A Variety of Specialized Receptors Are Employed by the Somatosensory System 414

Mechanoreceptors Mediate Touch and Proprioception 414

Specialized End Organs Contribute to Mechanosensation 416

Proprioceptors Measure Muscle Activity and Joint Positions 421

Thermal Receptors Detect Changes in Skin Temperature 422

Nociceptors Mediate Pain 424

Itch Is a Distinctive Cutaneous Sensation 425

Visceral Sensations Represent the Status of Internal Organs 426

Action Potential Codes Transmit Somatosensory Information to the Brain 426

Sensory Ganglia Provide a Snapshot of Population Responses to Somatic Stimuli 427

Somatosensory Information Enters the Central Nervous System Via Spinal or Cranial Nerves 427

Highlights 432

Selected Reading 433

References 433

19	Touch	• • • •	• • • •	 	35

Esther P. Gardner

Active and Passive Touch Have Distinct Goals 436

The Hand Has Four Types of Mechanoreceptors 437

A Cell's Receptive Field Defines Its Zone of Tactile Sensitivity 438

Two-Point Discrimination Tests Measure Tactile Acuity 439

Slowly Adapting Fibers Detect Object Pressure and Form 444

Rapidly Adapting Fibers Detect Motion and Vibration 446

Both Slowly and Rapidly Adapting Fibers Are Important for Grip Control 446

#### Tactile Information Is Processed in the Central Touch System 450

Spinal, Brain Stem, and Thalamic Circuits Segregate Touch and Proprioception 450

The Somatosensory Cortex Is Organized Into Functionally Specialized Columns 452

Cortical Columns Are Organized Somatotopically 454

The Receptive Fields of Cortical Neurons Integrate Information From Neighboring Receptors 457

# Touch Information Becomes Increasingly Abstract in Successive Central Synapses 460

Cognitive Touch Is Mediated by Neurons in the Secondary Somatosensory Cortex 460

Active Touch Engages Sensorimotor Circuits in the Posterior Parietal Cortex 463

### Lesions in Somatosensory Areas of the Brain Produce Specific Tactile Deficits 464

Highlights 466

Selected Reading 467

References 467

#### 

Allan I. Basbaum

Noxious Insults Activate Thermal, Mechanical, and Polymodal Nociceptors 471

Signals From Nociceptors Are Conveyed to Neurons in the Dorsal Horn of the Spinal Cord 474

Hyperalgesia Has Both Peripheral and Central Origins 476

Four Major Ascending Pathways Convey Nociceptive Information From the Spinal Cord to the Brain 484

Several Thalamic Nuclei Relay Nociceptive Information to the Cerebral Cortex 484

The Perception of Pain Arises From and Can Be Controlled by Cortical Mechanisms 485

Anterior Cingulate and Insular Cortex Are Associated With the Perception of Pain 485 Pain Perception Is Regulated by a Balance of Activity in Nociceptive and Nonnociceptive Afferent Fibers 488

Electrical Stimulation of the Brain Produces Analgesia 488

Opioid Peptides Contribute to Endogenous Pain Control 489

Endogenous Opioid Peptides and Their Receptors Are Distributed in Pain-Modulatory Systems 489

Morphine Controls Pain by Activating Opioid Receptors 490

Tolerance to and Dependence on Opioids Are Distinct Phenomena 493

Highlights 493

Selected Reading 494

References 494

### 21 The Constructive Nature of

### 

Charles D. Gilbert, Aniruddha Das

Visual Perception Is a Constructive Process 496

Visual Processing Is Mediated by the Geniculostriate Pathway 499

Form, Color, Motion, and Depth Are Processed in Discrete Areas of the Cerebral Cortex 502

The Receptive Fields of Neurons at Successive Relays in the Visual Pathway Provide Clues to How the Brain Analyzes Visual Form 506

The Visual Cortex Is Organized Into Columns of Specialized Neurons 508

Intrinsic Cortical Circuits Transform Neural Information 512

Visual Information Is Represented by a Variety of Neural Codes 517

Highlights 518

Selected Reading 519

References 519

### 22 Low-Level Visual Processing:

Markus Meister, Marc Tessier-Lavigne

# The Photoreceptor Layer Samples the Visual Image 522

Ocular Optics Limit the Quality of the Retinal Image 522

There Are Two Types of Photoreceptors: Rods and Cones 524

#### Phototransduction Links the Absorption of a Photon to a Change in Membrane Conductance 526

Light Activates Pigment Molecules in the Photoreceptors 528

Excited Rhodopsin Activates a Phosphodiesterase Through the G Protein Transducin 529

Multiple Mechanisms Shut Off the Cascade 530

Defects in Phototransduction Cause Disease 530

### Ganglion Cells Transmit Neural Images to the Brain 530

The Two Major Types of Ganglion Cells Are ON Cells and OFF Cells 530

Many Ganglion Cells Respond Strongly to Edges in the Image 531

The Output of Ganglion Cells Emphasizes Temporal Changes in Stimuli 531

Retinal Output Emphasizes Moving Objects 531

Several Ganglion Cell Types Project to the Brain Through Parallel Pathways 531

### A Network of Interneurons Shapes the Retinal Output 536

Parallel Pathways Originate in Bipolar Cells 536

Spatial Filtering Is Accomplished by Lateral Inhibition 536

Temporal Filtering Occurs in Synapses and Feedback Circuits 537

Color Vision Begins in Cone-Selective Circuits 538

Congenital Color Blindness Takes Several Forms 538

Rod and Cone Circuits Merge in the Inner Retina 540

### The Retina's Sensitivity Adapts to Changes in Illumination 540

Light Adaptation Is Apparent in Retinal Processing and Visual Perception 540

Multiple Gain Controls Occur Within the Retina 541

Light Adaptation Alters Spatial Processing 543

### Highlights 543

Selected Reading 543

References 544

### 23 Intermediate-Level Visual Processing and Visual Primitives......545

Charles D. Gilbert

Internal Models of Object Geometry Help the Brain Analyze Shapes 547

Depth Perception Helps Segregate Objects From Background 550

### Local Movement Cues Define Object Trajectory and Shape 554

Context Determines the Perception of Visual Stimuli 555

Brightness and Color Perception Depend on Context 555

Receptive-Field Properties Depend on Context 558

### Cortical Connections, Functional Architecture, and Perception Are Intimately Related 558

Perceptual Learning Requires Plasticity in Cortical Connections 559

Visual Search Relies on the Cortical Representation of Visual Attributes and Shapes 559

Cognitive Processes Influence Visual Perception 560

Highlights 562

Selected Reading 563

References 563

#### 

Thomas D. Albright, Winrich A. Freiwald

### High-Level Visual Processing Is Concerned With Object Recognition 564

### The Inferior Temporal Cortex Is the Primary Center for Object Recognition 565

Clinical Evidence Identifies the Inferior Temporal Cortex as Essential for Object Recognition 566

Neurons in the Inferior Temporal Cortex Encode Complex Visual Stimuli and Are Organized in Functionally Specialized Columns 568

The Primate Brain Contains Dedicated Systems for Face Processing 569

The Inferior Temporal Cortex Is Part of a Network of Cortical Areas Involved in Object Recognition 570

Object Recognition Relies on Perceptual Constancy 571

Categorical Perception of Objects Simplifies Behavior 572

Visual Memory Is a Component of High-Level Visual Processing 573

Implicit Visual Learning Leads to Changes in the Selectivity of Neuronal Responses 573

The Visual System Interacts With Working Memory and Long-Term Memory Systems 573

Associative Recall of Visual Memories Depends on Top-Down Activation of the Cortical Neurons That Process Visual Stimuli 578 Highlights 579 Selected Reading 580 References 580

#### 

Michael E. Goldberg, Robert H. Wurtz

The Brain Compensates for Eye Movements to Create a Stable Representation of the Visual World 582

Motor Commands for Saccades Are Copied to the Visual System 582

Oculomotor Proprioception Can Contribute to Spatially Accurate Perception and Behavior 587

Visual Scrutiny Is Driven by Attention and Arousal Circuits 588

The Parietal Cortex Provides Visual Information to the Motor System 592

Highlights 595

Selected Reading 596

References 596

### **26** Auditory Processing by

Pascal Martin, Geoffrey A. Manley

The Ear Has Three Functional Parts 599

Hearing Commences With the Capture of Sound Energy by the Ear 600

The Hydrodynamic and Mechanical Apparatus of the Cochlea Delivers Mechanical Stimuli to the Receptor Cells 603

The Basilar Membrane Is a Mechanical Analyzer of Sound Frequency 603

The Organ of Corti Is the Site of Mechanoelectrical Transduction in the Cochlea 604

### Hair Cells Transform Mechanical Energy Into Neural Signals 606

Deflection of the Hair Bundle Initiates Mechanoelectrical Transduction 606

Mechanical Force Directly Opens Transduction Channels 609

Direct Mechanoelectrical Transduction Is Rapid 610

Deafness Genes Provide Components of the Mechanotransduction Machinery 611

Dynamic Feedback Mechanisms Determine the Sensitivity of the Hair Cells 613

Hair Cells Are Tuned to Specific Stimulus Frequencies 613

Hair Cells Adapt to Sustained Stimulation 614

Sound Energy Is Mechanically Amplified in the Cochlea 616

Cochlear Amplification Distorts Acoustic Inputs 618

The Hopf Bifurcation Provides a General Principle for Sound Detection 618

### Hair Cells Use Specialized Ribbon Synapses 618

### Auditory Information Flows Initially Through the Cochlear Nerve 621

Bipolar Neurons in the Spiral Ganglion Innervate Cochlear Hair Cells 621

Cochlear Nerve Fibers Encode Stimulus Frequency and Level 622

Sensorineural Hearing Loss Is Common but Is Amenable to Treatment 624

Highlights 626

Selected Reading 626

References 627

#### 

J. David Dickman, Dora Angelaki

### The Vestibular Labyrinth in the Inner Ear Contains Five Receptor Organs 631

Hair Cells Transduce Acceleration Stimuli Into Receptor Potentials 631

The Semicircular Canals Sense Head Rotation 632

The Otolith Organs Sense Linear Accelerations 634

Central Vestibular Nuclei Integrate Vestibular, Visual, Proprioceptive, and Motor Signals 636

The Vestibular Commissural System Communicates Bilateral Information 636

Combined Semicircular Canal and Otolith Signals Improve Inertial Sensing and Decrease Ambiguity of Translation Versus Tilt 638

Vestibular Signals Are a Critical Component of Head Movement Control 639

### Vestibulo-Ocular Reflexes Stabilize the Eyes When the Head Moves 639

The Rotational Vestibulo-Ocular Reflex Compensates for Head Rotation 640

The Translational Vestibulo-Ocular Reflex Compensates for Linear Motion and Head Tilts 642

Vestibulo-Ocular Reflexes Are Supplemented by Optokinetic Responses 643

The Cerebellum Adjusts the Vestibulo-Ocular Reflex 643

The Thalamus and Cortex Use Vestibular Signals for Spatial Memory and Cognitive and Perceptual Functions 645

Vestibular Information Is Present in the Thalamus 645

Vestibular Information Is Widespread in the Cortex 645

Vestibular Signals Are Essential for Spatial Orientation and Spatial Navigation 646

#### Clinical Syndromes Elucidate Normal Vestibular Function 647

Caloric Irrigation as a Vestibular Diagnostic Tool 647

Bilateral Vestibular Hypofunction Interferes With Normal Vision 647

### Highlights 648

Selected Reading 649

References 649

### 28 Auditory Processing by the Central

Nervous System......651

Donata Oertel, Xiaoqin Wang

Sounds Convey Multiple Types of Information to Hearing Animals 652

The Neural Representation of Sound in Central Pathways Begins in the Cochlear Nuclei 652

The Cochlear Nerve Delivers Acoustic Information in Parallel Pathways to the Tonotopically Organized Cochlear Nuclei 655

The Ventral Cochlear Nucleus Extracts Temporal and Spectral Information About Sounds 655

The Dorsal Cochlear Nucleus Integrates Acoustic With Somatosensory Information in Making Use of Spectral Cues for Localizing Sounds 656

### The Superior Olivary Complex in Mammals Contains Separate Circuits for Detecting Interaural Time and Intensity Differences 657

The Medial Superior Olive Generates a Map of Interaural Time Differences 657

The Lateral Superior Olive Detects Interaural Intensity Differences 659

The Superior Olivary Complex Provides Feedback to the Cochlea 662

Ventral and Dorsal Nuclei of the Lateral Lemniscus Shape Responses in the Inferior Colliculus With Inhibition 663

### Afferent Auditory Pathways Converge in the Inferior Colliculus 664

Sound Location Information From the Inferior Colliculus Creates a Spatial Map of Sound in the Superior Colliculus 665

### The Inferior Colliculus Transmits Auditory Information to the Cerebral Cortex 665

Stimulus Selectivity Progressively Increases Along the Ascending Pathway 665

The Auditory Cortex Maps Numerous Aspects of Sound 668

A Second Sound-Localization Pathway From the Inferior Colliculus Involves the Cerebral Cortex in Gaze Control 669

Auditory Circuits in the Cerebral Cortex Are Segregated Into Separate Processing Streams 670

The Cerebral Cortex Modulates Sensory Processing in Subcortical Auditory Areas 670

### The Cerebral Cortex Forms Complex Sound Representations 671

The Auditory Cortex Uses Temporal and Rate Codes to Represent Time-Varying Sounds 671

Primates Have Specialized Cortical Neurons That Encode Pitch and Harmonics 673

Insectivorous Bats Have Cortical Areas Specialized for Behaviorally Relevant Features of Sound 675

The Auditory Cortex Is Involved in Processing Vocal Feedback During Speaking 677

Highlights 679

Selected Reading 680

References 680

### 29 Smell and Taste: The

Linda Buck, Kristin Scott, Charles Zuker

### A Large Family of Olfactory Receptors Initiate the Sense of Smell 683

Mammals Share a Large Family of Odorant Receptors 684

Different Combinations of Receptors Encode Different Odorants 685

### Olfactory Information Is Transformed Along the Pathway to the Brain 686

Odorants Are Encoded in the Nose by Dispersed Neurons 686

Sensory Inputs in the Olfactory Bulb Are Arranged by Receptor Type 687 The Olfactory Bulb Transmits Information to the Olfactory Cortex 688

Output From the Olfactory Cortex Reaches Higher Cortical and Limbic Areas 690

Olfactory Acuity Varies in Humans 691

#### Odors Elicit Characteristic Innate Behaviors 691

Pheromones Are Detected in Two Olfactory Structures 691

Invertebrate Olfactory Systems Can Be Used to Study Odor Coding and Behavior 691

Olfactory Cues Elicit Stereotyped Behaviors and Physiological Responses in the Nematode 694

Strategies for Olfaction Have Evolved Rapidly 695

### The Gustatory System Controls the Sense of Taste 696

Taste Has Five Submodalities That Reflect Essential Dietary Requirements 696

Tastant Detection Occurs in Taste Buds 696

Each Taste Modality Is Detected by Distinct Sensory Receptors and Cells 698

Gustatory Information Is Relayed From the Periphery to the Gustatory Cortex 702

Perception of Flavor Depends on Gustatory, Olfactory, and Somatosensory Inputs 702

Insects Have Modality-Specific Taste Cells That Drive Innate Behaviors 702

### Highlights 703

Selected Reading 704

References 705

### Part V

### Movement

#### 

Daniel M. Wolpert, Amy J. Bastian

The Control of Movement Poses Challenges for the Nervous System 714

Actions Can Be Controlled Voluntarily, Rhythmically, or Reflexively 715

Motor Commands Arise Through a Hierarchy of Sensorimotor Processes 715

Motor Signals Are Subject to Feedforward and Feedback Control 716 Feedforward Control Is Required for Rapid Movements 716

Feedback Control Uses Sensory Signals to Correct Movements 719

Estimation of the Body's Current State Relies on Sensory and Motor Signals 719

Prediction Can Compensate for Sensorimotor Delays 723

Sensory Processing Can Differ for Action and Perception 724

#### Motor Plans Translate Tasks Into Purposeful Movement 725

Stereotypical Patterns Are Employed in Many Movements 725

Motor Planning Can Be Optimal at Reducing Costs 726

Optimal Feedback Control Corrects for Errors in a Task-Dependent Manner 728

#### Multiple Processes Contribute to Motor Learning 729

Error-Based Learning Involves Adapting Internal Sensorimotor Models 730

Skill Learning Relies on Multiple Processes for Success 732

Sensorimotor Representations Constrain Learning 734

### Highlights 735

Selected Reading 735

References 735

### 31 The Motor Unit and Muscle Action ......737

Roger M. Enoka

### The Motor Unit Is the Elementary Unit of Motor Control 737

A Motor Unit Consists of a Motor Neuron and Multiple Muscle Fibers 737

The Properties of Motor Units Vary 739

Physical Activity Can Alter Motor Unit Properties 742

Muscle Force Is Controlled by the Recruitment and Discharge Rate of Motor Units 742

The Input–Output Properties of Motor Neurons Are Modified by Input From the Brain Stem 745

### Muscle Force Depends on the Structure of Muscle 745

The Sarcomere Is the Basic Organizational Unit of Contractile Proteins 745

Noncontractile Elements Provide Essential Structural Support 747

Contractile Force Depends on Muscle Fiber Activation, Length, and Velocity 747

Muscle Torque Depends on Musculoskeletal Geometry 750

### Different Movements Require Different Activation Strategies 754

Contraction Velocity Can Vary in Magnitude and Direction 754

Movements Involve the Coordination of Many Muscles 755

Muscle Work Depends on the Pattern of Activation 758

Highlights 758

Selected Reading 759

References 759

### 32 Sensory-Motor Integration in the Spinal Cord ......761

Jens Bo Nielsen, Thomas M. Jessell

### Reflex Pathways in the Spinal Cord Produce Coordinated Patterns of Muscle Contraction 762

The Stretch Reflex Acts to Resist the Lengthening of a Muscle 762

### Neuronal Networks in the Spinal Cord Contribute to the Coordination of Reflex Responses 762

The Stretch Reflex Involves a Monosynaptic Pathway 762

Gamma Motor Neurons Adjust the Sensitivity of Muscle Spindles 766

The Stretch Reflex Also Involves Polysynaptic Pathways 767

Golgi Tendon Organs Provide Force-Sensitive Feedback to the Spinal Cord 769

Cutaneous Reflexes Produce Complex Movements That Serve Protective and Postural Functions 770

Convergence of Sensory Inputs on Interneurons Increases the Flexibility of Reflex Contributions to Movement 772

### Sensory Feedback and Descending Motor Commands Interact at Common Spinal Neurons to Produce Voluntary Movements 773

Muscle Spindle Sensory Afferent Activity Reinforces Central Commands for Movements Through the Ia Monosynaptic Reflex Pathway 773

Modulation of Ia inhibitory Interneurons and Renshaw Cells by Descending Inputs Coordinate Muscle Activity at Joints 775 Transmission in Reflex Pathways May Be Facilitated or Inhibited by Descending Motor Commands 776

Descending Inputs Modulate Sensory Input to the Spinal Cord by Changing the Synaptic Efficiency of Primary Sensory Fibers 777

### Part of the Descending Command for Voluntary Movements Is Conveyed Through Spinal Interneurons 778

Propriospinal Neurons in the C3–C4 Segments Mediate Part of the Corticospinal Command for Movement of the Upper Limb 778

Neurons in Spinal Reflex Pathways Are Activated Prior to Movement 779

Proprioceptive Reflexes Play an Important Role in Regulating Both Voluntary and Automatic Movements 779

Spinal Reflex Pathways Undergo Long-Term Changes 779

#### Damage to the Central Nervous System Produces Characteristic Alterations in Reflex Responses 780

Interruption of Descending Pathways to the Spinal Cord Frequently Produces Spasticity 780

Lesion of the Spinal Cord in Humans Leads to a Period of Spinal Shock Followed by Hyperreflexia 780

Highlights 781

Selected Reading 781

References 781

#### 

Trevor Drew, Ole Kiehn

Locomotion Requires the Production of a Precise and Coordinated Pattern of Muscle Activation 786

### The Motor Pattern of Stepping Is Organized at the Spinal Level 790

The Spinal Circuits Responsible for Locomotion Can Be Modified by Experience 792

Spinal Locomotor Networks Are Organized Into Rhythm- and Pattern-Generation Circuits 792

### Somatosensory Inputs From Moving Limbs Modulate Locomotion 795

Proprioception Regulates the Timing and Amplitude of Stepping 795

Mechanoreceptors in the Skin Allow Stepping to Adjust to Unexpected Obstacles 798

Supraspinal Structures Are Responsible for Initiation and Adaptive Control of Stepping 799

Midbrain Nuclei Initiate and Maintain Locomotion and Control Speed 800

Midbrain Nuclei That Initiate Locomotion Project to Brain Stem Neurons 800

The Brain Stem Nuclei Regulate Posture During Locomotion 802

Visually Guided Locomotion Involves the Motor Cortex 804

Planning of Locomotion Involves the Posterior Parietal Cortex 806

The Cerebellum Regulates the Timing and Intensity of Descending Signals 806

The Basal Ganglia Modify Cortical and Brain Stem Circuits 807

Computational Neuroscience Provides Insights Into Locomotor Circuits 809

Neuronal Control of Human Locomotion Is Similar to That of Quadrupeds 809

Highlights 811

Suggested Reading 812

References 812

#### 

Stephen H. Scott, John F. Kalaska

### Voluntary Movement Is the Physical Manifestation of an Intention to Act 816

Theoretical Frameworks Help Interpret Behavior and the Neural Basis of Voluntary Control 816

Many Frontal and Parietal Cortical Regions Are Involved in Voluntary Control 818

Descending Motor Commands Are Principally Transmitted by the Corticospinal Tract 819

Imposing a Delay Period Before the Onset of Movement Isolates the Neural Activity Associated With Planning From That Associated With Executing the Action 821

### Parietal Cortex Provides Information About the World and the Body for State Estimation to Plan and Execute Motor Actions 823

The Parietal Cortex Links Sensory Information to Motor Actions 824

Body Position and Motion Are Represented in Several Areas of Posterior Parietal Cortex 824

Spatial Goals Are Represented in Several Areas of Posterior Parietal Cortex 825

Internally Generated Feedback May Influence Parietal Cortex Activity 827

### Premotor Cortex Supports Motor Selection and Planning 828

Medial Premotor Cortex Is Involved in the Contextual Control of Voluntary Actions 829

Dorsal Premotor Cortex Is Involved in Planning Sensory-Guided Movement of the Arm 831

Dorsal Premotor Cortex Is Involved in Applying Rules (Associations) That Govern Behavior 833

Ventral Premotor Cortex Is Involved in Planning Motor Actions of the Hand 835

Premotor Cortex May Contribute to Perceptual Decisions That Guide Motor Actions 835

Several Cortical Motor Areas Are Active When the Motor Actions of Others Are Being Observed 837

Many Aspects of Voluntary Control Are Distributed Across Parietal and Premotor Cortex 840

# The Primary Motor Cortex Plays an Important Role in Motor Execution 841

The Primary Motor Cortex Includes a Detailed Map of the Motor Periphery 841

Some Neurons in the Primary Motor Cortex Project Directly to Spinal Motor Neurons 841

Activity in the Primary Motor Cortex Reflects Many Spatial and Temporal Features of Motor Output 844

Primary Motor Cortical Activity Also Reflects Higher-Order Features of Movement 851

Sensory Feedback Is Transmitted Rapidly to the Primary Motor Cortex and Other Cortical Regions 852

The Primary Motor Cortex Is Dynamic and Adaptable 852

Highlights 856

Selected Reading 858

References 858

### **35** The Control of Gaze ...... 860

Michael E. Goldberg, Mark F. Walker

### The Eye Is Moved by the Six Extraocular Muscles 860

Eye Movements Rotate the Eye in the Orbit 860

The Six Extraocular Muscles Form Three Agonist–Antagonist Pairs 862

Movements of the Two Eyes Are Coordinated 862

The Extraocular Muscles Are Controlled by Three Cranial Nerves 862

Six Neuronal Control Systems Keep the Eyes on Target 866

An Active Fixation System Holds the Fovea on a Stationary Target 866

The Saccadic System Points the Fovea Toward Objects of Interest 866

### The Motor Circuits for Saccades Lie in the Brain Stem 868

Horizontal Saccades Are Generated in the Pontine Reticular Formation 868

Vertical Saccades Are Generated in the Mesencephalic Reticular Formation 870

Brain Stem Lesions Result in Characteristic Deficits in Eye Movements 870

#### Saccades Are Controlled by the Cerebral Cortex Through the Superior Colliculus 871

The Superior Colliculus Integrates Visual and Motor Information into Oculomotor Signals for the Brain Stem 871

The Rostral Superior Colliculus Facilitates Visual Fixation 873

The Basal Ganglia and Two Regions of Cerebral Cortex Control the Superior Colliculus 873

The Control of Saccades Can Be Modified by Experience 877

Some Rapid Gaze Shifts Require Coordinated Head and Eye Movements 877

### The Smooth-Pursuit System Keeps Moving Targets on the Fovea 878

The Vergence System Aligns the Eyes to Look at Targets at Different Depths 879

Highlights 880

Selected Reading 881

References 881

#### 

### Fay B. Horak, Gammon M. Earhart

#### Equilibrium and Orientation Underlie Posture Control 884

Postural Equilibrium Controls the Body's Center of Mass 884

Postural Orientation Anticipates Disturbances to Balance 886

### Postural Responses and Anticipatory Postural Adjustments Use Stereotyped Strategies and Synergies 886

Automatic Postural Responses Compensate for Sudden Disturbances 887

Anticipatory Postural Adjustments Compensate for Voluntary Movement 892

Posture Control Is Integrated With Locomotion 894

### Somatosensory, Vestibular, and Visual Information Must Be Integrated and Interpreted to Maintain Posture 894

Somatosensory Signals Are Important for Timing and Direction of Automatic Postural Responses 894

Vestibular Information Is Important for Balance on Unstable Surfaces and During Head Movements 895

Visual Inputs Provide the Postural System With Orientation and Motion Information 897

Information From a Single Sensory Modality Can Be Ambiguous 897

The Postural Control System Uses a Body Schema That Incorporates Internal Models for Balance 898

#### Control of Posture Is Task Dependent 900

Task Requirements Determine the Role of Each Sensory System in Postural Equilibrium and Orientation 900

### Control of Posture Is Distributed in the Nervous System 900

Spinal Cord Circuits Are Sufficient for Maintaining Antigravity Support but Not Balance 900

The Brain Stem and Cerebellum Integrate Sensory Signals for Posture 901

The Spinocerebellum and Basal Ganglia Are Important in Adaptation of Posture 902

Cerebral Cortex Centers Contribute to Postural Control 905

#### Highlights 906

Suggested Reading 906

References 906

#### 

Amy J. Bastian, Stephen G. Lisberger

# Damage of the Cerebellum Causes Distinctive Symptoms and Signs 909

Damage Results in Characteristic Abnormalities of Movement and Posture 909

Damage Affects Specific Sensory and Cognitive Abilities 909

The Cerebellum Indirectly Controls Movement Through Other Brain Structures 911

The Cerebellum Is a Large Subcortical Brain Structure 911

The Cerebellum Connects With the Cerebral Cortex Through Recurrent Loops 911

Different Movements Are Controlled by Functional Longitudinal Zones 911

The Cerebellar Cortex Comprises Repeating Functional Units Having the Same Basic Microcircuit 918

The Cerebellar Cortex Is Organized Into Three Functionally Specialized Layers 918

The Climbing-Fiber and Mossy-Fiber Afferent Systems Encode and Process Information Differently 918

The Cerebellar Microcircuit Architecture Suggests a Canonical Computation 920

### The Cerebellum Is Hypothesized to Perform Several General Computational Functions 922

The Cerebellum Contributes to Feedforward Sensorimotor Control 922

The Cerebellum Incorporates an Internal Model of the Motor Apparatus 922

The Cerebellum Integrates Sensory Inputs and Corollary Discharge 923

The Cerebellum Contributes to Timing Control 923

### The Cerebellum Participates in Motor Skill Learning 923

Climbing-Fiber Activity Changes the Synaptic Efficacy of Parallel Fibers 924

The Cerebellum Is Necessary for Motor Learning in Several Different Movement Systems 925

Learning Occurs at Several Sites in the Cerebellum 928

Highlights 929

Selected Reading 929

References 930

#### 

Peter Redgrave, Rui M. Costa

The Basal Ganglia Network Consists of Three Principal Input Nuclei, Two Main Output Nuclei, and One Intrinsic Nucleus 934

The Striatum, Subthalamic Nucleus, and Substantia Nigra Pars Compacta/Ventral Tegmental Area Are the Three Principal Input Nuclei of the Basal Ganglia 934

The Substantia Nigra Pars Reticulata and the Internal Globus Pallidus Are the Two Principal Output Nuclei of the Basal Ganglia 935

The External Globus Pallidus Is Mostly an Intrinsic Structure of the Basal Ganglia 935

The Internal Circuitry of the Basal Ganglia Regulates How the Components Interact 935 The Traditional Model of the Basal Ganglia Emphasizes Direct and Indirect Pathways 935

Detailed Anatomical Analyses Reveal a More Complex Organization 936

### Basal Ganglia Connections With External Structures Are Characterized by Reentrant Loops 937

Inputs Define Functional Territories in the Basal Ganglia 937

Output Neurons Project to the External Structures That Provide Input 937

Reentrant Loops Are a Cardinal Principle of Basal Ganglia Circuitry 937

### Physiological Signals Provide Further Clues to Function in the Basal Ganglia 939

The Striatum and Subthalamic Nucleus Receive Signals Mainly from the Cerebral Cortex, Thalamus, and Ventral Midbrain 939

Ventral Midbrain Dopamine Neurons Receive Input From External Structures and Other Basal Ganglia Nuclei 939

Disinhibition Is the Final Expression of Basal Ganglia Output 940

### Throughout Vertebrate Evolution, the Basal Ganglia Have Been Highly Conserved 940

### Action Selection Is a Recurring Theme in Basal Ganglia Research 941

All Vertebrates Face the Challenge of Choosing One Behavior From Several Competing Options 941

Selection Is Required for Motivational, Affective, Cognitive, and Sensorimotor Processing 941

The Neural Architecture of the Basal Ganglia Is Configured to Make Selections 942

Intrinsic Mechanisms in the Basal Ganglia Promote Selection 943

Selection Function of the Basal Ganglia Questioned 943

# Reinforcement Learning Is an Inherent Property of a Selection Architecture 944

Intrinsic Reinforcement Is Mediated by Phasic Dopamine Signaling Within the Basal Ganglia Nuclei 944

Extrinsic Reinforcement Could Bias Selection by Operating in Afferent Structures 946

### **Behavioral Selection in the Basal Ganglia Is Under Goal-Directed and Habitual Control** 946

Diseases of the Basal Ganglia May Involve Disorders of Selection 947

A Selection Mechanism Is Likely to Be Vulnerable to Several Potential Malfunctions 947

Parkinson Disease Can Be Viewed in Part as a Failure to Select Sensorimotor Options 948

Huntington Disease May Reflect a Functional Imbalance Between the Direct and Indirect Pathways 948

Schizophrenia May Be Associated With a General Failure to Suppress Nonselected Options 948

Attention Deficit Hyperactivity Disorder and Tourette Syndrome May Also Be Characterized by Intrusions of Nonselected Options 949

Obsessive-Compulsive Disorder Reflects the Presence of Pathologically Dominant Options 949

Addictions Are Associated With Disorders of Reinforcement Mechanisms and Habitual Goals 949

#### Highlights 950

Suggested Reading 951

References 951

### **39** Brain–Machine Interfaces ...... 953

Krishna V. Shenoy, Byron M. Yu

### BMIs Measure and Modulate Neural Activity to Help Restore Lost Capabilities 954

Cochlear Implants and Retinal Prostheses Can Restore Lost Sensory Capabilities 954

Motor and Communication BMIs Can Restore Lost Motor Capabilities 954

Pathological Neural Activity Can Be Regulated by Deep Brain Stimulation and Antiseizure BMIs 956

Replacement Part BMIs Can Restore Lost Brain Processing Capabilities 956

Measuring and Modulating Neural Activity Rely on Advanced Neurotechnology 956

### BMIs Leverage the Activity of Many Neurons to Decode Movements 958

Decoding Algorithms Estimate Intended Movements From Neural Activity 960

Discrete Decoders Estimate Movement Goals 961

Continuous Decoders Estimate Moment-by-Moment Details of Movements 961

#### Increases in Performance and Capabilities of Motor and Communication BMIs Enable Clinical Translation 962

Subjects Can Type Messages Using Communication BMIs 964

Subjects Can Reach and Grasp Objects Using BMI-Directed Prosthetic Arms 965

Subjects Can Reach and Grasp Objects Using BMI-Directed Stimulation of Paralyzed Arms 965

Subjects Can Use Sensory Feedback Delivered by Cortical Stimulation During BMI Control 967

BMIs Can Be Used to Advance Basic Neuroscience 968

BMIs Raise New Neuroethics Considerations 970

Highlights 971

Selected Reading 972

References 972

### Part VI

The Biology of Emotion, Motivation, and Homeostasis

#### 

Clifford B. Saper, Joel K. Elmquist

### The Cranial Nerves Are Homologous to the Spinal Nerves 982

Cranial Nerves Mediate the Sensory and Motor Functions of the Face and Head and the Autonomic Functions of the Body 982

Cranial Nerves Leave the Skull in Groups and Often Are Injured Together 985

### The Organization of the Cranial Nerve Nuclei Follows the Same Basic Plan as the Sensory and Motor Areas of the Spinal Cord 986

Embryonic Cranial Nerve Nuclei Have a Segmental Organization 987

Adult Cranial Nerve Nuclei Have a Columnar Organization 987

The Organization of the Brain Stem Differs From the Spinal Cord in Three Important Ways 992

### Neuronal Ensembles in the Brain Stem Reticular Formation Coordinate Reflexes and Simple Behaviors Necessary for Homeostasis and Survival 992

Cranial Nerve Reflexes Involve Mono- and Polysynaptic Brain Stem Relays 992

Pattern Generators Coordinate More Complex Stereotypic Behaviors 994

Control of Breathing Provides an Example of How Pattern Generators Are Integrated Into More Complex Behaviors 994

Monoaminergic Neurons in the Brain Stem Modulate Sensory, Motor, Autonomic, and Behavioral Functions 998 Many Modulatory Systems Use Monoamines as Neurotransmitters 998

Monoaminergic Neurons Share Many Cellular Properties 1001

Autonomic Regulation and Breathing Are Modulated by Monoaminergic Pathways 1002

Pain Perception Is Modulated by Monoamine Antinociceptive Pathways 1002

Motor Activity Is Facilitated by Monoaminergic Pathways 1004

Ascending Monoaminergic Projections Modulate Forebrain Systems for Motivation and Reward 1004

Monoaminergic and Cholinergic Neurons Maintain Arousal by Modulating Forebrain Neurons 1006

Highlights 1007

Selected Reading 1008

References 1008

### 41 The Hypothalamus: Autonomic, Hormonal, and Behavioral Control of Survival.....1010

Bradford B. Lowell, Larry W. Swanson, John P. Horn

Homeostasis Keeps Physiological Parameters Within a Narrow Range and Is Essential for Survival 1011

### The Hypothalamus Coordinates Homeostatic Regulation 1013

The Hypothalamus Is Commonly Divided Into Three Rostrocaudal Regions 1013

Modality-Specific Hypothalamic Neurons Link Interoceptive Sensory Feedback With Outputs That Control Adaptive Behaviors and Physiological Responses 1015

Modality-Specific Hypothalamic Neurons Also Receive Descending Feedforward Input Regarding Anticipated Homeostatic Challenges 1015

### The Autonomic System Links the Brain to Physiological Responses 1015

Visceral Motor Neurons in the Autonomic System Are Organized Into Ganglia 1015

Preganglionic Neurons Are Localized in Three Regions Along the Brain Stem and Spinal Cord 1016

Sympathetic Ganglia Project to Many Targets Throughout the Body 1016

Parasympathetic Ganglia Innervate Single Organs 1018

The Enteric Ganglia Regulate the Gastrointestinal Tract 1019

Acetylcholine and Norepinephrine Are the Principal Transmitters of Autonomic Motor Neurons 1019

Autonomic Responses Involve Cooperation Between the Autonomic Divisions 1021

Visceral Sensory Information Is Relayed to the Brain Stem and Higher Brain Structures 1023

Central Control of Autonomic Function Can Involve the Periaqueductal Gray, Medial Prefrontal Cortex, and Amygdala 1025

#### The Neuroendocrine System Links the Brain to Physiological Responses Through Hormones 1026

Hypothalamic Axon Terminals in the Posterior Pituitary Release Oxytocin and Vasopressin Directly Into the Blood 1027

Endocrine Cells in the Anterior Pituitary Secrete Hormones in Response to Specific Factors Released by Hypothalamic Neurons 1028

### Dedicated Hypothalamic Systems Control Specific Homeostatic Parameters 1029

Body Temperature Is Controlled by Neurons in the Median Preoptic Nucleus 1029

Water Balance and the Related Thirst Drive Are Controlled by Neurons in the Vascular Organ of the Lamina Terminalis, Median Preoptic Nucleus, and Subfornical Organ 1031

Energy Balance and the Related Hunger Drive Are Controlled by Neurons in the Arcuate Nucleus 1033

### Sexually Dimorphic Regions in the Hypothalamus Control Sex, Aggression, and Parenting 1039

Sexual Behavior and Aggression Are Controlled by the Preoptic Hypothalamic Area and a Subarea of the Ventromedial Hypothalamic Nucleus 1040

Parental Behavior Is Controlled by the Preoptic Hypothalamic Area 1041

Highlights 1041

Selected Reading 1042

References 1043

### 42 Emotion......1045

C. Daniel Salzman, Ralph Adolphs

The Modern Search for the Neural Circuitry of Emotion Began in the Late 19th Century 1047

### The Amygdala Has Been Implicated in Both Learned and Innate Fear 1050

The Amygdala Has Been Implicated in Innate Fear in Animals 1052

The Amygdala Is Important for Fear in Humans 1053

The Amygdala's Role Extends to Positive Emotions 1055

Emotional Responses Can Be Updated Through Extinction and Regulation 1055

Emotion Can Influence Cognitive Processes 1056

Many Other Brain Areas Contribute to Emotional Processing 1056

Functional Neuroimaging Is Contributing to Our Understanding of Emotion in Humans 1059

Functional Imaging Has Identified Neural Correlates of Feelings 1060

Emotion Is Related to Homeostasis 1060

Highlights 1062

Selected Reading 1063

References 1063

#### 

Eric J. Nestler, C. Daniel Salzman

### Motivational States Influence Goal-Directed Behavior 1065

Both Internal and External Stimuli Contribute to Motivational States 1065

Rewards Can Meet Both Regulatory and Nonregulatory Needs on Short and Long Timescales 1066

The Brain's Reward Circuitry Provides a Biological Substrate for Goal Selection 1066

Dopamine May Act as a Learning Signal 1068

### Drug Addiction Is a Pathological Reward State 1069

All Drugs of Abuse Target Neurotransmitter Receptors, Transporters, or Ion Channels 1070

Repeated Exposure to a Drug of Abuse Induces Lasting Behavioral Adaptations 1071

Lasting Molecular Adaptations Are Induced in Brain Reward Regions by Repeated Drug Exposure 1074

Lasting Cellular and Circuit Adaptations Mediate Aspects of the Drug-Addicted State 1075

Natural Addictions Share Biological Mechanisms With Drug Addictions 1077

#### Highlights 1078

Selected Reading 1079

References 1079

### 44 Sleep and Wakefulness ..... 1080

Clifford B. Saper, Thomas E. Scammell

Sleep Consists of Alternating Periods of REM Sleep and Non-REM Sleep 1081

The Ascending Arousal System Promotes Wakefulness 1082

The Ascending Arousal System in the Brain Stem and Hypothalamus Innervates the Forebrain 1084

Damage to the Ascending Arousal System Causes Coma 1085

Circuits Composed of Mutually Inhibitory Neurons Control Transitions From Wake to Sleep and From Non-REM to REM Sleep 1085

### Sleep Is Regulated by Homeostatic and Circadian Drives 1086

The Homeostatic Pressure for Sleep Depends on Humoral Factors 1086

Circadian Rhythms Are Controlled by a Biological Clock in the Suprachiasmatic Nucleus 1087

Circadian Control of Sleep Depends on Hypothalamic Relays 1090

Sleep Loss Impairs Cognition and Memory 1091

#### Sleep Changes With Age 1092

### Disruptions in Sleep Circuitry Contribute to Many Sleep Disorders 1092

Insomnia May Be Caused by Incomplete Inhibition of the Arousal System 1092

Sleep Apnea Fragments Sleep and Impairs Cognition 1093

Narcolepsy Is Caused by a Loss of Orexinergic Neurons 1093

REM Sleep Behavior Disorder Is Caused by Failure of REM Sleep Paralysis Circuits 1095

Restless Legs Syndrome and Periodic Limb Movement Disorder Disrupt Sleep 1095

Non-REM Parasomnias Include Sleepwalking, Sleep Talking, and Night Terrors 1095

Sleep Has Many Functions 1096

Highlights 1097

Selected Reading 1098

References 1098

### Part VII

Development and the Emergence of Behavior

### **45 Patterning the Nervous**

Development of the Neural Plate Is Induced by Signals From the Organizer Region 1108

Neural Induction Is Mediated by Peptide Growth Factors and Their Inhibitors 1110

### Rostrocaudal Patterning of the Neural Tube Involves Signaling Gradients and Secondary Organizing Centers 1112

The Neural Tube Becomes Regionalized Early in Development 1112

Signals From the Mesoderm and Endoderm Define the Rostrocaudal Pattern of the Neural Plate 1112

Signals From Organizing Centers Within the Neural Tube Pattern the Forebrain, Midbrain, and Hindbrain 1113

Repressive Interactions Divide the Hindbrain Into Segments 1115

### Dorsoventral Patterning of the Neural Tube Involves Similar Mechanisms at Different Rostrocaudal Levels 1115

The Ventral Neural Tube Is Patterned by Sonic Hedgehog Protein Secreted from the Notochord and Floor Plate 1117

The Dorsal Neural Tube Is Patterned by Bone Morphogenetic Proteins 1119

Dorsoventral Patterning Mechanisms Are Conserved Along the Rostrocaudal Extent of the Neural Tube 1119

### Local Signals Determine Functional Subclasses of Neurons 1119

Rostrocaudal Position Is a Major Determinant of Motor Neuron Subtype 1120

Local Signals and Transcriptional Circuits Further Diversify Motor Neuron Subtypes 1121

### The Developing Forebrain Is Patterned by Intrinsic and Extrinsic Influences 1123

Inductive Signals and Transcription Factor Gradients Establish Regional Differentiation 1123

Afferent Inputs Also Contribute to Regionalization 1124

### Highlights 1128

Selected Reading 1129

References 1129

### 46 Differentiation and Survival of Nerve Cells ...... 1130

Joshua R. Sanes, Thomas M. Jessell

The Proliferation of Neural Progenitor Cells Involves Symmetric and Asymmetric Cell Divisions 1131 Radial Glial Cells Serve as Neural Progenitors and Structural Scaffolds 1131

The Generation of Neurons and Glial Cells Is Regulated by Delta-Notch Signaling and Basic Helix-Loop-Helix Transcription Factors 1131

The Layers of the Cerebral Cortex Are Established by Sequential Addition of Newborn Neurons 1135

Neurons Migrate Long Distances From Their Site of Origin to Their Final Position 1137

Excitatory Cortical Neurons Migrate Radially Along Glial Guides 1137

Cortical Interneurons Arise Subcortically and Migrate Tangentially to Cortex 1138

Neural Crest Cell Migration in the Peripheral Nervous System Does Not Rely on Scaffolding 1141

### Structural and Molecular Innovations Underlie the Expansion of the Human Cerebral Cortex 1141

#### Intrinsic Programs and Extrinsic Factors Determine the Neurotransmitter Phenotypes of Neurons 1143

Neurotransmitter Choice Is a Core Component of Transcriptional Programs of Neuronal Differentiation 1143

Signals From Synaptic Inputs and Targets Can Influence the Transmitter Phenotypes of Neurons 1146

# The Survival of a Neuron Is Regulated by Neurotrophic Signals From the Neuron's Target 1147

The Neurotrophic Factor Hypothesis Was Confirmed by the Discovery of Nerve Growth Factor 1147

Neurotrophins Are the Best-Studied Neurotrophic Factors 1147

Neurotrophic Factors Suppress a Latent Cell Death Program 1151

Highlights 1153

Selected Reading 1154

References 1154

### 47 The Growth and Guidance

### of Axons ..... 1156

Joshua R. Sanes

Differences Between Axons and Dendrites Emerge Early in Development 1156

Dendrites Are Patterned by Intrinsic and Extrinsic Factors 1157

The Growth Cone Is a Sensory Transducer and a Motor Structure 1161

Molecular Cues Guide Axons to Their Targets 1166

### The Growth of Retinal Ganglion Axons Is Oriented in a Series of Discrete Steps 1168

Growth Cones Diverge at the Optic Chiasm 1171

Gradients of Ephrins Provide Inhibitory Signals in the Brain 1172

### Axons From Some Spinal Neurons Are Guided Across the Midline 1176

Netrins Direct Developing Commissural Axons Across the Midline 1176

Chemoattractant and Chemorepellent Factors Pattern the Midline 1176

Highlights 1179

Selected Reading 1179

References 1180

### 48 Formation and Elimination of Synapses......1181

Joshua R. Sanes

#### Neurons Recognize Specific Synaptic Targets 1182

Recognition Molecules Promote Selective Synapse Formation in the Visual System 1182

Sensory Receptors Promote Targeting of Olfactory Neurons 1184

Different Synaptic Inputs Are Directed to Discrete Domains of the Postsynaptic Cell 1186

Neural Activity Sharpens Synaptic Specificity 1187

### Principles of Synaptic Differentiation Are Revealed at the Neuromuscular Junction 1189

Differentiation of Motor Nerve Terminals Is Organized by Muscle Fibers 1190

Differentiation of the Postsynaptic Muscle Membrane Is Organized by the Motor Nerve 1194

The Nerve Regulates Transcription of Acetylcholine Receptor Genes 1196

The Neuromuscular Junction Matures in a Series of Steps 1197

#### Central Synapses and Neuromuscular Junctions Develop in Similar Ways 1198

Neurotransmitter Receptors Become Localized at Central Synapses 1198

Synaptic Organizing Molecules Pattern Central Nerve Terminals 1199

#### Some Synapses Are Eliminated After Birth 1204

Glial Cells Regulate Both Formation and Elimination of Synapses 1205

Highlights 1207 Selected Reading 1208 References 1208

### 49 Experience and the Refinement of Synaptic Connections......1210

Joshua R. Sanes

Development of Human Mental Function Is Influenced by Early Experience 1211

Early Experience Has Lifelong Effects on Social Behaviors 1211

Development of Visual Perception Requires Visual Experience 1212

#### Development of Binocular Circuits in the Visual Cortex Depends on Postnatal Activity 1213

Visual Experience Affects the Structure and Function of the Visual Cortex 1213

Patterns of Electrical Activity Organize Binocular Circuits 1215

#### Reorganization of Visual Circuits During a Critical Period Involves Alterations in Synaptic Connections 1219

Cortical Reorganization Depends on Changes in Both Excitation and Inhibition 1219

Synaptic Structures Are Altered During the Critical Period 1221

Thalamic Inputs Are Remodeled During the Critical Period 1221

Synaptic Stabilization Contributes to Closing the Critical Period 1223

### Experience-Independent Spontaneous Neural Activity Leads to Early Circuit Refinement 1224

Activity-Dependent Refinement of Connections Is a General Feature of Brain Circuitry 1225

Many Aspects of Visual System Development Are Activity-Dependent 1225

Sensory Modalities Are Coordinated During a Critical Period 1227

Different Functions and Brain Regions Have Different Critical Periods of Development 1228

#### Critical Periods Can Be Reopened in Adulthood 1229

Visual and Auditory Maps Can Be Aligned in Adults 1230

Binocular Circuits Can Be Remodeled in Adults 1231

Highlights 1233

### Selected Reading 1234

#### References 1234

of Acetylcholine Ma