Chapter 1
An Introduction: Overview of Nervous System and Brain Disorders

Maria Ayub and Antonello Mallamaci

1.1 Introduction to Nervous System

The nervous system is unique in the vast complexity of the processes it controls and the actions it performs. It gathers minute bits of information both externally and internally (sensory function), processes that information (integration), and sends out the required commands to the cell/tissue/organ in question to respond appropriately (motor function). The nervous system modulates every minute function of the body either directly or via sub-structures. Many of the functions that are regulated by the nervous system include higher cognitive abilities such as thought processing, and memory formation, and motor functions such as movement, posture, balance, and coordination. Sensory roles e.g., interpretation of information received from the hearing, taste, touch, homeostatic functions such as sleep, hunger, thirst, breathing, and many others. This complex array of functions regulated by the nervous system is the result of perfect coordination among its sub-structures and unique cellular organization. This system is further divided into two subsystems: the central nervous system (CNS) and the peripheral nervous system (PNS), one is responsible for voluntary control, and the other monitor involuntary actions. The brain and spinal cord make CNS and are the main relay centers of information to be processed. While cranial, spinal, and peripheral nerves together build PNS consisting of sensory and motor neurons [1].

M. Ayub (✉) · A. Mallamaci
Functional and Structural Genomics Area, Department of Neuroscience, International School for Advanced Studies (SISSA), Trieste, Italy
e-mail: mayub@sissa.it; amallama@sissa.it

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1.2 Nervous System Structural Organization

The nervous system is classified in general into two categories i.e., CNS and PNS, and PNS have further classification based on its autonomous and non-autonomous functions. These two divisions are somatic and autonomic, former is responsible for the voluntary actions of skeletal muscles while the latter is primarily involved in the autonomous regulation of internal organs such as cardiac myocytes, smooth muscles, and glandular epithelium. Autonomic PNS division has two subtypes, sympathetic and parasympathetic PNS, sympathetic PNS is well known for its "fight and flight response", it is activated during times of emergency and leads to increased heart rate and pupil size, the release of epinephrine/nor-epinephrine, inhibition of digestive and immune system activities and expansion of lungs. While parasympathetic PNS does the opposite of sympathetic PNS, its activation decreases heart rate and pupil size, enhances digestive and immune functions, and leads to the contraction of the lungs [2].

The structural organization of CNS builds its functional significance, it consists of the cerebrum, cerebellum, brainstem, and spinal cord. The Cerebrum, the largest part of the brain is divided into left and right hemispheres which are further classified into four lobes, each with its own set of functions: frontal, parietal, temporal, and occipital lobe. The frontal lobe is responsible for emotions, intelligence, and speech, parietal lobe regulates visual and spatial perception, constitutes language, and interprets sensory stimuli. Memory and hearing are controlled by the temporal lobe, and lastly, the occipital lobe is responsible for vision [3]. At deeper levels, these lobes are comprised of individual structures in the cerebrum such as the cortex, or deeper parts like the limbic system, hypothalamus, thalamus, pituitary gland, and pineal gland. Cerebellum is positioned at the base of the brain and monitors the balance of the body, and the brainstem acts as a relay center between the brain and spinal cord and observes sleep and breathing. The spinal cord is a cylindrical band of tissue running through the spine and connecting the brainstem and lower back of the body, carrying the information from the brain to the rest of the body via nerve bundles and cells. All this transportation of information to and from the brain via different sensory and motor routes is governed by the basic unit of CNS, called a neuron.

1.2.1 Role of CNS Individual Structures in Physiology

The cerebral cortex is the outer covering of the gray matter of the cerebrum, it has a large surface area due to its folded structure consisting of gyrus (ridges) and sulci (folds). Cortex contains 16 billion neurons arranged in such a way to give the cortex a layered structure (6 cortical layers), and the cell bodies of their neurons give the cerebrum gray color, thus called gray matter [4]. The newest part of the cortex that evolved is called the neocortex and makes up 90% of the whole cortex. While

evolutionary ancient cortexes are the allocortex and paleo cortex, which compared to the neocortex contain fewer cell layers. The two hemispheres of the cortex communicate through a C-shaped structure called the corpus callosum, which consists of white matter and nerve fibers. The left hemisphere is responsible for the proper functioning of the right side of the body, while the right hemisphere controls the left side of the body.

In general, the right hemisphere is in charge of spatial ability, and creativity like artistic and musical skills, while the left hemisphere, regulates learning abilities like speech, writing, or comprehension [5]. The cerebral cortex consists of sensory and motor areas; sensory areas of the cortex receive inputs from the thalamus and process the arrived information accordingly. On the other hand, motor areas include the motor cortex and premotor cortex which are responsible for the modulation of voluntary movements.

Given the structural contribution of the cortex in the brain and its subset areas, the cortex is involved in the monitoring and manipulation of a range of physiological functions. Some of the major functions modulated by the cortex are motor functions, language processing, decision-making, intelligence, personality determination, memory storage, thinking, learning, emotions, and consciousness [6]. On a deeper level, the four lobes that comprise the cortex have individual functions as discussed in the previous section, such as the frontal lobe of the cortex is mainly considered the action cortex and is involved in the brain reward system, skeletal movements, speech control, and expression of emotions. The parietal lobe also called the sensory cortex is responsible for the integration of the sensory information received through different areas. The temporal lobe interacts with the hippocampus and modulates long-term memory formation, and lastly, the occipital lobe known as a visual processing center of the brain is responsible for the processing of visual inputs (Fig. 1.1) [3].

Brainstem also called the middle brain is the structure that connects the cerebrum with the spinal cord and has substructures midbrain, pons, and medulla oblongata. Mesencephalon commonly called the midbrain is the uppermost part of the brainstem consisting of a complex network of neurons and neural pathways which

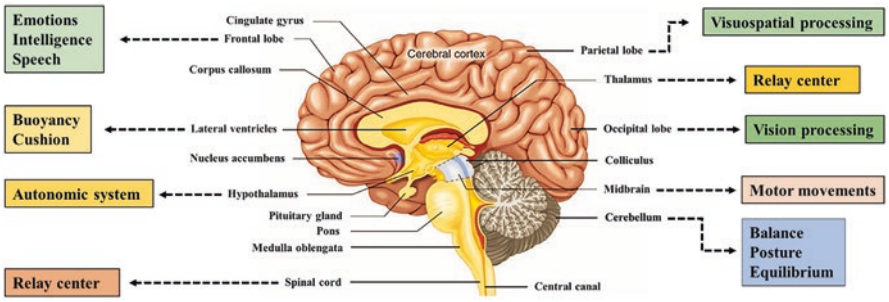

Fig. 1.1 Brain structural organization and associated physiological roles: Main structures of the brain like cerebral lobes, midbrain, limbic system, cerebellum, and spinal cord, and their associated functions in the brain

facilitates motor movements, particularly eye movements, and is involved in sensory information processing like visual and audio cues. Tectum, tegmentum, and ventral tegmental area are the subregions of the midbrain with their particular roles in the brain. The tectum forms the roof of the midbrain and processes the inputs received from the auditory cortex and peripheral brainstem nuclei. Tegmentum makes the base of the midbrain and is the house for nuclei and tracts of the reticular formation, which is a crucial brain network responsible for the survival of the being. The ventral tegmental area otherwise called VTA is involved in addiction behavior, memory, and reward system, and it does so by modulating dopaminergic neurons activity [7].

The word pons originates from the Latin word meaning "bridge", it connects the midbrain and medulla. It is the center of four of twelve cranial nerves origin, these nerves control functions such as tear production, facial expressions, blinking, chewing, and balance. Pons contain tracts carrying the sensory signals through different parts of the brain e.g., from the cerebrum to the medulla to the cerebellum, and thalamus. It coordinates the activity of cerebral hemispheres and houses the respiratory nuclei that modulates respiratory functions. At the bottom of the brainstem, a stem-like structure called medulla oblongata is positioned, which is crucial for the survival of organisms as it regulates some basic functions in the body such as breathing, rhythmic activities of the heart, blood, flow, and the body's oxygen and carbon dioxide levels. It is also responsible for sneezing, antiperistalsis movements (such as vomiting), coughing, and swallowing, altogether known as reflexes [8].

Cerebellum or little brain is a fist-size structure located at the back of the brain, above the brainstem. It consists of two hemispheres; the other outer part contains a neuronal network and the inner region communicates with the cerebral cortex. Cerebellum is mainly responsible for the posture, balance, and equilibrium of the body. It does so by monitoring the coordination of voluntary muscle movements. Cerebellum itself does not initiate any movements but contributes to coordination, precision, and timing. It receives sensory inputs from the spinal cord and other parts of the brain and integrates this information into finely tuned-motor actions. Anatomically speaking, the cerebellum is comprised of a specific set of neurons and axons i.e., Purkinje cells and granule cells, and three types of axons mossy fibers, climbing fibers, and parallel fibers that together make the cerebellar circuit. Animal and human studies have shown that damage to the cerebellum results in the loss of precisely coordinated body movements, equilibrium, posture, and motor learning [9]. Though after the damage, an individual continues to produce motor activity, precision is lost resulting in erratic, uncontrolled, and untimely movements, and actions. Before the 1990s, the sole function attributed to cerebellum was the motor activity. But advances in technology opened new avenues in the field of cerebellum research. For instance, functional imaging studies have shown the activity of the cerebellum in relation to language and attention, and correlation studies have shown the interaction between the cerebellum and non-motor parts of the cortex. Recent research is also trying to explore the role of the cerebellum in other functions such as emotions, memory, or social behaviors [10].

The limbic system is a structure buried deep within the brain underneath the cerebral cortex and consists of sub-structures, the hippocampus, hypothalamus, thalamus, and amygdala. This region is mainly involved in lower-order emotional information processing, long-term memory formation and storage, and olfaction. Hippocampus is one of the well-studied parts of the limbic system, specifically involved in cognitive functions: learning, memory formation and storage, particularly spatial learning, and memory. Morphologically speaking, the hippocampus is densely packed neurons into a seahorse-shaped structure located on the underside of the temporal lobe. Over the years, response inhibition, episodic memory, and spatial cognition have been associated with the hippocampus along with the monitoring of hypothalamic functions. In the past few decades, the hippocampus is attributed to carrying on neurogenesis in the adult stages of life, which before was considered not possible [11]. Amygdala, a small almond-like structure located next to the hippocampus is associated with the brain's reward system i.e., it regulates emotions like pleasure, fear, and anger, and is involved in fight and flight responses. Amygdala contains tracts that connect the hippocampus and entorhinal cortex [12]. Amygdala is responsible for affiliating emotional content to our memories and monitors how robustly these memories are stored [13]. Disruption of hippocampus physiology is observed in Alzheimer's disease, depression, schizophrenia, epilepsy, and many other neuropathies.

Hypothalamus is situated above the pituitary gland (master gland of the body) and is the main regulator of the autonomic system. It receives chemical stimuli from neurons of different brain regions and PNS and works to maintain an internal balance and homeostasis in the body thus called smart control of the body. It has a crucial role in monitoring some basic functions such as thirst, sleep, body temperature, blood pressure, secretion of hormones, and behaviors e.g., hunger, and sexual response [14]. And it does so by either directly influencing the autonomic system or by managing the endocrine system of the body i.e., by hormones. Hypothalamus itself synthesizes and releases some hormones to the pituitary gland such as growth hormone-releasing hormone (GHRH) which modulates the growth of long bones and muscles, gonadotrophin-releasing hormone (GnRH) that is responsible for the menstrual cycle in women, and testosterone secretion in men. It also secretes corticotropin-releasing hormone (CRH) which acts on adrenal glands during periods of stress and modulates the metabolism and immune responses, and many other hormones (Fig. 1.1) [15].

Thalamus is an egg-shaped structure present approximately in the middle of the brain, right above the mesencephalon, and its nerve fibers form multiple connections with the cerebral cortex and other parts of the brain. Thalamus consists of a bundle of nuclei mainly responsible for its function as a relay station. All the incoming information (touch, taste, hearing, and sight except smell) first pass through the thalamus and is then directed to the assigned cortical areas [16]. Thalamic nuclei are of excitatory and inhibitory nature, these neurons receive inputs from the body and present the selected information to the cortex via thalamocortical radiations. Thalamus is well connected to the hippocampus, mammillary bodies, and fornix via the mammillothalamic tract. This connection of the thalamus with the limbic

structures highlights its potential involvement in learning and episodic memory and regulation of sleep and wakefulness [17].

The pituitary gland known as the master gland of the body is a pea-sized structure situated below the hypothalamus involved in the synthesis and secretion of various hormones and monitors the hormonal homeostasis of the whole body by keeping a check on other hormone-secreting glandular structures. Some of the hormones synthesized and released by the pituitary gland are growth hormone (GH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH), prolactin, and luteinizing hormone (LH) [18]. GH secretion is mediated by the hypothalamus releasing GHRH, GH acts on almost every cell of the body, but its principal targets are skeletal muscles and bones. It has a direct effect on the metabolism of proteins, fats, and carbohydrates i.e., it is anabolic and stimulates protein synthesis in the growing tissues, it decreases glucose utilization and enhances the mobilization of the fatty acids from the adipose tissues. FSH and LH are synthesized by the pituitary gland under the instruction of hypothalamic GnRH. These two hormones regulate the functions of male and female gonads i.e., ovaries and testes. FSH stimulates the growth of follicles in ovaries and LH triggers ovulation and promotes the secretion of progesterone. While in males, FSH is required for spermatogenesis, and LH fosters testosterone secretion of Leydig cells of the testes [19]. The pituitary gland also regulates the body's responses during times of stress by ACTH, which is released under the control of hypothalamic CRH. The main function of ACTH is to act on the adrenal cortex and stimulates the production of stress hormones such as glucocorticoids during stress hours [20].

1.3 Brain Barriers System and Its Physiological Significance

The concept of brain barriers refers to the evolutionary formation of physical barriers in the brain that separates the flowing blood from the neurons and regulate communication between the periphery and the brain. The brain is protected by three main brain barriers: blood-brain barrier (BBB), blood-leptomeningeal barrier (BLMB), and blood-cerebrospinal fluid barrier (BCSB). The brain barrier system is mainly responsible for the protection of the CNS from foreign toxins and chemical insults. The BBB is a monolayered structure of endothelial cells firmly held together by transmembrane proteins. BBB also called absolute or true barrier is a structure of tightly junctioned endothelial cells, pericytes, basement membrane, and astrocyte end-feet. It encompasses the blood supply of the brain thus separating the blood from the CNS surroundings. BBB is mainly responsible for the dynamic exchange of ions, nutrients, molecules, and cells between the brain and blood. Each component of BBB has its functions, such as pericytes protecting endothelial cells and are involved in vascular development, astrocytes regulating glucose transport across BBB, and endothelial cells are responsible for the structural integrity of the BBB and vaso-regulation [21]. However, during

inflammatory insults or non-homeostatic conditions, BBB integrity is compromised, and it allows the unsupervised infiltration of peripheral immune components to the brain resulting in CNS dyshomeostasis [22].

BLMB is a structure made up of three layers: dura mater, arachnoid mater, and pia mater, altogether called meninges. It is also a true/absolute barrier due to its limiting nature like BBB i.e., it also restricts the entry of peripheral components into the CNS. Three layers of BLMB and subarachnoid space act as a cushion for the brain and provide support and a route for cerebrospinal fluid (CSF) circulation. The arachnoid layer of the BLMB contains CSF within the subarachnoid space and limits the invasion of activated immune cells from dural blood vessels into the CSF. Leptomeningeal cells line the stroma of the choroid plexus (ChP) and facilitate CSF drainage into the blood and lymphatics. In addition to this, leptomeningeal cells extend deep into the CNS along the outer walls of arteries and ease the CSF entry into the CNS. During homeostatic conditions, BLMB allows negligible transport of peripheral components into the brain, while in inflammatory states, BLMB's restrictive nature is disrupted leading to enhanced infiltration of leukocytes from the periphery into the CNS, resulting in neuroinflammation [23].

BCSFB on the other hand is an immunoregulatory or educational barrier i.e., it functions as a controlled junction between the brain and periphery and monitors neuroimmune communication. It is composed of ChP (structure responsible for CSF production) and CSF, together known as the ChP-CSF system (Fig. 1.2). It provides the brain a physical barrier, helps in the removal of CNS debris by CSF circulation, and acts as an immunosurveillance system owing to its diverse immune cell populations [24]. The unique anatomy of BCSFB regulates the migration of immune cells to the CNS by modulating the expression of adhesion molecules, chemokines, and cytokines at ChP and in the CSF. BCSFB physiological roles are classified as immunosurveillance and immunoprotection and the disruption of this barrier system is termed immunopathology. Immunopathology i.e., ChP-CSF system in disease, this disruption of the ChP-CSF system is highlighted in various neuropathies such as Alzheimer's disease, depression, multiple sclerosis, physiological aging, and many others.

1.3.1 Blood Supply of the Brain

Internal carotid arteries and vertebral arteries are two paired arteries that are the main supplier of blood to the brain. The internal carotid arteries give rise to two cerebral arteries (anterior and middle) which are mainly responsible for the blood flow of the cerebrum. While the cerebellum, brainstem, and base of the cerebrum get their blood intake from the vertebral arteries. The right and left vertebral arteries come together at the pons and join to form a basilar artery. At the bottom of the brain, the Circle of Willis, which is the joining area of the basilar artery and internal carotid arteries is located. This Circle of Willis is a safety feature of the brain i.e., it provides collateral blood flow to the brain in the event of blood vessel damage, thus protecting the brain from ischemia [25].

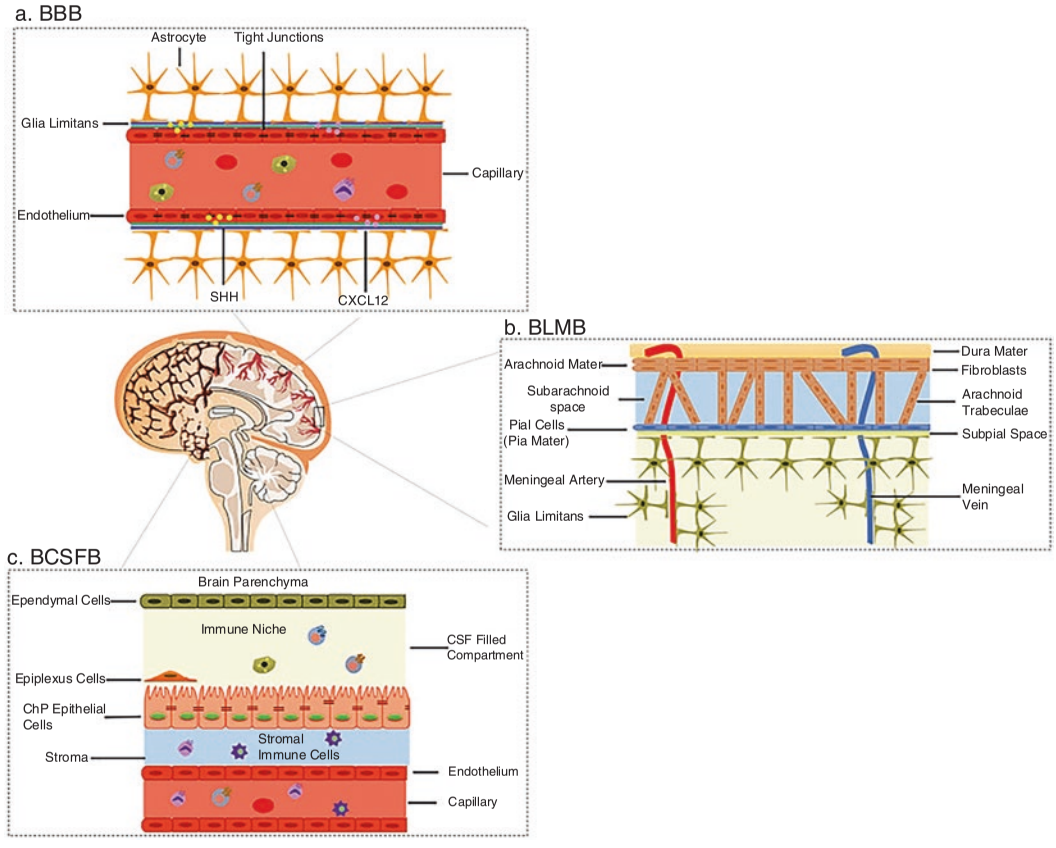

Fig. 1.2 CNS barriers system: Adapted from Ayub, Jin and Bae, 2021 from Fig. 1.1. Three main barriers of the brain i.e., Blood brain barrier, blood leptomeningeal barrier, and blood cerebrospinal fluid barrier

1.4 CNS at the Cellular Level: Structural and Functional Contributions of Various CNS Cells

1.4.1 Neuron

Neuron is the basic structural and functional unit of the nervous system. CNS is made up of more than 100 billion neurons alone excluding the supporting cells to be discussed in the coming sections. Morphologically speaking, a neuron consists of three basic substructures: soma/cell body, dendrites (receiving ends), and axons (transmitting ends). The functional classification of neurons divides them into three categories: sensory neurons, motor neurons, and interneurons [26]. Apart from this classification, neurons are also categorized based on their number of neurites i.e., unipolar, bipolar, and multipolar neurons (Fig. 1.3). A unipolar neuron has one nerve process which extends on both sides of the cell body forming one axon and one dendrite, and sensory neurons fall in this category. Bipolar neurons have two extensions i.e., one axon and one dendrite, and the majority of interneurons are bipolar. While multipolar neurons have a single axon but consist of multiple dendritic extensions and motor neurons fall into this category. There is another category of neurons not very common called anaxonic neurons which lack axons. Neurons are also subtyped based on the shape of dendrites, such as stellated neurons (star-shaped) and pyramidal neurons (of pyramid shape) [27].

Sensory neurons make the sensory part of the nervous system i.e., they collect the information from different sensory receptors across the body and carry it to the brain for processing. Such as visual receptors in the eyes to perceive visual stimuli, auditory receptors for hearing, tactile receptors for touch, and other kinds of sensory

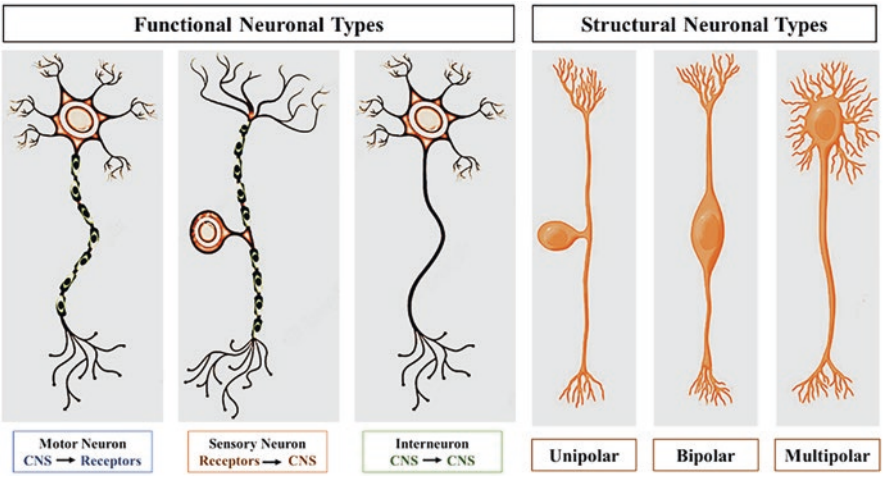

Fig. 1.3 Functional and structural neuronal types: Functional neuronal types include motor, sensory and interneurons. Structural phenotypes include unipolar, bipolar, and multipolar neurons

receptors. The information enters the brain through sensory neurons via the following pathway: the spinal cord to the brainstem, cerebellum, thalamus, and finally to the allocated regions of the cerebrum for the processing of sensory input. Integrative functions i.e., processing any kind of information entering the brain before conducting any response is the fundamental task of the nervous system. 99% of the sensory input received is discarded as unimportant and irrelevant such as continuous contact of the bodily parts with clothing or seat strain while sitting. But at the arrival of important, novel, or alarming stimuli, the information is channeled to the proper integrative areas for processing and motor regions for the desired actions. This phenomenon of channeling and processing of inputs is called the integrative function of the nervous system [28].

After the integration of the sensory inputs, the motor neurons also called effectors come into the function to elicit the desired and the best response to the received stimuli. For instance, the movement of skeletal muscles in times of physical activity or the contraction of smooth muscles in the internal organs. As sensory inputs enter the brain via a specific pathway and each structure in this pathway has its role in monitoring the input, motor output is also regulated at various levels: the spinal cord, brainstem, cerebellum, and motor cortex. Higher regions deliberate the thought process involved in controlling the movement by the lower regions involved in the motor function of the nervous system. This transition of information from sensory inputs to motor actions highlights the working of CNS at different levels for a single or multiplex of stimuli i.e., regulation at the spinal cord level, subcortical or cortical levels. These three levels of CNS have major functional significance in monitoring the input and output of information, ensuring the maximum efficacy of the system [29].

1.4.2 Functional Order in CNS

As described above, CNS has three major levels of functional specificity in information processing and taking an action. Spinal cord level: spinal cord in terms of its functionality has been undermined, as through the years it has been considered only as a conduit for the signals from the body to the brain and vice versa. But recent research and accumulating evidence in literature have started to highlight the cruciality of the spinal cord in the proper functioning of the nervous system and other systems. For instance, reflex arc/reflexes which are the immediate response of the body towards a painful or harmful stimulus are processed in the spinal cord for instantaneous actions. Walking movements, or reflexes that support the movement of legs and body against gravitational resistance or control of local blood supply, digestive system movements, are all monitored by the spinal cord. The higher levels of the nervous system often send commands to control centers in the spinal cord to take action rather than sending signals directly to the peripheral systems [30].

Subcortical or lower brain levels such as the medulla, pons, cerebellum, and basal ganglia are mainly responsible for the subconscious activities of the body. For

example, body equilibrium is calibrated by the joint action of the cerebellum and reticular substance of the pons and medulla, and normal respiration and monitoring of arterial blood pressure are regulated by the pons and medulla. Feeding reflexes such as hunger are controlled by areas in the pons, medulla, amygdala, and hypothalamus. Research has also highlighted that many emotional responses such as anger, sexual responses, excitement, or reaction to pain or pleasure can still occur even after the damage to the cortex, which points out both the physiological and pathological significance of these areas of a lower order [31]. Lastly, the cortical, or higher level is responsible for thought processing and memory storage. And most importantly, lower CNS levels are precisely controlled by the actions of the cortical level, and this intercommunication between these levels is the foundation of proper and maintained functioning of the nervous system in specific and the whole body in general. All this intercommunication occurs at the neuronal level and more specifically at the synapse level, which are the junctions between two communicating neurons and responsible for intraneuronal information transfer [32].

1.4.3 Synapses of the Nervous System

The processing of information in the CNS occurs through a series of electrical and chemical reactions occurring between connected neurons. The electrical transmission of information otherwise called nerve impulse happens mainly in the form of action potentials. Each impulse reaching a neuron might be blocked, changed into repetitive impulses, or can be transformed into intricate patterns of impulses by the integration of signals from other neurons. This interneuronal communication at the chemical level is governed by the release of specific chemicals called neurotransmitters at the neuronal junction. This release of chemicals for information transmission or manipulation of electrical impulses is termed as synaptic function of neurons in the CNS.

The communicative role of synapses in the CNS is governed by their anatomical features. Morphologically speaking, a typical synapse has a presynaptic terminal, synaptic gap (space between two consecutive neurons), and postsynaptic neuronal terminal. Presynaptic terminals are also called knobs, boutons, or end feet owing to small round or oval knob-like anatomical features. This part of the synapse is responsible for the regulation of neurotransmitter release into the synaptic cleft. Presynaptic terminals are equipped with transmitter vesicles (containing required neurotransmitters) and mitochondria which provide energy in the form of adenosine triphosphate (ATP) for the release of neurotransmitters from the vesicles into the synaptic cleft (Fig. 1.4). Depending on the type of nerve impulse received at the presynaptic neuron, either excitatory or inhibitory neurotransmitters are synthesized in the transmitter vesicles. So far, more than 40 neurotransmitters have been reported and some of the best knows are glutamate, epinephrine, nor-epinephrine (excitatory transmitters), gamma-aminobutyric acid, serotonin, and glycine (inhibitory neurotransmitters). These synthesized transmitters are then emptied into the synaptic

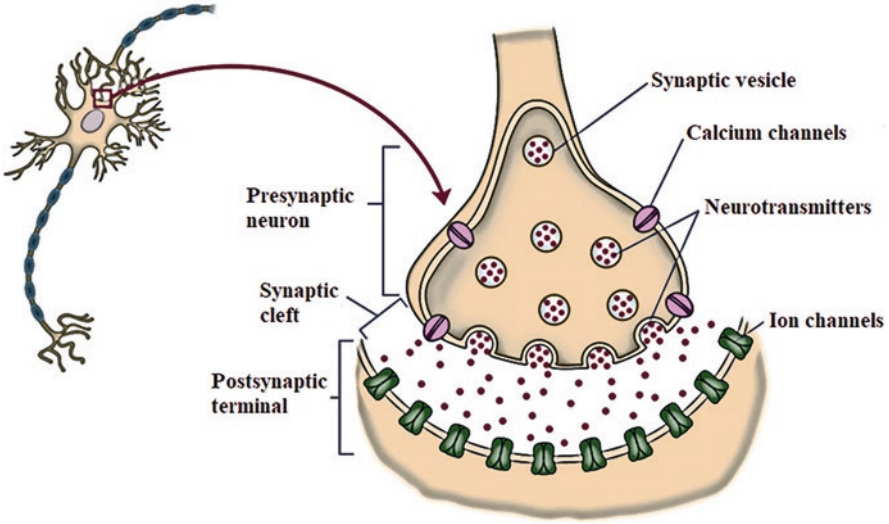

Fig. 1.4 Structural organization of a synapse: Illustration of a typical chemical synapse, consisting of presynaptic terminal containing neurotransmitters in synaptic vesicles, voltage gated calcium channels, synaptic cleft where neurotransmitters are released, and postsynaptic terminal

cleft, which is then recognized by the receptors expressed at the postsynaptic neuronal terminal and leads to either excitatory or inhibitory responses [33].

Based on their functionality, synapses are classified into two categories named electrical and chemical synapses. The majority of synapses in the human CNS are of chemical origin. As described in the paragraph above, these synapses pass signals from one neuron to the other via neurotransmitter release at the presynaptic terminals which in turn will either excite, inhibit, or modify the sensitivity of the signal at the postsynaptic terminal. While electrical synaptic communication occurs via open fluid channels which act as electrical conductors. Most of these channels are the tubular structure of proteins called gap junctions, which make the free movement of ions from one neuron to the other possible. The best examples of electric synapses are the transmission of action potentials between smooth and cardiac muscles [34].

1.4.4 Supporting Cells of CNS

Though neurons are largely responsible for the accurate functioning of the nervous system, the performance of neurons is highly dependent on supporting cells called neuroglia or glial cells. This term was coined in 1907 by Emilio Lugaro, who suggested that neuroglia control the neuronal environment by monitoring the exchange of substances with the extracellular fluid. Advancements over time in glial biology have found evidence that neurons and glia exist in a 1:1 ratio, and are easily distinguishable as they don't possess axons, these cells do not form synapses and can

divide throughout the lifespan of an individual. Six types of neuroglia i.e., microglia, astrocytes, oligodendrocytes, and ependymal cells exist in CNS, satellite glial cells, and Schwann cells are present in the PNS (Fig. 1.5).

Astrocytes is a name derived from the Greek word Astron meaning star. These star-shaped cells are the most abundant type of neuroglia and have various physiological roles ranging from making BBB to migration of cells, from regulating metabolic activities in the CNS to facilitating the formation of synaptic connections. The most studied role of astrocytes is their contribution to the formation and maintenance of BBB. The astrocytic-end feet or foot processes, wrap around the blood capillaries, forming the physical barrier which separates the circulating blood and neurons. They regulate the exchange of substances at the BBB and are effective in filtering out inflammatory or harmful substances, preventing the onset of pathology [35]. Metabolic activities governed by astrocytes ensure the steady supply of energy to neurons for proper functioning, for instance, they serve as reservoirs of glycogen, which can be utilized by the brain in the hours of need. Apart from this, these star-shaped cells also help in the removal of byproducts generated as the result of cellular metabolism. Piling evidence has reported that defective astrocytic metabolism can lead to many neurological abnormalities such as depression, anxiety, bipolar disorder, or neurodegenerative pathologies like Alzheimer's disease [36]. Astrocytes guide the migration of progenitor cells in the CNS, which then differentiate into different cell types. Literature also suggests astrocytes ensheath the neuronal synapses to form tripartite synapses, where they tend to influence synaptic communication and neuronal plasticity. Some reports also point out their role in the release of specific neurotransmitters also called gliotransmitters such as glutamate, ATP, D-serine, and many others. These released transmitters then act on both pre and post-synaptic neuronal terminals to regulate synaptic transmission [37].

Microglia also known as brain macrophages or immune cells of the CNS are the second most abundant neuroglia. They have small oval-shaped nuclei and

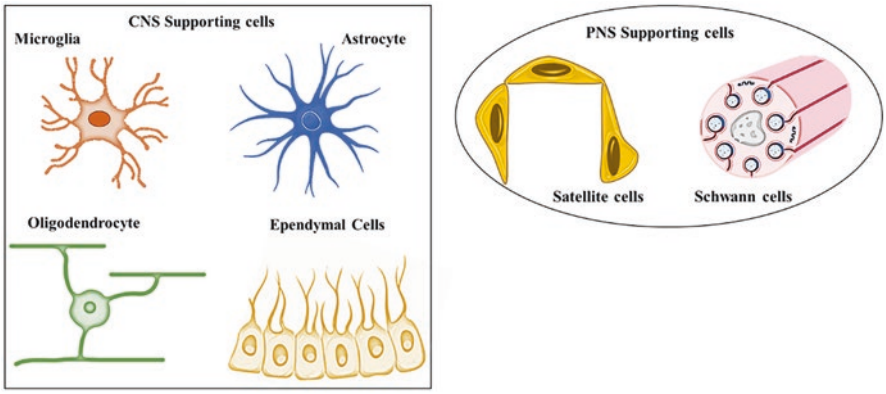

Fig. 1.5 CNS and PNS supporting cells: CNS supporting cells also known as neuroglia include microglia, astrocytes, oligodendrocytes, and ependymal cells. PNS supporting cells are Schwann cells and satellite cells

projections from their cell soma, which help their chemotactic movement in the CNS. These cells enter the CNS during embryonic development and attain the role of brain immune cells. Their origin differs from other neuroglia, while other glial cells originate from neuroectoderm (embryonic layer which gives rise to nervous tissue), microglia are derived from mesoderm, which forms blood and immune cells. During homeostatic conditions, microglia patrol the brain, and clear out any damaged or toxic substances. Microglia have different physiological states, and each type possesses a particular function in a particular condition. For instance, ameboid microglia also called surveilling microglia are prevalent during brain development and have scavenger properties. Ramified microglia have long branches, and maintain an immunologically stable environment in the adult brain. While activated microglia are the type of microglia present in neuroinflammatory conditions, these microglia are in a fully active phagocytic form, have short thick branches, are neurotoxic, and act as antigen-presenting cells. Apart from this classification, microglia also have M1 and M2 forms, former proinflammatory and later anti-inflammatory. In different pathological environments, such as inflammatory or degenerative, the polarization of microglia from M2 to M1 form is commonly observed, which exacerbates the ongoing pathology. Microglia also regulate the infiltration of peripheral immune cells such as monocytes into the brain via the release of specific chemokines, influencing BBB permeability [38]. Recent literature has pointed out the critical role of microglia specifically in depression and Alzheimer's disease, in the former it regulates the inflammatory response while in the latter it is involved in the phagocytosis of amyloid-beta (Aβ) plaques. Microglia also monitor synaptic pruning, which is the elimination process of extra synapses during early childhood and adulthood. Studies in mice lacking microglia have shown delayed synaptic pruning and synaptic abnormalities resulting in developmental disorders [39].

Oligodendrocytes are myelin sheath-synthesizing glial cells, which are derived from oligodendrocyte precursor cells. The term oligodendrocyte is derived from a Greek word meaning a cell with few branches, and these few branches of oligodendrocytes are wrapped around the adjacent neuronal processes to provide myelin sheath protection, while soma and nucleus remain separated. The myelin-containing cells in the PNS are called Schwann cells, which serve the same function of providing myelin protection to the nerves in the PNS. Unlike Schwann cells, oligodendrocytes can wrap around multiple axons at the same time, for example, one oligodendrocyte can cover almost 50 axons at a time while Schwann cells can wrap around only one neuronal process. The main purpose of this cellular ensheathing is to ensure the effective and fast transfer of nerve impulses without the loss of signal intensity by preventing the leakage of ions and decreasing the cell membrane capacitance.

The ideal example of this type of fast travel of nerve impulse is observed at the nodes of Ranvier (myelin sheath gaps) called saltatory conduction (which is the propagation of action potential along the myelinated axons) at the speed of 150 m/s [40]. Apart from increasing the signal velocity, myelin sheath also ensures an energy-efficient process, by reducing the energy expenditure over the axonal

membrane. With advances in the studies in this field, oligodendrocytes have been reported to also secrete some neuronal trophic factors such as glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), or insulin-like growth factor-1 (IGF-1). Any injury, infection, or autoimmune action which results in demyelination can result in serval pathological states as the most common disorder associated with demyelination of neurons in multiple sclerosis. Demyelination results in the loss of effective signal transmission over the neurons, which can lead to various signs and symptoms such as muscle weakness, blindness, double vision, and disrupted coordination [41].

Ependymal cells are ciliated cuboidal to columnar epithelial cells that develop from radial glia and line the brain ventricles and central canal in the spinal cord. Given their location in the brain, these cells are primarily responsible for monitoring CSF homeostasis. Their apical surface is provided with cilia which facilitate the CSF circulation in the CNS, and microvilli which serve the function of CSF absorption. In addition to the lining of the ventricles, within brain ventricles, a modified form of ependymal cells exists in conjunction with capillaries called tela choroidea, which form ChP, the structure responsible to produce CSF. The tight junctions between these ependymal cells regulate the exchange of nutrients, ions, and other factors between ventricles and peripheral blood. These epithelial cells also secrete some chemokines to attract immune cells such as monocytes, memory $CD4^+$ T cells, or peripheral macrophages into the CNS, hence explaining the complex immune profile of the CSF. The clinical significance of these cells can be highlighted by the fact that any abnormality or dysregulation of their function will ultimately affect the functioning of ChP and CSF. Ependymoma, the tumor of ependymal cells is the most common pathology associated with these cells, dysregulation of their functionality can affect the physiology of ChP which can lead to several neurodevelopmental disorders such as autism, schizophrenia, intellectual disability, or in some cases neurodegenerative pathologies [42].

Satellite glial cells (SGCs) are exclusively found in PNS ganglia, particularly in sensory, sympathetic, and parasympathetic ganglia, where they form neuronal envelopes by covering the cell bodies of neurons. SGCs are equipped with potassium channels and glutamate transporters via which they monitor the microenvironment around neurons. SGCs share many molecular markers with other neuroglia such as they express glutamine synthetase, potassium channels, and glutamate aspartate transporter like astrocytes. SGCs express transcription factor Sox10 like oligodendrocytes, they contain cadherin19, a Schwann cell marker, and share many other morphological and molecular similarities. Closely located SCGs tend to form strong interactions, otherwise called SGCs-SGCs coupling, or with neurons, neuron-SGCs coupling. This neuronal-SGCs and SGCs-SGCs coupling plays a critical role during injury to the PNS and pain sensation. Recent research has reported the contribution of SGCs in sensory glia during pain pathology. Research has observed that inflammation or peripheral nerve damage can activate SGCs in sensory ganglions. This results in the upregulation of astrocyte marker glial fibrillary acidic protein (GFAP), an increase in SGCs-SGCs coupling, and enhanced reactivity of SGCs to the ATP (pain mediator). In addition to that, SGCs upon activation also release proinflammatory cytokines such

as interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor, and fractalkine, which in turn can act on the neurons and result in hyperexcitability. The working mechanism of SGCs has been explored in many clinical pathologies related to pain such as systemic inflammation, chronic post-surgical pain, diabetic neuropathic pain, and post-herpetic neuralgia. Though the potential contribution of SGCs in pain has been explored in rodent models, a lot is still needed to be explored about the physiological significance of SGCs in homeostatic states [43].

Schwann cells are the oligodendrocytes of PNS except they only wrap myelin sheath around a single neuron, unlike oligodendrocytes which can wrap multiple axons at a time. These cells are derived from the neural crest, neural crest cells differentiate into Schwann cell precursors, which migrate to the periphery along the axonal tracts and proliferate. These cells play a significant role in PNS nerve development, maintenance, functioning, and regeneration. Schwann cells are categorized into two types based on their myelinating properties: myelinating and non-myelinating cells. Myelinating Schwann cells associate and ensheath a single axon, and like oligodendrocytes, this process is not continuous. Myelinating Schwann cells help the fast and energy-efficient transmission of nerve impulses over the axons. While non-myelinating Schwann cells associate with several smaller axons such as those involved in transmitting pain and temperature stimuli and make Remak bundle (group C nerve fiber). And this non-myelinating gap exists between the myelinated axons and make-up nodes of Ranvier as described in the oligodendrocyte section. Schwann cells can lose their myelinating properties in demyelinating neuropathies, autoimmune reactions, or external toxin attacks. These pathological states can displace the Schwann cells away from the nerve fibers which can ultimately lead to the loss of proper nerve conduction or in some cases complete blockade of nerve impulse transmission down the axons as in Guillain-Barré syndrome and diphtheria [44].

The comprehensive description of supporting cells of CNS and PNS highlights their critical physiological contribution and how dysfunction of any of these can lead to neuropathies, and not only this but how this can affect the proper functioning of neurons. The following section underlines the several pathologies ranging from neurodevelopmental disorders to autoimmune disorders to neurodegeneration and how all cellular populations play a role in either contributing to or alleviating these pathologies.

1.5 Brain in Disease: Overview of Various Brain Pathologies

A wide range of pathologies can affect the brain, and their incidence is increasing with the increase in the aging population and genetic and environmental alterations. Not every brain disorder can be categorized into a particular classification but there are some established main classes of brain diseases that encompass a variety of pathologies: neurodevelopmental disorders, autoimmune brain diseases, infections, epilepsy, stroke, traumatic brain injuries, mental illness, and neurodegenerative

pathologies. The subsequent section shed light on some of these disorders which will then be discussed in detail in the coming chapter.

1.5.1 Neurodevelopmental Disorders

Neurodevelopmental disorders are a group of disorders that affect the normal development of the CNS, resulting in abnormal brain functions such as emotional, social, and memory deficits, difficulty in learning and processing, and self-control and persist through the lifespan of an individual. Autism spectrum disorder (ASD), Attention-Deficit/Hyperactivity disorder (ADHD), and intellectual disability (ID) are the main pathologies included in this category. The pathophysiology of these disorders is very complex and ranges from genetic mutations to environmental factors or in most cases the combined effect of these two and other biological stimulants such as psychosocial risks. For instance, intellectual disability is specifically associated with mutations in specific genes, and some variants of ASD and ADHD also result from genetic alteration. While the majority of ASD and ADHD cases result from the mutual effect of genetic and environmental factors such as during pregnancy abuse of alcohol, tobacco, or drugs by the mother, poor socioeconomic state, childhood traumas, or environmental contaminants (lead, methylmercury), low birth weight, or preterm birth.

ASD, previously known as autism or pervasive disorder is a lifelong condition characterized by deficits in social interactions and communication, repetitive behaviors like flapping arms, poor motor coordination, learning problems, and enhanced sensitivity to sensory stimuli like loud noises. According to the world health organization (WHO), about 1 in 100 children is affected by autism. Literature reports that specific genetic causes account for up to 10–20% of ASD cases, while the rest of them are the result of the combined effect of genetic and environmental risk factors. There are no specific diagnostic techniques to determine ASD, but healthcare workers receive specific training in behavioral screenings and evaluations to assess the disorder. No drugs have been produced so far that can cure the pathology completely, and the medicine given to the affected individuals is used only to alleviate some of the signs and symptoms. Autistic children and adults mainly go through behavioral therapies aimed to address the core behavioral abnormalities and to reduce their severity. Apart from the affected individuals, the entire family is also advised to undergo specific training that helps in educating the parents and other members of the family about autism, which can help in improving living conditions for both family and the autistic person [45].

ADHD also a neurodevelopmental disorder is characterized by inattentiveness, impulsivity, and hyperactivity more pronounced in affected persons than in individuals of the same age. ADHD symptoms usually appear around the age of 7 years, and children suffering from ADHD exhibit specific behavioral activities like distractedness, diminish academic performance, social problems, and difficulty in following instructions or completing a task. Systematic reviews report

that about 2–7% of people are suffering from ADHD globally. ADHD share somewhat the same pathophysiology as ASD, but with different disease outcome and different brain regions involved. ADHD in children, teens, and adults is diagnosed via an established protocol i.e., identification of ADHD symptoms, ruling out of alternative causes of symptoms, and identification of comorbid conditions such as depression or anxiety. Unlike ASD, ADHD is treatable and some drugs have proved effective in the treatment of ADHD. Psychostimulants (drugs used to stimulate CNS), methylphenidates (often known as Ritalin), and dextroamphetamine are the most used psychostimulants for ADHD. These drugs help individuals with ADHD focus their attention and ignore unnecessary thoughts and stimulants. Data reports that stimulant medicines are 70–90% effective in patients with ADHD [46].

ID also called mental retardation is characterized by diminished intellectual functioning in a person before the age of 18, or put in other words IQ of less than 70. These individuals also display impaired communicative, interpersonal, and social skills, difficulty with self-care, and in some cases severe retardation. Genetic mutations, traumatic brain injuries, maternal use of alcohol or drugs, or infection during pregnancy are observed to be the major causes of ID according to the reports. However, the main causes of intellectual disability are still unknown in 30–50% of the cases, but the identification of triggers in severe retardation (IQ less than 50) is more frequent than in individuals with mild retardation (IQ between 50 and 70) which remains unknown in more than 75% of cases. To diagnose an intellectual disability, a series of tests are performed which include IQ tests, psychological testing, special education tests, hearing, speech, and vision tests, and many others to formulate a conclusive diagnosis. Currently, there is no treatment for this disorder, but there is occupational therapy (self-care training, employment activities, skills, domestic activities), speech therapy (to improve communication skills, vocabulary, speech articulations, and language skills), and physical therapy (improves sensory integration, quality of life, and educating the individuals to adaptive solutions to mobility problems) [47].

1.5.2 Neurodegenerative Diseases

Neurodegeneration refers to the progressive loss of either structure or function of a neuron, ultimately resulting in neuronal death, and pathologies occurring because of neurodegeneration are called neurodegenerative diseases. These diseases occur at several brain levels i.e., from molecular to systemic, and affect memory, motor movements, coordination, speech, and breathing and so far, these are incurable. Neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), Huntington's disease including many others. Many of these disorders are of genetic origin and result from alterations at

the genetic level, but in some reported cases infections, alcoholism, toxins, tumor, or stroke can result in the diseased outcome.

AD is the most common neurodegenerative disease mainly occurring in people over the age of 60 and is the prevalent cause of dementia (memory loss). It is characterized by loss of memory, affected learning, difficulty in managing daily routine tasks and coping with unfamiliar situations, and disorientation. Abnormal protein aggregation especially of Aβ plaques and tau neurofibrillary tangles lead to neuronal damage and loss in the cerebral cortex and some subcortical areas resulting in the temporal and parietal lobe and some parts of the frontal cortex atrophied. Research reports that the first symptoms of AD can appear after 10 years of the disease onset, thus making an early and timely diagnosis difficult. The current diagnostic methods used are brain imaging, mental status testing, neuropsychological, and blood testing. As neurodegeneration is an irreversible process, no cure exists at the moment for the treatment of AD or other neurodegenerative diseases, but some drugs are assigned to the patients to alleviate symptoms [48].

PD is the second most common chronic neurodegenerative disease affecting 1% of the population over the age of 60. The signs and symptoms of PD are categorized into motor and non-motor, former include bradykinesia (slow movements due to muscle weakness), tremors, loss of body coordination, rigidity, and stiffness, and later includes dysphagia (trouble with swallowing), drooling or monotonous facial expressions. PD shares some similar pathological features with AD but the affected area in question is different. In PD mainly dopaminergic neurons are lost in substantia nigra (a structure in basal ganglia that regulates body movements) presumably due to the accumulation of aggregated alpha-synuclein complexes in Lewy bodies within the affected neurons. PD like AD is both familial and sporadic i.e., it can be hereditary or occur at later stages in life due to some non-genetic factors. PD is diagnosed based on blood tests, computerized tomography (CT) scans, magnetic resonance imaging (MRI), and genetic testing. There are some drugs available to treat the symptoms of PD but no medication for a cure exists for now [49].

ALS or Lou Gehrig's disease is a neurodegenerative disease that particularly affects the neuromuscular system causing muscle weakness and leading to difficulty in talking, eating, or moving. It is a progressive disorder and throughout the disease, the symptoms get worse, and with time muscle atrophy and wasting occur. As the symptoms get worse, the individual starts to experience breathing problems and most ALS patients die of respiratory failure because of weakened muscle contraction. ALS affects both upper-level neurons (in the brain) and lower levels (spinal cord and brainstem) and both genetic and environmental factors can lead to the disease. Sporadic cases of ALS have reported the aggregation of TAR DNA-binding protein 43 (TDP-43) and RNA-binding FUS proteins in the affected motor neurons. ALS is diagnosed by a couple of tests including an electromyogram (EMG), MRI, nerve conduction study, spinal fluid test, and muscle and/or nerve biopsy [50].

1.5.3 Autoimmune Brain Diseases

Autoimmune brain diseases occur when the body's immune system mistakenly attacks the healthy cells and tissues of the nervous system resulting in the inflammation of the affected area. This inflammation of the affected tissue or cells can lead to neurological and psychological signs and symptoms. Affected individuals can develop symptoms like seizures, loss of vision, muscle weakness, sleep problems, depression, hallucinations, and an overall decline in the quality of life. Autoimmune brain diseases include Multiple sclerosis (MS), autoimmune encephalitis, autoimmune-related epilepsy, and many others.

In MS, the immune system attacks the healthy myelin-producing cells in the brain and spinal cord, resulting in the disruption of proper nerve signal transmission. This impaired signal transduction can lead to optic neuritis (blurriness or pain in the eye), muscle weakness or spasms particularly in arms and legs, fatigue, loss of coordination, changes in the gait, and memory problems. Epidemiological studies suggest that MS is more prevalent in women than men and affected individuals fall in the age group of 20–40 years. Many factors can trigger the onset of MS like viral or bacterial infections, living in an environment with less sun exposure can lead to vitamin D deficiency (a risk factor for MS), how your immune system works, and genetic mutations. How genetics play a role in the onset of MS is still unclear but having a family member with MS increases the risk of MS development. MS is diagnosed by multiple tests which particularly include MRI to look for the lesions in the brain or spinal cord resulting due to damage to the myelin sheath, physical examination, and some blood and urine tests. Currently, there is no cure for MS, the treatment focuses on managing symptoms and slowing the disease progression [51].

1.5.4 Neuropsychiatric Disorders

Neuropsychiatric disorders are a class of mental, behavioral, and emotional diseases that occur both at cellular and systemic levels and affect a person's ability to carry out daily life tasks and diminish the quality of life. The pathologies in this category mostly result from environmental factors such as psychological traumas, poor socioeconomic status, infections, comorbidity with other diseases, and in some cases genetic predisposition. At the cellular level, microglia and neuronal communication are highlighted in the pathology of these orders, and their contributions are now explored in the research to establish some mechanisms and pathways. Neuropsychiatric disorders include anxiety, depression, bipolar disorder, schizophrenia, and many others.

Anxiety, depression, and bipolar disorder: These three disorders share some similar signs and symptoms, and pathophysiology. The shared symptoms include nervousness, panic, anhedonia (sadness), mood swings, mania, and changes in thinking patterns. These disorders also have some common causative initiators like traumas,

chemical imbalances in the brain, medical conditions, long-lasting stress, or sometimes genetics or hereditary. The diagnosis of any of these disorders requires an extensive observation of affected individuals' behavior, for instance, in case of depression, symptoms of sadness or hopelessness lasting for more than 2 weeks, physical examination, blood tests, and thorough examination of family medical history are required. The common treatment for these disorders is a combination of medication (anxiolytics, anti-depressants), psychotherapy, and counseling. Establishing a healthy lifestyle such as exercise, meditation or yoga has also been observed to improve the quality of life for individuals [52].

Schizophrenia refers to a spectrum of conditions that fall in the range of psychosis and involve a disconnection from reality like suffering from hallucinations or delusions. The common symptoms of schizophrenia include slow/unusual movements, incoherent/disorganized speech, delusions, hallucinations, depression/anxiety, paranoia, and alcohol or drug abuse. According to statistics, about 2.27 million new cases are reported each year globally, and about 22.1 million people are suffering from this disease at the moment. For schizophrenia diagnosis, a person must have at least two of five main symptoms lasting for no less than a month. Other medical tests are performed to rule out other problems like stroke, injuries, tumors, or other diseases. Schizophrenia is treatable but for now, no full cure exists for this disease. This treatment includes medication (anti-psychotic drugs), psychotherapy, and in some cases electroconvulsive therapy [53].

1.6 Conclusion

This chapter discussed nervous system structural organization and shed light on the cellular composition of the nervous system and the various roles performed by specific parts and cells. And lastly, an overview of some of the common brain disorders is provided, detail of which will be discussed in the coming chapter. This discussion laid the foundation for the coming section as the basic knowledge of brain anatomy and physiology is essential to understanding and comprehending neuropathies in the light of structural, molecular, and behavioral abnormalities.

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