Contents in Brief

Contents xiii
Preface xxxix
Acknowledgments xli
Contributors xliii
How to Use This Book xlv

Part I
An Overall View 2
1 Brain and Behavior 5
2 Nerve Cells and Behavior 18

Part II
Cell and Molecular Biology of the Neuron 34
3 The Cytology of Neurons 37
4 Synthesis and Trafficking of Neuronal Proteins 49
5 Ion Channels 66
6 Membrane Potential 81
7 Passive Membrane Properties of the Neuron 95
8 Voltage-Gated Ion Channels and the Generation of the Action Potential 104

Part III
Elementary Interactions Between Neurons: Synaptic Transmission 120
9 Synaptic Transmission 123

10 Directly Gated Transmission at the Nerve–Muscle Synapse 135
11 Directly Gated Transmission at Central Synapses 153
12 Synaptic Transmission Mediated By Second Messengers 173
13 Transmitter Release 194
14 Chemical Messengers: Small Molecules and Peptides 213
15 Synaptic Vesicles 225
16 Diseases of Chemical Transmission at the Nerve–Muscle Synapse: Myasthenia Gravis 235
17 Diseases of the Motor Unit 244
18 Reactions of Neurons to Injury 258

Part IV
Functional Anatomy of the Central Nervous System 270
19 Anatomical Organization of the Nervous System 273
20 The Neural Basis of Perception and Movement 283
21 Development as a Guide to the Regional Anatomy of the Brain 296
22 Imaging the Living Brain 309
### Part V
**Sensory Systems of the Brain: Sensation and Perception**

23 Coding and Processing of Sensory Information 329
24 Modality Coding in the Somatic Sensory System 341
25 Anatomy of the Somatic Sensory System 353
26 Touch 367
27 Pain and Analgesia 385
28 Phototransduction and Information Processing in the Retina 400
29 Central Visual Pathways 420
30 Perception of Motion, Depth, and Form 440
31 Color Vision 467
32 Hearing 481
33 The Sense of Balance 500
34 Smell and Taste: The Chemical Senses 512

### Part VI
**Motor Systems of the Brain: Reflex and Voluntary Control of Movement**

35 The Control of Movement 533
36 Muscles: Effectors of the Motor Systems 548
37 Muscle Receptors and Spinal Reflexes: The Stretch Reflex 564
38 Spinal Mechanisms of Motor Coordination 581
39 Posture 596
40 Voluntary Movement 609
41 The Cerebellum 626
42 The Basal Ganglia 647
43 The Ocular Motor System 660

### Part VII
**The Brain Stem and Reticular Core: Integration of Sensory and Motor Systems**

44 The Brain Stem: Cranial Nerve Nuclei and the Monoaminergic Systems 683
45 Trigeminal System 701
46 Clinical Syndromes of the Spinal Cord and Brain Stem 711

### Part VIII
**Hypothalamus, Limbic System, and Cerebral Cortex: Homeostasis and Arousal**

47 Hypothalamus and Limbic System: Peptidergic Neurons, Homeostasis, and Emotional Behavior 735
48 Hypothalamus and Limbic System: Motivation 750
49 The Autonomic Nervous System 761
50 The Collective Electrical Behavior of Cortical Neurons: The Electroencephalogram and the Mechanisms of Epilepsy 777
51 Sleep and Dreaming 792
52 Disorders of Sleep and Consciousness 805

### Part IX
**Localization of Higher Functions and the Disorders of Language, Thought, and Affect**

53 Localization of Higher Cognitive and Affective Functions: The Association Cortices 823
54 Disorders of Language: The Aphasias 839
55 Disorders of Thought: Schizophrenia 853
56 Disorders of Mood: Depression, Mania, and Anxiety Disorders 869

### Part X
**Development, Critical Periods, and the Emergence of Behavior**

57 Control of Cell Identity 887
58 Cell Migration and Axon Guidance 908
59 Neuronal Survival and Synapse Formation 929
60 Early Experience and the Fine Tuning of Synaptic Connections 945
61 Sexual Differentiation of the Nervous System 959
62 Aging of the Brain: Dementia of the Alzheimer's Type 974

Part XI
Genes, Environmental Experience, and the Mechanisms of Behavior 984

63 Genetic Determinants of Behavior 987
64 Learning and Memory 997
65 Cellular Mechanisms of Learning and the Biological Basis of Individuality 1009

Appendices
A Current Flow in Neurons 1033
B Cerebral Circulation: Stroke 1041
C Cerebrospinal Fluid: Blood–Brain Barrier, Brain Edema, and Hydrocephalus 1050

Index 1061
Contents

Preface xxxix
Acknowledgments xli
Contributors xliii
How to Use This Book xlv

Part I
An Overall View 2

1 Brain and Behavior 5
Eric R. Kandel
Two Alternative Views Have Been Advanced on the Relationship Between Brain and Behavior 6
Regions of the Brain Are Specialized for Different Functions 7
Language and Other Cognitive Functions Are Localized Within the Cerebral Cortex 7
Affective and Character Traits Are Also Anatomically Localized 12
Mental Processes Are Represented in the Brain by Their Elementary Operations 15
Selected Readings 16
References 16

Nerve Cells Are the Signaling Units of Behavioral Responses 24

Signaling Is Organized in the Same Way in All Nerve Cells 26
Signals Represent Changes in the Electrical Properties of Neurons 26
The Input Component Produces Graded Local Signals 27
The Integrative Component Makes the Decision to Generate an Action Potential 28
The Conductile Component Propagates an All-or-None Action Potential 29
The Output Component Releases Transmitter 29
The Information Carried by a Signal Is Transformed As It Passes from One Component to the Next 30
Nerve Cells Differ Most at the Molecular Level 31
Patterns of Interconnection Allow Relatively Stereotyped Nerve Cells to Convey Unique Information 31

Selected Readings 32
References 32

2 Nerve Cells and Behavior 18
Eric R. Kandel
The Nervous System Has Two Classes of Cells 19
Nerve Cells 19
Glial Cells 22

Part II
Cell and Molecular Biology of the Neuron 34

3 The Cytology of Neurons 37
James H. Schwartz
The Neurons That Mediate the Stretch Reflex Differ in Their Morphology and Transmitter Substance 38
The Sensory Neuron 38
The Motor Neuron 38
The Axons of Both Sensory and Motor Neurons Are Ensheathed in Myelin 43
A Major Function of the Neuron's Cell Body Is the Synthesis of Macromolecules 45
An Overall View 47
Selected Readings 47
References 47

4 Synthesis and Trafficking of Neuronal Proteins 49
James H. Schwartz
Messenger RNA Gives Rise to Three Classes of Proteins 49
Cytoplasmic Proteins 51
Nuclear, Mitochondrial, and Peroxisomal Proteins 52
Cell Membrane Proteins and Secretory Proteins 52
Fate of Major Membrane Proteins 55
Axonal Transport Controls the Distribution of Membranes and Secretory Proteins in the Neuron 57
Fast Anterograde Transport 57
Slow Axonal Transport 58
Fast Retrograde Transport 59
Fibrillar Proteins of the Cytoskeleton Are Responsible for the Shape of Neurons 60
The Dynamics of Polymerization 62
An Overall View 64
Selected Readings 65
References 65

5 Ion Channels 66
Steven A. Siegelbaum and John Koester
Ions Cross the Cell Membrane Through Channels 67
Ion Channels Can Now Be Investigated by Functional and Structural Methods 68
Single-Channel Recording Can Measure the Activity of a Single Protein Molecule 68
Ion Channels Can Now Be Studied Through Molecular Biological Approaches 69
Ion Channels Share Several Characteristics 73

Ion Channels Facilitate the Passive Flux of Ions Across the Cell Membrane 73
The Opening and Closing of a Channel Involves Conformational Changes 75
Variants of Each Type of Ion Channel Are Found in Different Tissues 78
Genes That Encode Ion Channels Can Be Grouped into Families 78
An Overall View 78
Selected Readings 79
References 79

6 Membrane Potential 81
John Koester
Membrane Potential Results from the Separation of Charge Across the Cell Membrane 82
The Resting Membrane Potential Is Determined by the Relative Abundance of Different Types of Nongated Ion Channels 82
Nongated Channels in Glial Cells Are Selective Only for Potassium 84
Nongated Channels in Nerve Cells Are Selective for Several Ion Species 84
The Passive Fluxes of Sodium and Potassium Through Nongated Channels Are Balanced by Active Pumping of Sodium and Potassium Ions 86
Chloride Ions Are Often Passively Distributed 88
The Action Potential Is Generated by the Sequential Opening of Voltage-Gated Channels Selective for Sodium and Potassium 88
The Resting and Action Potentials Can Be Quantified by the Goldman Equation 88
The Neuron Can Be Represented by an Electrical Equivalent Circuit 89
Each Ion Channel Acts as a Conductor and Battery 89
An Equivalent Circuit Model of the Membrane Includes Batteries, Conductors, a Capacitor, and a Current Generator 90
An Overall View 92
Postscript 92
Calculation of Membrane Potential from the Equivalent Circuit Model of the Neuron 92
The Equation for Membrane Potential Can Be Written in a More General Form 93
The Sodium–Potassium Pump Counteracts the Passive Fluxes of Sodium and Potassium 94
Selected Readings 94
References 94
7 Passive Membrane Properties of the Neuron 95
John Koester
Membrane Capacitance Prolongs the Time Course of Electrical Signals 95
Membrane and Axoplasmic Resistance Affect the Efficiency of Signal Conduction 97
Axon Diameter Affects the Current Threshold 100
Passive Membrane Properties and Axon Diameter Affect the Velocity of Action Potential Propagation 100
An Overall View 102
Selected Readings 103

8 Voltage-Gated Ion Channels and the Generation of the Action Potential 104
John Koester
The Action Potential Is Generated by the Flow of Ions Through Voltage-Gated Sodium and Potassium Channels 105
Voltage-Gated Channels Can Be Studied by Use of the Voltage Clamp 105
The Voltage-Gated Sodium and Potassium Channels Have Different Kinetics 105
Sodium and Potassium Membrane Conductances Are Calculated from Their Currents 108
The Action Potential Can Be Reconstructed from the Known Electrical Properties of the Neuron 109
The Hodgkin–Huxley Model of Excitability Is Universally Applicable: Modifications Reflect the Diversity and Distribution of Voltage-Gated Channels 110
The Basic Mechanism of Action Potential Generation Is the Same in All Neurons 110
The Nervous System Expresses a Rich Variety of Voltage-Gated Ion Channels 111
Gating of Voltage-Sensitive Ion Channels Can Be Influenced by Changes in Intracellular Ion Concentrations 111
Excitability Properties Vary Among Neurons 111
Excitability Properties Vary Within Regions of the Neuron 112
Voltage-Gated Channels Have Characteristic Molecular Properties 112
Voltage-Gated Sodium Channels Are Sparsely Distributed 112

Part III
Elementary Interactions Between Neurons: Synaptic Transmission 120

9 Synaptic Transmission 123
Eric R. Kandel, Steven A. Siegelbaum, and James H. Schwartz
Synaptic Transmission Can Be Electrical or Chemical 124
Electrical Synapses Can Be Either Unidirectional or Bidirectional 124
Electrical Transmission Allows for Rapid and Synchronous Firing of Interconnected Cells 125
In Electrical Synapses the Pre- and Postsynaptic Elements Are Bridged by Gap Junctions 129
At Chemical Synapses the Pre- and Postsynaptic Elements Are Separated by a Synaptic Cleft 131
Chemical Transmission Involves Transmitter Release and Receptor Activation 131
Chemical Receptors Use Two Major Molecular Mechanisms to Gate Ion Channels 132
An Overall View 133
Selected Readings 134
References 134

10 Directly Gated Transmission at the Nerve–Muscle Synapse 135
Eric R. Kandel and Steven A. Siegelbaum
The Neuromuscular Junction Is a Simple Synapse for Studying Directly Gated Transmission 135

Voltage-Gated Channels Open in an All-or-None Fashion 113
Charges Are Redistributed Within the Membrane When Voltage-Gated Sodium Channels Open 113
The Voltage-Gated Sodium Channel Selects for Sodium on the Basis of Size, Charge, and Energy of Hydration of the Ion 115
The Voltage-Gated Potassium, Sodium, and Calcium Channels Belong to One Gene Family 115
An Overall View 118
Selected Readings 118
References 118
Excitatory and Inhibitory Synaptic Actions Are Integrated at a Common Trigger Zone 166

Synapses onto a Single Central Neuron Are Grouped According to Function 168
Synapses on Cell Bodies Are Often Inhibitory 168
Synapses on Dendritic Spines Are Often Excitatory 170
Synapses on Axon Terminals Are Often Modulatory 170
Excitatory and Inhibitory Synapses Have Distinct Ultrastructures 170

An Overall View 171
Selected Readings 172
References 172

12 Synaptic Transmission Mediated By Second Messengers 173
James H. Schwartz and Eric R. Kandel

Different Second-Messenger Pathways Share a Common Molecular Logic 175
The Cyclic AMP Pathway Involves a Polar and Diffusible Cytoplasmic Messenger 177
Some Second Messengers Are Generated Through Hydrolysis of Phospholipids 179

Second-Messenger Pathways Can Interact with One Another 182
Second Messengers Often Act Through Protein Phosphorylation to Open or Close Ion Channels 182
Second Messengers and G-Proteins Can Sometimes Act Directly on Ion Channels 185
Second Messengers Can Alter the Properties of Transmitter Receptors: Desensitization 186
Second Messengers Can Regulate Gene Expression and Thereby Endow Synaptic Transmission with Long-Lasting Consequences 187
Other Second-Messenger Pathways: Tyrosine Kinases and Cyclic GMP 191

An Overall View 191
Selected Readings 192
References 192

13 Transmitter Release 194
Eric R. Kandel

Transmitter Release Is Controlled by Calcium Influx 194
Sodium influx Is Not Necessary 195
Potassium Efflux Is Not Necessary 196
Calcium Influx Is Essential 197

Transmitter Is Released in Quantal Units 198
Calcium Influx Affects the Probability That a Quantum of Transmitter Will Be Released 199
Each Quantum of Transmitter Is Stored in a Specialized Organelle Called a Synaptic Vesicle 201
Transmitter Is Discharged from Synaptic Vesicles by Exocytosis at the Active Zone 203
The Docking of Synaptic Vesicles, Fusion, and Exocytosis Are Controlled by Calcium Influx 203
Calcium Influx Is Greatest in the Region of the Active Zone 206
Calcium Mobilizes Vesicles from the Cytoskeleton 206
The Number of Transmitter Vesicles Released Can Be Modulated by Altering Calcium Influx 206
Intrinsic Cellular Mechanisms Regulate the Concentration of Free Calcium 206
Synaptic Connections on Presynaptic Terminals Also Regulate Intracellular Free Calcium 207
An Overall View 209
Postscript: Calculating the Probability of Transmitter Release 210
Selected Readings 211
References 212

15 Synaptic Vesicles 225
James H. Schwartz
Transmitters Are Stored in Vesicles 225
Subcellular Fractionation Allows Biochemical Study of Vesicles 226
Transmitter Is Actively Taken up into Vesicles 226
Vesicles Are Involved in Transmitter Release 227
Synaptic Vesicle Membranes Contain Specific Proteins 227
Synaptic Vesicles Are Recycled 228
Vesicle Membranes Differ with the Type of Neuron 231
Transmitter Can Be Released by Carrier Mechanisms 232
Removal of Transmitter from the Synaptic Cleft Terminates Synaptic Transmission 232
An Overall View 233
Selected Readings 233
References 233

16 Diseases of Chemical Transmission at the Nerve–Muscle Synapse: Myasthenia Gravis 235
Lewis P. Rowland
Myasthenia Gravis Affects Transmission at the Nerve–Muscle Synapse 236
Physiological Studies Showed a Disorder of Neuromuscular Transmission 236
Immunological Studies Indicated That Myasthenia Is an Autoimmune Disease 236
Identification of Antibodies to the Acetylcholine Receptor Initiated the Modern Period of Research 237
Immunological Changes Cause the Physiological Abnormality 238
The Basis of Antibody Binding in Myasthenia Gravis Has Been Defined 239
The Molecular Basis of the Autoimmune Reaction Has Been Defined 241
Myasthenia Gravis May Be More than One Disease 241
Current Therapy for Myasthenia Gravis Is Effective But Not Ideal 242

Other Disorders of Neuromuscular Transmission: Presynaptic (Facilitating) Neuromuscular Block 242

An Overall View 242

Selected Readings 243

References 243

17 Diseases of the Motor Unit 244
Lewis P. Rowland

The Motor Unit Includes the Neuron, Peripheral Nerve, and Muscle Cell 244

Neurogenic and Myopathic Diseases Are Distinguished by Clinical and Laboratory Criteria 245
Clinical Criteria Help to Identify Neurogenic and Myopathic Conditions 245
Laboratory Criteria 246

Diseases of Motor Neurons Are Acute or Chronic 248
Motor Neuron Diseases Do Not Affect Sensory Neurons 248
Motor Neuron Disease Is Characterized by Fasciculation and Fibrillation 250

Diseases of Peripheral Nerves Are Also Acute or Chronic 250
Neuropathies Can Have Positive or Negative Symptoms 251
Demyelination Leads to a Slowing of Conduction Velocity 251

Diseases of Skeletal Muscle Can Be Inherited or Acquired 252
Muscular Dystrophies Are the Most Common Inherited Myopathies 252
Dermatomyositis Is an Acquired Myopathy 253
Weakness in Myopathies Need Not Be Due to Loss of Muscle Fibers 253

Molecular Genetics Illuminates the Physiology and Pathology of Duchenne Muscular Dystrophy 253

An Overall View 257

Selected Readings 257

References 257

18 Reactions of Neurons to Injury 258
Thomas M. Jessell

Severing the Axon Causes Degenerative Changes in the Neuron 259
Synaptic Transmission Is Lost Rapidly 259
The Distal Axon Segment Degenerates Slowly 260
The Membrane Compartments of the Cell Body Are Disrupted 260
Glial Cells and Macrophages Scavenge the Debris Caused by Injury 260

Cells That Have Synaptic Connections with Injured Neurons Also Degenerate 261

Neurons in the Peripheral Nervous System Can Regenerate Their Axons 262
Trophic Factors Prevent the Degeneration of Peripheral Neurons after Axotomy 262
Schwann Cells Contribute to the Regeneration of Peripheral Axons 264

Neurons in the Adult Central Nervous System Have Only Limited Capacity to Regenerate Their Axons 264

Several Potential Manipulations Can Promote the Recovery of Function after Damage to the Central Nervous System 265
Peripheral Nerve Grafts Promote the Growth of Central Axons 265
Transplantation of Embryonic Neurons into Adult Brain Promotes Recovery of Function after Damage 266
In Some Animals New Neurons Can Be Generated in the Adult Brain 268

An Overall View 268

Selected Readings 268

References 268

Part IV
Functional Anatomy of the Central Nervous System 270

19 Anatomical Organization of the Nervous System 273
James P. Kelly and Jane Dodd

The Nervous System Has Peripheral and Central Components 273
The Peripheral Nervous System 273
The Central Nervous System 274

The Central Nervous System Consists of Six Main Regions 275
The Cerebral Cortex Is Divided into Four Lobes Concerned with Different Functions 276
The Motivational System Influences Behavior by Acting on the Somatic and Autonomic Motor Systems 279

Even Simple Behavior Involves the Activity of the Sensory, Motor, and Motivational Systems 279

Four Principles Govern the Organization of the Major Functional Systems 279
Each System Contains Synaptic Relays 279
Each System Is Composed of Several Distinct Pathways 280
Each Pathway Is Topographically Organized 280
Most Pathways Cross the Midline 281

An Overall View 282
Selected Readings 282
References 282

20 The Neural Basis of Perception and Movement 283
James P. Kelly

The Spinal Cord Provides Sensory and Motor Innervation to the Trunk and Limbs 283
The Internal Structure of the Spinal Cord Varies at Different Levels 284
Sensory Axons Innervating the Trunk and Limbs Originate in the Dorsal Root Ganglia 286
Central Axons of Dorsal Root Ganglion Neurons Are Arranged Somatotopically in the Dorsal Column 287
The Dorsal Column–Medial Lemniscal System Is the Principal Pathway for Somatosensory Perception 287

The Thalamus Is the Principal Synaptic Relay for Information Reaching the Cerebral Cortex 287

The Highest Level of Information Processing Occurs in the Cerebral Cortex 292

The Corticospinal Tract Is a Direct Pathway for Voluntary Movement 293
Voluntary Movements Recruit the Actions of the Entire Motor System 294

Selected Readings 295
References 295

21 Development as a Guide to the Regional Anatomy of the Brain 296
John H. Martin and Thomas M. Jessell

The Neural Tube Is the Embryonic Precursor of the Six Brain Regions 296
The Neural Tube Develops from the Neural Plate 297
The Neural Epithelium Gives Rise to the Entire Nervous System 297

The Spinal Cord and Brain Stem Follow Similar Developmental Plans 300
The Hindbrain and Spinal Cord Become Segmented by Different Mechanisms 302
The Cavities of the Brain Vesicles Become the Ventricular System of the Brain 303

The Ventricular System Provides a Guide to Understanding the Regional Anatomy of the Diencephalon and Cerebral Hemispheres 304
The Caudate Nucleus Becomes C-Shaped Like the Lateral Ventricles 306
The Major Components of the Limbic System Also Develop into a C Shape 307

An Overall View 308
Selected Readings 308
References 308

22 Imaging the Living Brain 309
John H. Martin, John C. M. Brust, and Sadek Hilal

Imaging the Brain with X-Rays Depicts Structures with Large Differences in Absorbency of Radiation 309
Brain Asymmetry Is Revealed on Conventional Radiographs 310
Computerized Tomography Has Improved the Depiction of Brain Structures within the Skull 311

Positron Emission Tomography Yields Images of Biochemical Processes of the Living Brain 312

Magnetic Resonance Imaging Reveals the Structure and the Functional State of the Central Nervous System 314
Proton Images Show Structural Lesions in the Brain 321
The Paramagnetic Effects of Iron Allow Imaging of Specific Neural Systems 321
Sodium and Phosphorus Scans Reveal Cerebral Infarcts, Neoplastic Changes, and Metabolism 323

An Overall View 323
Selected Readings 324
References 324
23 Coding and Processing of Sensory Information 329
John H. Martin

Sensory Information Underlies Motor Control and Arousal As Well As Sensation 330

Sensory Systems Mediate Four Attributes of a Stimulus That Can Be Correlated Quantitatively with a Sensation 331
Modality 331
Intensity 331
Duration 333
Location 333

Sensory Systems Have a Common Plan 333
Sensory Receptors and Sensory Neurons in the Central Nervous System Have a Receptive Field 334
Sensory Information Is Processed by the Thalamus and Transmitted to the Cerebral Cortex 335
Sensory Systems Are Organized in Both a Hierarchical and Parallel Fashion 335
Sensory Systems Are Topographically Organized 335

Sensory Receptors Transduce Stimulus Features into Neural Codes 336
Stimulus Intensity Is Encoded by Frequency and Population Codes 336
Stimulus Duration Is Encoded in the Discharge Patterns of Rapidly and Slowly Adapting Receptors 337
Modality Is Encoded by a Labeled Line Code 338

Stimulus Information Is Transmitted to the Central Nervous System by Conducted Action Potentials 338
An Overall View 339
Selected Readings 339
References 339

24 Modality Coding in the Somatic Sensory System 341
John H. Martin and Thomas M. Jessell

The Dorsal Root Ganglion Neuron Is the Sensory Receptor in the Somatic Sensory System 342

Different Sensory Receptors Have Distinguishing Anatomical Features 342
Pain Is Mediated by Nociceptors 343
Warmth and Cold Are Mediated by Thermal Receptors 343
Touch Is Mediated by Mechanoreceptors in the Skin 344
Glabrous and Hairy Skin Have Different Types of Mechanoreceptors 345
Mechanoreceptors Differ in Their Ability to Resolve Spatial and Temporal Features of Stimuli 346
Limb Proprioception Is Mediated Primarily by Muscle Afferent Fibers 347
Afferent Fibers of Different Diameters Convey Action Potentials at Different Rates 349
An Overall View 352
Selected Readings 352
References 352

25 Anatomy of the Somatic Sensory System 353
John H. Martin and Thomas M. Jessell

Afferent Fibers Enter the Spinal Cord Through the Dorsal Roots 353
The Spinal Cord Is the First Relay Point for Somatic Sensory Information 354
Spinal Gray Matter Contains Nerve Cell Bodies 354
Spinal White Matter Contains Myelinated Axons 356
Dorsal Root Fibers Branch in the White Matter and Terminate in the Gray Matter 356
Afferents Conveying Different Somatic Sensory Modalities Have Distinct Terminal Projections 357
Two Major Ascending Systems Convey Somatic Sensory Information to the Cerebral Cortex 359
The Dorsal Column–Medial Lemniscal System Mediates Tactile Sense and Arm Proprioception 360
The Anterolateral System Mediates Pain and Temperature Sense 362
The Primary Somatic Sensory Cortex Is Divided into Four Functional Areas 364
Pyramidal Cells Are the Output Cells of the Primary Somatic Sensory Cortex 364
An Overall View 365
26 Touch 367
Eric R. Kandel and Thomas M. Jessell
Sensory Information About Touch Is Processed by a Series of Relay Nuclei 367
The Body Surface Is Represented in the Brain in an Orderly Fashion 370
Somatic Sensations Are Localized to Specific Regions of Cortex 370
Electrophysiological Studies Have Correlated Body Areas and Cortical Areas 370
Each Central Neuron Has a Specific Receptive Field 374
Sizes of Receptive Fields Vary in Different Areas of the Skin 374
Receptive Fields of Central Neurons Have Inhibitory and Excitatory Components 374
Lateral Inhibition Can Aid in Two-Point Discrimination 374
Inputs to the Somatic Sensory Cortex Are Organized into Columns by Submodality 377
Detailed Features of a Stimulus Are Communicated to the Brain 378
In the Early Stages of Cortical Processing the Dynamic Properties of Central Neurons and Receptors Are Similar 378
In the Later Stages of Cortical Processing the Central Nerve Cells Have Complex Feature-Detecting Properties and Integrate Various Sensory Inputs 380
An Overall View 381
Selected Readings 383
References 383

27 Pain and Analgesia 385
Thomas M. Jessell and Dennis D. Kelly
Noxious Insults to the Body
Activate Nociceptors 386
Nociceptors Are Activated by Mechanical, Thermal, or Chemical Stimuli 386
Tissue Damage Can Sensitize Nociceptors 386
Local Pain Can Be Sensed Even When Nociceptive Pathways Are Damaged 387
Pain Syndromes Can Result From Surgery Intended to Alleviate Pain 388
Primary Afferent Fibers Synapse with Dorsal Horn Neurons 389
Primary Afferent Fibers Use Amino Acids and Peptides As Transmitters 389
Nociceptive Information Is Conveyed to the Brain Along Several Ascending Pathways 390
Pain Can Be Modulated by the Balance of Activity Between Nociceptive and Other Afferent Inputs 392
Pain Can Be Controlled by Central Mechanisms 393
Direct Electrical Stimulation of the Brain Produces Analgesia 393
Nociceptive Control Pathways Descend to the Spinal Cord 393
Opiate Analgesia Involves the Same Pathways As Stimulation-Produced Analgesia 394
Endogenous Opioid Peptides and Their Receptors Are Located at Key Points in the Pain Modulatory System 394
Supraspinal and Spinal Networks Coordinateably Modulate Nociceptive Transmission 396
Local Dorsal Horn Circuits Modulate Afferent Nociceptive Input 396
Behavioral Stress Can Induce Analgesia Through Both Opioid and Nonopioid Mechanisms 397
An Overall View 398
Selected Readings 398
References 398

28 Phototransduction and Information Processing in the Retina 400
Marc Tessier-Lavigne
The Retina Contains the Eye's Receptor Sheet 401
There Are Two Types of Photoreceptors: Rods and Cones 402
Light Is Absorbed by Visual Pigments in the Outer Segments of Rods and Cones 403
Phototransduction Results from a Cascade of Biochemical Events in the Outer Segment of Photoreceptors 403
Light Activates Pigment Molecules in Photoreceptors 404
Activated Pigment Molecules Affect the Cytoplasmic Concentration of Cyclic GMP 406
Cyclic GMP Gates Specialized Ion Channels in the Plasma Membrane of the Photoreceptor 406
Closing of Cyclic GMP-Gated Ion Channels in the Outer Segment Hyperpolarizes the Photoreceptor 406
Changes in Intracellular Calcium Underlie Light Adaptation in Photoreceptors 408
Ganglion Cells Are the Output Neurons of the Retina 408
Ganglion Cell Receptive Fields Have a Center and Antagonistic Surround 409
The Properties of Ganglion Cells Enhance the Ability to Detect Weak Contrasts and Rapid Changes in the Visual Image 411
Ganglion Cells Are Also Specialized for Processing Specific Aspects of the Visual Image 412

Bipolar Cells and Other Interneurons
Relay Signals from Photoreceptors to Ganglion Cells 412
Cone Signals Are Conveyed to Ganglion Cells Through Direct or Lateral Pathways 412
Bipolar Cells Also Have Center-Surround Receptive Fields 412
Each Class of Bipolar Cells Has Excitatory Connections with Ganglion Cells of the Same Class 414
Different Pathways Convey Rod Signals to Ganglion Cells in the Moderately and Extremely Dark-Adapted Eye 414
Some Chemical Synapses in the Retina Have Distinctive Morphologies 415

An Overall View 416
Selected Readings 416
References 416

29 Central Visual Pathways 420
Carol Mason and Eric R. Kandel
The Retinal Image Is an Inversion of the Visual Field 420
The Retina Projects to Three Subcortical Regions in the Brain 423
The Pretectal Area of the Midbrain Controls Pupillary Reflexes 424
The Superior Colliculus Controls Saccadic Eye Movements 424
The Lateral Geniculate Nucleus Processes Visual Information 425

Neurons in the Lateral Geniculate Nucleus Have Concentric Receptive Fields 426
The Primary Visual Cortex Transforms Concentric Receptive Fields into Linear Segments and Boundaries 427
Simple and Complex Cells Decompose the Outlines of a Visual Image into Short Line Segments of Various Orientations 430
Some Feature Abstraction Can Be Accomplished by Progressive Convergence Within the Primary Visual Cortex 431

The Primary Visual Cortex Is Organized into Vertical Columns 431
Columnar Units Are Linked by Horizontal Connections 434
The Visual and Somatic Sensory Cortices Are Functionally Similar 436
Lesions in the Retino-Geniculate-Cortical Pathway Cause Predictable Changes in Vision 436
An Overall View 438
Selected Readings 438
References 438

30 Perception of Motion, Depth, and Form 440
Eric R. Kandel
Visual Perception Is a Creative Process 441
Vision Is Thought to Be Mediated by Three Parallel Pathways That Process Information for Motion, Depth and Form, and Color 445
Psychological Evidence Supports the Idea That Separate Pathways Carry Different Visual Information 448
Clinical Evidence Is Also Consistent with Parallel Processing of Visual Information 448

Motion in the Visual Field Is Analyzed by a Special Neural System 449
Motion Is Represented in the Middle Temporal Area (V5) and Medial Superior Temporal Area (V5a) 450
Lesions of the Middle Temporal Area Selectively Impair the Ability to Analyze Motion 452
The Perceptual Judgment of Motion Direction Can Be Influenced by Microstimulation of Cells Within the Middle Temporal Area 452

Three-Dimensional Vision Depends on Monocular Depth Cues and Binocular Disparity 454
Monocular Cues Create Far-Field Depth Perception 454
Stereoscopic Cues Create Near-Field Depth Perception 455
Information from the Two Eyes Is First Combined in the Primary Visual Cortex 457

Recognition of Faces and Other Complex Forms Occurs in the Inferior Temporal Cortex 458
Visual Attention Focuses Perception by Facilitating Coordination Between Separate Visual Pathways 459
The Analysis of Visual Attention May Provide Important Clues Toward Understanding ConsciousAwareness 462
### 31 Color Vision 467

Peter Gouras

Three Separate Cone Systems Respond Best to Different Parts of the Visible Spectrum 468

Color Discrimination Requires at Least Two Types of Photoreceptors with Different Spectral Sensitivities 468

Color Opponency, Simultaneous Color Contrast, and Color Constancy Are Key Features of Color Vision 470

In the Retina and Lateral Geniculate Nucleus Color Is Coded by Color Opponent Cells 471

In the Cortex Color Information Is Processed by Double-Opponent Cells in the Blob Zones 473

Double-Opponent Cells Help Explain Color Opponency, Color Contrast, and Color Constancy 476

Color Experience Is Based on Impressions of Hue, Saturation, and Brightness 476

Color Blindness Can Be Caused by Genetic Defects in Photoreceptors or by Retinal Disease 477

An Overall View 479

Selected Readings 479

References 479

### 32 Hearing 481

James P. Kelly

Sound Is Produced by Vibrations and Is Transmitted Through Air by Pressure Waves 481

Vibrations of the Conductive Apparatus Generate Fluid Waves in the Cochlea 482

Fluid Waves in the Cochlea Vibrate Hair Cells 483

Different Regions of the Cochlea Respond Selectively to Different Frequencies of Sound 486

Individual Hair Cells at Different Points Along the Cochlea Are Tuned to Different Frequencies of Vibration 487

Vibrations of Hair Cells Are Transformed into Electrical Signals in the Auditory Nerve 489

Central Auditory Neurons Are Specialized Physiologically to Preserve Time and Frequency Information 491

Bilateral Auditory Pathways Provide Cues to Localize Sound 493

The Auditory Cortex Is Composed of Separate Functional Areas 494

An Overall View 498

Selected Readings 498

References 498

### 33 The Sense of Balance 500

James P. Kelly

The Organs of Balance Are Located in the Inner Ear 501

The Vestibular Labyrinth Is Filled with Endolymph 501

Specialized Regions of the Vestibular Labyrinth Contain Hair Cells 501

Vestibular Hair Cells Respond to Changes in Movement or Position of the Head 503

The Hair Cells Are Polarized Structurally and Functionally 503

The Semicircular Ducts Respond to Angular Acceleration in Specific Directions 506

The Utricle Responds to Linear Acceleration in All Directions 506

The Central Connections of the Vestibular Labyrinth Reflect Its Dynamic and Static Functions 508

The Lateral Vestibular Nucleus Participates in the Control of Posture 508

The Medial and Superior Vestibular Nuclei Mediate Vestibulo-Ocular Reflexes 509

The Inferior Vestibular Nucleus Integrates Inputs from the Vestibular Labyrinth and the Cerebellum 510

An Overall View 510

Selected Readings 510

References 511

### 34 Smell and Taste: The Chemical Senses 512

Jane Dodd and Vincent F. Castellucci

Smell and Taste Result from the Activation of Specific Receptors 513

The Sensation of Smell Is Transduced by Neurons Within the Olfactory Epithelium 513
Presentation of Odorants to the Receptor Cell 514
May Involve an Olfactory Binding Protein 514
Olfactory Transduction Involves Second Messenger-Regulated Ion Channels 515
Individual Olfactory Neurons Respond to a Variety of Odorants 515
Olfactory Information Is First Encoded in the Paleocortex and Then Projects to the Neocortex via the Thalamus 516
Abnormalities of Olfaction Can Give Rise to Both Sensory Loss and Hallucination 518
The Sensation of Taste Is Transduced by Gustatory Receptor Cells 518
Taste Receptor Cells Are Innervated by Primary Afferent Neurons 519
Four or Five Basic Stimulus Qualities Can Be Distinguished 521
There Are Distinct Representations of Taste in the Thalamus and Cortex 524
Afferents from Taste Buds Project to the Gustatory Nucleus 524
Taste Sensations Are Encoded by Specific Pathways and by Patterns of Activity Across These Pathways 525
Both Inborn and Learned Taste Preferences Are Important for Behavior 527
An Overall View 527
Selected Readings 528
References 528

Part VI
Motor Systems of the Brain:
Reflex and Voluntary Control of Movement 530

35 The Control of Movement 533
Claude Ghez
Sensory Information Is Necessary for the Control of Movement 534
Sensory Information Is Used to Correct Errors Through Feedback and Feed-forward Mechanisms 535
Patients with Impaired Sensation in the Limbs Show Deficits in Both Feedback and Feed-forward Control of Movement 535
There Are Three Levels in the Hierarchy of Motor Control 537
The Spinal Cord, the Brain Stem, and Cortical Motor Areas Are Organized Hierarchically and in Parallel 537

36 Muscles: Effectors of the Motor Systems 548
Claude Ghez
Movement and Force Are Produced by the Contraction of Sarcomeres 548
Contraction Results from the Sliding of Filamentous Proteins within the Muscle Fiber 548
The Force of Contraction Depends on the Length of the Muscle 551
The Force of Contraction Also Depends on the Relative Rates of Movement of the Thick and Thin Filaments 552
Muscles Contract Slowly and the Force Generated by a Train of Impulses Summates 553
Repeated Activation of Muscles Causes Fatigue 555
A Single Motor Neuron and the Muscle Fibers It Innervates Constitute a Motor Unit 555
Three Types of Motor Units Are Distinguished by the Properties of Their Muscle Fibers 555
The Properties of Motor Neurons Are Closely Matched to Muscle Fibers 556
The Nervous System Grades the Force of Muscle Contraction in Two Ways 556
Motor Units Are Recruited in a Fixed Order from Weakest to Strongest 556
Increases in Firing Rate of Motor Units Produce Increasing Force Output 559
Muscle Properties Limit the Strategies Available to Control Movement 560
Several Strategies Can Produce a Given Joint Angle 560
Skeletal Muscles Are Low-Pass Filters of Neural Input 561
An Overall View 562
Selected Readings 563
References 563

37 Muscle Receptors and Spinal Reflexes: The Stretch Reflex 564
James Gordon and Claude Ghez
Muscles Contain Specialized Receptors That Sense Different Features of the State of the Muscle 565
Muscle Spindles Respond to Stretch of Specialized Muscle Fibers 566
Golgi Tendon Organs Are Sensitive to Changes in Tension 567
Functional Differences Between Spindles and Tendon Organs Derive from Their Different Anatomical Arrangements within Muscle 568
Muscle Spindles Are Sensitive to Muscle Stretch 569
The Primary and Secondary Endings of Spindle Afferents Respond Differently to Phasic Changes in Length 569
Two Types of Gamma Motor Neurons Alter the Responsiveness of Spindles 570
Spindle Afferents and Efferents Innervate Different Types of Intrafusal Fibers 570
The Central Nervous System Can Control Sensitivity of the Muscle Spindles Through the Gamma Motor Neurons 571
The Fusimotor System Maintains Spindle Sensitivity During Muscle Contraction 571
Fusimotor Output Can Be Adjusted Independently of Motor Output 573
Discharge of Muscle Spindle Afferents Produces Stretch Reflexes 574
The Stretch Reflex Has Phasic and Tonic Components 574
Group la Afferents Make Monosynaptic Connections to Motor Neurons 575
The Main Connections of Group II and Group Ib Afferents to Motor Neurons Are Polysynaptic 576
Stretch Reflexes Contribute to Muscle Tone 577
Stretch Reflexes Regulate Muscle Tone Through Negative Feedback 577
Stretch Reflexes Allow Muscles to Respond Smoothly to Stretch and Release 578
An Overall View 578
Selected Readings 579
References 580

38 Spinal Mechanisms of Motor Coordination 581
James Gordon
Interneurons Are the Building Blocks of Spinal Reflexes 582
Convergent and Divergent Connections Are the Basis of Reflex Pathways 582
Networks of Interneurons Coordinate the Timing of Reflex Components 582
Inhibitory Interneurons Coordinate Muscle Action Around a Joint 584
Group la Inhibitory Interneurons Coordinate Opposing Muscles 585
Renshaw Cells Are Part of a Negative Feedback Loop to Motor Neurons 585
Group Ib Inhibitory Interneurons Receive Convergent Input from Several Types of Receptors 586
Cutaneous Stimuli Elicit Complex Reflexes That Serve Protective and Postural Functions 586
Cutaneous Stimuli Modulate the Excitability of Specific Motor Neuron Pools 586
Flexion Reflex Pathways Coordinate Whole Limb Movements 587
Certain Reflexes Consist of Rhythmic Movements 589
Certain Reflexes Adapt to Different Body Postures 590
Spinal Circuits Generate Rhythmic Locomotor Patterns 591
xxvi Contents

Tonic Descending Signals from the Brain Stem Activate the Spinal Circuits Responsible for Locomotion 591
NMDA Receptors Are Involved in Generating the Locomotor Pattern 593
Goal-Directed Locomotion Requires Intact Supraspinal Systems 593
Afferent Information Modifies the Rhythmic Locomotor Pattern 593
An Overall View 594
Selected Readings 594
References 594

39 Posture 596
Claude Ghez

Postural Stability During Standing and Walking Is Maintained by Both Feedforward Control and Rapid Feedback Compensatory Corrections 597
Three Classes of Sensory Input Are Important for Triggering Postural Responses but Are Normally Used in Different Ways 597
The Topography of Rapid Postural Responses Is Dependent on Context 598
Postural Responses Are Triggered Centrally Before Voluntary Movements 599

Vestibular and Neck Reflexes Stabilize the Head and Eyes 600
Vestibulocollic and Vestibulospinal Reflexes Maintain the Head Vertical with Respect to Gravity 600
Neck and Vestibular Reflexes Are Synergistic in the Neck but Antagonistic in the Limbs: Cervicocollic and Cervicospinal Reflexes 601
Vestibular and Neck Afferents Converge on the Vestibular Nuclei and Propriospinal Neurons 602

Brain Stem and Spinal Mechanisms Play a Major Role in the Control of Posture 602
The Pontine Reticular Nuclei Facilitate Motor Neurons Whereas Medullary Reticular Nuclei Produce Both Facilitation and Inhibition 602
Section of the Brain Stem above the Vestibular Nuclei Produces Decerebrate Rigidity 604
Lesions of the Cerebellum Modify Vestibular and Reticular Influences on Posture 604
Spasticity Is a Common Manifestation of Supraspinal Lesions in Humans 606
An Overall View 606
Selected Readings 606
References 607

40 Voluntary Movement 609
Claude Ghez

The Motor Areas of the Cerebral Cortex Are Organized Somatotopically 610
The Primary Motor, Supplementary Motor, and Premotor Areas Contribute the Majority of Axons in the Corticospinal Tract 611
Inputs to Motor Areas from the Periphery, Cerebellum, and Basal Ganglia Are Mediated by Other Areas of Cortex and the Thalamus 611
Corticospinal Axons Influence Segmental Motor Neurons Through Direct and Indirect Connections 612

Neurons of the Primary Motor Cortex Encode the Direction of the Force Exerted 613
Individual Corticospinal Neurons Control Small Groups of Muscles 613
Neurons in the Primary Motor Cortex Encode the Amount of Force to be Exerted 613
Movement Direction Is Encoded by Populations of Neurons, Not By Single Cells 614
Neurons in the Motor Cortex Are Informed of the Consequences of Movements 616

Premotor Cortical Areas Prepare the Motor Systems for Movement 619
Motor Preparation Time Is Longer Than the Response Time to Stimuli 619
Lesions of the Premotor Cortex, Supplementary Motor, and Posterior Parietal Areas Impair the Ability to Execute Purposeful Movements 619
The Supplementary Motor Area Is Important in Programming Motor Sequences and in the Coordination of Bilateral Movements 619
The Premotor Cortex Controls the Proximal Movements that Project the Arm to Targets 620

The Posterior Parietal Lobe Plays a Critical Role in Providing the Visual Information for Targeted Movements 622
An Overall View 624
Selected Readings 624
References 624

41 The Cerebellum 626
Claude Ghez

The Regional Organization of the Cerebellum Reflects Its Different Functions 627
The Cerebellum Is Divided into Three Lobes 627
Two Longitudinal Furrows Divide the Cerebellum into Medial and Lateral Regions 628

The Cellular Organization of the Cerebellum Is Highly Regular 630
The Cerebellar Cortex Is Divided into Three Distinct Layers 630
The Purkinje Cells Provide the Output of the Cerebral Cortex and Receive Excitatory Input from Three Fiber Systems 631
Purkinje Cells Are Inhibited by Local Interneurons 632

The Cerebellum Has Three Functional Divisions 632

The Vestibulocerebellum Controls Balance and Eye Movements 634
The Vestibulocerebellum Receives Input Directly from the Vestibular Nuclei 634
Diseases of the Vestibulocerebellum Cause Disorders in the Control of Eye Movements and Disturbances of Equilibrium 634

The Spinocerebellum Adjusts Ongoing Movements 634
The Spinocerebellum Contains Complete Somatosensory Maps of the Body 634
Somatic Sensory Information Reaches the Spinocerebellum Mainly Through Direct and Indirect Mossy Fiber Pathways 635
Efferent Spinocerebellar Projections Control the Medial and Lateral Descending Systems in the Brain Stem and Cerebral Cortex 635
The Spinocerebellum Uses Sensory Feedback to Control Muscle Tone and the Execution of Movement 637

The Cerebrocerebellum Coordinates the Planning of Limb Movements 637
The Cerebrocerebellum Is the Center of a Complex Feedback Circuit That Modulates Cortical Motor Commands 637
Lesions of the Cerebrocerebellum Produce Delays in Movement Initiation and in Coordination of Limb Movement 637

The Cerebellum Participates in Motor Learning 642
Cerebellar Diseases Have Distinctive Symptoms and Signs 644
An Overall View 645
Selected Readings 645
References 645

43 The Ocular Motor System 660
Michael E. Goldberg, Howard M. Eggers, and Peter Gouras
Five Neuronal Control Systems Keep the Fovea on Target 661
The Vestibulo-ocular and Optokinetic Reflexes Compensate for Head Movement 661
The Smooth Pursuit System Keeps Moving Targets in the Fovea 663
The Saccadic System Points the Fovea Toward Objects of Interest 664
The Vergence Movement System Aligns the Eyes to Look at Targets with Different Depths 664

The Eye Is Moved by Three Complementary Pairs of Muscles 664
Eye Position and Velocity Are Signaled by Extraocular Motor Neurons 665
The Vestibulo-ocular Reflex Is Coordinated in the Brain Stem 667
The Semicircular Canals Send an Eye Velocity Signal to Brain Stem Oculomotor Centers 667
Disease of the Vestibular System Causes Nystagmus 668
A Brain Stem Network Coordinates the Horizontal Vestibulo-ocular Reflex 668
A Neural Integrator Maintains Eye Position After the Head Has Stopped Moving 669
Modulation of the Vestibulo-ocular Reflex Requires the Cerebellum 670
Subcortical and Cortical Structures Contribute to the Optokinetic Reflex 671
Saccades and Smooth Pursuit Are Organized in Pontine and Mesencephalic Reticular Centers 671
Horizontal Saccades Are Generated in the Pontine Reticular Formation 671
Vertical Saccades Are Generated in the Mesencephalic Reticular Formation 672
Modulation of the Saccadic System by Experience Requires the Cerebellum 672
Smooth Pursuit Requires the Cerebral Cortex, Cerebellum, and Pons 672
Vergence Is Organized in the Midbrain 673
Patients with Brain Stem Lesions Have Characteristic Deficits in Eye Movements 673
The Saccade Generator in the Brain Stem Is Controlled in the Cerebral Cortex 674
The Superior Colliculus Transmits Cortical Oculomotor Signals to the Brain Stem 674
The Frontal Eye Field Sends a Specific Movement Signal to the Superior Colliculus 675
An Overall View 675
Selected Readings 676
References 676

Part VII
The Brain Stem and Reticular Core: Integration of Sensory and Motor Systems 680

44 The Brain Stem: Cranial Nerve Nuclei and the Monoaminergic Systems 683
Lorna W. Role and James P. Kelly
Most Cranial Nerves Are Located in the Brain Stem 683
Cranial Nerves Contain Motor, Visceral, and Somatic Afferent Fibers 684
There Are Three Classes of Motor Neurons in the Brain Stem 686
There Are Four Classes of Sensory Neurons 687
The Cranial Nerve Nuclei Are Organized into Columns 687
The Motor Nuclei 687
The Sensory Nuclei 690
Several Principles Govern the Organization of the Brain Stem 691
Most Motor Nuclei in the Brain Stem Project to Their Targets Through a Single Cranial Nerve 691
The Sensory Nuclei in the Brain Stem Receive Input from Several Cranial Nerves 691
Somatic Sensory and Motor Tracts Traverse the Brain Stem 691
Cranial Nerve Fiber Types May Intermingle in the Periphery 691
Nuclei in the Reticular Formation Form Widespread Networks 692
There Are Three Major Monoaminergic Systems in the Brain Stem 693
The Noradrenergic System Originates in Two Nuclear Groups: The Locus Ceruleus and the Lateral Tegmental Nucleus 696
The Dopaminergic System Originates in the Midbrain and Projects to the Striatum, Limbic System, and Neocortex 697
The Serotonergic System Originates in the Raphe Nuclei 698
An Overall View 698
Selected Readings 699
References 699

45 Trigeminal System 701
Jane Dodd and James P. Kelly
The Trigeminal Nerve Has Three Major Branches That Innervate the Face, Oral Cavity, and Dura Mater 701
Trigeminal Nerve Fibers Ascend to the Principal Sensory Nucleus and Descend to the Spinal Nucleus 702
Tactile Sensation from the Face Is Mediated by the Principal Sensory Nucleus 702
Pain and Temperature Sensation Are Mediated by the Spinal Nucleus 702
Lesions of the Trigeminal Sensory System Have Elucidated the Functional Organization of the Spinal Nucleus 705
Neurons in the Hypothalamus Undergo Structural and Biochemical Changes in Response to Behavioral Demands 746

The Hypothalamus Helps Regulate the Autonomic Nervous System and Is Involved in Emotional Behavior 746

An Overall View 747

Selected Readings 748

References 748

48 Hypothalamus and Limbic System: Motivation 750
Irving Kupfermann

Motivation Is an Inferred Internal State Postulated to Explain Variability of Behavioral Responses 750

Homeostatic Processes Such as Temperature Regulation, Feeding, and Thirst Correspond to Motivational States 751

Temperature Regulation Involves Integration of Autonomic, Endocrine, and Skeletomotor Responses 752

Feeding Behavior Is Regulated by a Great Variety of Mechanisms 753
Body Weight Is Regulated Around a Set Point 753

Dual Controlling Elements Are Involved in the Control of Food Intake 754
Chemical Stimulation of the Hypothalamus Alters Feeding Behavior 756

Thirst Is Regulated by Tissue Osmolality and Vascular Volume 757

Motivational States Can Be Regulated by Factors Other Than Tissue Needs 758
Ecological Constraints 758
Anticipatory Mechanisms 758
Hedonic Factors 759

Intracranial Stimulation Can Simulate Motivational States and Reinforce Behavior 759

An Overall View 759

Selected Readings 759

References 760

49 The Autonomic Nervous System 761
Jane Dodd and Lorna W. Role

The Autonomic Nervous System Is a Visceral and Largely Involuntary Motor System 762

The Autonomic Nervous System Is Organized into Three Divisions 763

The Sympathetic (Thoracolumbar) Division 764
The Parasympathetic (Craniosacral) Division 766
The Enteric Division 766

The Hypothalamus and the Nucleus of the Solitary Tract Play a Major Role in Controlling the Output of the Autonomic Nervous System 766

The Autonomic Nervous System Has Been Studied at the Cellular Level 768

Synaptic Transmission in Autonomic Ganglia Is Predominantly Cholinergic 768
Autonomic Targets Are Regulated by Both Cholinergic and Noradrenergic Input 769
Autonomic Control of Target Function Is Coordinately Regulated 770

An Overall View 774

Selected Readings 774

References 775

50 The Collective Electrical Behavior of Cortical Neurons: The Electroencephalogram and the Mechanisms of Epilepsy 777
John H. Martin

The Collective Behavior of Neurons Can Be Studied Noninvasively in Humans with Macroelectrodes 778

The Cellular Mechanisms Underlying Electroencephalography 779

The EEG Is Generated in the Cortex by the Flow of Synaptic Currents Through the Extracellular Space 781
The EEG Reflects Primarily Synaptic Potentials in Pyramidal Cells 784

Epilepsy Interrupts Normal Brain Function 785
Partial and Generalized Seizures Have Different Clinical and EEG Features 785
Large Populations of Neurons Are Activated Synchronously During an Epileptic Seizure 786
A Depolarization Shift Underlies Focal Seizures 787
Excitatory Connections Between Cortical Neurons Synchronize Discharges in an Epileptic Focus 789
Synaptic Inhibition May Limit Seizure Spread 789
Generalized Epilepsy Can Be Produced Experimentally 789
An Overall View 790
Selected Readings 790
References 791

51 Sleep and Dreaming 792
Dennis D. Kelly

Sleep Is an Active and Rhythmic Neural Process 793
Normal Sleep Is Composed of a Recurring Succession of Identifiable Stages 793
Slow-Wave Sleep Stages Are Distinguished Principally by Electroencephalographic Criteria 793
An Active Sleep Stage Can Be Distinguished by Rapid Eye Movements (REM Sleep) 794
Sleep Architecture Refers to the Pattern of Sleep Stages Throughout the Night 795
There Are Several Clues to the Biological Importance of REM Sleep 795
Selective Deprivation of REM Sleep Results in a REM Rebound 795
The Need for REM Sleep Steadily Declines During Early Development 795
The Need for REM Sleep Differs Markedly Across Species 796
REM Sleep Can Occur Without Atonia Following Damage to the Pons 797
The Mental Content of Dreams Is Linked to the Physiology of Sleep 797
Several Neural Mechanisms May Be Responsible for the Sleep–Wake Cycle 798
Sleep Factors Interact with the Immune System 798
Early Concepts of the Reticular Activating System Cast Sleep as a Passive Process 799
Active Sleep-Inducing Neurons Reside in the Brain Stem 799
The Suprachiasmatic Nucleus Serves as the Biological Clock for the Sleep–Wake Cycle 800
Distinct Regions of the Brain Stem May Trigger REM Sleep 801

An Overall View 802
Selected Readings 803
References 803

52 Disorders of Sleep and Consciousness 805
Dennis D. Kelly
Insomnia Is a Symptom with Many Causes, Not a Unitary Disease 806
The Sleep of Insomniacs Differs Physiologically from That of Normal Sleepers 806
Anticipation of Insomnia May Cause Insomnia 807
Psychopathology Is Often Mirrored in Disturbed Sleep 807
Temporary Insomnia Is a Natural Consequence of Altered Circadian Rhythms 807
Sleep Problems Are Magnified in the Elderly 808
The Barbiturates: Earlier Sleep Medications Initially Helped, Then Harmed Sleep 808
The Benzodiazepines: Subjective Benefits to Insomniacs May Exceed Objective Improvements in Sleep Measures 809
Parasomnias Are Behavioral Dysfunctions Associated with Sleep, Sleep Stages, or Partial Arousals 810
Nocturnal Enuresis Is Not Caused by Dreaming 810
Sleepwalking Is Triggered by Arousal from Slow-Wave Sleep 810
REM Behavior Disorder: REM Sleep Without Atonia Causes Violent Episodes in Human Sleepers 811
Night Terrors, Nightmares, and Terrifying Dreams Occur in Different Stages of Sleep 811
Sleep Apnea: Persistent Nocturnal Arousals Can Result from Lapses in Breathing 812
Narcolepsy: Irresistible Sleep Attacks Are Accompanied by Several REM-Related Symptoms 813
Loss of Consciousness: Coma Is Not Deep Sleep 815
Transient Losses of Consciousness Can Result from Decreased Cerebral Blood Flow 815
Coma Has Many Causes 815
The Determination of Cerebral Death Constitutes a Medical, Legal, and Social Decision 817
Selected Readings 818
References 818
Part IX
Localization of Higher Functions and the Disorders of Language, Thought, and Affect 820

53 Localization of Higher Cognitive and Affective Functions: The Association Cortices 823
Irving Kupfermann
The Three Association Areas Are Involved in Different Higher Functions 825
The Association Areas of the Frontal Region Are Thought to Be Involved in Cognitive Behavior and Motor Planning 826
Lesions of the Principal Sulcus in Monkeys Interfere with Specific Motor Tasks 827
Lesions of the Inferior Prefrontal Convexity Interfere with Appropriate Motor Responses 829
The Association Areas of the Limbic Cortex Are Involved in Memory and in Aspects of Emotional Behavior 829
The Orbitofrontal Cortex and Cingulate Gyrus Are Concerned with Emotional Behavior 829
The Temporal Lobe Portion of the Limbic Association Cortex Is Thought to Be Concerned with Memory Functions 830
The Association Areas of the Parietal Lobes Are Involved in Higher Sensory Functions and Language 831
The Two Hemispheres Are Not Fully Symmetrical and Differ in Their Capabilities 832
Split-Brain Experiments Reveal Important Asymmetries and Show That Consciousness and Self-Awareness Are Not Unitary 833
Why Is Function Lateralized to One Hemisphere? 835
Cognitive Functions Can Be Simulated by Connectionist Networks Capable of Parallel Distributed Processing 836
An Overall View 837
Selected Readings 838
References 838

54 Disorders of Language: The Aphasiases 839
Richard Mayeux and Eric R. Kandel
Language Is Distinctive from Other Forms of Communication 840
Animal Models of Human Language Have Been Largely Unsatisfactory 840

What Is the Origin of Human Language? 841
Is the Capability for Language an Innate Skill or Learned? 842
Aphasiases Are Disorders of Language that Also Interfere with Other Cognitive Functions 843
The Wernicke-Geschwind Model for Language Is a Useful Clinical Model for Distinguishing Damage to the Two Major Language Regions of the Brain 843
Recent Cognitive and Imaging Studies of Normal Subjects and Aphasic Patients Have Clarified the Interconnections of the Two Language Regions 845

Seven Types of Aphasia Can Be Distinguished and Related to Different Anatomical Systems 846
Wernicke's Aphasia 846
Broca's Aphasia 847
Conduction Aphasia 847
Anomic Aphasia 848
Global Aphasia 848
Transcortical Aphasias 848
Subcortical Aphasia 848
Certain Affective Components of Language Are Affected by Damage to the Right Hemisphere 848
Some Disorders of Reading and Writing Can Be Localized 849
Alexias and Agraphias Are Acquired Disorders of Reading and Writing 849
Dyslexia and Hyperlexia Are Developmental Disorders of Reading 850
An Overall View 850
Selected Readings 850
References 851

55 Disorders of Thought: Schizophrenia 853
Eric R. Kandel
Defining a Psychiatric Syndrome Poses Unusual Difficulties 853
There Are Now Reliable Clinical Criteria for Classifying Mental Illnesses 854
Schizophrenia Has Been Studied Extensively to Improve Classification and Diagnosis of the Illness 854
Schizophrenia Is Characterized by Psychotic Episodes Preceded by Prodromal Signs and Followed by Residual Symptoms 855
Schizophrenia Has an Important Genetic Predisposition 856
Some People with Schizophrenia Have Prominent Anatomical Changes in the Brain 857
Antipsychotic Drugs Are Effective in the Treatment of Schizophrenia 858
Antipsychotic Drugs Block Dopamine Receptors 860
Excess Dopaminergic Transmission May Contribute to the Development of Schizophrenia 861
Schizophrenic Symptoms Have Been Associated with Distinct Anatomical Components Within the Dopaminergic System 863
Abnormalities in Dopaminergic Transmission Do Not Account for All Aspects of Schizophrenia 865
An Overall View 866
Selected Readings 867
References 867

Part X
Development, Critical Periods, and the Emergence of Behavior 884

57 Control of Cell Identity 887
Thomas M. Jessell and Samuel Schacher
Cell Lineage Can Control the Fate of Neural Cells 888
In Most Species the Fate of Neural Cells Is Not Determined by Cell Lineage 891
Neural and Epidermal Cell Fate Is Regulated by Local Cell Interactions 891
Induction of the Neural Plate from the Ectoderm Is Dependent on Interactions with the Adjacent Mesoderm 891
Regional Differentiation Within the Neural Plate Is Also Controlled by the Mesoderm 896
Studies of Invertebrate Embryos Have Identified Genes that Control the Fate of Ectodermal Cells 896
Diffusible Factors Control Glial Cell Differentiation in the Central Nervous System 898
Cell Position Controls the Identity of Photoreceptors in the Drosophila Eye 899
The Fate of Neural Crest Cells Is Controlled by the Local Environment 902
The Transmitter Choice of Peripheral Neurons Is Controlled by Signals from Neighboring Cells 904
An Overall View 905
Selected Readings 906
References 906

58 Cell Migration and Axon Guidance 908
Thomas M. Jessell
The Migration Pattern of Neurons Establishes the Basic Plan of the Central Nervous System 908
The Birthday of a Neuron Defines Its Eventual Position and Properties 909
Immature Neurons in the Brain Migrate on a Scaffold of Radial Glial Cells 909
The Growth Cone Guides the Axon to Its Target 911
The Pathways of Developing Axons Are Accurate 914
Studies in Invertebrates Reveal the Precision of Axon Pathfinding and the Existence of Specific Cellular Cues 915
Guidance Cues Can Be Inhibitory 916
Some Growth Cones Are Guided by Chemotropic Molecules 916
Adhesion Molecules Are Involved in Axon Extension 917
Several Major Classes of Glycoproteins Are Involved in Neural Cell Adhesion 918
Many Glycoproteins Involved in Axon Fasciculation Are Members of the Immunoglobulin Superfamily 921
Axons Often Pause As They Project to Their Targets 921
Molecular Gradients May Help Axons Find Their Correct Location Within a Target Field 921
Pruning of Axons Focuses Their Projection to Targets 922
The Initial Formation of Synaptic Connections Is Often Accurate 923
An Overall View 926
Selected Readings 926
References 926

59 Neuronal Survival and Synapse Formation 929
Thomas M. Jessell
The Survival of Neurons Is Regulated by Interactions with Their Targets 929
The Survival of Many Classes of Neurons Depends on Nerve Growth Factor 930
The Activity of Target Muscle Regulates the Survival of Motor Neurons 933
Synapse Formation Is a Gradual Process 935
The Presynaptic Nerve Terminal Triggers Biochemical and Morphological Changes in the Postsynaptic Membrane 936
The Distribution and Stability of Nicotinic Acetylcholine Receptors Change After Innervation of Skeletal Muscle 937
The Functional Properties of Nicotinic Acetylcholine Receptors in Muscle Change After Innervation 939
Other Components of the Nerve–Muscle Synapse Are Also Regulated by Innervation of Muscle 940
Innervation Changes the Contractile Properties of Muscle 941
Presynaptic Neurons Also Regulate the Development of Nicotinic Receptors in Neurons 941
The Postsynaptic Muscle Cell Regulates the Differentiation of the Motor Nerve Terminal 941
Some Synapses Are Eliminated During Development 942
An Overall View 943
Selected Readings 943
References 943

60 Early Experience and the Fine Tuning of Synaptic Connections 945
Eric R. Kandel and Thomas Jessell
Normal Development Depends on Sensory Experience and Social Interaction 946
There Is an Early Critical Period in the Development of Social and Perceptual Competence 946
Isolated Young Monkeys Do Not Develop Normal Social Behavior 946
Early Sensory Deprivation Alters Perceptual Development 947
Early Sensory Deprivation Alters the Development of Neural Circuits 947
The Development of Ocular Dominance Columns Is an Important Example for Understanding the Development of Behavior 949
Cooperation and Competition Are Important for Segregating Afferent Inputs into the Ocular Dominance Columns 950
Cooperation Requires Synchronous Activity 953
Different Regions of the Brain Have Different Critical Periods of Development 956
Studies of Development Are Important Clinically 957
An Overall View 957
Selected Readings 957
References 958

61 Sexual Differentiation of the Nervous System 959
Dennis D. Kelly
The Gene for the Testes Determining Factor Is Located on the Y Chromosome 960
The Developing Gonads Are Embryologically Bipotential, Becoming Testes If the TDF Gene Is Present and Ovaries If It Is Not 961
Sexual Differentiation Is Regulated by Gonadal Hormones from Both Mother and Male Fetus 962
Gonadal Hormones Exert Both Organizational and Regulatory Effects upon Nervous Tissue Depending upon the Stage of the Life Cycle 962
Perinatal Hormones Impose a Permanent Sex-Specific Blueprint upon the Developing Nervous System 963
Fetal Exposure to Male Hormones Causes Pseudohermaphroditism in Genetic Females 963
Steroid Hormones Influence Perinatal Development Only During Critical Periods 964
The Brain Can Be Masculinized Not Only by Male Hormones But Also by Many Other Compounds 964
Alpha-Fetoprotein Binds Estrogen in the Rat and Thus Protects Female Fetuses from Masculinization 965
Receptors in the Cell Nucleus Mediate the Effects of Gonadal Steroid Hormones 965
Sexually Differentiated Brains Have Different Physiological Properties and Behavioral Tendencies 967
Perinatal Hormones Also Determine the Degree to Which Sex-Linked Behaviors Are Expressed by Normal Males and Females 968
Sexual Differentiation Is Reflected in the Structure of Certain Neurons 968
The Cellular Mechanisms Involved in the Development of Sex Differences in the Brain Can Be Studied in Vitro 969
A Wide Range of Behaviors Is Influenced by Sex Differences in the Organization of the Brain 970
Sexual Dimorphism is Evident in Cognitive Development in Monkeys 970
Human Cerebral Asymmetry Is Sexually Dimorphic 971
An Overall View 971
Selected Readings 972
References 972

Aging of the Brain: Dementia of the Alzheimer’s Type 974
James Goldman and Lucien Côté
Several Hypotheses Have Been Proposed for the Molecular Mechanisms of Aging 974
Normal Aging Produces Characteristic Changes in the Brain and Behavior 976
Progressive Decline in Mental Function Is Not An Inevitable Consequence of Aging 976
Alzheimer’s Disease Is the Most Common Form of Dementia 976
There Is a Genetic Component to Certain Forms of Alzheimer’s Disease 977
Extracellular Plaques Containing Amyloid Deposition Are a Prominent Feature of Alzheimer’s Disease 977
Neurofibrillary Tangles Are an Intracellular Characteristic of Alzheimer’s Disease 979
There Are Neurotransmitter Deficits in Alzheimer’s Disease 981
Other Degenerative Diseases Also Produce Dementia 981
An Overall View 982
Selected Readings 982
References 982

Part XI
Genes, Environmental Experience, and the Mechanisms of Behavior 984

63 Genetic Determinants of Behavior 987
Irving Kupfermann
Are Aspects of Behavior Genetically Determined? 987
Ethologists Define Instincts as Inborn Motor Patterns 988
Can a Behavior Be Inherited? 988
Some Species-Specific Behaviors Are Elicited by Sign Stimuli 989
Each Species Has a Repertory of Fixed-Action Patterns Generated by Central Programs 989
The Role of Genes in the Expression of Behavior Can Be Studied Directly 991
Higher Mammals and Humans Seem to Have Certain Innate Behavioral Patterns 993
Certain Human Behavioral Traits Have a Hereditary Component 993
Many Human Behaviors Are Universal 993
Stereotyped Sequences of Movements Resemble Fixed-Action Patterns 993
Certain Complex Patterns Require Little or No Learning 994
The Brain Sets Limits on the Structure of Language 994
An Overall View 995
Learning and Memory 997
Irving Kupfermann

Certain Elementary Forms of Learning Are Nonassociative 998

Classical Conditioning Involves Associating a Conditioned and an Unconditioned Stimulus 999
Conditioning Involves the Learning of Predictive Relationships 1000
Operant Conditioning Involves Associating an Animal's Own Behavior with a Subsequent Reinforcing Environmental Event 1000
Food-Aversion Conditioning Illustrates How Biological Constraints Influence the Efficacy of Reinforcers 1001

Conditioning Is Used as a Therapeutic Technique 1001

Learning and Memory Can Be Classified as Reflexive or Declarative on the Basis of How Information Is Stored and Recalled 1002

The Neural Basis of Memory Can Be Summarized in Four Generalizations 1003
Memory Has Stages 1003
Long-Term Memory May Be Represented by Plastic Changes in the Brain 1004
The Plastic Changes Encoding Memory Are Often Localized in Different Places Throughout the Nervous System 1005
Reflexive and Declarative Memories May Involve Different Neuronal Circuits 1005

An Overall View 1007

Cellular Mechanisms of Learning and the Biological Basis of Individuality 1009
Eric R. Kandel

Simple Forms of Reflexive Learning Lead to Changes in the Effectiveness of Synaptic Transmission 1010
Habituation Involves Depression of Synaptic Transmission 1010
Sensitization Involves Enhancement of Synaptic Transmission 1012

Long-Term Memory Requires Synthesis of New Proteins and the Growth of New Synaptic Connections 1014

Classical Conditioning Involves an Associative Enhancement of Presynaptic Facilitation That Is Dependent on Activity 1016

Long-Term Potentiation in the Hippocampus Is an Example for Both Associative and Nonassociative Learning in the Mammalian Brain 1019
Long-Term Potentiation in the CA1 Region Is Associative 1019
Associative Long-Term Potentiation Is Thought to Be Important for Spatial Memory 1022
Long-Term Potentiation in the CA3 Region Is Nonassociative 1023
Is There a Molecular Grammar for Learning? 1023

The Somatotopic Map in the Brain Is Modifiable by Experience 1024
Changes in the Somatotopic Map Produced by Learning May Contribute to the Biological Expression of Individuality 1025
Changes in the Somatotopic Map May Reflect Common Cellular Mechanisms for Associative Plasticity 1026

Studies of Neuronal Changes with Learning Provide Insights into Psychiatric Disorders 1027

An Overall View 1028

Appendices

Current Flow in Neurons 1033
John Koester

Definition of Electrical Parameters 1033
Potential Difference (V or E) 1033
Current (I) 1034
Conductance (g) 1034
Capacitance (C) 1034

Rules for Circuit Analysis 1036
Conductance 1036
Current 1036
Capacitance 1037
Potential Difference 1037

Current Flow in Circuits with Capacitance 1038
Circuit with Capacitor 1038
B Cerebral Circulation: Stroke 1041
John C. M. Brust
The Blood Supply of the Brain Can Be Divided into Arterial Territories 1041
The Cerebral Vessels Have Unique Physiological Responses 1043
A Stroke Is the Result of Disease Involving Blood Vessels 1045
Clinical Vascular Syndromes May Follow Vessel Occlusion, Hypoperfusion, or Hemorrhage 1045
Infarction Can Occur in the Middle Cerebral Artery Territory 1045
Infarction Can Occur in the Anterior Cerebral Artery Territory 1046
Infarction Can Occur in the Posterior Cerebral Artery Territory 1046
The Anterior Choroidal and Penetrating Arteries Can Become Occluded 1046
The Carotid and Basilar Arteries Can Become Occluded 1047
Diffuse Hypoperfusion Can Cause Ischemia or Infarction 1047
The Rupture of Microaneurysms Causes Intraparenchymal Stroke 1047
The Rupture of Saccular Aneurysms Causes Subarachnoid Hemorrhage 1048
Stroke Alters the Vascular Physiology of the Brain 1048
Selected Readings 1049

C Cerebrospinal Fluid: Blood–Brain Barrier, Brain Edema, and Hydrocephalus 1050
Lewis P. Rowland, Matthew E. Fink, and Lee Rubin
Cerebrospinal Fluid Is Secreted by the Choroid Plexus 1050
Cerebrospinal Fluid Has Several Functions 1053
Specific Permeability Barriers Exist Between Blood and Cerebrospinal Fluid and Between Blood and Brain 1053
The Properties of the Brain Capillary Endothelial Cells Account for the Blood–Brain Barrier 1054
The Blood–Brain Barrier Develops Early 1055
Some Areas of the Brain Do Not Have a Blood–Brain Barrier 1055
Why Is a Blood–Brain Barrier Necessary? 1056
Disorders of the Blood–Brain Barrier 1056
Drug Delivery to the Brain 1057
The Composition of Cerebrospinal Fluid May Be Altered in Disease 1057
Increased Intracranial Pressure May Harm the Brain 1057
Brain Edema Is a State of Increased Brain Volume Due to Increased Water Content 1058
Vasogenic Edema Is a State of Increased Extracellular Fluid Volume 1058
Cytotoxic Edema Is the Swelling of Cellular Elements 1058
Interstitial Edema Is Attributed to Increased Sodium in Periventricular White Matter 1058
Hydrocephalus Is an Increase in the Volume of the Cerebral Ventricles 1059
Selected Readings 1060
References 1060

Index 1061