Chapter 1
Neuroplasticity

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1.1 Introduction

Functional recovery after nervous system injury remains a paradox. Following non-fatal brain damage, neural function takes days, weeks, or months to improve, many a time dramatically, and sometimes the process can continue for years. The extent to which the nervous system recovery occurs depends on many factors, including the age, location, amount of tissue damage, rapidity of damage, rehabilitation program, and environmental and psychosocial factors. The ability of the nervous system to adapt or modify functions and compensate for damage has played an imperative role in recovery; however, the importance of this ability has been appreciated only recently.

The term "plasticity," used in neuroscience for well over a century, is a loosely defined concept that stands in contrast to elasticity and brittleness. Following an impact, an elastic object returns to its original form, whereas a brittle object shatters. A plastic object may survive and continue to function but is changed by the impact. Injury to the nervous system causes similar "plastic" changes, which form the physical basis of rehabilitation. Neural plasticity "or" neuroplasticity can be defined broadly or narrowly. In the broad sense, all learning processes can be included in the concept, whereas in the latter, evidence of morphologic changes such as sprouting and synaptogenesis is essential. Neuroplasticity can also be defined as the ability to adapt or modify the neural structural organization and function to the imposed change. The mechanisms underlying neuroplasticity can include

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A. M. Joshua (ed.), *Physiotherapy for Adult Neurological Conditions*,
https://doi.org/10.1007/978-981-19-0209-3_1

neurochemical, receptor, end plate, and neuronal structural changes. The concept of plasticity is less often stretched to those adaptations to external circumstances that fall outside the normal range. Even such plastic changes can be physiological or structural, which usually require time to form. For instance, regular marathon running can increase the oxidative metabolism in largely anaerobic muscles of a healthy subject who is not used to such physical activity.

It is essential to know the concept of plasticity, which is central to the work of physiotherapists. In clinical practice, many of the problems a physiotherapist faces result from too little or excess amount of plasticity. For instance, damaged motor axons within the spinal cord will not regenerate, causing permanent motor impairment, whereas injured axons in a peripheral nerve may grow easily but indiscriminately, limiting the functional recovery of reinnervated muscles. One must realize that many of the procedures used in physiotherapy exploit the plasticity inherent in the neuromuscular system to maximize rehabilitation.

1.2 Historical Background

In 1890, William James, an American philosopher and psychologist, was the first to suggest the theory of neuroplasticity in his work "Principles of Psychology." He suggested that the human brain is capable of continuous functional changes. In subsequent years, Santiago Ramón y Cajal, a Spanish neuroanatomist who first defined the neuron as the anatomical, physiological, genetic, and metabolic unit of the nervous system, suggested that an increase in the number of connections could augment the capacity of the brain. In 1893, Eugenio Tanzi, an Italian neuropsychiatrist, proposed that during the process of learning or practice, repetitive activity in a neuronal pathway produces hypertrophy, thus reinforcing the already existing connections. Michael Foster and Charles Scott Sherrington, in the year 1897, coined the term "synapse" (known as "junction" by Cajal) and identified it as the device that ensures unidirectional transmission of signals along neural pathways. Interestingly, Sherrington did not elaborate on any possible relations between learning and synaptic plasticity. Later on, in 1906, Ernesto Lugaro suggested the chemical nature of synaptic transmission and formulated the link between Tanzi's theories and Cajal's ideas of neurotropism. Though Tanzi and Lugaro were considered to be the supporters of Cajal's ideas, there remains a mystery about who first coined the term plasticity.

For a very long time, it was believed that the improvement does not occur in man beyond a period of 2 years and that paralysis is permanent following a cerebral accident. In 1915, Shepherd Ivory Franz and coworkers in an article titled "The Possibility of Recovery of Motor Function in Long-standing Hemiplegia," stated that the return of function in a paralyzed segment exists much beyond the time limit set by some neurologists. In the same article, they explained the assumption of function by other portions of the brain as the possible reason for the recoveries. Robert Ogden and Shepherd Ivory Franz, in 1917, provided the initial

evidence for functional recovery in the affected upper limb through forced use, following immobilization of the unaffected upper limb of rhesus monkeys. They hypothesized that the return of function was due to behavioral recovery and possible plasticity of the cortex and suggested that the "vicarious" functions of other cerebral parts had to be investigated. In 1923, during the experimental research on monkeys, Karl Lashley demonstrated specific neuronal pathway changes as evidence of plasticity.

The twentieth century witnessed an enormous body of work focused on the properties of synaptic transmission. The Canadian psychologist Donald Olding Hebb, in his publication "The Organization of Behaviour," in 1949, articulated a theory regarding the possible neural mechanisms of learning and memory, which subsequently came to be known as "Hebb's postulates" and had a vast influence on neurophysiological studies. Though "Hebb's postulates" and "Hebbian plasticity" are two terminologies widely used in the literature, Hebb himself expressed a mixture of amusement and irritation and admitted that he did not propose anything new. In 1948, Jerzy Konorski, a Polish neurophysiologist, was the first to define the term "neuroplasticity" and postulated that morphological changes in neural connections could be the substrate of learning. Konorski suggested a theory by which neurons that have been activated by the closeness of an active neural circuit can change and incorporate themselves into that circuit. Stanley Cohen and Rita Levi-Montalcini in the 1950s first discovered the nerve growth-stimulating factor from mice sarcomas. Eric Richard Kandel and Ladislav Tauc, in 1965, published the first evidence linking short-term plasticity to behavioral modifications in *Aplysia*, a large, shell-less marine snail or sea hare.

Several behavioral and neurophysiological experiments suggested that the sensory pathways are plastic. Paul Bach-y-Rita, an American neuroscientist, proposed the concept of sensory substitution and, in 1969, demonstrated sensory plasticity by delivering cutaneous vibratory stimuli to the back of the blind patients. The optical images from a TV camera were real-time converted to cutaneous vibratory stimuli, which helped the blind patients to see.

About 20 years after the introduction of Hebb's theory, experimental evidence supporting Hebb's long-term potentiation was discovered in the dentate gyrus of the rabbit hippocampus. In 1986, Caroline Herron and coworkers demonstrated the involvement of N-methyl-D-aspartate (NMDA) receptors in synaptic plasticity. Wickliffe Abraham and Mark Bear, in the year 1996, introduced the term metaplasticity, a phenomenon that involves the activity-dependent changes in neuronal function that modulate synaptic plasticity, also known as "the plasticity of synaptic plasticity." The role of metaplasticity is unclear and might be serving to maintain synapses within a dynamic range of activity, allowing synapses and networks to respond to a changing environment.

During the late nineteenth and early twentieth century, several scientists had to fight against an academic dogma, which disapproved the existence of neuroplasticity among the adults, except during the developmental phase and younger ages of life. Michael Merzenich identified two distinct periods of brain plasticity: the critical period, a period when the child's brain establishes neural processes for the

stimuli to which it is presented, and the period of adult plasticity, a period when the adult brain refines its neural processes as it masters a variety of tasks.

Though a considerable body of work has focused on evaluating dynamic changes in neural circuitry, there is mounting evidence that motor training can induce structural changes, which include changes in gray and white matter density. In 2008, Lynne Gauthier and co-researchers, in a study on constraint-induced movement therapy, a treatment proposed to improve motor function after stroke, demonstrated increased matter density in the affected cerebral hemisphere. An important factor that contributed to substantial advances in the understanding of neuroplasticity has been the development of noninvasive techniques for measurement of plastic changes. Noninvasive techniques like positron emission tomography (PET), magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), real-time fMRI, magnetoencephalography (MEG), and transcranial magnetic stimulation (TMS) have all played crucial roles in the evaluation of plastic processes associated with functional recovery following central nervous system lesions.

1.3 Plasticity Within the Developing Brain

Though the plasticity in development and young age group is not a topic for elaboration in this textbook, the author believes that a short description of the same is appropriate. The brain is most sensitive to experience during development and childhood, particularly when the changes are most dramatic. For instance, the language acquisition capacity of a toddler is remarkable as compared to an adult. Even the cells within a developing neuromuscular system have a higher capacity for adaptability than mature ones. Such capacity is essential to facilitate interaction between different types of cells within the neuromuscular system and is particularly crucial for matching the function of the different components and promoting specificity of motor control. Fortunately or unfortunately, this has both beneficial and harmful consequences. For example, the programmed cell death associated with neuromuscular system development reduces the number of motor neurons by about 50% to match the number of neurons to the muscle and is partly regulated by a retrograde signal from the muscle. It is assumed that these neurons appear to compete for this signal, and an increase in the number of muscle fibers available for the motor neuron increases the survival possibility, while reduction increases motor neuron death.

Developmental plasticity has four special features. The first feature is found in the cells within the subventricular zone, a region situated on the wall of each lateral ventricle and the dentate gyrus of the hippocampus (Fig. 1.1). Both the abovementioned regions contain stem cells that remain active throughout life. The subventricular zone cells produce both glial and neural progenitor cells, which have the potential to migrate into cerebral gray or white matter, even in adulthood. In humans, these cells appear mostly quiescent but can become activated, largely in response to stress to the health of the brain. The stem cells in the hilus of the dentate gyrus

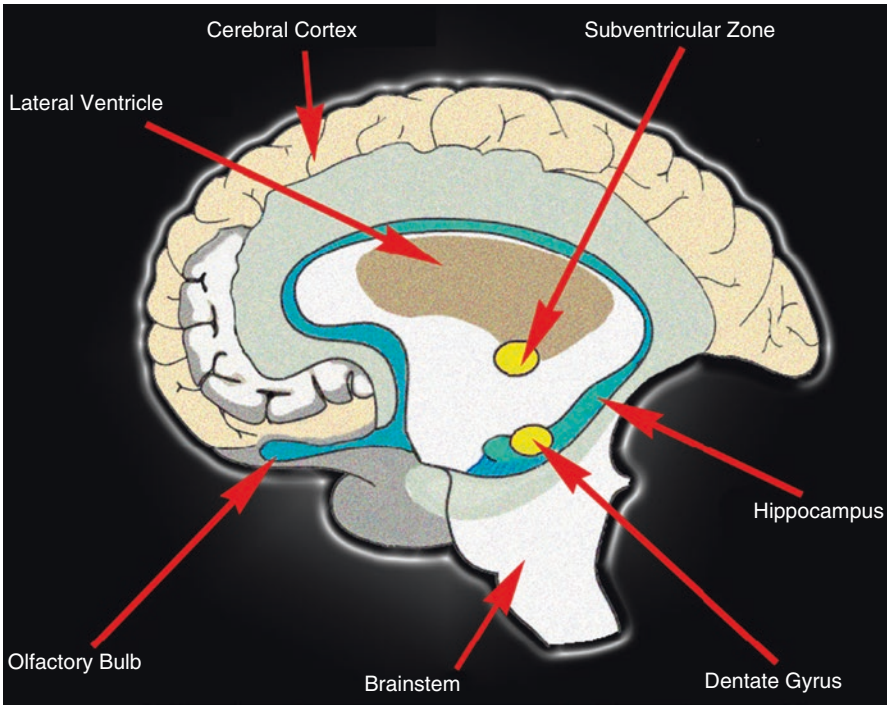

Fig. 1.1 The subventricular zone and the dentate gyrus of the hippocampus

produce new neurons at a slow and steady pace throughout life; however, the potential for generating new neurons (neurogenesis) declines with aging. The functional role of these new neuronal cells is not entirely understood, but these cells do integrate with the existing neurons and may play a role in the formation of new memories.

The second special feature consists of the three types of plasticity distinguished in the developing brain: experience-independent, experience-expectant, and experience-dependent. Experience-independent plasticity involves nervous system changes regardless of the environment and unfolds over time through a tightly regulated series of molecular events. It occurs mostly during the prenatal developmental phase when the genome generates a rough approximation of connectivity that is modified by certain specific events. Neuronal cell connectivity increases when they are active together and weakens their connections when not coincidentally active. Experience-expectant plasticity occurs mostly during early postnatal development and describes the normal, generalized development of neuronal connections and will not unfold until they are triggered by specific environmental cues that the brain expects to encounter. For instance, the visual cortex will not be fully functional until the neonates open their eyes for the first time, and the young children will not learn the language until they hear others' speech. Experience-dependent plasticity refers to ways neural pathways are strengthened through repeated engagement, which

begins in early postnatal life and continues for a lifetime. Experience-dependent plastic changes are unique to each person and reflect the range of social and cultural environments and the specific activities in which the person engages. Enriched experience (discussed later in this chapter) is an example of experience-dependent plasticity.

The speed at which dendrites modify their structure to form or delete synapses in response to experience is the third special feature of plasticity. The period of heightened sensitivity to environment and experience is called a critical period for that circuit, which is the fourth special feature. The experiences during these critical periods play a crucial role in shaping the brain and are important for experience-expectant plasticity. Once the critical period ceases, substantial alteration of neural circuits will be difficult. For instance, closure of one eye of a kitten soon after birth, for a period of few months, expands the territory of the open eye at the expense of the closed eye and may result in permanent loss of spatial vision. In the past 5–6 decades, considerable effort has been made to elucidate molecular and cellular mechanisms underlying the activation and regulation of critical periods in the brain. Unraveling these mechanisms may potentially assist scientists to augment the plasticity in the adult brain.

Plasticity in the young has both positive and negative consequences. Clinical and experimental studies had indicated that young animals and children have a remarkable degree of functional sparing after central nervous system (CNS) injuries, which were devastating when they occurred in adulthood. However, on the contrary, the recovery in children can be minimal after certain types of injury, and in others, it may be at a high cost. For instance, sparing of language after early left hemisphere damage is accompanied by substantial intellectual and perceptual deficits, which are not seen after equivalent lesions in adults. In the same way, some extreme plastic responses may exacerbate a developmental abnormality.

1.4 Plasticity: An Ongoing Process

Scientists once believed that the brain's capacity to develop ceases after the first few years of life. They believed that connections between neurons develop only until the first few years of life. This implies that only young brains would be "plastic" and be able to form new connections. Because of this belief, they also thought that if a particular area of the adult brain is damaged, the nerve cells could not form new connections or regenerate, and the functions controlled by that area of the brain would be permanently lost. However, new research on animals and humans has overturned such a mistaken old view. It is recognized that the brain continues to reorganize itself by forming new neural connections throughout life. This phenomenon, called neuroplasticity, allows the neuronal cells within the brain to compensate for injury and adjust their activity in response to new situations or changes in their environment and also plays an essential role in CNS functions such as learning and memory, both throughout the lifetime and post-brain injury.

Human brains have the extraordinary capacity for structural and functional change. The ability of the neuronal cells to change their physical structure as a result of learning is known as structural plasticity. Structural plasticity could be defined in terms of dendritic and axonal arborization, spine density, number and size of synapses, and receptor density. Neurogenesis, the formation of new neurons in certain regions of the brain, and neuronal migration, a process in which neurons travel from their "place of birth" toward their final position within the brain, are instances of structural plasticity during development and growth. The changes of gray matter volume or proportion in the brain following learning can also be considered as instances of structural neuroplasticity. On the contrary, functional plasticity refers to the brain's ability to adapt and/or modify the physiological properties of neurons. Activity-dependent plasticity (changes in response to previous activity) and reactive plasticity (changes in response to damage or malfunction of neuronal cells) are forms of functional and structural neuroplasticity. Activity-dependent plasticity involving the synapses, known as synaptic plasticity, includes long-term potentiation, long-term depression, and intrinsic and extrinsic plasticity. In reactive plasticity, the neuronal functions of the injured brain area are transferred to another region for recovery. Structures like the hippocampus display both structural and functional plasticity into adulthood.

1.4.1 Learning and Memory

For the past many years, research workers had spent enormous time in understanding the biological basis of learning and memory among vertebrates, especially in mammals, including humans. Our memory is very crucial to our sense of self, and diseases like brain injuries and Korsakoff's syndrome (caused by long-term alcohol abuse) prevent the patients from acquiring new memories, and they live in a world where every experience is new and do not benefit at all from their past. Neuroplasticity is a necessity for learning and memory. Advancing knowledge about synaptic transmission has contributed to a better understanding of the cellular and molecular changes associated with learning and memory responsible for changes in behavior in organisms, including humans. About eight decades ago, Hebb proposed that learning was mediated by changes in synaptic strength or "efficacy." According to Hebb, when an animal learned a new act, some synapses became stronger; that is, those particular synapses in the neuronal pathways that were responsible for the learned behavior gave a large postsynaptic response to the stimulation of the presynaptic neuron. However, he did not specify whether this increased efficacy was caused presynaptically (like an increased release of neurotransmitters) or postsynaptically (like an increased number of receptors). Even though this basic hypothesis was very appealing, it took many years to conclude that Hebb was essentially correct.

Evidence is now accumulating that other parts of the brain, mainly those concerned with motor function, which includes the cerebellum and basal ganglia,

mediate the learning and memory of motor skills. Most of this evidence comes from studies of brain lesions in humans and animals upon the acquisition of motor tasks, and its validity depends upon distinguishing learning from performance deficits. It is believed that the hippocampus is concerned with the formation of declarative memory, such as remembering words, faces, or facts, and structures like the cerebellum and basal ganglia are required for forming procedural memories, which involve learning tasks like driving a car or playing a musical instrument. Patients with hippocampal damage can often learn new procedures but not the new declarative information. For instance, the patient may learn to drive a car but may fail to remember the rules pertaining to it. The cerebellum and basal ganglia, structures important for procedural memories, show long-term potentiation like the cerebral cortex, where the higher cognitive functions such as comprehension, planning, reasoning, and decision-making are located.

1.4.1.1 Long-Term Potentiation and Long-Term Depression

Decades ago, a form of synaptic plasticity was discovered that was called long-term potentiation (LTP). Many neuroscientists believed LTP as an essential part of the process of learning, and as a result, an enormous amount of time and effort was allotted to understand the cellular changes underlying LTP, especially in a region of the mammalian brain called the hippocampus (Box 1.1).

Box 1.1 Features of Hippocampus

Hippocampus

Phylogenetically, hippocampus is considered as one of the oldest parts of the cerebrum, and the damage to the same will produce striking amnesia. In mammals, it is known to play an important role in memory acquisition. Following damage to the hippocampus, mammals, including humans, have great difficulty learning new things but not recalling things that they already learned. Though it is involved in an early stage of memory formation, it is not involved in the long-term storage or recall of memories.

In addition to LTP, a contrary phenomenon called long-term depression (LTD) occurs in various regions of the brain, including the hippocampus. LTD may be a process involved in selective forgetting or ignoring irrelevant information, which is another kind of learning that is important in an animal's function. Scientific evidence is available to prove that the NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors located within the synapses are involved in both learning new information and actively unlearning old ones. In 1949, Hebb

first used the phrase "neurons that fire together, wire together," to describe how pathways in the brain are formed and reinforced through synaptic strengthening. Contrary to that, the "neurons that fire apart, wire apart" can explain synaptic weakening, which is a fundamental feature of LTD.

Experimental studies have found that the neurotransmitter at the LTP synapses is almost always glutamate, and at least two or three types of glutamate receptors, including the NMDA and the AMPA receptors on the postsynaptic neurons, have been identified. The molecular mechanism subserving LTP or LTD is unsettled, but it is known to be mediated by calcium and probably involves changes in both postsynaptic glutamate receptors and presynaptic transmitter release. Studies have also suggested that structural changes in dendritic spines may also be involved in learning. Further details regarding LTP and LTD are given in Boxes 1.2 and 1.3, respectively.

Box 1.2 Details Regarding Long-Term Potentiation

Long-Term Potentiation

The synaptic strength is defined as the average amount of voltage excursion produced in the postsynaptic neuron by an action potential in the presynaptic neuron. LTP is an example of synaptic plasticity, a process by which the synaptic strength between neuronal cells becomes stronger with repeated stimulation. It is believed to be a way in which the brain changes its response to experience and maybe a mechanism underlying learning and memory. There are many ways in which LTP is produced. Glutamate released from the presynaptic neuron first activates a subtype of glutamate receptor known as the AMPA receptor on the postsynaptic membrane. Low-level release of glutamate will not activate the NMDA receptors found nearby the AMPA receptors due to the presence of magnesium ion blocking the ion channel of the NMDA receptor. Repeated and stronger stimulation of AMPA receptors will cause the depolarization of the postsynaptic neuron, eventually causing the voltage-dependent magnesium blockage of the NMDA receptor to be removed, allowing calcium ions to flow through the NMDA receptor (Fig. 1.2). The calcium influx initiates cellular mechanisms that cause more AMPA receptors to be inserted into the postsynaptic neuronal membrane. The new AMPA receptors being more responsive to glutamate will allow more positively charged ions to enter the cell when activated, thus making the postsynaptic cell more sensitive to glutamate, making the synapse stronger and more likely to be activated in the future. In addition to the above, the signals that travel back across the synapse are believed to stimulate greater levels of glutamate release. The process is also associated with changes in gene transcription in the neuron, which can lead to the production of new receptors or modifications of cell structure augmenting the LTP.

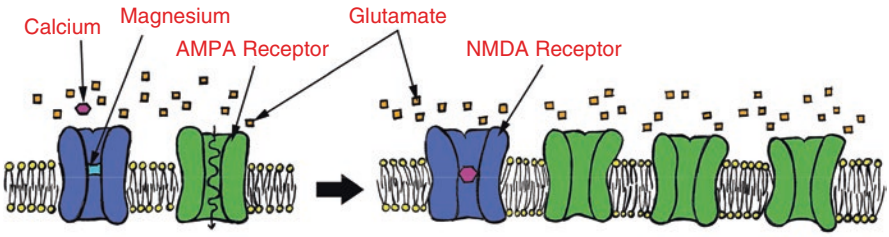

Fig. 1.2 An illustration of long-term potentiation

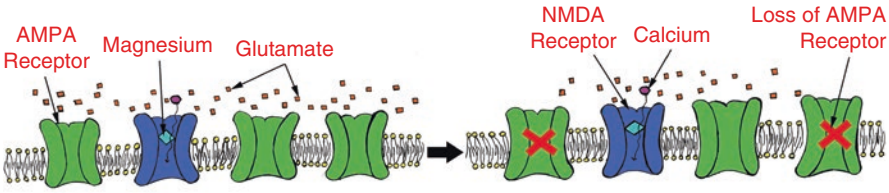

Fig. 1.3 An illustration of long-term depression

Box 1.3 Details Regarding Long-Term Depression

Long-Term Depression

Long-term depression is another example of synaptic plasticity, a process by which the synaptic strength between neuronal cells becomes weaker. It is a process that is opposite to that of LTP and believed to be important for learning and memory, perhaps by resetting previous synaptic changes to allow for new memories. The best-understood mechanism for the production of LTD involves the same glutamate receptors (NMDA and AMPA receptors) involved in LTP. The LTP typically occurs after brief high-intensity stimulation of a postsynaptic neuron, whereas the LTD typically occurs after prolonged low-intensity stimulation. Inadequate depolarization fails to remove the magnesium ions blocking many of the NMDA receptors on the postsynaptic membrane, allowing only a few of the NMDA receptors to pass calcium ions through them. This low-level calcium is insufficient to activate the enzymes that facilitate LTP and, on the contrary, activates a cellular process that causes removal of AMPA receptors, thus reducing the number of glutamate receptors on the postsynaptic membrane leading to a weaker synapse (Fig. 1.3). In addition to the above, the LTD may also decrease the amount of glutamate released from the presynaptic neuron by involving other glutamate receptors.

1.4.2 Muscle Activity and Plasticity

Muscle plasticity is defined as the ability of a skeletal muscle to alter its structural and functional properties secondary to certain conditions imposed on it. It is well known that intense physical training can cause strengthening and hypertrophy of the muscles, and the effects can be further augmented by neuromuscular electrical stimulation. By endurance training, the oxidative metabolism of muscles will increase and tends to convert fast-contracting motor units into slow ones, indicating that the individual muscles can be enlarged and strengthened by selective patterns of intensive training. On the contrary, a reduction in muscle activity can lead to muscle wasting.

Functional adaptations to reduced muscle activity depend upon the nature of the reduction. The absence of weight-bearing tends to cause muscle weakness and atrophy, whereas immobilization can lead to resorption of sarcomeres as an adaptation to being held in a shortened position. In animal model studies, unloading muscle revealed preferential atrophy of Type 1 muscle fibers and increased proportions of Type 2 fibers. Experimental studies on humans revealed significant atrophy of Type 1 and 2 muscle fibers as a major finding. With regard to the type of muscle fibers involved, the results among humans were mixed. The variability seen across human studies could be due to the differences in the choice of muscle studied, the type and intensity of physical activity before the period of inactivity, or the muscle contractions performed during the period of immobility. Studies during space flight have found differences in the pattern of fiber atrophy between rodents and humans. Rodents were found to show more significant atrophy in Type 1 than Type 2A fibers, whereas humans showed more atrophy in Type 2A than Type 1 fibers, and the difference in the pattern may be related to initial fiber size.

Muscle inactivity causes major changes, and such changes are initiated within a matter of few hours following inactivity or immobilization. Reduction in the rate of protein synthesis is one of the dominant characteristics of muscle atrophy. In rodents, a 35% reduction in protein synthesis was recorded within hours after the onset of inactivity. A decline in contractile protein concentration can lead to a reduction in the number of active cross-bridges per muscle volume reducing the electromechanical efficiency. Even prolonged periods of reduced muscle activity can lead to significant reductions in maximal voluntary contraction. It is believed that reduced neural input is also partly responsible for the reduction in maximal voluntary force during periods of muscle inactivity.

Increased muscle activity or training results in a change in expression of myosin heavy chain isoforms characterized by greater expression of slow myosin heavy chain and hence more Type 1 fibers; however, the nature of the activity also determines their expression. For instance, heavy weight-lifting induces a greater expression of fast myosin heavy chain. Even moderate loads are capable of inducing a greater expression, but the minimum threshold required to induce the transformation is yet to be clear. Animal model studies on training have revealed hyperplasia that contributes further to muscle hypertrophy.

Appropriate strategies must be used to counteract the ill effects of immobilization or muscle inactivity. For instance, strengthening exercise programs to hasten the recovery of muscle functions after periods of immobilization or use of electrical stimulation in addition to passive limb exercises in paralytic or paretic neurological conditions can counteract the ill effects of such changes. Similarly, the four main principles of training skeletal muscles, namely, overload, specificity, reversibility, and individuality, have to be used to improve muscle strength and endurance to minimize the deleterious effects of muscle inactivity.

1.4.3 Peripheral Nerve Injury and Plasticity

The response of the neuromuscular system to interruption of nerve axon (excluding neurapraxia or demyelination) can be considered in two different ways. The first one consists of the new growth of neural processes by protoplasmic extension from the severed axon end, and the second one requires synaptic plasticity, which operates locally. Both these mechanisms are necessary for full functional recovery of the neuromuscular system.

1.4.3.1 Nerve Regeneration

Damage to the nerve fiber disrupts nutritive contact between the proximal and distal parts of the axon. As a result, the distal part degenerates along with its myelin sheath. Many mature neurons that survive an injury to their axons respond by attempting to regenerate a new axon. The regeneration process begins with axonal elongation after a latent period of a day or two, the time required for the modification of biosynthetic activity in the cell body. The severed axon stump or the zone just proximal to it may emit 1–20 sprouts and can advance at the rate of approximately 2 mm per day. To guide the regenerating sprouts, the surviving Schwann cells present in the distal nerve segment proliferate and become aligned in strands to form the bands of Büngner (Fig. 1.4). Ultimately, the fate of these sprouts depends upon their success at entering the distal nerve stump and reaching an appropriate peripheral target.

The axonal sprouts are capable of growing long distances along empty nerve sheaths and will even grow through artificial conduits to reach their synaptic targets. In the process of crossing the zone of injury, fibers are strongly influenced by local mechanical factors. Many grow in a retrograde direction back along the proximal nerve, often forming spirals around parent axons or blood vessels, whereas others are arrested or escape from the nerve bundle. However, sprouts that reach the distal stump track along the bands of Büngner toward the peripheral target. The trophic substance picked up by the successful sprout in the periphery may be responsible for shunting the flow of structural metabolites selectively toward the connected sprout to foster its maturation. The mechanism for “culling” the unsuccessful

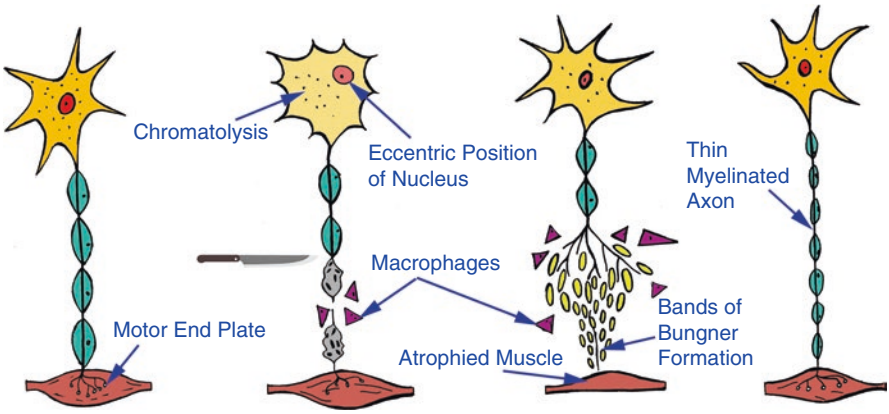

Fig. 1.4 An illustration of the axonal degeneration and regeneration post-trauma

sprouts during regeneration may be similar to those involved in the natural death of excess sensory, motor, and autonomic neurons in developing the nervous system or the elimination of polyneuronal innervation in maturing muscle fibers. Like the normal unmyelinated axons, the young regenerating sprouts conduct impulses in the continuous (non-saltatory) mode. Shortly after reconnection, a wave of diameter increases, and myelination sweeps over the axon from the point of injury distal ward, and conduction becomes saltatory, and, gradually, the velocity of conduction accelerates.

The death of axon till the nearest node of Ranvier, widening of nodes, fragmentation and/or blistering of the myelin sheath, chromatolytic changes in the cell body and dendritic retractions, and stripping off some afferent synapse of the dendrites are certain proximal nerve segment changes seen soon after nerve fiber severance. These changes are considered to be a process of metabolic mobilization in preparation for axon repair. The process is reversed upon successful regeneration, and the absence or delay in successful regeneration can lead to the progression of these changes, and, eventually, the cell may die. The incidence of retrograde cell death depends on several factors, including the particular neural system involved, time after axotomy, age, location of the injury, and the existence of axon collateral branches.

Even if the injured nerve regenerates, it is only half the battle for recovery. Reinnervation of nerve fibers must be specific if it has to be functionally beneficial. Experimental and clinical studies suggest that the mechanisms, which guide the innervation of appropriate targets during embryonic development, do not operate during reinnervation. For instance, following the transection of a large mixed nerve, some sensory axons will innervate muscles, and some motor axons will innervate cutaneous receptors making it functionless. Apart from the abovementioned, individual muscles may be reinnervated by motor neurons from other motor pools and will, therefore, be activated inappropriately. Microsurgical repair of severed nerves by closing or bridging the gap while minimizing tissue obstructions and

maintaining as good a fascicular alignment may optimize the specific reinnervation. Studies on reinnervation in animals suggest that the precision of motor reinnervation may improve with time even if the reinnervation may be nonspecific initially, due to the selective withdrawal of misdirected collateral axonal branches over many weeks.

The term "sprouting," a necessary neuronal process that follows nerve injury, can be reactive, regenerative, or compensatory type. The reactive (collateral) sprouting refers to the new growth of intact nerve fibers in response to denervation in the adjacent areas. Regenerative sprouting refers to new growth from near the severed end of the nerve fiber, and compensatory sprouting refers to the new growth of one branch of an axonal tree when a distant branch is cut. It is unclear what induces axons to sprout in the event of injury and to what extent the mechanism underlying sprouting in these three situations is different. Some of the factors believed to regulate the sprouting are given in Box 1.4.

Box 1.4 Factors Believed to Regulate the Neuronal Sprouting

Possible Factors Regulating Sprouting

- Sprouts tend to move in mechanical adherence to preexisting axonal or glial processes.
- The environment through which the sprouts pass can alter neural processes, and abnormal tissue configurations can fail the growth of sprouts.
- Nerve sprouts and cells may recognize their proper target utilizing specific "cytochemical position markers" made up of specific tissue-target recognition molecules.
- Sprouts may be partially directed by preexisting chemical "fields" or gradients.
- By attractive and/or repulsive "forces," individual axons within an outgrowing population may interact with one another to constrain the growth of its neighbor.
- Temporal factors like the time of arrival of earlier axons for connection exclude the connection of later arriving ones.
- In certain systems, neurons and neuronal processes are produced in excess, and those that fail to form functional connections are eliminated.
- Mutual dependence may be seen in certain neural elements, i.e., in the absence of one, the second may fail to differentiate or may atrophy.
- The axonal system competes for the exclusive occupation of available terminal space that is left vacant by the degeneration of neighboring axons.
- Certain axonal populations of the neural system tend to conserve the total amount of their axonal arborization, i.e., if growth in one part is limited, branches in another part will sprout extra collaterals.

At least, weeks or months are taken for the regenerating sprouts to return to the denervated tissue. During this period, there are certain changes in intact fibers that normally share the distribution field of the injured ones or that innervate adjacent zones. It is believed that the motor unit can expand even up to five times its original size, compensating for the considerable deficiencies in innervation. This explains why in conditions like motor neuron disease, muscle weakness does not become apparent until about 50% of motor neurons have degenerated. Even in the early stages of muscular dystrophy, sprouting occurs when newly developing muscle fibers replace degenerating muscle fibers. The trigger for motor neuron sprouting in muscle is unclear but probably involves a local signal from inactive denervated muscle fibers. Such return or improvement of function also occurs in the sensory system, and sprouting of neighboring sensory nerves accounts for the same.

1.4.4 Denervation Hypersensitivity

Another important category of plastic change secondary to axonal damage is the increase in chemosensitivity of postsynaptic elements known as denervation hypersensitivity or denervation supersensitivity. Denervation hypersensitivity results in a permanent increase in neuronal responsivity to diminished input and maybe even a factor in CNS reorganization. An increase in the number of receptors or the receptor site becoming more sensitive can be considered as the reason for the same. For instance, following denervation of muscles, acetylcholine sensitivity spreads over the whole membrane surface (postsynaptic junctional membrane), and the changes produced within the muscle membrane, concomitant cellular changes, and the loss of muscle activity generally tend to persist until innervation is restored.

1.4.5 Synaptic Plasticity

Many researchers believe that synaptic plasticity is central to understanding the mechanisms of learning and memory. Decades ago, the synapse was simply considered a junction for the transfer of information between one neuron and another neuron or between a neuron and a muscle cell. Once established during development, these synapses were believed to be relatively permanent in their strength. Nevertheless, the developments in science during the past five to six decades have realized that most synapses are incredibly plastic, and they are capable of changing their strength as a result of their own activity (intrinsic or homosynaptic plasticity) or through activity in another pathway (extrinsic or heterosynaptic plasticity).

Short-term synaptic depression and short-term synaptic facilitation are two types of homosynaptic plasticity, and, typically, both of them are not found at the same synapse. Such plastic changes are thought to play crucial roles in short-term adaptations to sensory inputs, transient changes in behavioral states, and short-term forms of memory. Most forms of short-term synaptic plasticity are triggered by short bursts of activity, causing a transient accumulation of calcium in presynaptic nerve terminals. The mechanism of synaptic depression varies and is attributed to the depletion of the readily releasable vesicles, and the efficacy of synaptic transmission depends upon the frequency of stimulation. Paired-pulse facilitation and post-tetanic potentiation are a few types of synaptic facilitation. The plausible mechanism contributing to paired-pulse facilitation is the presence of residual calcium ions. Longer-lasting forms of plasticity are observed following repetitive or tetanic stimulation of synapses with prolonged trains of stimulation. Post-tetanic potentiation describes an enhancement of transmitter release lasting for several minutes and may lead to biochemical modifications of proteins in the presynaptic terminal.

Even heterosynaptic plasticity is either of presynaptic inhibition or presynaptic facilitation type. The axoaxonic synapses (synapse made between the axon of one neuron and the axon of another neuron) mediate presynaptic inhibition and presynaptic facilitation. In presynaptic inhibition, a third neuron, which makes an axoaxonic synapse with the presynaptic neuron near its terminal button, reduces the effect of the presynaptic neuron on the postsynaptic neuron. Presynaptic inhibition is quite prominent in the spinal cord and regulates the propagation of potentials to higher brain centers. For instance, the pain gate theory proposed by Ronald Melzack and Patrick Wall in 1965 is based on presynaptic inhibition of pain produced by mechanical stimulation, the basic rationale for transcutaneous electrical nerve stimulation. In presynaptic facilitation, a third neuron, which makes an axoaxonic synapse with the presynaptic neuron near its terminal button, increases the effect of the presynaptic neuron on the postsynaptic neuron.

1.5 Plasticity Within the Adult Central Nervous System

One of the most striking differences between the peripheral nervous system and CNS is that the axonal injury in the CNS does not lead to regeneration, and the consequence is more or less permanent impairment. In the brain of some lower vertebrates, including organisms like a lamprey, even in their adult forms, severed fiber trunks such as optic and spinal tracts may regenerate much as in the peripheral nervous system. The processes of axon outgrowth after peripheral nerve injury in mammalian adults are reminiscent of initial axon outgrowth in the developing nervous system, and for evolutionary reasons that are entirely unclear, the mammalian CNS has lost a great deal of this lability when compared to the peripheral nervous system.

The major difference between a developing and a developed system is that in a developed system, the surrounding milices are mature and do not unfold

themselves. Following CNS damage, neuroplasticity in the form of sprouting, denervation supersensitivity, unmasking of latent synapses, or behavioral compensation may occur in the absence of unfolding of surrounding milices. However, the presence of inhibitory environment can make successful regeneration practically impossible for functional restoration. Early pathophysiological processes such as the decline of edema and recovery from ion-imbalances are certain reasons for functional restitution following nervous system injury and will not be dealt with in this chapter.

Unmasking Quiescent neuronal connections that are inhibited in the normal state may be unmasked following brain damage. Unmasking may be another important mechanism of recovery of function and may also produce negative effects. The appearance of "pathologic" reflexes such as a tonic labyrinthine reflex and tonic neck reflex following a brain injury can be considered as instances for the unmasking of reflexes that were normal in infancy but became inhibited during development.

Both in animal and human stroke studies, ipsilesional peri-infarct activation was observed after partial damage of the primary motor cortex. Such a finding suggests the unmasking of preexisting, yet functionally silent, areas in the vicinity of the lesion or the progressive activation of neural networks normally not devoted to the lost function. Changes in glutamatergic transmission and LTP have been reported in the peri-infarct cortex and beyond in the first week after stroke. Evidence suggests that the brain-derived neurotrophic factor (BDNF) appears directly linked to the activity-dependent early unmasking of existing connections. Studies on mammalian CNS have proved the presence of silent synapses that lack functional AMPA-type glutamate receptors but possess NMDA-type glutamate receptors. Even evidence from electrophysiological measurements has established the existence of silent synapses and their emergence as active synapses with appropriate stimulation.

Behavioral Compensation A considerable extent of recovery of function after brain damage can be due to the development of compensatory behavioral strategies, a new combination of behaviors that circumvent impairments. For instance, the patient may use different groups of muscles or cognitive strategies for fulfilling the functional activities or spontaneously develop over-reliance on the uninvolved limb for normal postural support behaviors and transitions. Animal model studies have revealed that unilateral lesions can result in remarkable neuroanatomical changes in the motor cortex opposite and homotopic to the lesions associated with a sequence of changes in the neuronal and glial cells in this region. Soon after the lesion, there will be loss of axonal processes presumably arising from the damaged cortex and reactive changes in glial cells, and there will be an increased presence of neurotrophic factors, followed by major axonal, dendritic, and synaptic connections growth within this region. Synaptic connections also show structural changes that are characteristic of increased potency.

Larger lesions of the sensorimotor cortex can cause the contralesional motor cortex to contribute new axonal projections to subcortical regions underlying the lesion. After unilateral lesions, animals progressively rely on the uninvolved limb.

Animal model studies have also revealed that restriction of uninvolved limb soon after brain lesion for 15 days prevented the dendritic growth usually seen in the contralesional cortex. Though the compensatory behaviors have shown certain improvement in the functional level in animal studies, such behaviors can be stubborn to correction in humans, especially when there is a potential for further improvement.

1.5.1 Brain Plasticity

Even though it is customary to explain brain functions in terms of "centers," it is not known to what extent brain functions are localized to "centers." The functional loss following the damage of a particular group of cells means only that the rest of the brain cannot perform the function without the contribution normally made by the damaged cells. This contribution might be a minor one, say, setting the level of excitability of some other group of cells, or be a major one such as organizing the neural impulse sequence required. There are many ways by which the excitability of the target cells could be restored, but if a specific, localized group of cells that organizes the neural impulse sequences is destroyed, the recovery might require massive and perhaps impossible reorganization of remaining neural aggregates. This implies that when a vital circuit element is destroyed, plastic changes such as the substitution of parallel channels or the mobilization of redundant capacity could still support the need for therapeutic exercise.

Synaptic plastic changes occur in the brain in response to both local and peripheral injuries. It was presumed that such adaptation was possible only when the injury happens in early development or when young. However, more recent works suggest that substantial reorganizations also occur after injury to the adult brains. Recently, positron emission tomography of adult patients who have suffered striatocapsular stroke has demonstrated bilateral activation of motor pathways and the recruitment of additional sensorimotor cortical areas associated with the recovery of motor function.

There is growing evidence that the glial cells are involved in short- and long-term plasticity. The belief that they are passive bystanders in neuronal brain circuits and required for housekeeping and brain metabolism is incorrect, and they play an active role in regulating physiological function and synaptic plasticity. With their intimate association with synapses, astrocytes and perisynaptic Schwann cells are well-positioned to regulate synapses. They have an established role in the clearance of neurotransmitters and control of extracellular ionic gradients and excitability.

Functional radio-imaging studies on post-stroke patients have identified the role of the healthy hemisphere in recovery. Earlier studies on rodents have demonstrated enhanced activity of the contralesional hemisphere in the very acute stage after stroke, followed by perilesional activation at later stages during the recovery phase. Experimental silencing of the healthy hemisphere (using muscimol, an ionotropic gamma-aminobutyric acid [GABA] receptor agonist) within hours after

a stroke has demonstrated improvement in functional recovery, and the duration of the inactivation was directly correlated with the improvement. There is scientific evidence that the activity of the healthy hemisphere can worsen motor recovery. For instance, a recent quantitative noninvasive study among acute stroke survivors could relate an increased contralesional hemispheric activity to the negative final outcome. Conversely, when the sensorimotor cortex lesion is considerably extensive, the healthy hemisphere could be important to vicariate lost functions. Studies have shown that stroke patients can demonstrate a significant increase in contralesional motor cortex activity during movement of the affected extremities, and TMS-induced disruption of the function within this area has shown impairments in the recovered movement of the affected extremity. However, controversy still exists whether the healthy hemisphere has a positive or negative impact on recovery.

1.5.2 Experience-Dependent Neuroplasticity

Experience can change the synaptic efficacy, neuronal structure, and rate of neurogenesis and remodel vasculature and glial processes. Experience is also crucial for function following brain lesions, such as stroke and traumatic brain injury. Manipulations of behavioral experience, including physical activities and physical exercises, are the primary tools currently available for the treatment of functional deficits following brain injury. Behavioral experiences, including rehabilitation strategies and interventions and self-taught compensatory strategies, have a powerful impact on post-injury brain remodeling and functional outcomes.

The type and site of brain remodeling vary with different types of experience. For instance, aerobic exercise drives hippocampal neurogenesis and angiogenesis in the cerebellum and hippocampus. Learning a motor skill is associated with changes in neuronal architecture, synaptogenesis, and dendritic spine plasticity in the cerebral motor cortex and cerebellum, which is in addition to the motor map reorganization. Animal model studies have shown that rodents socially housed in a large cage with many objects to explore and manipulate, an enriched environment (Fig. 1.5), resulted in dendritic growth, synaptogenesis, and angiogenesis in cerebral cortices and other regions. Following are the principles of the experience-dependent plasticity which are likely to impact the neurological physiotherapy treatment efficacy for post-brain injury:

Use It or Lose It Neural circuits not actively engaged while performing the task for an extended period of time tend to degrade. Behavioral experiences post-injury can protect neurons and enhance performance and restore neuroplasticity that would otherwise be lost after the injury. The loss can be prevented, and functional reorganization can be promoted by appropriate use of rehabilitation strategies, including the task-oriented approach and the constraint-induced movement therapy.

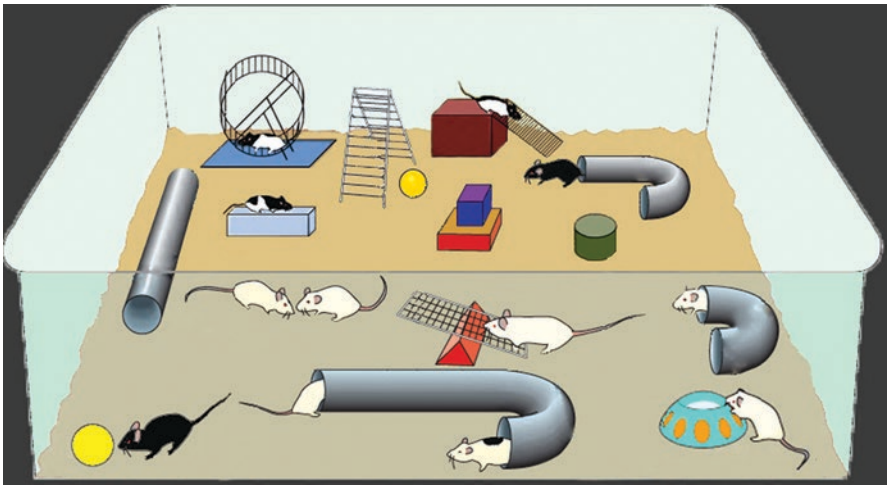

Fig. 1.5 An illustration of an animal model enriched environment

Use It and Improve It Training in an enriched environment can enhance the function and attribute to synaptogenesis and increased synaptic responses. Primates trained to perform fine movements had an increase in digit representation area within the primary motor cortex. It is hypothesized that similar neural changes occur in response to exercise training and mediate functional improvement. Several research works indicate that behavioral experience can enhance performance and optimize restorative brain plasticity post-injury.

Specificity The nature of the plasticity depends on the nature of the training experience. For instance, individuals trained to perform skilled movements exhibited enhanced corticospinal excitability, compared to those trained to repeat unskilled movements. Learning-induced neuroplasticity also shows regional specificity. For instance, unilateral task training in rodents caused dendritic growth in the contralateral motor cortex with a modest effect on the ipsilateral motor cortex. Skill acquisition is associated with changes in gene expression, dendritic growth, synapse addition, and neuronal activity in the cerebral cortex and cerebellum.

Repetition Matters An adequate amount of repetition is required to induce brain plasticity. Merely engaging a neural circuit in task performance is not adequate to drive brain plasticity. Animal models have revealed that the skilled reaching task performed several days increased the synaptic strength, synapse number, or map reorganization, emphasizing the importance of repetition in driving plasticity and concomitant learning, which is critical for rehabilitation.

Intensity Matters The intensity of stimulation or training is another essential factor for the induction of brain plasticity as indicated by the fact that low-intensity

stimulation can weaken the synaptic response (LTD), and high-intensity stimulation can strengthen the synaptic response (LTP). However, care has to be taken to avoid overuse to prevent the possible worsening of function, especially during a vulnerable early period, due to exaggeration of excitotoxicity in the susceptible tissue surrounding the primary injury.

Time Matters The plasticity of the brain, underlying learning can be considered as a process rather than a single measurable event. Neuroplasticity is a complex cascade of molecular, cellular, structural, and physiological events. For instance, during motor skill learning, gene expression precedes synapse formation, which in turn precedes motor map reorganization. Theoretically, if training promotes neural restructuring, then it should work anytime. On the contrary, there appears to be a time frame when it is particularly useful in inducing plasticity. For instance, a rehabilitative regimen initiated 1 month after cerebral infarct tends to be far less effective in improving functional outcomes and promoting cortical dendritic growth compared to the same regimen initiated 5 days post-infarct. The time delay may also encourage establishing self-taught compensatory behaviors that may interfere with rehabilitation.

Salience Matters The training experience must be sufficiently salient to induce plasticity. For an organism to function effectively, there must be a system in place to weigh the importance of any given experience such that it can be encoded. As in classical conditioning, merely playing a tone without the reward does not alter the topography of the auditory maps. Sufficient motivation and attention are essential to promote engagement in the task.

Age Matters Plasticity occurs more readily in younger brains as compared to older brains. Healthy aging is associated with widespread neuronal and synaptic atrophy and physiological degradation and is a known fact that neuroplastic responses such as experience-dependent synaptic plasticity, synaptogenesis, and cortical map reorganization reduce with aging. However, the effects of aging vary with lifespan experiences and are generally better in individuals with greater physical and mental activity. In animal models, ischemic injury triggers an increased production of new neurons (neurogenesis), and such a response is significantly reduced in aged rodents.

Transference Plasticity induced by one training experience can augment the acquisition of similar behaviors. It is the ability of plasticity within one set of neural circuits to promote concurrent or subsequent plasticity. Learning a particular skill can generalize or transfer to similar real-world skills to improve independence in the home environment.

Interference Plasticity induced by one experience can interfere with the acquisition of another one. It refers to the plastic ability within a given neural circuitry to impede the induction of a new one within the same circuitry. For instance, the com-

pensatory strategies, including circumduction gait, developed in the post-brain injury patients are stubborn to correction when training for the appropriate or more effective strategies.

1.5.3 Enriched Environment and Plasticity

Several environmental factors may influence the normal physiological functions of the brain and its ability to counteract pathological changes. Experimental studies have demonstrated that experience shapes the neural circuits, making them more functional, keeping them "young." Experience is a factor that makes our brain more plastic. The brain plasticity represents the biological basis of "cerebral reserves," an apparent protection from the onset of cerebral disease and/or cognitive decline during the process of aging.

There is clinical evidence that individuals with a higher level of education show a slower level of cognitive decline. The two types of cerebral reserves recognized are the brain reserve and the cognitive reserve. The former one is based on the protective potential of anatomical features like brain size, neuronal density, and synaptic connectivity. The brain reserve is passive and is defined as the amount of brain damage that can be sustained before reaching a threshold for clinical expression. On the contrary, the cognitive reserve represents a functional reserve and is the brain's ability to improvise its function or change the way it functions to cope with challenges. It is developed by a lifetime of education and experience and is an active process of coping with brain damage or functional decline by using preexisting cognitive processes or compensatory mechanisms.

In humans, the development of cognitive reserves can be influenced by several factors, such as educational level, physical activity, social integration, and emotional involvement. Cognitively stimulating experiences and regular physical activity are associated with neurogenesis, increased levels of neurotrophic factors, and diminution of neuronal apoptosis. Evidence provides that individuals with a high level of education who maintain regular physical activity and healthy food habits have more cognitive reserve as compared to the rest. Exposing the animals to an enriched environment (Fig. 1.5) is similar to that which occurs in the human lifestyle. In animal models, all these factors are provided by the environmental complexity and novelty to which the animals are exposed. When they are reared in an enriched environment, the animals show significant functional and structural effects consisting of cellular level changes such as neurogenesis, synaptogenesis, dendritic arborization, dendritic spine density, gliogenesis and angiogenesis, and molecular level alterations such as changes in neurotransmitter and neurotrophin expression. In addition to the above, enriched environment and physical activity are proven to have a neuroprotective role against neurodegenerative diseases. Studies suggest that enriched environment exposure up to middle age can provide a reserve-like advantage for specific spatial capabilities in old age.

1.5.4 Physical Activity, Exercise, and Plasticity

The effects of physical activity on the brain are relatively widespread; however, there is also some specificity, such that prefrontal and hippocampal areas appear to be more influenced than other areas of the brain. Six months of light aerobic activity among elderly adults exhibited a 2% increase in the hippocampal volume when compared to the elderly who did not participate in the aerobic activity. Physical fitness appears to prevent cortical decay and improve cognitive performance. In humans, exercise has shown enhancement of spatial learning, pattern separation, working memory, processing speed, and executive function. Physical activity triggers a variety of neurobiological mechanisms to produce both acute and chronic neurological effects on many brain regions.

Exercise modulates neurotransmitters that communicate information in the brain and may play a role in exerting its neurological effects. Physical activity directly influences the central dopaminergic, noradrenergic, and serotonergic systems. Alterations in such systems may cause disorders, including depression. Exercise increases the levels of such neurochemicals and may restore normal brain function, as shown by the transient elevations in plasma tryptophan (a serotonin precursor) following 16 weeks of aerobic training, performed 45 min per session, 3 days per week. Even animal models also demonstrate a similar link between exercise, neurotransmitters, and improvement in brain function.

Exercise has shown that alteration in the levels of monoamines alleviates the symptoms of Parkinson's disease and Huntington's disease in rodents. Dopamine appears to play a crucial role in the acquisition of skilled motor tasks, and studies on rodents have demonstrated the impaired function of learning new tasks after depletion of dopamine. Similarly, an interaction exists between exercise and hormones and may be vital for proper brain function. Physical activity levels are strongly associated with salivary levels of estradiol among regularly menstruating women. Cessation of estradiol and progesterone production by the ovaries, as seen in postmenopausal women, is associated with a variety of symptoms that include short-term memory loss and difficulty concentrating. Hormone therapy is commonly utilized for the treatment of postmenopausal cognitive decline; however, the efficiency is considerable when exercise is combined with hormone therapy.

Neurotrophic factors are peptides or small proteins that support the neuronal growth, survival, and differentiation of both developing and mature brains. Exercise increases the concentration of several neurotrophic factors such as fibroblast growth factor-2, insulin-like growth factor-1, vascular endothelial growth factor, and BDNF, which are likely to support morphological changes in the brain. Evidence suggests that an increase in the levels of BDNF in the spinal cord, cerebellum, cerebral cortex, and hippocampus post-physical activity promotes the differentiation, neurite extension, and survival of neuronal populations. In addition to the above, it potentiates synaptic transmission, participates in gene transcription, modifies synaptic morphology, and enhances neuronal resilience, implicating the importance of BDNF as a prime candidate behind exercise-induced neuronal plasticity and

learning enhancement. Forced treadmill training exercises and intense rowing exercises performed by adults have exhibited increased levels of plasma BDNF. Physical activity can also produce neurological changes by altering cerebral blood flow, microvasculature, and vascular endothelial growth factor expression. The presence of angiogenesis in animal studies is considered to be pre-requisition for many forms of neural and behavioral plasticity. Animal models have shown that continuous exercise exposure is essential to produce substantial changes in the microvasculature and blood flow and its neurological effects diminish when physical inactivity returns.

Physical activity or exercise may reduce oxidative stress levels in the brain. Oxidative stress occurs when an organism cannot eliminate the oxygen-free radicals, the chemically reactive molecules that attack and degrade important molecules for biological functions. Animal studies have revealed that exercise increases the levels of antioxidants and reduces the levels of reactive oxygen-free radicals and oxidative protein damage. Studies on rodents have also revealed the significance of exercise in extending the lifespan and improving the behavioral performance on spatial and nonspatial tasks. Exercise is also known to alter the levels of apoptosis in the brain and may cause a transient increase in apoptosis that triggers neuroprotective mechanisms. Animal model studies have shown transient apoptosis at the onset of exercise in the hippocampus, followed by neurogenesis and enhanced function.

1.5.5 Spinal Cord Plasticity

Given its clinical importance, a good deal of research has been devoted to plastic changes related to spinal cord transection. Recovery from a spinal cord injury in mammals is minimal, and the results have been disappointing for those seeking a cure for complete spinal cord injuries (quadriplegia or paraplegia), but they have produced valuable data on fundamental aspects of sprouting. Several researchers have documented the beginning of sprout outgrowth at the severed ends of spinal tracts. These sprouts are arrested at the spinal scar, proliferate within the proximal gray matter and form numerous synaptic complexes. Usually, the sprout outgrowth is soon aborted, and, at best, only a handful of fibers cross the gap at the severed end. The poor response of central neurons to injury is not due to the inability to grow their axons but due to the presence of an inhibitory environment. However, the CNS does undergo synaptic plasticity, and hence some recovery of motor function can be possible. Many authors have found a rapid replacement of degenerating synapses near the transected spinal cord with new synapses emerging from local neuron populations, which is in addition to those emerging from dorsal roots and long descending tracts.

During the past 5–6 decades, research has shown a remarkable degree of plasticity within the spinal cord. Many of the characteristics of hippocampal LTP have been identified in the spinal cord, providing a potential cellular mechanism for

central sensitization. Even the glial cells located within the spinal cord have been implicated in spinal LTP. The capacity for glial cells to affect glutamatergic signaling through the release of a host of neuromodulators has led researchers to assess the importance of glia in CNS plasticity. The spinal cord may also mediate plastic changes relevant to the acquisition of motor skills. Alteration of the spinal stretch reflex in response to reward-driven motor training, which is retained independently of supraspinal influences, is an example of such plastic changes in the spinal cord. It may be that all structures in the CNS concerned with motor function undergo plastic changes during the learning of motor skills.

Most studies on cortical plasticity after spinal cord injury have shown that the topographical organization of the sensorimotor cortex is not static but undergoes considerable reorganization after cord injury. Both animal and human studies have shown that the adult body and cerebral cortex are in constant and intimate interaction. Injuries to the spinal cord that convey ascending or descending information disrupt this interaction and cause plasticity changes at the cortical level. Stimulation of a body part above the cord injury level causes activation of the cortex that normally represents a body part below the level. Spinal cord injuries cause structural changes in subcortical substrates, including the thalamus, and the changes generally resemble the cortical changes. At the cellular level, the primary injury causes cell death, and the secondary injury is likely to induce a spread of damage. In the dorsal column and other spinal cord regions, spinal cord injury often leads to degeneration, apoptosis, atrophy, and transneuronal changes. Regardless of the above changes, spinal regeneration and sprouting are often observed simultaneously after chronic spinal cord injury.

Spinal plasticity is not limited to maladaptive plasticity. It also demonstrates several forms of adaptive motor plasticity. It can be considered as a two-edged sword: an adaptive process that can foster sensorimotor recovery and reduce neuropathic pain and a maladaptive mechanism that can lead to pain, spasticity, and lack of functional recovery. Several preclinical studies have claimed functional improvements following spinal cord injury using regenerative approaches. However, most of the studies have shown a weak correlation between regeneration and recovery and "failed to stand the test of time and scrutiny." Even several clinical trials using stem cells, the relatively recent approach which claimed to offer a potential treatment for complete spinal cord injury, have been terminated due to the lack of any noticeable functional improvement. On the contrary, considerable functional recovery can be anticipated for incomplete spinal cord lesions, even in the absence of any regenerative approaches.

The current data suggest that in addition to the regenerated inputs (motor and sensory) and locomotor networks within the spinal cord, which are essential for recovery, the recovery requires appropriate changes and interactions within and between different components of the spinal cord motor system. Though spontaneous recovery from complete spinal cord injury is unheard of in mammals, including humans, experimental studies on lamprey (primitive fishlike jawless vertebrates) have shown remarkable recovery of locomotor function within 12 weeks after a complete spinal cord transection, which is supported by repair of the spinal lesion,

axon regeneration, and synapse formation. However, studies on lamprey reveal that several aspects complicate the link between regeneration and recovery of the spinal cord. The regeneration is never complete, axons grow short distances and project to ectopic locations, and regenerated synapses are sparse and small. The robust functional recovery from cord injury in such organisms, when the regenerated synapses are sparse and small, suggests that functional recovery is due to a complex set of compensatory changes throughout the spinal network.

1.6 Neuroplasticity and Neurological Physiotherapy

For a long time, the hardware of the brain was considered "hard," and the structure and the function of the brain were believed to be never regainable or restorable following neurological conditions like stroke or traumatic brain injury. The existing data suggest that neurons possess a remarkable ability to alter their structure and function in response to a variety of internal and external pressures, including rehabilitative training. The gamut of clinical and research evidence strongly suggests that rehabilitative training is the most successful means to enhance functional recovery following such incidences.

Neuroplasticity is considered to be the physical basis of rehabilitation. The key principle of neuroplasticity is that brain activity promotes brain reorganization. In other words, "brain workouts" help the brain to reorganize connections more quickly and stimulate reorganization when the brain is not capable of reorganizing on its own. Presenting oneself to challenging intellectual environments, interacting in social situations, and getting involved in physical activities are some examples of brain workouts. However, generalized stimulation may not be beneficial for rebuilding a specific damaged area of the brain.

Currently, the approaches to improve brain function post-injury focus on limiting the severity of the initial injury to minimize functional loss or reorganizing the brain to restore and compensate for those functions already impaired or lost. Even in the absence of overt rehabilitation efforts after damage, the brain has the potential to adapt. Those patients developing compensatory movement strategies to perform daily activities using the less-involved limb are associated with plastic changes in the contralesional hemisphere. Such behavioral changes can be adaptive and can contribute to functional outcomes. However, they can also be maladaptive and interfere and limit the propensity of individuals to engage in behaviors that improve the function of the involved side using rehabilitation strategies or training.

Brain plasticity can produce a considerable degree of spontaneous recovery, and therapeutic training may modify and boost the neuronal plasticity processes. Experimental studies on animals have extended these findings and provided insight into a broad range of underlying molecular and physiological events. Typically, the best recoveries are associated with the greatest return toward the normal state of functional organization. Reorganization of surviving CNS neuronal cells supports functional recovery through changes in the interhemispheric lateralization, the

activity of cortices adjoining the injured zones, and the organization of cortical representational maps. Studies involving the extremity of the rodents have described a shift in laterality of activation after stroke. The rodents, soon after a stroke, exhibited contralesional cortical activation during affected paw stimulation, and later, the activation shifted back to the normal pattern in the ipsilesional cortex. However, larger ischemic insult produced stronger activity in the contralesional primary motor cortex with no functional shift back to the ipsilesional site.

Similarly, the destruction of the forelimb primary motor cortex causes the neurons in the hind limb area to take over the functional recovery of the forelimb. The significant gains in the recovery of forelimb were obtained when exercise training was initiated within 5 days post-stroke as compared to 2–4 weeks post-stroke. Recovery was also associated with increased dendritic branching of layer V neurons of the primary motor cortex in the ipsilesional hemisphere.

Activity-dependent modification of synaptic connections and reorganization within adult brain areas are thought to involve LTP and LTD mechanisms by which information is stored in the mammalian CNS. Synaptic plasticity in cortical horizontal connections has been proposed to underlie cortical map reorganization. Topographical maps are shaped during the early part of life and remain quite stable in adulthood. However, they can change even in the adult by experience-dependent plasticity or post-brain damage. Remapping of the motor cortical areas has been observed in stroke patients using fMRI or TMS.

Animal data show that skilled learning leads to a profound rewiring of the motor cortex, observable both anatomically and physiologically. Such findings are not limited to laboratory animals but can be demonstrated in the human motor cortex. Noninvasive techniques like TMS have demonstrated similar learning-dependent neuroplasticity in the human motor cortex. Individuals trained on a one-handed, five-finger piano playing task demonstrated increased motor cortex area representation for the hand muscles trained during the task. Similarly, studies have shown that highly skilled racket players have a larger representation of muscles of the trained hand in comparison to less proficient players and nonplaying controls.

Building on the principle that neuronal activity promotes reorganization of its complex mass of synapses and neurotransmitters, the therapist should attempt to stimulate those neurons that have not been active for some time. Here, the goal is to promote selective self-repair and reorganization through specific motor activity. Brain reorganization generally becomes more difficult as we age (for reasons not yet fully understood), and, in such a situation, the damaged brain needs a specific "neuroplasticity jump-start" to rebuild. For instance, practicing a particular movement over and over again, as seen in "forced" rehabilitation or constraint-induced movement therapy, helps the brain to form and strengthen the connections necessary for that movement. The use of treadmills and partial body weight support systems for patients who have lost the ability to walk are believed to enable neural reorganization evident clinically by improvement in gait parameters. Like "forcing" the subject to use the affected extremity, "timing" of physical therapy is another important aspect that can influence brain reorganization. If a subject who has

suffered from brain damage does not practice a lost movement, the damaged neurons and surrounding neurons starved of stimulation will be unable to reconnect.

Research on nonhuman animals indicates that the use of involved limbs immediately after the injury to the brain can further worsen the area of damage. A higher rate of mortality was observed among acute stroke patients who underwent high-intensity very early mobilization compared to those who received the usual care. Even studies on very early mobilization among stroke patients were not associated with beneficial effects when carried out during the initial 24–48 h after the onset of a stroke.

For rehabilitation to be successful, it is mandatory to commence rehabilitation only when the patient's medical and hemodynamic conditions are stable. Following the stabilization of the condition, the use of the injured limb stimulates damaged connections that would otherwise atrophy without input. Even excessive practice of certain movements can have untoward effects, i.e., if practiced too many times per day for months and years, the pattern of connections can grow so much that it inhibits or "squeezes out" other patterns of connection, resulting in the inability to perform other movements. For instance, some of the compensatory techniques like circumduction gait, if habituated, can impede the possibilities of normal or near-normal gait.

Appropriate therapeutic exercises, right timing and intensity of exercise to facilitate normal movement and purposeful activity, optimal environmental setting, correct sensory and proprioceptive feedback, and strategies to minimize abnormal movements and spasticity are often used in rehabilitation to optimize sensorimotor recovery. Such methods and strategies might strengthen synaptic chains, guide axonal sprouting, facilitate function by unmasking latent synapses, or compensate by behavioral changes to promote optimal or near-optimal motor recovery in patients with motor deficits. Therefore, rehabilitation therapy should take advantage of the brain's natural flexibility for forming new neural connections; however, this is a delicate process that must be done carefully and under professional guidance.

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