

# 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

### 2 Genes and Behavior ..... 26

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

## 10 Propagated Signaling: The Action Potential ..... 211

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 Transmission ..... 241

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

## 13 Synaptic Integration in the Central Nervous System. .... 273

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

<b>14 Modulation of Synaptic Transmission and Neuronal Excitability: Second Messengers.....</b>	<b>301</b>
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>3</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
<b>15 Transmitter Release .....</b>	<b>324</b>
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
<b>16 Neurotransmitters.....</b>	<b>358</b>
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**

### **18 Receptors of the Somatosensory System.....408**

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.....435**

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

## **20 Pain ..... 470**

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 Visual Processing ..... 496**

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: The Retina ..... 521**

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**

**24 High-Level Visual Processing: From Vision to Cognition ..... 564**

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

## 25 Visual Processing for Attention and Action ..... 582

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 the Cochlea ..... 598

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

## 27 The Vestibular System ..... 629

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 Chemical Senses . . . . . 682

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**

**30 Principles of Sensorimotor Control..... 713**

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

**33 Locomotion..... 783**

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**

## **34 Voluntary Movement: Motor Cortices . . . . . 815**

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

**36 Posture..... 883**

- 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**

**37 The Cerebellum..... 908**

- 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**

**38 The Basal Ganglia . . . . . 932**

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

---

#### 40 The Brain Stem ..... 981

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**

**43 Motivation, Reward, and Addictive States . . . . . 1065**

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 System . . . . . 1107**

Joshua R. Sanes, Thomas M. Jessell

**The Neural Tube Arises From the Ectoderm 1108**

**Secreted Signals Promote Neural Cell Fate 1108**

- 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

**50 Repairing the Damaged Brain . . . . 1236**

Joshua R. Sanes

**Damage to the Axon Affects Both the Neuron and Neighboring Cells 1237**

Axon Degeneration Is an Active Process 1237

Axotomy Leads to Reactive Responses in Nearby Cells 1240

**Central Axons Regenerate Poorly After Injury 1241****Therapeutic Interventions May Promote Regeneration of Injured Central Neurons 1242**

Environmental Factors Support the Regeneration of Injured Axons 1243

Components of Myelin Inhibit Neurite Outgrowth 1244

Injury-Induced Scarring Hinders Axonal Regeneration 1246

An Intrinsic Growth Program Promotes Regeneration 1246

Formation of New Connections by Intact Axons Can Lead to Recovery of Function Following Injury 1247

**Neurons in the Injured Brain Die but New Ones Can Be Born 1248****Therapeutic Interventions May Retain or Replace Injured Central Neurons 1250**

Transplantation of Neurons or Their Progenitors Can Replace Lost Neurons 1250

Stimulation of Neurogenesis in Regions of Injury May Contribute to Restoring Function 1254

Transplantation of Nonneuronal Cells or Their Progenitors Can Improve Neuronal Function 1255

Restoration of Function Is the Aim of Regenerative Therapies 1255

**Highlights 1256****Selected Reading 1257****References 1257****51 Sexual Differentiation of the Nervous System . . . . . 1260**

Nirao M. Shah, Joshua R. Sanes

**Genes and Hormones Determine Physical Differences Between Males and Females 1261**

Chromosomal Sex Directs the Gonadal Differentiation of the Embryo 1261

Gonads Synthesize Hormones That Promote Sexual Differentiation 1262

Disorders of Steroid Hormone Biosynthesis Affect Sexual Differentiation 1263

**Sexual Differentiation of the Nervous System Generates Sexually Dimorphic Behaviors 1264**

Erectile Function Is Controlled by a Sexually Dimorphic Circuit in the Spinal Cord 1266

Song Production in Birds Is Controlled by Sexually Dimorphic Circuits in the Forebrain 1267

Mating Behavior in Mammals Is Controlled by a Sexually Dimorphic Neural Circuit in the Hypothalamus 1272

**Environmental Cues Regulate Sexually Dimorphic Behaviors 1272**

Pheromones Control Partner Choice in Mice 1272

Early Experience Modifies Later Maternal Behavior 1274

A Set of Core Mechanisms Underlies Many Sexual Dimorphisms in the Brain and Spinal Cord 1275

**The Human Brain Is Sexually Dimorphic 1277**

Sexual Dimorphisms in Humans May Arise From Hormonal Action or Experience 1279

Dimorphic Structures in the Brain Correlate with Gender Identity and Sexual Orientation 1279

**Highlights 1281****Selected Reading 1282****References 1283****Part VIII****Learning, Memory, Language and Cognition****52 Learning and Memory . . . . . 1291**

Daphna Shohamy, Daniel L. Schacter, Anthony D. Wagner

**Short-Term and Long-Term Memory Involve Different Neural Systems 1292**

Short-Term Memory Maintains Transient Representations of Information Relevant to Immediate Goals 1292

Information Stored in Short-Term Memory Is Selectively Transferred to Long-Term Memory 1293

**The Medial Temporal Lobe Is Critical for Episodic Long-Term Memory 1294**

Episodic Memory Processing Involves Encoding, Storage, Retrieval, and Consolidation 1297

Episodic Memory Involves Interactions Between the Medial Temporal Lobe and Association Cortices 1298

Episodic Memory Contributes to Imagination and Goal-Directed Behavior 1300

The Hippocampus Supports Episodic Memory by Building Relational Associations 1300

**Implicit Memory Supports a Range of Behaviors in Humans and Animals 1303**

Different Forms of Implicit Memory Involve Different Neural Circuits 1303

Implicit Memory Can Be Associative or Nonassociative 1304

Operant Conditioning Involves Associating a Specific Behavior With a Reinforcing Event 1306

Associative Learning Is Constrained by the Biology of the Organism 1307

**Errors and Imperfections in Memory Shed Light on Normal Memory Processes 1308**

Highlights 1309

Suggested Reading 1310

References 1310

**53 Cellular Mechanisms of Implicit Memory Storage and the Biological Basis of Individuality..... 1312**

Eric R. Kandel, Joseph LeDoux

**Storage of Implicit Memory Involves Changes in the Effectiveness of Synaptic Transmission 1313**

Habituation Results From Presynaptic Depression of Synaptic Transmission 1314

Sensitization Involves Presynaptic Facilitation of Synaptic Transmission 1316

Classical Threat Conditioning Involves Facilitation of Synaptic Transmission 1317

**Long-Term Storage of Implicit Memory Involves Synaptic Changes Mediated by the cAMP-PKA-CREB Pathway 1319**

Cyclic AMP Signaling Has a Role in Long-Term Sensitization 1319

The Role of Noncoding RNAs in the Regulation of Transcription 1323

Long-Term Synaptic Facilitation Is Synapse Specific 1324

Maintaining Long-Term Synaptic Facilitation Requires a Prion-Like Protein Regulator of Local Protein Synthesis 1327

Memory Stored in a Sensory-Motor Synapse Becomes Destabilized Following Retrieval but Can Be Restabilized 1330

**Classical Threat Conditioning of Defensive Responses in Flies Also Uses the cAMP-PKA-CREB Pathway 1330**

**Memory of Threat Learning in Mammals Involves the Amygdala 1331**

**Learning-Induced Changes in the Structure of the Brain Contribute to the Biological Basis of Individuality 1336**

Highlights 1336

Selected Reading 1337

References 1337

**54 The Hippocampus and the Neural Basis of Explicit Memory Storage ..... 1339**

Edvard I. Moser, May-Britt Moser, Steven A. Siegelbaum

**Explicit Memory in Mammals Involves Synaptic Plasticity in the Hippocampus 1340**

Long-Term Potentiation at Distinct Hippocampal Pathways Is Essential for Explicit Memory Storage 1342

Different Molecular and Cellular Mechanisms Contribute to the Forms of Expression of Long-Term Potentiation 1345

Long-Term Potentiation Has Early and Late Phases 1347

Spike-Timing-Dependent Plasticity Provides a More Natural Mechanism for Altering Synaptic Strength 1349

Long-Term Potentiation in the Hippocampus Has Properties That Make It Useful as A Mechanism for Memory Storage 1349

Spatial Memory Depends on Long-Term Potentiation 1350

**Explicit Memory Storage Also Depends on Long-Term Depression of Synaptic Transmission 1353**

**Memory Is Stored in Cell Assemblies 1357**

**Different Aspects of Explicit Memory Are Processed in Different Subregions of the Hippocampus 1358**

The Dentate Gyrus Is Important for Pattern Separation 1359

The CA3 Region Is Important for Pattern Completion 1360

The CA2 Region Encodes Social Memory 1360

**A Spatial Map of the External World Is Formed in the Hippocampus 1360**

Entorhinal Cortex Neurons Provide a Distinct Representation of Space 1361

Place Cells Are Part of the Substrate for Spatial Memory 1365

**Disorders of Autobiographical Memory Result From Functional Perturbations in the Hippocampus 1367****Highlights 1367****Selected Reading 1368****References 1368****55 Language..... 1370**

Patricia K. Kuhl

**Language Has Many Structural Levels: Phonemes, Morphemes, Words, and Sentences 1371****Language Acquisition in Children Follows a Universal Pattern 1372**

The "Universalist" Infant Becomes Linguistically Specialized by Age 1 1373

The Visual System Is Engaged in Language Production and Perception 1376

Prosodic Cues Are Learned as Early as In Utero 1376

Transitional Probabilities Help Distinguish Words in Continuous Speech 1376

There Is a Critical Period for Language Learning 1377

The "Parentese" Speaking Style Enhances Language Learning 1377

Successful Bilingual Learning Depends on the Age at Which the Second Language Is Learned 1378

**A New Model for the Neural Basis of Language Has Emerged 1378**

Numerous Specialized Cortical Regions Contribute to Language Processing 1378

The Neural Architecture for Language Develops Rapidly During Infancy 1380

The Left Hemisphere Is Dominant for Language 1381

Prosody Engages Both Right and Left Hemispheres Depending on the Information Conveyed 1382

**Studies of the Aphasias Have Provided Insights into Language Processing 1382**

Broca's Aphasia Results From a Large Lesion in the Left Frontal Lobe 1382

Wernicke's Aphasia Results From Damage to Left Posterior Temporal Lobe Structures 1384

Conduction Aphasia Results From Damage to a Sector of Posterior Language Areas 1384

Global Aphasia Results From Widespread Damage to Several Language Centers 1386

Transcortical Aphasias Result From Damage to Areas Near Broca's and Wernicke's Areas 1386

Less Common Aphasias Implicate Additional Brain Areas Important for Language 1386

**Highlights 1388****Selected Reading 1389****References 1390****56 Decision-Making and Consciousness ..... 1392**

Michael N. Shadlen, Eric R. Kandel

**Perceptual Discriminations Require a Decision Rule 1393**

A Simple Decision Rule Is the Application of a Threshold to a Representation of the Evidence 1393

Perceptual Decisions Involving Deliberation Mimic Aspects of Real-Life Decisions Involving Cognitive Faculties 1395

**Neurons in Sensory Areas of the Cortex Supply the Noisy Samples of Evidence to Decision-Making 1397****Accumulation of Evidence to a Threshold Explains the Speed Versus Accuracy Trade-Off 1401****Neurons in the Parietal and Prefrontal Association Cortex Represent a Decision Variable 1401****Perceptual Decision-Making Is a Model for Reasoning From Samples of Evidence 1404****Decisions About Preference Use Evidence About Value 1408****Decision-Making Offers a Framework for Understanding Thought Processes, States of Knowing, and States of Awareness 1409****Consciousness Can be Understood Through the Lens of Decision Making 1412****Highlights 1415****Selected Reading 1415****References 1416**



**Part IX**  
**Diseases of the Nervous System**

**57 Diseases of the Peripheral Nerve and Motor Unit . . . . . 1421**

Robert H. Brown, Stephen C. Cannon,  
 Lewis P. Rowland

**Disorders of the Peripheral Nerve, Neuromuscular Junction, and Muscle Can Be Distinguished Clinically 1422**

**A Variety of Diseases Target Motor Neurons and Peripheral Nerves 1426**

Motor Neuron Diseases Do Not Affect Sensory Neurons (Amyotrophic Lateral Sclerosis) 1426

Diseases of Peripheral Nerves Affect Conduction of the Action Potential 1428

The Molecular Basis of Some Inherited Peripheral Neuropathies Has Been Defined 1430

**Disorders of Synaptic Transmission at the Neuromuscular Junction Have Multiple Causes 1432**

Myasthenia Gravis Is the Best-Studied Example of a Neuromuscular Junction Disease 1433

Treatment of Myasthenia Is Based on the Physiological Effects and Autoimmune Pathogenesis of the Disease 1435

There Are Two Distinct Congenital Forms of Myasthenia Gravis 1435

Lambert-Eaton Syndrome and Botulism Also Alter Neuromuscular Transmission 1436

**Diseases of Skeletal Muscle Can Be Inherited or Acquired 1437**

Dermatomyositis Exemplifies Acquired Myopathy 1437

Muscular Dystrophies Are the Most Common Inherited Myopathies 1437

Some Inherited Diseases of Skeletal Muscle Arise From Genetic Defects in Voltage-Gated Ion Channels 1441

**Highlights 1445**

**Selected Reading 1445**

**References 1445**

**58 Seizures and Epilepsy . . . . . 1447**

Gary Westbrook

**Classification of Seizures and the Epilepsies Is Important for Pathogenesis and Treatment 1448**

Seizures Are Temporary Disruptions of Brain Function 1448

Epilepsy Is a Chronic Condition of Recurrent Seizures 1449

**The Electroencephalogram Represents the Collective Activity of Cortical Neurons 1450**

**Focal Onset Seizures Originate Within a Small Group of Neurons 1454**

Neurons in a Seizure Focus Have Abnormal Bursting Activity 1454

The Breakdown of Surround Inhibition Leads to Synchronization 1456

The Spread of Seizure Activity Involves Normal Cortical Circuitry 1460

**Generalized Onset Seizures Are Driven by Thalamocortical Circuits 1461**

**Locating the Seizure Focus Is Critical to the Surgical Treatment of Epilepsy 1463**

**Prolonged Seizures Can Cause Brain Damage 1465**

Repeated Convulsive Seizures Are a Medical Emergency 1465

Excitotoxicity Underlies Seizure-Related Brain Damage 1466

**The Factors Leading to Development of Epilepsy Are Poorly Understood 1467**

Mutations in Ion Channels Are Among the Genetic Causes of Epilepsy 1467

The Genesis of Acquired Epilepsies Is a Maladaptive Response to Injury 1469

**Highlights 1470**

**Selected Reading 1471**

**References 1471**

**59 Disorders of Conscious and Unconscious Mental Processes. . . . 1473**

Christopher D. Frith

**Conscious and Unconscious Cognitive Processes Have Distinct Neural Correlates 1474**

**Differences Between Conscious and Unconscious Processes in Perception Can Be Seen in Exaggerated Form After Brain Damage 1476**

**The Control of Action Is Largely Unconscious 1479**

**The Conscious Recall of Memories Is a Creative Process 1482**

**Behavioral Observation Needs to Be Supplemented With Subjective Reports 1483**

- Verification of Subjective Reports Is Challenging 1484
- Malingering and Hysteria Can Lead to Unreliable Subjective Reports 1485

**Highlights 1485**

**Selected Reading 1486**

**References 1486**

**60 Disorders of Thought and Volition in Schizophrenia ..... 1488**

Steven E. Hyman, Joshua Gordon

**Schizophrenia Is Characterized by Cognitive Impairments, Deficit Symptoms, and Psychotic Symptoms 1489**

- Schizophrenia Has a Characteristic Course of Illness With Onset During the Second and Third Decades of Life 1490
- The Psychotic Symptoms of Schizophrenia Tend to Be Episodic 1490

**The Risk of Schizophrenia Is Highly Influenced by Genes 1490**

**Schizophrenia Is Characterized by Abnormalities in Brain Structure and Function 1492**

- Loss of Gray Matter in the Cerebral Cortex Appears to Result From Loss of Synaptic Contacts Rather Than Loss of Cells 1494
- Abnormalities in Brain Development During Adolescence May Be Responsible for Schizophrenia 1494

**Antipsychotic Drugs Act on Dopaminergic Systems in the Brain 1497**

**Highlights 1499**

**Selected Reading 1499**

**References 1499**

**61 Disorders of Mood and Anxiety ..... 1501**

Steven E. Hyman, Carol Tamminga

**Mood Disorders Can Be Divided Into Two General Classes: Unipolar Depression and Bipolar Disorder 1501**

- Major Depressive Disorder Differs Significantly From Normal Sadness 1502
- Major Depressive Disorder Often Begins Early in Life 1503
- A Diagnosis of Bipolar Disorder Requires an Episode of Mania 1503

**Anxiety Disorders Represent Significant Dysregulation of Fear Circuitry 1504**

**Both Genetic and Environmental Risk Factors Contribute to Mood and Anxiety Disorders 1506**

**Depression and Stress Share Overlapping Neural Mechanisms 1508**

**Dysfunctions of Human Brain Structures and Circuits Involved in Mood and Anxiety Disorders Can Be Identified by Neuroimaging 1509**

- Identification of Abnormally Functioning Neural Circuits Helps Explain Symptoms and May Suggest Treatments 1509
- A Decrease in Hippocampal Volume Is Associated With Mood Disorders 1512

**Major Depression and Anxiety Disorders Can Be Treated Effectively 1512**

- Current Antidepressant Drugs Affect Monoaminergic Neural Systems 1512
- Ketamine Shows Promise as a Rapidly Acting Drug to Treat Major Depressive Disorder 1515
- Psychotherapy Is Effective in the Treatment of Major Depressive Disorder and Anxiety Disorders 1515
- Electroconvulsive Therapy Is Highly Effective Against Depression 1518
- Newer Forms of Neuromodulation Are Being Developed to Treat Depression 1518
- Bipolar Disorder Can Be Treated With Lithium and Several Anticonvulsant Drugs 1519
- Second-Generation Antipsychotic Drugs Are Useful Treatments for Bipolar Disorder 1520

**Highlights 1520**

**Selected Reading 1521**

**References 1521**

**62 Disorders Affecting Social Cognition: Autism Spectrum Disorder ..... 1523**

Matthew W. State

**Autism Spectrum Disorder Phenotypes Share Characteristic Behavioral Features 1524**

**Autism Spectrum Disorder Phenotypes Also Share Distinctive Cognitive Abnormalities 1525**

- Social Communication Is Impaired in Autism Spectrum Disorder: The Mind Blindness Hypothesis 1525
- Other Social Mechanisms Contribute to Autism Spectrum Disorder 1527

People With Autism Show a Lack of Behavioral Flexibility 1528

Some Individuals With Autism Have Special Talents 1528

**Genetic Factors Increase Risk for Autism Spectrum Disorder 1529**

**Rare Genetic Syndromes Have Provided Initial Insights Into the Biology of Autism Spectrum Disorders 1531**

Fragile X Syndrome 1531

Rett Syndrome 1531

Williams Syndrome 1532

Angelman Syndrome and Prader-Willi Syndrome 1533

Neurodevelopmental Syndromes Provide Insight Into the Mechanisms of Social Cognition 1534

**The Complex Genetics of Common Forms of Autism Spectrum Disorder Are Being Clarified 1534**

**Genetics and Neuropathology Are Illuminating the Neural Mechanisms of Autism Spectrum Disorder 1537**

Genetic Findings Can Be Interpreted Using Systems Biological Approaches 1537

Autism Spectrum Disorder Genes Have Been Studied in a Variety of Model Systems 1538

Postmortem and Brain Tissue Studies Provide Insight Into Autism Spectrum Disorder Pathology 1539

**Advances in Basic and Translational Science Provide a Path to Elucidate the Pathophysiology of Autism Spectrum Disorder 1540**

Highlights 1540

Selected Reading 1541

References 1541

**63 Genetic Mechanisms in Neurodegenerative Diseases of the Nervous System..... 1544**

Huda Y. Zoghbi

**Huntington Disease Involves Degeneration of the Striatum 1545**

**Spinobulbar Muscular Atrophy Is Caused by Androgen Receptor Dysfunction 1546**

**Hereditary Spinocerebellar Ataxias Share Similar Symptoms but Have Distinct Etiologies 1546**

**Parkinson Disease Is a Common Degenerative Disorder of the Elderly 1548**

**Selective Neuronal Loss Occurs After Damage to Ubiquitously Expressed Genes 1550**

**Animal Models Are Productive Tools for Studying Neurodegenerative Diseases 1552**

Mouse Models Reproduce Many Features of Neurodegenerative Diseases 1552

Invertebrate Models Manifest Progressive Neurodegeneration 1553

**The Pathogenesis of Neurodegenerative Diseases Follows Several Pathways 1553**

Protein Misfolding and Degradation Contribute to Parkinson Disease 1553

Protein Misfolding Triggers Pathological Alterations in Gene Expression 1555

Mitochondrial Dysfunction Exacerbates Neurodegenerative Disease 1556

Apoptosis and Caspases Modify the Severity of Neurodegeneration 1556

**Understanding the Molecular Dynamics of Neurodegenerative Diseases Suggests Approaches to Therapeutic Intervention 1556**

Highlights 1558

Selected Reading 1558

References 1558

**64 The Aging Brain ..... 1561**

Joshua R. Sanes, David M. Holtzman

**The Structure and Function of the Brain Change With Age 1561**

**Cognitive Decline Is Significant and Debilitating in a Substantial Fraction of the Elderly 1566**

**Alzheimer Disease Is the Most Common Cause of Dementia 1567**

**The Brain in Alzheimer Disease Is Altered by Atrophy, Amyloid Plaques, and Neurofibrillary Tangles 1568**

Amyloid Plaques Contain Toxic Peptides That Contribute to Alzheimer Pathology 1570

Neurofibrillary Tangles Contain Microtubule-Associated Proteins 1573

Risk Factors for Alzheimer Disease Have Been Identified 1574

**Alzheimer Disease Can Now Be Diagnosed Well but Available Treatments Are Unsatisfactory 1576**

Highlights 1579

Selected Reading 1580

References 1580

Index 1583