

CONTENTS

Chapter 1			
An Invitation to Neurobiology	1		
NATURE AND NURTURE IN BRAIN FUNCTION AND BEHAVIOR	1		
1.1 Human twin studies can reveal the contributions of nature and nurture	1	2.2 While some dendritic and axonal proteins are synthesized from mRNAs locally, most are actively transported from the soma	30
1.2 Examples of nature: Animals exhibit instinctive behaviors	3	2.3 The cytoskeleton forms the basis of neuronal polarity and directs intracellular trafficking	32
1.3 An example of nurture: Barn owls adjust their auditory map to match an altered visual map	4	2.4 Channels and transporters move solutes passively or actively across neuronal membranes	34
HOW IS THE NERVOUS SYSTEM ORGANIZED?	6	2.5 Neurons are electrically polarized at rest because of ion concentration differences across the plasma membrane and differential ion permeability	38
1.4 The nervous system consists of neurons and glia	7	2.6 Neuronal plasma membrane can be described in terms of electrical circuits	40
1.5 Individual neurons were first visualized by Golgi staining in the late nineteenth century	8	2.7 Electrical circuit models can be used to analyze ion flows across glial and neuronal plasma membrane	43
1.6 Twentieth-century technology confirmed the neuron doctrine	10	2.8 Passive electrical properties of neurons: electrical signals evolve over time and decay across distance	44
1.7 In vertebrate neurons, information generally flows from dendrites to cell bodies to axons	11	2.9 Active electrical properties of neurons: depolarization above a threshold produces action potentials	47
1.8 Neurons use membrane potential changes and neurotransmitter release to transmit information	13	HOW DO ELECTRICAL SIGNALS PROPAGATE FROM THE NEURONAL CELL BODY TO ITS AXON TERMINALS?	49
1.9 Neurons function in the context of specific neural circuits	15	2.10 Action potentials are initiated by depolarization-induced inward flow of Na ⁺	49
1.10 Specific brain regions perform specialized functions	18	2.11 Sequential, voltage-dependent changes in Na ⁺ and K ⁺ conductances account for action potentials	50
1.11 The brain uses maps to organize information	19	2.12 Action potentials are all-or-none, are regenerative, and propagate unidirectionally in the axon	52
1.12 The brain is a massively parallel computational device	21	2.13 Action potentials propagate more rapidly in axons with larger diameters and in myelinated axons	53
GENERAL METHODOLOGY	23	2.14 Patch clamp recording enables the study of current flow across individual ion channels	57
1.13 Observations and measurements are the foundations for discovery	23	2.15 Cloning of genes that encode ion channels allows their structure–function relationship to be studied	59
1.14 Perturbation experiments establish causes and mechanisms	24	2.16 Crystal structures reveal the atomic bases of ion channel properties	62
SUMMARY	25	SUMMARY	65
FURTHER READING	25	FURTHER READING	66
Chapter 2			
Signaling within Neurons	27		
CELL BIOLOGICAL AND ELECTRICAL PROPERTIES OF NEURONS	28		
2.1 Neurons follow the central dogma of molecular biology and rules of intracellular vesicle trafficking	28		

Chapter 3	
Signaling across Synapses	69
HOW IS NEUROTRANSMITTER RELEASE CONTROLLED AT THE PRESYNAPTIC TERMINAL?	69
3.1 Action potential arrival at the presynaptic terminal triggers neurotransmitter release	69
3.2 Neurotransmitters are released in discrete packets	70
3.3 Neurotransmitters are released when synaptic vesicles fuse with the presynaptic plasma membrane	72
3.4 Neurotransmitter release is controlled by Ca^{2+} entry into the presynaptic terminal	74
3.5 SNARE and SM proteins mediate synaptic vesicle fusion	75
3.6 Synaptotagmin serves as a Ca^{2+} sensor to trigger synaptic vesicle fusion	78
3.7 The presynaptic active zone is a highly organized structure	79
3.8 Neurotransmitters are efficiently cleared from the synaptic cleft by enzymatic cleavage or transport into presynaptic and glial cells	80
3.9 Synaptic vesicle recycling by endocytosis is essential for continual synaptic transmission	81
3.10 Synapses can be facilitating or depressing	83
3.11 The nervous system uses many neurotransmitters	85
HOW DO NEUROTRANSMITTERS ACT ON POSTSYNAPTIC NEURONS?	87
3.12 Acetylcholine opens a nonselective cation channel at the neuromuscular junction	88
3.13 The skeletal muscle acetylcholine receptor is a ligand-gated ion channel	90
3.14 Neurotransmitter receptors are ionotropic or metabotropic	91
3.15 AMPA and NMDA glutamate receptors are activated by glutamate under different conditions	93
3.16 The postsynaptic density is organized by scaffolding proteins	95
3.17 Ionotropic GABA and glycine receptors are Cl^- channels that mediate inhibition	96
3.18 All metabotropic neurotransmitter receptors trigger G protein cascades	99
3.19 A GPCR signaling paradigm: β -adrenergic receptors activate cAMP as a second messenger	100
3.20 α and $\beta\gamma$ G protein subunits trigger diverse signaling pathways that alter membrane conductance	102
3.21 Metabotropic receptors can act on the presynaptic terminal to modulate neurotransmitter release	104
3.22 GPCR signaling features multiple mechanisms of signal amplification and termination	106
3.23 Postsynaptic depolarization can induce new gene expression	106
3.24 Dendrites are sophisticated integrative devices	110
3.25 Synapses are strategically placed at specific locations in postsynaptic neurons	113
SUMMARY	116
FURTHER READING	118
Chapter 4	
Vision	121
HOW DO RODS AND CONES DETECT LIGHT SIGNALS?	121
4.1 Psychophysical studies revealed that human rods can detect single photons	122
4.2 Electrophysiological studies identified the single-photon response of rods: light hyperpolarizes vertebrate photoreceptors	123
4.3 Light activates rhodopsin, a prototypical G-protein-coupled receptor	124
4.4 Photon-induced signals are greatly amplified by a transduction cascade	125
4.5 Light-triggered decline of cyclic-GMP level directly leads to the closure of cation channels	126
4.6 Recovery enables the visual system to respond to light continually	127
4.7 Adaptation enables the visual system to detect contrast over a wide range of light levels	129
4.8 Cones are concentrated in the fovea for high-acuity vision	130
4.9 Cones are less sensitive but faster than rods	131
4.10 Photoreceptors with different spectral sensitivities are needed to sense color	132
4.11 Humans have three types of cones	133
4.12 Cloning of the cone opsin genes revealed the molecular basis of color detection	134
4.13 Defects in cone opsin genes cause human color blindness	135
HOW ARE SIGNALS FROM RODS AND CONES ANALYZED IN THE RETINA?	135
4.14 Retinal ganglion cells use center-surround receptive fields to analyze contrast	136

4.15	Bipolar cells are either depolarized or hyperpolarized by light based on the glutamate receptors they express	137	5.4	Gradients of ephrins and Eph receptors instruct retinotectal mapping	172
4.16	Lateral inhibition from horizontal cells constructs the center-surround receptive fields	138	5.5	A single gradient is insufficient to specify an axis	174
4.17	Diverse retinal cell types and their precise connections enable parallel information processing	140	5.6	To cross, or not to cross: that is the question	178
4.18	Direction-selectivity of RGCs arises from asymmetric inhibition by amacrine cells	142	HOW DO EXPERIENCE AND NEURONAL ACTIVITY CONTRIBUTE TO WIRING?		180
4.19	Color is sensed by comparing signals from cones with different spectral sensitivities	143	5.7	Monocular deprivation markedly impairs visual cortex development	180
4.20	The same retinal cells and circuits can be used for different purposes	145	5.8	Competing inputs are sufficient to produce spatial segregation at the target	182
HOW IS INFORMATION PROCESSED IN THE VISUAL CORTEX?		146	5.9	Ocular dominance columns in V1 and eye-specific layers in LGN develop by gradual segregation of eye-specific inputs	183
4.21	Retinal information is topographically represented in the lateral geniculate nucleus and visual cortex	146	5.10	Retinal neurons exhibit spontaneous waves of activity before the onset of vision	184
4.22	Receptive fields of LGN neurons are similar to those of RGCs	148	5.11	Retinal waves and correlated activity drive segregation of eye-specific inputs	185
4.23	Primary visual cortical neurons respond to lines and edges	149	5.12	Hebb's rule: correlated activity strengthens synapses	187
4.24	How do visual cortical neurons acquire their receptive fields?	150	5.13	A Hebbian molecule: the NMDA receptor acts as a coincidence detector	189
4.25	Cells with similar properties are vertically organized in the visual cortex	151	HOW DO MOLECULAR DETERMINANTS AND NEURONAL ACTIVITY WORK TOGETHER?		190
4.26	Information generally flows from layer 4 to layers 2/3 and then to layers 5/6 in the neocortex	154	5.14	Ephrins and retinal waves act in parallel to establish the precise retinocollicular map	192
4.27	Visual information is processed in parallel streams	157	5.15	Ephrins and retinal waves also work together to establish the retinotopic map in the visual cortex	193
4.28	Face recognition cells form a specialized network in the primate temporal cortex	159	5.16	Different aspects of visual system wiring rely differentially on molecular cues and neuronal activity	195
4.29	Linking perception to decision and action: microstimulation of MT neurons biased motion choice	160	VISUAL SYSTEM DEVELOPMENT IN DROSOPHILA: LINKING CELL FATE TO WIRING SPECIFICITY		197
SUMMARY		163	5.17	Cell-cell interactions determine photoreceptor cell fates: R7 as an example	198
FURTHER READING		164	5.18	Multiple parallel pathways participate in layer-specific targeting of R8 and R7 axons	201
Chapter 5			SUMMARY		203
Wiring of the Visual System		167	FURTHER READING		204
HOW DO RETINAL GANGLION CELL AXONS FIND THEIR TARGETS?		167	Chapter 6		
5.1	Optic nerve regeneration experiments suggested that RGC axons are predetermined for wiring	168	Olfaction, Taste, Audition, and Somatosensation		207
5.2	Point-to-point connections between retina and tectum arise by chemoaffinity	169	HOW DO WE SENSE ODORS?		207
5.3	The posterior tectum repels temporal retinal axons	171	6.1	Odorant binding leads to opening of a cyclic nucleotide-gated channel in olfactory receptor neurons	208

CONTENTS

6.2	Ca ²⁺ coordinates olfactory recovery and adaptation	210	AUDITION: HOW DO WE HEAR AND LOCALIZE SOUNDS?	238	
6.3	Odorants are represented by combinatorial activation of olfactory receptor neurons	210	6.22	Sounds are converted to electrical signals by mechanically gated ion channels in the stereocilia of hair cells	239
6.4	Odorant receptors are encoded by many hundreds of genes in mammals	210	6.23	Sound frequencies are represented as a tonotopic map in the cochlea	240
6.5	Polymorphisms in odorant receptor genes contribute to individual differences in odor perception	213	6.24	Motor properties of outer hair cells amplify auditory signals and sharpen frequency tuning	243
6.6	Each olfactory receptor neuron (ORN) expresses a single odorant receptor	214	6.25	Auditory signals are processed by multiple brainstem nuclei before reaching the cortex	245
6.7	ORNs expressing a given odorant receptor are broadly distributed in the nose	214	6.26	In the owl, sound location is determined by comparing the timing and levels of sounds reaching two ears	246
6.8	ORNs expressing the same odorant receptor project their axons to the same glomerulus	215	6.27	Mechanisms of sound location in mammals differ from those in the owl	249
6.9	Olfactory bulb circuits transform odor representation through lateral inhibition	217	6.28	The auditory cortex analyzes complex and biologically important sounds	250
6.10	Olfactory inputs are differentially organized in distinct cortical areas	218	SOMATOSENSATION: HOW DO WE SENSE BODY MOVEMENT, TOUCH, TEMPERATURE, AND PAIN?	255	
HOW DO WORMS AND FLIES SENSE ODORS?		222	6.29	Many types of sensory neurons are used to encode diverse somatosensory stimuli	257
6.11	<i>C. elegans</i> encodes olfactory behavioral choices at the sensory neuron level	223	6.30	Merkel cells and some touch sensory neurons employ Piezo2 as a mechanotransduction channel	259
6.12	<i>C. elegans</i> sensory neurons are activated by odorant withdrawal and engage ON- and OFF-pathways	224	6.31	TRP channels are major contributors to temperature, chemical, and pain sensation	262
6.13	The olfactory systems in insects and mammals share many similarities	225	6.32	Sensation can be a product of central integration: the distinction of itch and pain as an example	264
6.14	The antennal lobe transforms ORN input for more efficient representation by projection neurons	226	6.33	Touch and pain signals are transmitted by parallel pathways to the brain	266
6.15	Odors with innate behavioral significance use dedicated olfactory processing channels	230	6.34	Pain is subjected to peripheral and central modulation	268
6.16	Odor representation in higher centers is stereotyped or stochastic depending on whether the center directs innate or learned behavior	231	6.35	Linking neuronal activity with touch perception: from sensory fiber to cortex	269
TASTE: TO EAT, OR NOT TO EAT?		232	SUMMARY	272	
6.17	Mammals have five classic taste modalities: sweet, bitter, umami, salty, and sour	233	FURTHER READING	273	
6.18	Sweet and umami are sensed by heterodimers of the T1R family of G-protein-coupled receptors	233	Chapter 7	Wiring of the Nervous System	277
6.19	Bitter is sensed by a family of ~30 T2R G-protein-coupled receptors	234	HOW DOES WIRING SPECIFICITY ARISE IN THE DEVELOPING NERVOUS SYSTEM?	278	
6.20	Sour and salty tastes involve specific ion channels	236	7.1	The nervous system is highly patterned as a consequence of early developmental events	278
6.21	Activation of specific taste receptor cells confers specific taste perceptions	236	7.2	Orderly neurogenesis and migration produce many neuronal types that occupy specific positions	280

7.3	Cell fates are diversified by asymmetric cell division and cell–cell interactions	281	HOW DO ~20,000 GENES SPECIFY 10¹⁴ CONNECTIONS?	316	
7.4	Transcriptional regulation of guidance molecules links cell fate to wiring decision	283	7.24	Some genes can produce many protein variants	316
7.5	Crossing the midline: Combinatorial actions of guidance receptors specify axon trajectory choice	286	7.25	Protein gradients can specify different connections	318
7.6	Crossing the midline: Axons switch responses to guidance cues at intermediate targets	288	7.26	The same molecules can serve multiple functions	318
7.7	The cell polarity pathway participates in determining whether a neuronal process becomes an axon or a dendrite	290	7.27	The same molecules can be used at multiple times and places	318
7.8	Local secretory machinery is essential for dendrite morphogenesis and microtubule organization	292	7.28	Combinatorial use of wiring molecules can reduce the number of wiring molecules needed	319
7.9	Homophilic repulsion enables self-avoidance of axonal and dendritic branches	293	7.29	Dividing wiring decisions into multiple steps can conserve molecules and increase fidelity	319
7.10	Subcellular site selection of synaptogenesis uses both attractive and repulsive mechanisms	295	7.30	Many connections do not need to be specified at the level of individual synapses or neurons	320
7.11	Bidirectional trans-synaptic communication directs the assembly of synapses	297	7.31	Wiring can be instructed by neuronal activity and experience	320
7.12	Astrocytes stimulate synapse formation and maturation	299	SUMMARY	321	
7.13	Activity and competition refine neuromuscular connectivity	300	FURTHER READING	322	
7.14	Developmental axon pruning refines wiring specificity	301	Chapter 8		
7.15	Neurotrophins from target cells support the survival of sensory, motor, and sympathetic neurons	302	Motor and Regulatory Systems	325	
ASSEMBLY OF OLFACTORY CIRCUITS: HOW DO NEURAL MAPS FORM?		305	HOW IS MOVEMENT CONTROLLED?	326	
7.16	Neural maps can be continuous, discrete, or a combination of the two	305	8.1	Muscle contraction is mediated by sliding of actin and myosin filaments and is regulated by intracellular Ca ²⁺	326
7.17	In mice, odorant receptors instruct ORN axon targeting by regulating expression of guidance molecules	307	8.2	Motor units within a motor pool are recruited sequentially from small to large	329
7.18	ORN axons sort themselves by repulsive interactions before reaching their target	309	8.3	Motor neurons receive diverse and complex input	330
7.19	Activity-dependent regulation of adhesion and repulsion refines glomerular targeting	310	8.4	Central pattern generators coordinate rhythmic contraction of muscles during locomotion	332
7.20	<i>Drosophila</i> projection neurons' lineage and birth order specify the glomeruli that their dendrites target	312	8.5	Intrinsic properties of neurons and their connection patterns produce rhythmic output in a model central pattern generator	334
7.21	Graded determinants and discrete molecular labels control the targeting of projection neuron dendrites	313	8.6	The spinal cord uses multiple central pattern generators to control locomotion	336
7.22	Sequential interactions among ORN axons limit their target choice	314	8.7	The brainstem contains specific motor control nuclei	338
7.23	Homophilic matching molecules instruct connection specificity between synaptic partners	315	8.8	The cerebellum is required for fine control of movement	340
			8.9	The basal ganglia participate in initiation and selection of motor programs	343
			8.10	Voluntary movement is controlled by the population activity of motor cortical neurons in a dynamical system	346

8.11	Population activity of motor cortical neurons can be used to control neural prosthetic devices	349	9.2	<i>Fruitless</i> (<i>Fru</i>) is essential for many aspects of sexual behavior	379	
HOW DOES THE BRAIN REGULATE THE FUNCTIONS OF INTERNAL ORGANS?			351	9.3	A sex-determination hierarchy specifies sex-specific splicing of <i>Fru</i> that produces male-specific <i>Fru^M</i>	379
8.12	The sympathetic and parasympathetic systems play complementary roles in regulating body physiology	351	9.4	Expression of <i>Fru^M</i> in females is sufficient to produce most aspects of male courtship behavior	380	
8.13	The autonomic nervous system is a multilayered regulatory system	353	9.5	Activity of <i>Fru^M</i> neurons promotes male courtship behavior	381	
8.14	The hypothalamus regulates diverse basic body functions via homeostasis and hormone secretion	354	9.6	<i>Fru^M</i> sensory neurons process mating-related sensory cues	382	
HOW IS EATING REGULATED?			356	9.7	<i>Fru^M</i> central neurons integrate sensory information and coordinate the behavioral sequence	384
8.15	Hypothalamic lesion and parabiosis experiments suggested that eating is inhibited by a negative feedback signal from the body	356	9.8	<i>Fru^M</i> neurons in the ventral nerve cord regulate mating-related behavioral output	385	
8.16	Studies of mouse mutants led to the discovery of the leptin feedback signal from adipose tissues	357	9.9	<i>Fru^M</i> -equivalent neurons in females promote female receptivity to courtship	386	
8.17	POMC and AgRP neurons in the arcuate nucleus are central regulators of eating	358	9.10	<i>Fru^M</i> and <i>Doublesex</i> (<i>Dsx</i>) regulate sexually dimorphic programmed cell death	386	
8.18	Multiple feedback signals and neural pathways act in concert to regulate eating	360	9.11	<i>Dsx</i> and <i>Fru^M</i> control sexually dimorphic neuronal wiring	389	
HOW ARE CIRCADIAN RHYTHMS AND SLEEP REGULATED?			362	9.12	Even innate behavior can be modified by experience	390
8.19	Circadian rhythms are driven by an auto-inhibitory transcriptional feedback loop that is conserved from flies to mammals	362	HOW ARE MAMMALIAN SEXUAL BEHAVIORS REGULATED?			390
8.20	Entrainment in flies is accomplished by light-induced degradation of circadian rhythm regulators	365	9.13	The <i>Sry</i> gene on the Y chromosome determines male differentiation via testosterone production	393	
8.21	Pacemaker neurons in the mammalian suprachiasmatic nucleus integrate input and coordinate output	366	9.14	Testosterone and estradiol are the major sex hormones	393	
8.22	Sleep is widespread in the animal kingdom and exhibits characteristic electroencephalogram patterns in mammals	367	9.15	Early exposure to testosterone causes females to exhibit male-typical sexual behavior	395	
8.23	The mammalian sleep-wake cycle is regulated by multiple neurotransmitter and neuropeptide systems	369	9.16	Testosterone exerts its organizational effect mainly through the estrogen receptors in rodents	396	
8.24	Why do we sleep?	372	9.17	Dialogues between the brain and gonads initiate sexual maturation at puberty and maintain sexual activity in adults	396	
SUMMARY			374	9.18	Sex hormones specify sexually dimorphic neuronal numbers by regulating programmed cell death	398
FURTHER READING			375	9.19	Sex hormones also regulate sexually dimorphic neuronal connections	399
Chapter 9				9.20	Sexually dimorphic nuclei define neural pathways from olfactory systems to the hypothalamus	400
Sexual Behavior			377	9.21	Whereas the main olfactory system is essential for mating, the accessory olfactory system discriminates sex partners in mice	401
HOW DO GENES SPECIFY SEXUAL BEHAVIOR IN THE FLY?			378	9.22	The same neuronal population can control multiple behaviors in females and males	402
9.1	<i>Drosophila</i> courtship follows a stereotyped ritual that is instinctive	378				

9.23	Parental behavior is activated by mating and regulated by specific populations of hypothalamic neurons	405	WHAT IS THE RELATIONSHIP BETWEEN LEARNING AND SYNAPTIC PLASTICITY?	434	
9.24	Two neuropeptides, oxytocin and vasopressin, regulate pair bonding and parental behavior	407	10.14	Animals exhibit many forms of learning	434
SUMMARY		410	10.15	Habituation and sensitization in <i>Aplysia</i> are mediated by changes of synaptic strength	437
FURTHER READING		412	10.16	Both short-term and long-term memory in <i>Aplysia</i> engage cAMP signaling	439
Chapter 10			10.17	Olfactory conditioning in <i>Drosophila</i> requires cAMP signaling	441
Memory, Learning, and Synaptic Plasticity	415		10.18	<i>Drosophila</i> mushroom body neurons are the site of CS-US convergence for olfactory conditioning	442
PRELUDE: WHAT IS MEMORY, AND HOW IS IT ACQUIRED BY LEARNING?	415		10.19	In rodents, spatial learning and memory depend on the hippocampus	446
10.1	Memory can be explicit or implicit, short-term, or long-term: Insights from amnesic patients	415	10.20	Many manipulations that alter hippocampal LTP also alter spatial memory	447
10.2	Hypothesis I: Memory is stored as strengths of synaptic connections in neural circuits	417	10.21	From correlation to causation: the synaptic weight matrix hypothesis revisited	449
10.3	Hypothesis II: Learning modifies the strengths of synaptic connections	420	WHERE DOES LEARNING OCCUR, AND WHERE IS MEMORY STORED IN THE BRAIN?	451	
HOW IS SYNAPTIC PLASTICITY ACHIEVED?	420		10.22	The neocortex contributes to long-term storage of explicit memory	451
10.4	Long-term potentiation (LTP) of synaptic efficacy can be induced by high-frequency stimulation	421	10.23	The amygdala plays a central role in fear conditioning	454
10.5	LTP at the hippocampal CA3 → CA1 synapse exhibits input specificity, cooperativity, and associativity	421	10.24	Dopamine plays a key role in reward-based learning	456
10.6	The NMDA receptor is a coincidence detector for LTP induction	423	10.25	Early experience can leave behind long-lasting memory traces to facilitate adult learning	459
10.7	Recruitment of AMPA receptors to the postsynaptic surface is the predominant mechanism of LTP expression	423	SUMMARY	463	
10.8	CaMKII auto-phosphorylation creates a molecular memory that links LTP induction and expression	425	FURTHER READING	464	
10.9	Long-term depression weakens synaptic efficacy	426	Chapter 11	467	
10.10	Spike-timing-dependent plasticity can adjust synaptic efficacy bidirectionally	428	Brain Disorders		
10.11	Dendritic integration in the postsynaptic neuron also contributes to synaptic plasticity	428	ALZHEIMER'S DISEASE AND OTHER NEURODEGENERATIVE DISEASES	467	
10.12	Postsynaptic cells can produce retrograde messengers to regulate neurotransmitter release by their presynaptic partners	429	11.1	Alzheimer's disease is defined by brain deposition of numerous amyloid plaques and neurofibrillary tangles	468
10.13	Long-lasting changes of connection strengths involve formation of new synapses	431	11.2	Amyloid plaques mainly consist of aggregates of proteolytic fragments of the amyloid precursor protein (APP)	469
			11.3	Mutations in human APP and γ -secretase cause early-onset familial Alzheimer's disease	470
			11.4	Animal models offer crucial tools to investigate pathogenic mechanisms	472
			11.5	An apolipoprotein E (ApoE) variant is a major risk factor for Alzheimer's disease	473

CONTENTS

11.6	Microglia dysfunction contributes to late-onset Alzheimer's disease	474	11.26	Synaptic dysfunction is a common cellular mechanism that underlies neurodevelopmental and psychiatric disorders	506
11.7	How can we treat Alzheimer's disease?	475	11.27	Studies of brain disorders and basic neurobiology research advance each other	507
11.8	Prion diseases are caused by propagation of protein-induced protein conformational change	477	SUMMARY		510
11.9	Aggregation of misfolded proteins is associated with many neurodegenerative diseases	479	FURTHER READING		511
11.10	Parkinson's disease results from death of substantia nigra dopamine neurons	480	Chapter 12		
11.11	α -Synuclein aggregation and spread are prominent features of Parkinson's pathology	480	Evolution of the Nervous System		513
11.12	Mitochondrial dysfunction is central to the pathogenesis of Parkinson's disease	482	GENERAL CONCEPTS AND APPROACHES IN EVOLUTIONARY ANALYSIS		
11.13	Treating Parkinson's disease: L-dopa, deep brain stimulation, and cell-replacement therapy	483	12.1	Phylogenetic trees relate all living organisms in a historical context	514
11.14	The various neurodegenerative diseases have common themes and exhibit unique properties	487	12.2	Cladistic analysis distinguishes processes of evolutionary change	515
PSYCHIATRIC DISORDERS		487	12.3	Gene duplication, diversification, loss, and shuffling provide rich substrates for natural selection	517
11.15	Schizophrenia can be partially alleviated by drugs that interfere with dopamine function	488	12.4	Altering patterns of gene expression is an important mechanism for evolutionary change	519
11.16	Mood disorders have been treated by manipulating monoamine neurotransmitter metabolism	490	12.5	Natural selection can act on multiple levels in the developing and adult nervous systems to enhance fitness	520
11.17	Modulating GABAergic inhibition can alleviate symptoms of anxiety disorders	491	EVOLUTION OF NEURONAL COMMUNICATION		521
11.18	Addictive drugs hijack the brain's reward system by enhancing the action of VTA dopamine neurons	493	12.6	Ion channels appeared sequentially to mediate electrical signaling	522
11.19	Human genetic studies suggest that many genes contribute to psychiatric disorders	495	12.7	Myelination evolved independently in vertebrates and large invertebrates	523
NEURODEVELOPMENTAL DISORDERS		498	12.8	Synapses likely originated from cell junctions in early metazoans	524
11.20	Intellectual disabilities and autism spectrum disorders are caused by mutations in many genes	499	12.9	Neurotransmitter release mechanisms were co-opted from the secretory process	525
11.21	Rett syndrome is caused by defects in MeCP2, a regulator of global gene expression	500	EVOLUTION OF SENSORY SYSTEMS		526
11.22	MeCP2 acts predominantly in post-mitotic neurons to regulate their maturation and function	502	12.10	G-protein-coupled receptors (GPCRs) are ancient chemosensory receptors in eukaryotes	527
11.23	Restoring MeCP2 expression in adulthood reverses symptoms in a mouse model of Rett syndrome	503	12.11	Chemosensory receptors in animals are predominantly GPCRs	530
11.24	Fragile-X syndrome is caused by loss of an RNA-binding protein that regulates translation	504	12.12	Two distinct families of ligand-gated ion channels cooperate to sense odors in insects	532
11.25	Reducing mGluR signaling ameliorates fragile-X symptoms in animal models	505	12.13	Retinal- and opsin-based light-sensing apparatus evolved independently at least twice	532

12.14	Photoreceptor neurons evolved in two parallel paths	535	13.7	Reverse genetics disrupts pre-designated genes to assess their functions	563
12.15	Diversification of cell types is a crucial step in the evolution of the retinal circuit	538	13.8	RNA interference (RNAi)-mediated knockdown can also be used to assess gene function	567
12.16	Trichromatic color vision in primates originated from variations and duplications of a cone opsin gene	540	13.9	Genetic mosaic analysis can pinpoint which cell is critical for mediating gene action	568
12.17	Introducing an extra cone opsin in dichromatic animals enables superior spectral discrimination	542	13.10	Transgene expression can be controlled in both space and time in transgenic animals	569
EVOLUTION OF NERVOUS SYSTEM STRUCTURE AND DEVELOPMENT		543	13.11	Transgene expression can also be achieved by viral transduction and other transient methods	571
12.18	All bilaterians share a common body plan specified by conserved developmental regulators	544	13.12	Accessing specific neuronal types facilitates functional circuit dissection	572
12.19	Eye development is controlled by evolutionarily conserved transcription factors	546	13.13	Gene expression patterns can be determined by multiple powerful techniques	572
12.20	The mammalian neocortex underwent rapid expansion recently	547	13.14	Genome sequencing reveals connections across species and identifies genetic variations that contribute to diseases	574
12.21	The size of the neocortex can be altered by modifying the mechanisms of neurogenesis	548	ANATOMICAL TECHNIQUES		575
12.22	Cortical area specialization can be shaped by input patterns	550	13.15	Histological analyses reveal the gross organization of the nervous system	575
SUMMARY		553	13.16	Visualizing individual neurons opens new vistas in understanding the nervous system	578
FURTHER READING		555	13.17	Fine structure studies can identify key facets of molecular organization within neurons	579
Chapter 13			13.18	Mapping neuronal projections allows the tracking of information flow across different brain regions	582
Ways of Exploring		557	13.19	Mapping synaptic connections reveals neural circuitry	584
ANIMAL MODELS IN NEUROBIOLOGY RESEARCH		557	RECORDING AND MANIPULATING NEURONAL ACTIVITY		586
13.1	Some invertebrates provide large, identifiable neurons for electrophysiological investigations	557	13.20	Extracellular recordings can detect the firing of individual neurons	587
13.2	<i>Drosophila</i> and <i>C. elegans</i> allow sophisticated genetic manipulations	558	13.21	Intracellular and whole-cell patch recordings can measure synaptic input in addition to firing patterns	589
13.3	Diverse vertebrate animals offer technical ease or special faculties	559	13.22	Optical imaging can measure the activity of many neurons simultaneously	591
13.4	Mice, rats, and nonhuman primates are important models for mammalian neurobiology research	560	13.23	Neuronal inactivation can be used to reveal which neurons are essential for circuit function and behavior	596
13.5	Human studies are facilitated by a long history of medicine and experimental psychology and by the recent genomic revolution	560	13.24	Neuronal activation can establish sufficiency of neuronal activity in circuit function and behavior	598
GENETIC AND MOLECULAR TECHNIQUES		561	13.25	Optogenetics allows control of the activity of genetically targeted neurons with millisecond precision	599
13.6	Forward genetic screens use random mutagenesis to identify genes that control complex biological processes	562			

CONTENTS

13.26	Synaptic connections can be mapped by physiological and optogenetic methods	601
	BEHAVIORAL ANALYSES	602
13.27	Studying animal behavior in natural environments can reveal behavioral repertoires and their adaptive value	603
13.28	Studying behaviors in highly controlled conditions facilitates investigation of their neural basis	604
13.29	Behavioral assays can be used to evaluate the functions of genes and neurons and to model human brain disorders	606
	SUMMARY AND PERSPECTIVES	608
	FURTHER READING	610
	GLOSSARY	612
	INDEX	

SPECIAL FEATURES

Box 1–1	The debate between Ramón y Cajal and Golgi: why do scientists make mistakes?	9
Box 1–2	Commonly used neural circuit motifs	17
Box 2–1	How were kinesins discovered?	35
Box 2–2	A deeper look at <i>R-C</i> circuits	42
Box 2–3	Axon–glia interactions in health and disease	55
Box 2–4	Diverse ion channels for diverse functions	63
Box 3–1	Binomial distribution, Poisson distribution, and calculating neurotransmitter release probability	72
Box 3–2	From toxins to medicines	77
Box 3–3	G proteins are molecular switches	101
Box 3–4	Signal transduction and receptor tyrosine kinase signaling	107
Box 3–5	Electrical synapses	115
Box 4–1	Vision research uses diverse animal models	124
Box 4–2	Intrinsically photosensitive retinal ganglion cells have multiple functions	147
Box 4–3	Cracking neocortical microcircuits	155
Box 5–1	Molecular biology of axon guidance	174
Box 5–2	Cell biology and signaling at the growth cone	179
Box 5–3	Activity-dependent wiring of the rodent whisker-barrel system depends on the NMDA receptor	190
Box 6–1	The mammalian accessory olfactory system is specialized for detecting pheromones and predator cues	221
Box 6–2	The vestibular system senses movement and orientation of the head	253
Box 6–3	Mechanotransduction channels in worms and flies	260
Box 8–1	Neuromodulatory systems	370
Box 9–1	Bird song: nature, nurture, and sexual dimorphism	391
Box 9–2	Courtship in unisexual lizards	403
Box 9–3	An ancestral function of oxytocin/vasopressin-like neuropeptide in sexual behavior	409
Box 10–1	Synaptic tagging: maintaining input specificity in light of new gene expression	432
Box 10–2	Place cells, grid cells, and representations of space	444
Box 10–3	How to find an engram	450
Box 10–4	Microcircuits of the central amygdala	456
Box 10–5	Memory can be formed by the activation of random populations of cortical neurons	459
Box 11–1	Rational drug development to treat brain disorders	476
Box 11–2	Producing neurons from embryonic stem cells, induced pluripotent cells, and fibroblasts	485
Box 11–3	How to collect and interpret human genetics data for brain disorders	497
Box 11–4	Epilepsy is a disorder of neuronal network excitability	508
Box 12–1	When did the nervous system first emerge?	517
Box 12–2	Chemotaxis: from bacteria to animals	528
Box 12–3	Darwin and the evolution of the eye	537
Box 12–4	Transcription factor FoxP2 and the evolution of language	552
Box 13–1	Genome engineering by the CRISPR–Cas9 system	565
Box 13–2	Patch clamp recordings can serve many purposes	590
Box 13–3	From in vitro preparations to awake, behaving animals: a comparison of recording methods	594