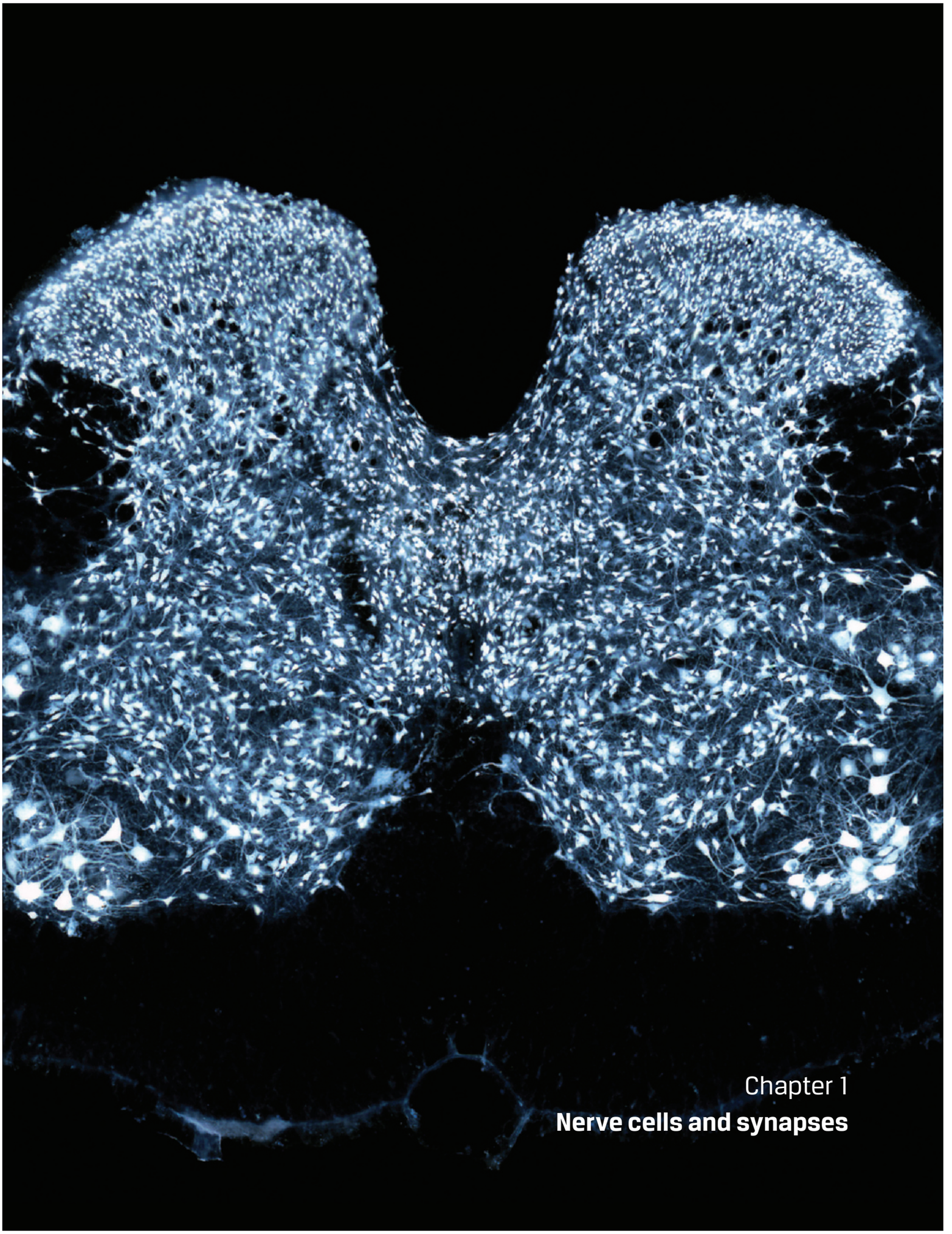


Chapter 1

Nerve cells and synapses

1 Nerve cells and synapses

In this chapter:

The nervous system is made up of two types of cells–neurons and glia. A typical neuron has dendrites, which receive input from other neurons or from sensory receptors, and a single axon, which carries signals to other neurons or to muscles. When the dendrites are stimulated, the neuron generates an electrical signal, which is transmitted along the axon. Axons can vary in size from being very short to very long, even up to half the body length of an animal. When the electrical signal reaches the end of the axon, a chemical transmitter is released, which influences a second neuron.

Neurons come in many shapes and sizes. Some have cell bodies as large as 50 micrometers (one twentieth of a millimeter), and some are as small as 10 micrometers (one hundredth of a millimeter). For comparison, the average diameter of a human hair is 100 micrometers.

The second cell type in the nervous systems is the glial cell. Glia were originally thought to have simple nutritive and protective functions, but our understanding of their roles has expanded considerably in recent years. Glia are now viewed as functional partners to neurons, with key roles in regulating the activity of neurons and the communication between them. Various subtypes of glia protect and buffer the central nervous system against chemical changes; others provide immune surveillance or alter the properties of neuronal signaling.

Membrane potentials and action potentials

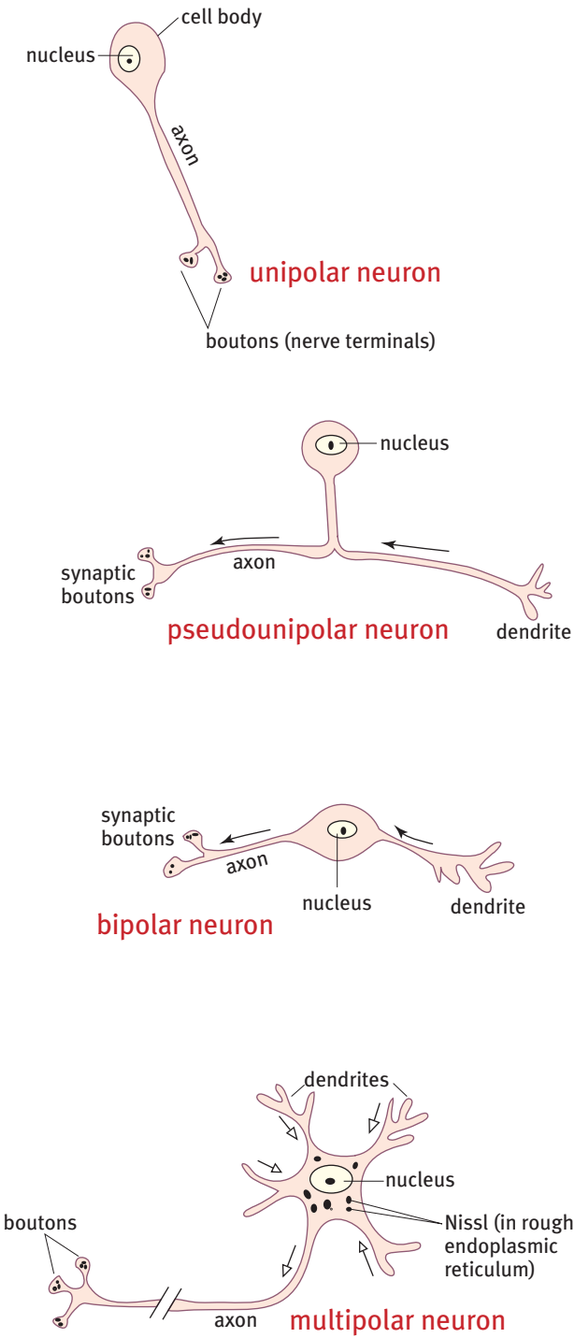
Living cells maintain their internal chemical environment by controlling the movement of ions and molecules across their membranes. Neurons can pump large quantities of ions across their membranes to produce a voltage difference (an electrical potential) between the inside and outside of the cell. This is called the membrane potential[1]. Stimulating a neuron can trigger a large, brief jump in membrane potential, called an action potential or 'spike.' An action potential at one point on the surface of a cell will set off action potentials around it in a chain reaction, spreading almost instantly across the entire cell and down its axon. Transmission of action potentials is the basis of most communication within the nervous system.

Neurons and their connections

Neurons receive stimuli on their sensitive filaments called dendrites. The membrane covering each dendrite has many tiny channels which control the flow of positive and negative ions across the membrane. Some of these ion channels are sensitive to chemical or physical stimuli, and can cause changes in the electrical charge on the membrane. If enough of these small membrane voltage changes happen at the same time, they trigger an action potential. When an action potential is triggered, this sharp, clear signal is transmitted along the axon. At its far end, the axon breaks up into a number of terminal branches. Specialized swellings on these branches are called axon terminals or terminal boutons. An action potential causes the boutons to release chemical signaling compounds called neurotransmitters. These neurotransmitters connect in a key-and-lock fashion with receptors on the target cell. Receptors are protein structures that are shaped to receive specific transmitters. The combination of the neurotransmitters with the receptors can

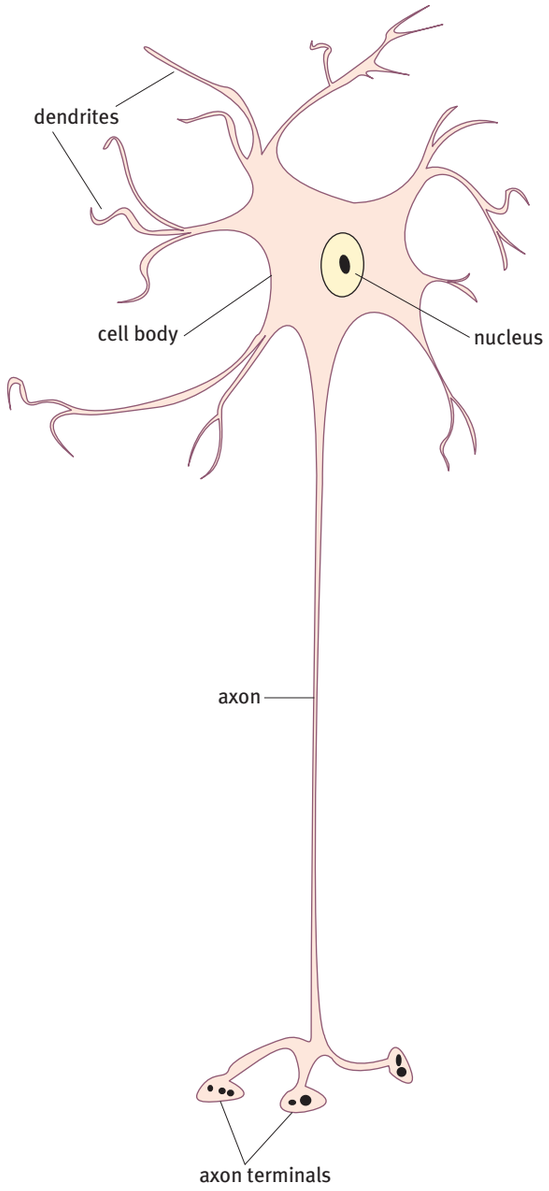
1 See Appendix for more about membrane and action potentials.

Figure 1.1 Different types of neurons



This diagram shows some of the different types of neurons found in the nervous system of different animals. Unipolar neurons have an axon but no dendrites. Pseudounipolar neurons have an axon and a single dendrite but the dendrite and axon are fused near the cell body. Bipolar neurons have an axon and a single dendrite whereas multipolar neurons have many dendrites. (Adapted from Brodal, 2004, p 7)

Figure 1.2 The parts of a neuron



This diagram shows the basic structures that make up a neuron. The neuron cell body has many branching dendrites. A long thin axon extends away from the cell body. The axon will eventually break up into many fine branches which end in swellings called terminal boutons. The boutons make synaptic contact with other neurons or with muscle cells.

open ion channels or trigger other changes. Neurotransmitter receptors are mostly found on the dendrites of other neurons, but they are also found on the surface of muscle cells, glial cells, or gland cells. The close physical pairing between an axon terminal and a concentration of receptors on another cell is called a synapse.

Synapses

Neurons are able to receive and integrate information from multiple stimuli, and can send messages to distant regions of the nervous system. The activity of a single neuron in the central nervous system may be influenced by tens of thousands of synaptic inputs. In the cerebellum up to a quarter of a million synapses are connected to a single Purkinje cell. The axon that carries information away from the neuron may branch into hundreds or even thousands of terminals. Conversely, there are neurons dedicated to a single input, like a photoreceptor in the eye.

Synapses are just one of the influences on neuronal firing. Other influences include the activity of nearby glia, the composition of extra-cellular fluid, and the presence of circulating hormones. Direct electrical links also exist between the membranes of some neurons. To further complicate the picture, many of these types of communication can be two-way, so that an axon terminal that synapses on a dendrite might also be influenced by feedback from the dendrite. Because receptors often have effects on internal biochemistry and gene expression, the communication between

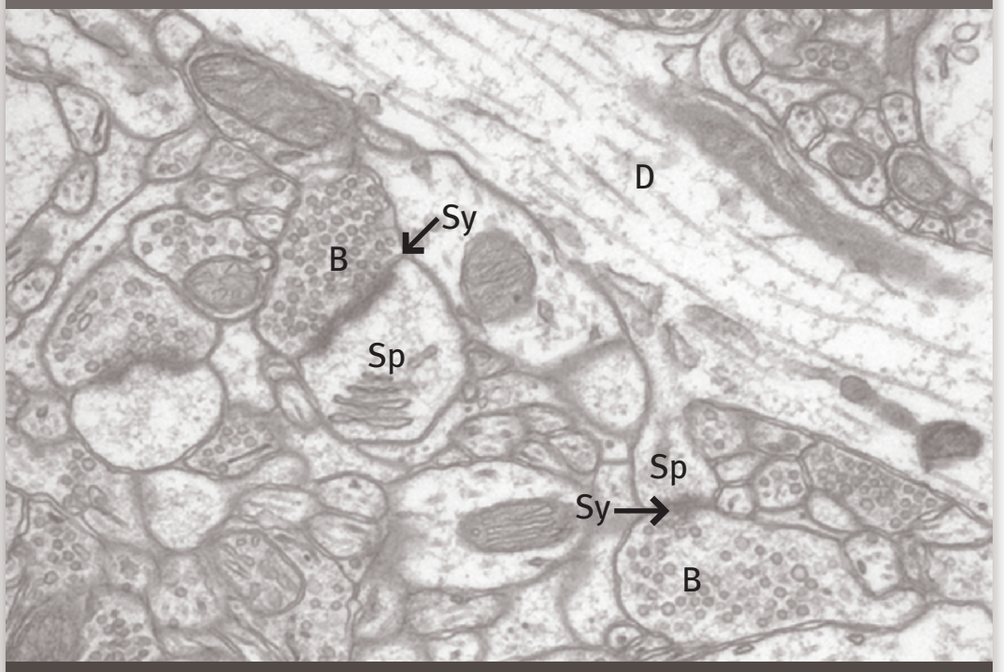
Synapse

A synapse is a small region of close proximity between the terminal branch of an axon and another cell. Messages are transmitted across the synapse by neurotransmitters.

How many neurons?

The rat brain contains 200 million neurons. The rhesus monkey brain contains six billion neurons. The human brain has 86 billion neurons (Herculano-Houzel, 2009).

Figure 1.3 Electron microscope picture of a synapses in the cerebral cortex



This is an electron micrograph of a very thin section of cerebral cortex. A large dendrite (D) runs diagonally across the section. Most of the unstained (white) structures are dendritic spines (Sp), one of which is attached to the large dendrite. Most of the darker staining structures are terminal boutons (B) full of round synaptic vesicles. Dark synaptic thickenings (Sy) are seen at the junction of some dendritic spines and boutons.

cells in the nervous system is rich and diverse, much more so than simplistic models of neurons as integrators of their inputs. (See box, Computers and nervous systems, p10).

Synapses can be changed. Even in the adult brain, synapses may be discarded and new ones formed according to need. This process of tuning and revising connections is termed plasticity. Plasticity is the basis of developmental maturation, learning, memory, recovery from injury, and indeed every functional adaptation of the nervous system. All regions of the nervous system are plastic to some extent, but the extent of plasticity varies a great deal. Generally, the juvenile nervous system is more plastic than the adult, and the cerebral cortex is more functionally plastic than the brainstem and spinal cord.

Most communication between neurons occurs by the release of chemical neurotransmitters from axon terminals and the detection of these chemicals on the surface of cell membrane. Synapses are the spaces in which this communication takes place. They may be small and relatively open to the extracellular space, or large and enclosed, but they share common structural features. The neuron or sensory receptor that secretes a neurotransmitter is called the presynaptic cell, and the corresponding receptors are in the membrane of the postsynaptic cell. Synapses are activated by action potentials that travel to the axon terminals. The action potential causes calcium ions to enter the terminals, and this in turn activates cellular machinery to deliver vesicles full of neurotransmitter to the presynaptic membrane. The number and size of vesicles delivered, as well as the way in which they release their contents, vary greatly with cell type. Neurotransmitter molecules are released from the presynaptic memebrane and diffuse rapidly across the nanometer-sized fluid space of the synaptic cleft. The neurotransmitter binds to and activates a receptor on the postsynaptic membrane. Receptor binding is a dynamic process, with transmitters occupying active sites for only a fraction of the time they are present in the cleft. Their time for activation is limited by the action of enzymes, which break down the transmitter. In other situations the transmitters are pumped away by specialized transport systems on glia or presynaptic cell membranes. This all happens within milliseconds. For example, visual stimuli are signaled by interruptions in the steady stream of neurotransmitter flowing from the visual receptors. Retinal glia take up the neurotransmitter so fast that light flickering tens of times per second is easily noticeable.

Chemical communication between neurons and their targets can also occur outside synapses. For example, in the autonomic nervous system it is common for receptors to be activated by neurotransmitter leaking from nearby axons, or by substances circulating in the blood.

Neurotransmitters

The chemical compounds used by neurons to signal to each other are collectively called neurotransmitters. Many different neurotransmitters have been identified. Here we will summarize the action of the more common neurotransmitters.

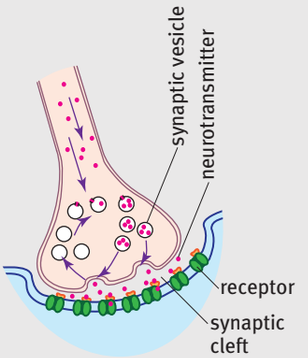


Figure 1.4
Structure of the synapse

This diagram shows the basic components of a synapse. The terminal bouton of the axon contains synaptic vesicles, each of which encloses many neurotransmitter molecules (shown here as pink dots). The neurotransmitter molecules are released into the synaptic cleft. The neurotransmitter diffuses across the synaptic cleft and binds to receptors on the post-synaptic cell membrane. (Adapted from Campbell, 1996, p 1004)

Table 1.1 A table of common neurotransmitters

Neurotransmitter	Descriptive name	Typical functions
glutamate (glu)	glutamatergic	CNS excitation
aspartate (asp)		brain, spinal cord excitation
γ-aminobutyric acid (GABA)	GABAergic	CNS inhibition
glycine (gly)	glycinergic	rapid inhibition in spinal cord
acetylcholine (ACh)	cholinergic	muscle/autonomic activation; attention
dopamine (DA)	dopaminergic	reward; movement
noradrenaline (NA) [a.k.a. norepinephrine (NE)]	noradrenergic	arousal; smooth muscle control
serotonin (5-HT)	serotonergic	relaxation; mood; sensory processing
substance P (SP)	peptidergic	pain signaling, other functions
neuropeptide Y (NPY)		appetite control
opioids (Enk)		pain modulation; satiety
adenosine triphosphate (ATP)	purinergic	many functions

Receptors[2]

Neurotransmitter release can have two kinds of effects on the post-synaptic cell, depending on the number and type of receptors in its membrane. The first is ionotropic, in which a receptor allows ions to pass through the membrane when activated. The second is metabotropic, in which a receptor triggers internal biochemical signaling when activated.[3] Most neurotransmitters can activate specific receptors of both kinds. The post-synaptic cell can change its response by altering the number and type of receptors on the post-synaptic membrane.

Ionotropic receptors that are linked to sodium channels will excite a neuron and make it more likely to fire, whereas those linked to chloride channels tend to suppress firing by returning membrane potential to its resting state. The resulting changes in membrane potential are called post-synaptic potentials. Post-synaptic potentials can be either excitatory (EPSP) or inhibitory (IPSP), depending on whether they make the neuron more or less likely to fire. Dozens of different synapses may be activated in close proximity to each other, opposing or reinforcing each other's effects in a mix of competing influences. These effects spread passively across the membrane, but the effects diminish with distance. Whether or not the charge on the cell membrane reaches the threshold and triggers an action potential is determined by the mix of influences felt at the trigger zone, usually located where the axon leaves the cell body at the axon hillock. This means that the influence of a synapse varies according to how close it is to the axon hillock. For example, the chandelier cells of the cerebral cortex activate ionotropic chloride channels located directly on the axon hillock, so their effect is to instantly cancel whatever activity might be pushing the postsynaptic neuron towards triggering an action potential. This enables them to function as a silencer of axonal outputs.[4]

Metabotropic receptors activate internal signaling molecules to produce a wide variety of effects on postsynaptic cells. These effects are typically longer-lasting than the brief gushes of ions through ionotropic receptors. Some metabotropic receptors cause opening or closing of ion

2 The term *receptor* can refer either to cells that are sensitive to stimuli such as light and touch, or to these membrane protein structures that respond to neurotransmitters.

3 These functional classes are not clearly separated. Some ionotropic receptors let calcium into the cell, which can also affect biochemical pathways by activating calcium-dependent enzymes. Conversely, some metabotropic receptors activate or close membrane ion channels via internal second messengers.

4 The distance between a synapse and the hillock is usually a good predictor of influence, but the shape and thickness of dendrites also influences the spread of synaptic influence. In addition, actively propogated potential spikes may be triggered, exerting far more influence than simple synaptic potentials.

channels by means of internal messenger molecules, while others change the expression of genes and the production of proteins. Another type of metabotropic receptor releases calcium from intracellular stores, sparking oscillating cycles of enzyme activity or causing changes to the structure of the synapse itself. It is not unusual for a synapse to have both ionotropic and metabotropic receptors.

Gap junctions

Gap junctions are small openings in the cell membrane that connect neurons together, allowing ions and therefore electric currents to pass from one neuron to another with no physical barrier. Because of this, changes in membrane potential in one cell can have an instant influence on connected cells.

In some cases, the gap junction system is combined with chemical synaptic communication. Certain large networks of inhibitory neurons in the brain are gap-junction coupled, and also make inhibitory synapses on each other. In this situation, an action potential in one neuron causes a

Figure 1.5 Glial cells in the human cerebral cortex

A drawing of different types of glial cells of the cerebral cortex stained with the Golgi method. The original drawing was by Retzius in 1894. (Illustration courtesy of De Felipe, 2010, p 89)

Gene expression

Gene expression involves the decoding of genetic information in DNA to make some sort of non-DNA product, usually a protein. The proteins are molecules that build the various parts of the body. Gene expression in individual neurons can be detected by a number of techniques, including in situ hybridization.

Neuroglia

The neuroglia are supporting cells in the nervous system. The main types are astrocytes, oligodendrocytes, microglia, and Schwann cells.

brief simultaneous electrical excitation in neurons linked to it by gap junctions, which is followed by a synaptic inhibition. The timing of these two actions causes specific frequencies of activity to spread more easily between neurons, and the network may end up firing in synchrony. This large-scale coordination is thought to be important in the activity of large areas of cerebral cortex, and may even contribute to the neuronal basis of attention.

Glia

Glia were long regarded as the simple glue filling in the space between neurons, but they are now recognized as important functional partners to neurons. While neurons tend to communicate with fast, specific signals, glial activity in the same region may take the form of gradual shifts in electrical excitability. Glial impulses spread through the tissue at a slower rate and alter neuronal activity, neurotransmitter kinetics, metabolic activity, blood flow, and the extracellular environment. Since glia and neurons are in contact across almost every part of their membranes, they interact and influence each other in a tight, reciprocal relationship, which is not completely understood.

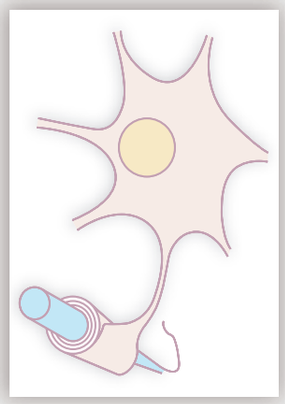
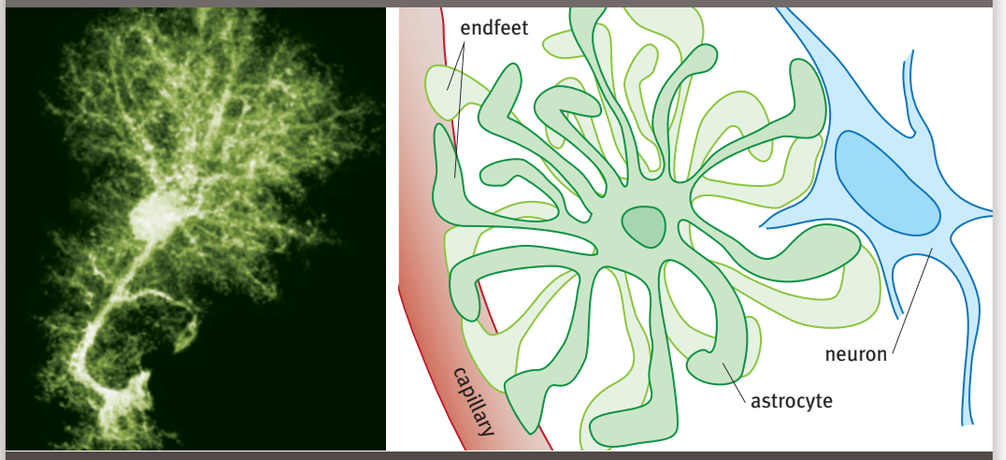


Figure 1.6
Oligodendrocyte

A diagram of a process of an oligodendrocyte which has wrapped around an axon to form a myelin sheath.

Figure 1.7 Astrocyte



A filled cell (left) shows the complex fluffy structure of a typical astrocyte (image courtesy of CCDB, National Center for Microscopy and Imaging Research, University of California, San Diego). On the right is a diagram illustrating the buffering role of an astrocyte that lies between a blood capillary and a neuron.

Astrocytes

The principal glial type in the central nervous system is the astrocyte–a general-purpose cell whose functions include buffering the cellular environment, tending synapses, metabolic regulation, signaling and communication, and governing capillary flow and traffic between neural tissue and the bloodstream. Individual astrocytes fill non-overlapping domains with fine, fluffy processes surrounding virtually every square micron of neuronal membranes and capillary walls. A single astrocyte interacts with dozens of neurons, regulating their environment and metabolism, and communicating back and forth to regulate synapses and neuron excitability. Astrocytes also provide neurons with pre-processed food to meet their energy demands. This relationship, combined with their ability to alter the size of brain capillaries, allows them to change blood flow according to neuronal energy use. Apart from meeting metabolic demands efficiently, these changes are the basis of functional magnetic resonance imaging (See Chapter 11).

Oligodendrocytes

These cells manufacture myelin, the multiple layers of fatty cell membrane that encircle many axons. The myelin sheath is not continuous; there is a small gap between the sheath made by one oligodendrocyte and the next. This gap is called a node. Myelin sheaths speed up signaling along the axon by allowing action potentials to jump from one node to the next. Not a lot is known about the other functions of oligodendrocytes. However, they have recently been shown to respond to synaptic events with post-synaptic potentials and action-potential-like spikes, further blurring the line between the functions of neurons and glia.

Schwann cells

Outside the central nervous system, the myelinating role of oligodendrocytes is taken by Schwann cells. Schwann cells manufacture myelin that encircles the axons of peripheral nerves. As in the central nervous system, the myelin sheath of peripheral nerve axons is not continuous; there are gaps between the sheath made by one Schwann cell and the next. Besides their role in myelination, Schwann cells have similar functions to the astrocytes of the central nervous system. Schwann cells are important in the maintenance of the extracellular environment around neural tissue, and in the uptake and processing of neurotransmitters around synapses, particularly at the neuro-muscular junction.

Microglia

Microglia are specialized macrophage cells. Macrophages are immune system cells that are found in blood and other tissues of the body. When macrophages enter the brain, they change into microglia. Microglia assume a stationary sentry role, exploring the tissue around them with fine processes that continuously extend and retract. If the brain is damaged or infected, microglia are activated and can resume their mobile form, which is able to engulf and destroy pathogens, foreign material, and necrotic tissue. They also signal to other cells of the immune system for assistance.

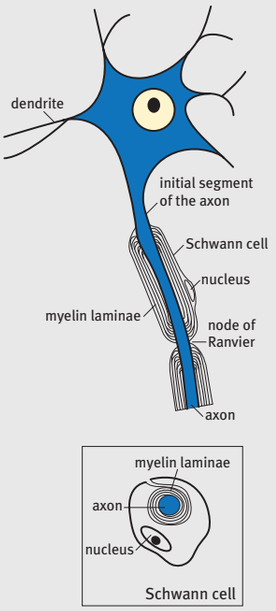


Figure 1.8
Myelinated axon

A diagram of the first part of a myelinated axon. The initial unmyelinated segment of the axon is called the axon hillock. In this case two myelin condensations are seen, the first of which is associated with the nucleus of a Schwann cell. The myelin in each condensation is produced by cell membrane extensions of a Schwann cell. Between adjacent condensations of myelin is a short length of axon not covered by myelin. This is called a node of Ranvier. (Adapted from Brodal, 2004, p 20)

Oligodendrocyte precursor cells–polydendrocytes

In addition to the mature glia described above, the central nervous system contains precursor cells which can be transformed into oligodendrocytes, astrocytes and possibly even neurons. These cells are also called polydendrocytes. They are capable of communicating and signaling in neuron-like ways, and play an important role in regeneration after injury.

Ependymal cells

The fluid spaces of the brain (the ventricles) are lined by ependymal cells. In some places the ependymal cells form specialized clusters with blood vessels called choroid plexuses. The choroid plexuses secrete cerebrospinal fluid into the ventricles. Some ependymal cells have the ability to divide and produce new neurons throughout the life of the organism. Steady streams of developing neurons from the ependymal layer migrate to the olfactory bulb and the dentate gyrus of the hippocampus, where they replace old neurons, which may have died or become dysfunctional.

Cerebrospinal fluid

Cerebrospinal fluid is a clear watery fluid that fills the ventricles of the brain and the space surrounding the brain.

How many glial cells?

Old estimates put the number of glial cells in the brain as at least 10 times the number of neurons, but recent work shows that the number of glial cells is about the same as the number of neurons.

Computers and nervous systems

Biologists and computer scientists have often compared nervous systems with the functions and properties of computers. This analogy has been useful for some understanding some neural functions, and has suggested new paradigms and algorithms to assist the design of computer architectures and applications. However, these comparisons are limited by the fact that computers and nervous systems operate in fundamentally different ways.

Computer models of neural activity have taken two basic forms–simulations of the activity of actual neurons, and simulations of neural networks, using neuron-like connection patterns and rules derived from physiology, to solve computational problems. The latter has allowed new approaches to computationally difficult problems, but is nearly always implemented using standard computer hardware and programming languages, which make it no more similar to neural activity than conventional computer programs. The modeling of actual neural activity is really a scaled-up and more sophisticated version of the neural network paradigm, except that individual neurons are modeled in much greater detail. Neither approach captures much of the biological character of neural tissue, particularly the ability of neural systems to continually modify themselves by changing gene expression and other variables. The models allow simple ideas about neural activity patterns to be explored, but they are not realistic enough to be very useful.

It could be argued that by describing nervous systems in terms of computational activity, these models are missing the point entirely, since they exhibit no evidence of awareness or consciousness.