BIEN 500- fall 2023
Lecture 14

- Dr.DeCoster:

- The nervous system: General principles and cellular integration:

1. Cells of the Nervous System

Cells of the Nervous System

- Neurons
- Astrocytes
- Microglia
- Endothelial cells

Overview 1:

- Several types of cellular elements (cells) are integrated to yield normally functioning brain tissue:
- The *neuron* is the <u>communicating</u> cell, and a wide variety of neuronal subtypes are connected to one another via complex circuits usually involving multiple *synapses*.
- Neurons convert stimuli into electrochemical signals that are conducted through the nervous system

Overview 2:

- Neurons are supported by *glial* cells, which function in myelination, secretion of *trophic factors*, maintenance of the extracellular milieu, and scavenging of molecular and cellular debris from it.
- Also participate in formation and maintenance of *BBB*, a multi-component structure interposed between brain and bloodstream, thus serving as the gateway to the brain.

Nerve cells carry electrical signals

- Nerve cells or *neurons*, receive, conduct, and transmit signals. Neurons in general are extremely elongated- more so than any other class of cells in the body.
- Neurons are highly morphologically ***polarized***, developing distinct subcellular domains that subserve different functions: the *cell soma* (body), *dendrites*, and the *axon*
- (Figure 18-2)

Neurons: Highly Polarized Cells

>>>Dendrites bring signals <u>in</u>   Axons send signals <u>away >>></u>

Cells of the Nervous System: A Preliminary Sketch   **1015**

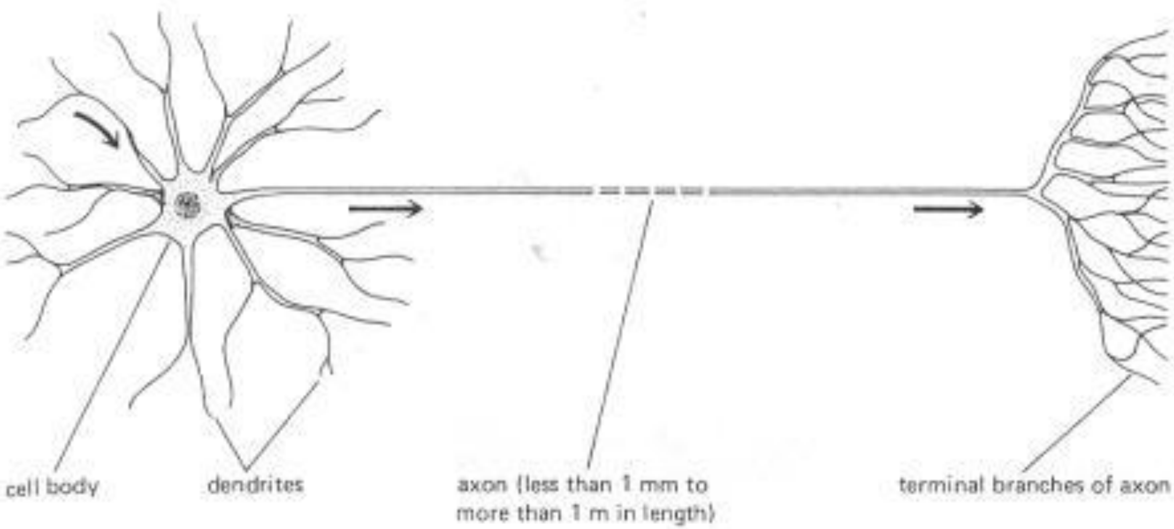


Figure 18–2 Schematic diagram of a typical neuron of a vertebrate. The arrows indicate the direction in which signals are conveyed.

Neurons communicate chemically at synapses

- Neuronal signals are transmitted from one cell to another at specialized sites of contact known as synapses
- Neurons making up the synapse are electrically isolated from each other, the <u>presynaptic</u> neuron being separated from the <u>postsynaptic</u> neuron by a <u>synaptic cleft</u>.
- A change in electrical potential in the presynaptic cell triggers it to release a chemical known as a *neurotransmitter*, which diffuses across the synaptic cleft and provokes an electrical change in the postsynaptic cell.

(Fig. 18-3)

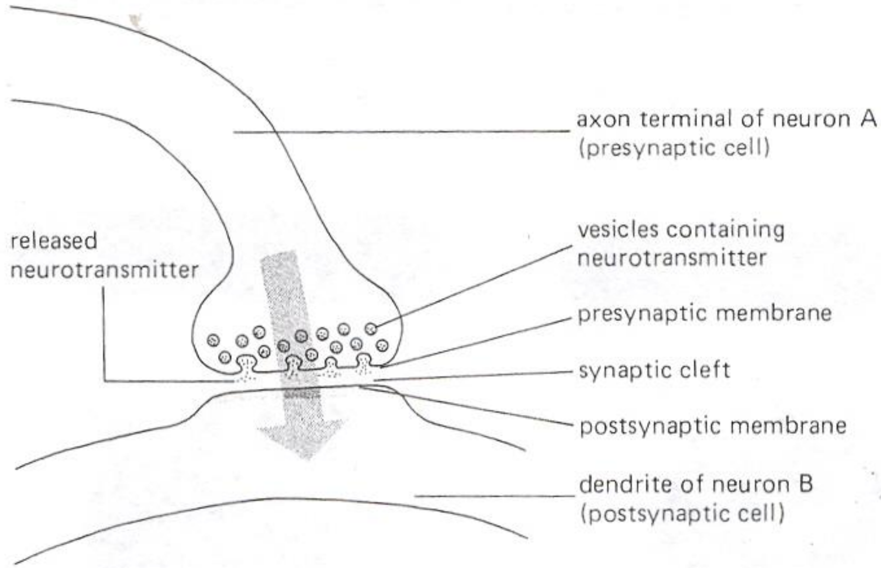
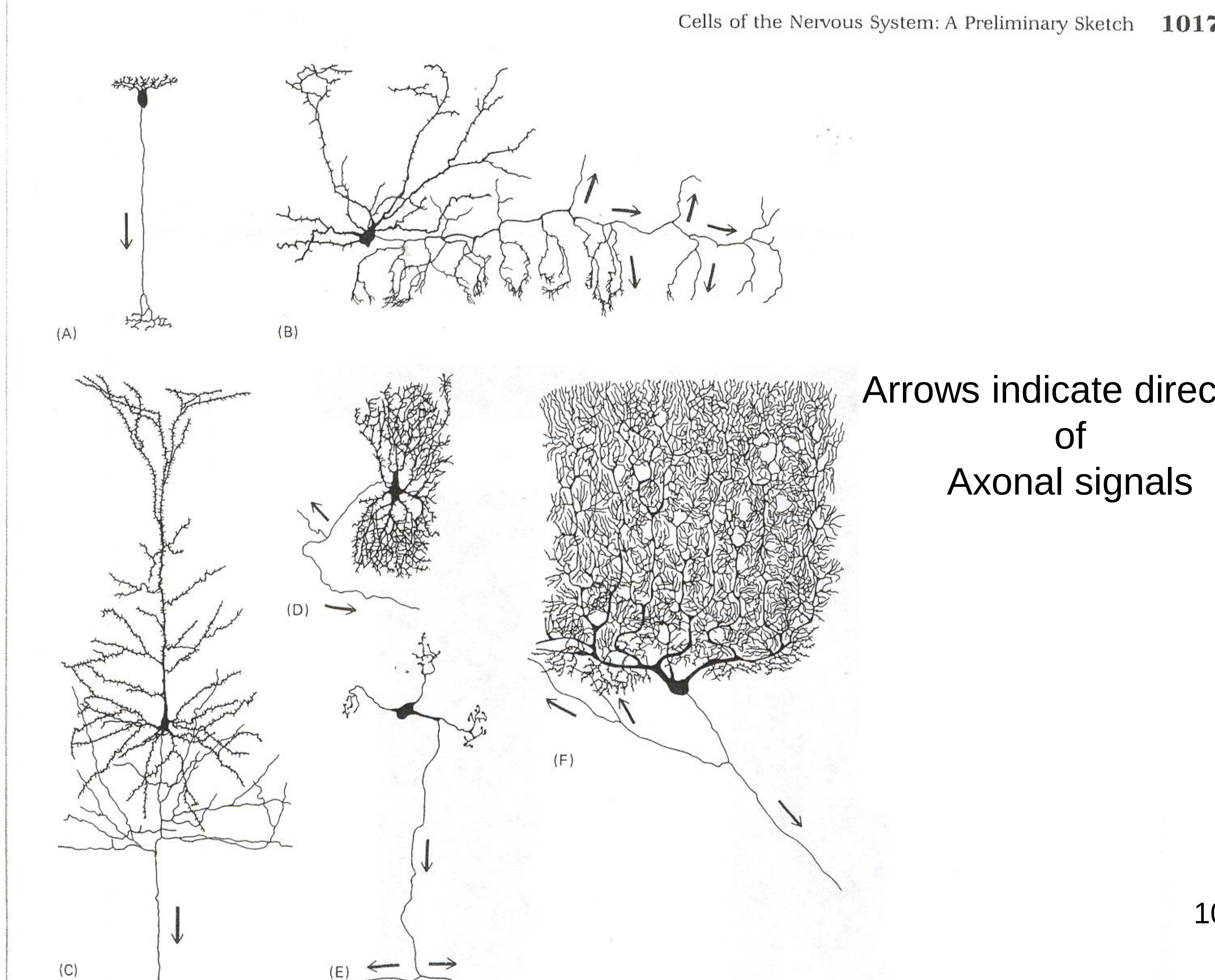


Figure 18–3 Schematic diagram of a typical synapse. An electrical signal arriving at the axon terminal of neuron A triggers the release of a chemical messenger (the neurotransmitter), which crosses the synaptic cleft and causes an electrical change in the membrane of a dendrite of neuron B. A broad arrow indicates the direction of signal transmission. The axon of a single neuron such as that shown in Figure 18–2 may make thousands of synaptic connections with other cells. Conversely, the neuron may receive signals through thousands of synaptic connections on its dendrites and cell body.

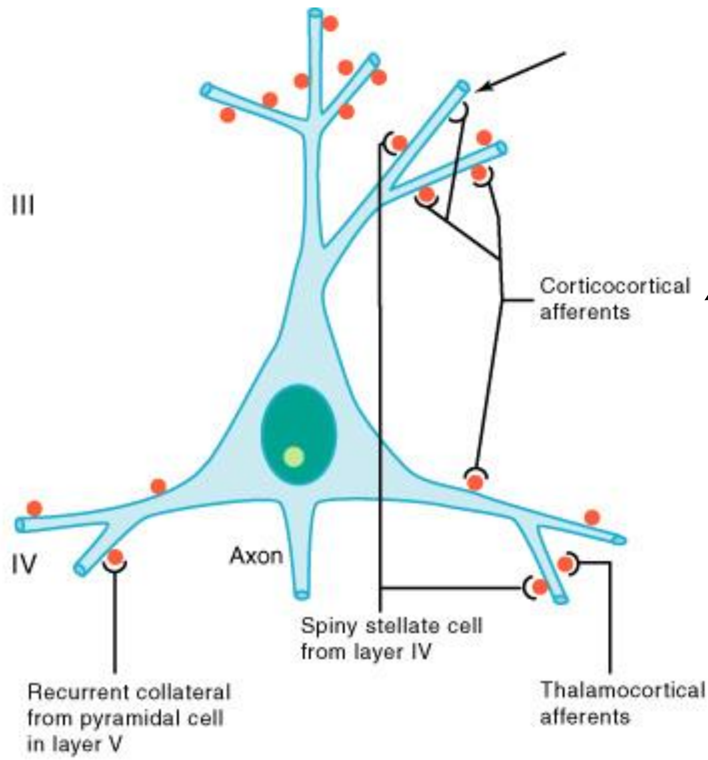
Neurons are diverse in the neurotransmitters they release and in their shape and size



Arrows indicate direction of Axonal signals

Examples of Neurons

- Pyramidal Neurons:
- -- Are the main *excitatory* neurons in the cerebral cortex. Pyramidal cells are highly polarized neurons, with a major orientation axis perpendicular to the pial surface of the cerebral cortex (explain).
- --In cross section, the cell body is roughly triangular (*often the function of a neuron depends on its shape*).– Figure 1.2



Afferents are axonal contacts coming from other neurons

FIGURE 1.2 Schematic representation of four major excitatory inputs to pyramidal neurons. A pyramidal neuron in layer III is shown as an example. Note the preferential distribution of synaptic contacts on spines. Spines are labeled in red. Arrow shows a contact directly on the dendritic shaft.

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The cortex of the brain is highly laminar, with neurons distributed into defined cell layers

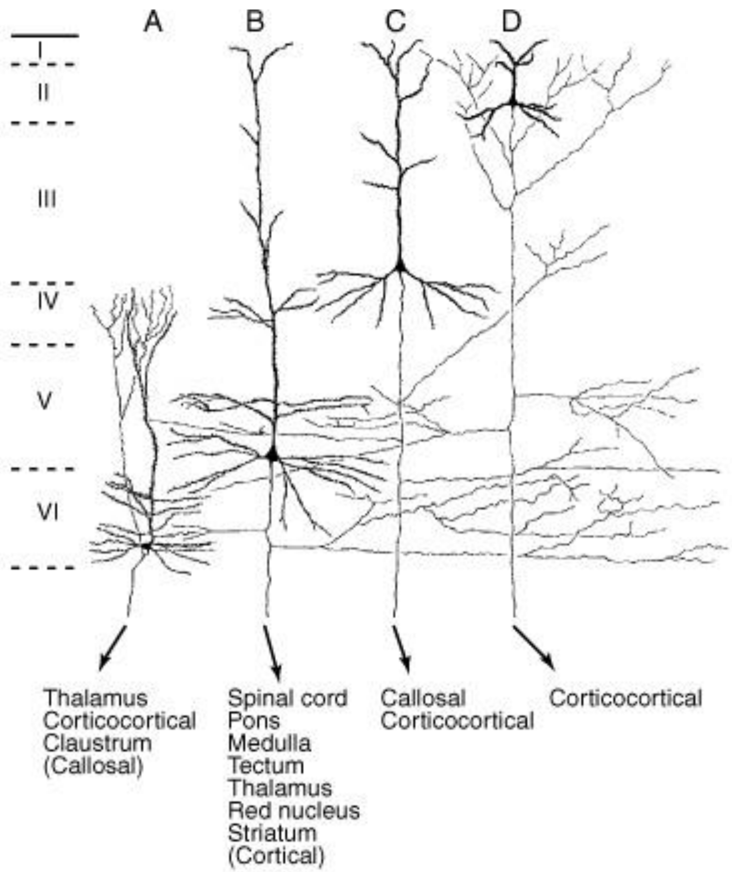

FIGURE 1.4 Morphology and distribution of neocortical pyramidal neurons. Note the variability in cell size and dendritic arborization as well as the presence of axon collaterals, depending on the laminar localization (I–VI) of the neuron. Also, different types of pyramidal neurons with a precise laminar distribution project to different regions of the brain. Adapted with permission, from Jones (1984).

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Examples of *inhibitory* Neurons

- Basket, chandelier, and double bouquet cells are <u>inhibitory</u> <u>interneurons</u>.
- These neurons contain the inhibitory neurotransmitter gamma-aminobutyric acid (*GABA*), and exert strong local inhibitory effects.

Chandelier Cells-1: Inhibitory

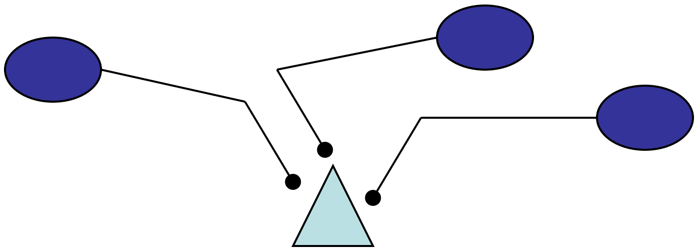
- Has generally bitufted or multipolar dendritic tree (variable).
- Defining characteristic is axonal endings. In Golgi or <u>immunohistochemical</u> staining, axon terminals are shown to be characterized by series of axonal *boutons* or swellings, linked together by thin connecting processes (looks like a chandelier?).

Chandelier Cells-2: Inhibitory

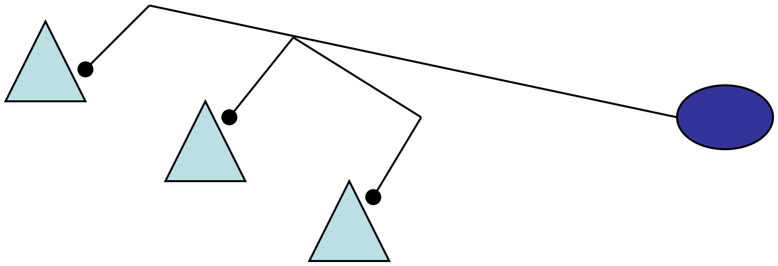
- Chandelier cells show extraordinary specificity in it *synaptic* target. These neurons synapse exclusively on the axon initial segment of pyramidal cells (also called axoaxonic).
- One pyramidal may receive inputs from multiple chandeliers, and one chandelier may innervate more than one pyramidal (draw)

Chandelier-Pyramidal Synapses

1. Pyramidal receiving many inputs from many Chandeliers:



2. Chandelier innervating more than one pyramidal:



Chandelier Cells-3: Inhibitory

- Because of the high density of chandelier cell axon endings in cortical layer III of the brain, this type of neuron may be involved in controlling corticortical circuits.
- Because strength of synaptic input is correlated directly with proximity to the axon initial segment, the chandelier inhibitory input to a pyramidal is very strong– presumably chandelier interneurons could completely shut down the firing of a pyramidal cell.

Examples of non-cortical neurons (distinct morphologies and relevance to disease)- Purkinje Cells (disorders of the cerebellum)

- The structure of the cerebellar cortex, in contrast with that of the cerebral cortex, is basically identical all over– composed of three layers with distinct neuronal types. One of these layers contains Purkinje cells, which are the most salient cellular elements of the cerebellar cortex.

- Purkinje cells arranged in a single row throughout the entire cerebellar cortex between the molecular (outer) layer and granular (inner) layer. They are the largest cerebellar neurons, with round perikaryon and highly branched dendritic tree. The apical dendrites of Purkinje cells have enormous number of spines (more than 80,000 per cell). A particular feature of the dendritic tree of Purkinje cells is that it is distributed in one plane, and thus each dendritic arbor determines a separate domain of cerebellar cortex.
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- Humans have approx. 15 million Purkinje cells; they contain the inhibitory neurotransmitter GABA. A severe disorder combining ataxic gait and impairment of fine hand movements accompanied by tremor, has been documented in some families and is related directly to Purkinje cell degeneration.
- (Figure 1.1)---

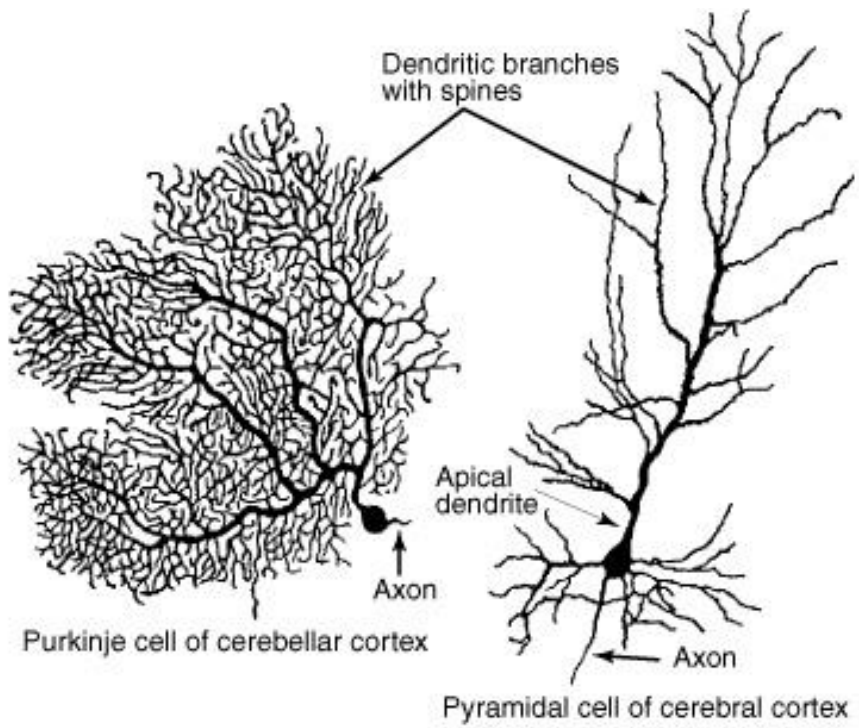

FIGURE 1.1 Typical morphology of projection neurons. On the left is a Purkinje cell of the cerebellar cortex, and on the right, a pyramidal neuron of the neocortex. These neurons are highly polarized. Each has an extensively branched, spiny apical dendrite, shorter basal dendrites, and a single axon emerging from the basal pole of the cell.

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Spinal Motor Neurons (ALS)

- The motor cells of the ventral horns of the spinal cord, also called alpha motor neurons, have their cell bodies within the spinal cord and send their axons outside the central nervous system (CNS) to innervate the muscles. The spinal motor neurons use **acetylcholine** as their neurotransmitter.
- Larger motor neurons are severely affected in lower motor neuron disease (a form of amyotrophic lateral sclerosis-ALS), a neurodegenerative disorder characterized by progressive muscular weakness and wasting due to denervation.
- Neuropathologically, a massive loss of ventral horn motor neurons occurs, and the remaining motor neurons appear shrunken and pyknotic (degeneration of the cell nucleus).

The Neuroglia (or Glia)

- Neuroglia (“nerve glue”) was coined in 1859 by Rudolph Virchow, who conceived of the neuroglia as inactive connective tissue holding neurons together in the CNS. (“Glia” may be used to indicate these type of cells, and as we will learn, glia are much more than inactive connective tissue).

Glia-2

- In addition to the ependymal cells lining the ventricles and central canal of the brain, three types of supporting cells in the CNS were identified, which can all be considered glia:
- oligodendrocytes, astrocytes, and microglia. In the peripheral nervous system (PNS), the Schwann cell is the major glia component.

Glia-3

- Oligodendrocytes and Schwann cells synthesize myelin

- Astrocytes play important roles in CNS homeostasis.
- As the name suggests, astrocytes are star shaped process-bearing cells distributed throughout the CNS.
- Constitute 20-50% of the volume of most brain areas. Astrocytes come in many shapes and forms; by shape the two main forms are protplasmic, and fibrous astrocytes .

Astrocytes: Migration support for neurons

- Embryonically, astrocytes develop from radial glial cells, which compartmentalize the neural tube.
- Radial glial cells serve as scaffolding for the migration of neurons and play a critical role in defining the cytoarchitecture of the CNS.

Astrocytes: support for neurons and integration with other cells

- Astrocytes fence in neurons and oligodendrocytes.
- They isolate the brain tissue by extending long processes projecting to the pia mater (towards the surface of the brain) and to the ependyma (lining the ventricles), to form the glia limitans, by covering the surface of capillaries, and by making a cuff around the nodes of Ranvier.
- Astrocytes also ensheathe synapses and dendrites and project processes to cell somas (Fig. 1.18).

Integration of Astrocytes within the brain

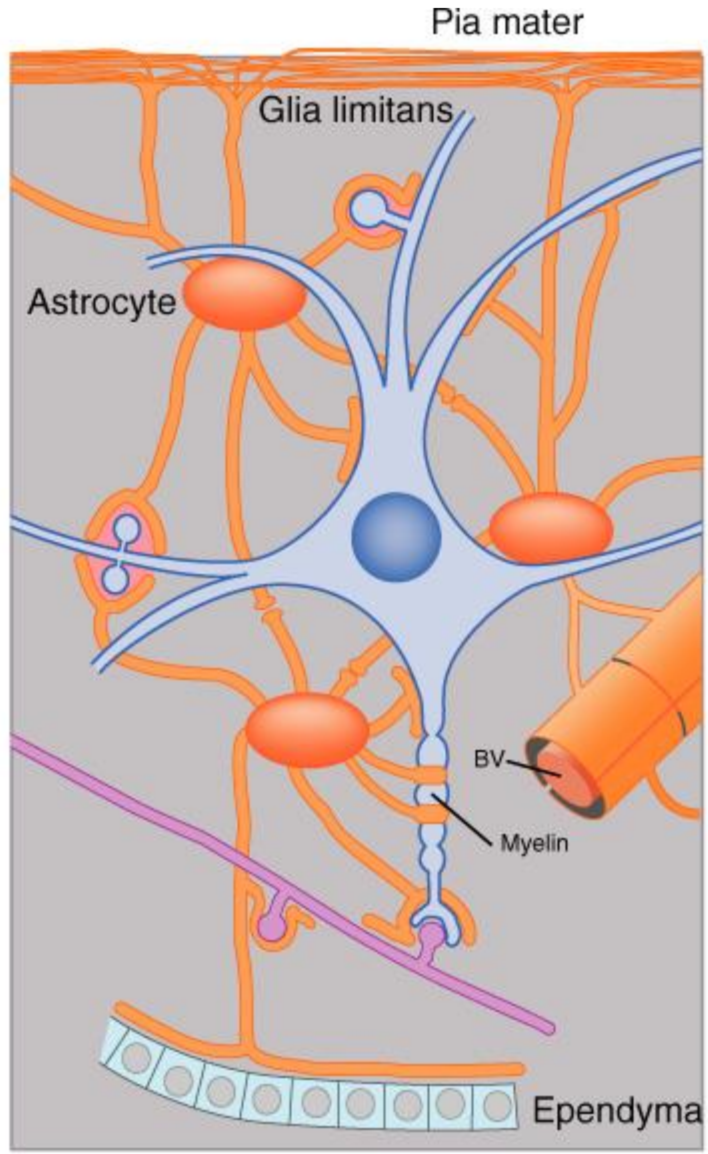

FIGURE 1.18 Astrocytes (in orange) are depicted *in situ* in schematic relationship with other cell types with which they are known to interact. Astrocytes send processes that surround neurons and synapses, blood vessels, and the region of the node of Ranvier and extend to the ependyma as well as to the pia mater, where they form the glia limitans.

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Astrocyte Functions-3

- During neurotransmission, neurotransmitters and ions are released at high concentrations into the synaptic cleft. Rapid removal of these substances is essential for future signaling.
- The presence of astrocyte processes around synapses position them well to regulate neurotransmitter uptake and inactivation.
- For example, the uptake of *glutamate (the major excitatory neurotransmitter in the brain),* is performed mostly by astrocytes, which convert glutamate to *glutamine*, and then release it into the extracellular space.
- --Glutamine is taken up by neurons, which is used to generate glutamate and GABA, potent excitatory and inhibitory neurotransmitters, respectively. Fig. 1.19.

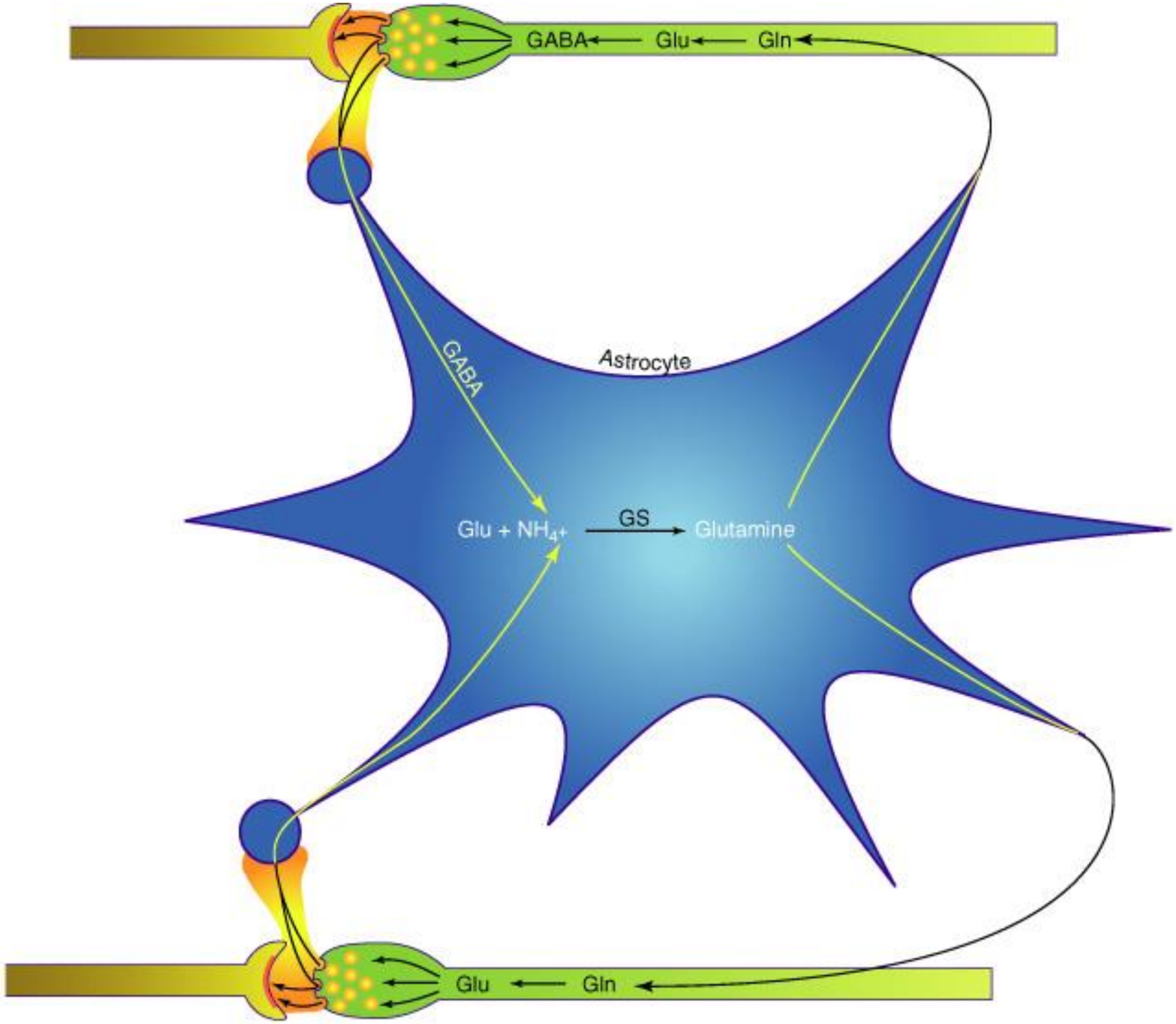

FIGURE 1.19 The glutamate–glutamine cycle is an example of a complex mechanism that involves an active coupling of neurotransmitter metabolism between neurons and astrocytes. The systems of exchange of glutamine, glutamate, GABA, and ammonia between neurons and astrocytes are highly integrated. The postulated detoxification of ammonia and inactivation of glutamate and GABA by astrocytes are consistent with the exclusive localization of glutamine synthetase in the astroglial compartment. Gln, glutamine.

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Microglia are mediators of immune responses in nervous tissue

- The brain has traditionally been considered to be an immunologically privileged site because the blood brain barrier (BBB) normally restricts the access of immune cells from the blood.
- However, it is now known that immunological reactions do take place in the brain, particularly during cerebral inflammation.
- Microglia cells have been called the tissue macrophages of the CNS. A hallmark of microglia is their ability to become reactive and to respond to pathological challenges in a variety of ways.

Microglia-2

- Many microglia appear to be derived from bone-marrow derived monocytes, which enter the brain during early stages of brain development.
- These cells help phagocytose degenerating cells (cell debris) that undergo programmed cell death (apoptosis) as part of normal development.
- Microglia retain the ability to divide (proliferate) and have the immunophenotypic properties of monocytes and macrophages;
- microglia may also secrete cytokines or growth factors important in neuronal fiber tract development, gliogenesis, and angiogenesis (growth of blood vessels).

Summary of Glia in the Brain:

- Glia in the brain are a set of cell types that together subserve supportive and trophic roles critical for the normal functioning of the neurons.
- The myelinating glia have clear functional roles, facilitating rapid conduction of the action potential along small-caliber axons.
- Astrocytes and microglia (non-myelinating cells) also have major and extremely important functions in development and in brain injury:
- these cells react to, contain, and limit tissue damage, and they also contribute in a major way to repair mechanisms.

End of Part I