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Chapter

The Modulation of Hippocampus Plasticity

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Abstract

The hippocampus is a brain region that plays a vital role not only in learning and memory but also in a variety of cognitive processes. Additionally, the hippocampus is known for its plasticity or its ability to adapt structural and functional properties in response to internal and external factors. This plasticity is intricately modulated by a variety of factors, including neurotransmitters (such as glutamate), neurotrophic factors (such as BDNF, IGF-1, VEGFα, and NGF), cytokines, chemokines, adipokines (such as leptin and adiponectin), and hormones (such as cortisol, beta-endorphins, thyroid hormones, and noradrenaline). Changes in the number, length, type, and shape of dendritic spines within the hippocampus can influence neurotransmission, and subsequently behavior, through modulation of glutamatergic neurons. There are several interventions, including pharmacological treatments (such as antidepressants or multimodal drugs) and non-pharmacological interventions (such as non-invasive brain stimulation of targeted regions, physical exercise, and an enriched environment) that promote neurogenesis in the dentate gyrus, resulting in beneficial effects on cognition and mood. Both types of therapies have the potential to increase connectivity between the hippocampus and other areas of the brain involved in motor and cognitive control, and thus, improve performance in specific tasks.

Keywords: hippocampus, plasticity, cognitive control, neurotrophic factors, non-pharmacological interventions

1. Introduction

The hippocampus is a crucial brain region that plays a vital role in learning and memory, particularly in the acquisition of new memories. It is also involved in the regulation of emotion and mood. The hippocampus is affected by aging and age-related cognitive disorders, such as the progressive atrophy of its volume.

The hippocampus is composed of a heterogeneous population of neurons that are distinguished by their age, morphological characteristics, and connectivity. It is anatomically organized into three main areas: CA1, CA3 (short for Cornu Ammonis), and the dentate gyrus (DG). Area CA1 is responsible for encoding memories while area CA3 is thought to mediate the retrieval of complete memories from partial information (pattern completion). The DG is important for spatial pattern separation,

the process by which similar incoming information or stimuli are transformed into distinct, non-overlapping experiences. The hippocampus is thought to support the recollection of episodic events by representing the complex spatiotemporal patterns that uniquely define typical real-world events. Patients with lesions to the hippocampus have marked deficits in episodic and spatial memory [1–5].

This chapter focuses first on the modulation of hippocampal plasticity in terms of neurogenesis, structural, and functional plasticity, as well as on the relevant factors. It then examines how the connectivity between the hippocampus and other cerebral structures leads to the creation of new associations starting from familiar concepts or the construction of new concepts and categories. The second half of the chapter outlines the medical interventions designed to modulate hippocampal plasticity, including both pharmacological (such as therapy with Cerebrolysin, antidepressant medication, and even drug abuse) and non-pharmacological interventions (such as transcranial electrical stimulation, transcranial magnetic stimulation, and physical exercise).

2. Plasticity

2.1 Introducing neuroplasticity

2.1.1 From neurogenesis to reorganized or new connections

Neuroplasticity refers to the brain's ability to change and adapt with input and repetitive use. This capacity allows the brain to adjust to environmental changes, learn, and repair itself after lesions or disease. Genetic, neuronal, and neurochemical factors all play a role in neuroplasticity, and its limits can be manipulated through clinical and pharmacological interventions [1, 2]. The hippocampus is a highly adaptable structure that is particularly prone to neuroplasticity. This process involves neurogenesis, which is the proliferation and differentiation of neural stem cells (NSCs) and the subsequent changes in the morphology and activity of the differentiated neurons. In adult mammals, the subventricular and subgranular zones of the hippocampus are the two neurogenic niches where NSCs proliferate and differentiate to generate new neurons [2, 4].

The central nervous system undergoes structural and functional changes during development years and adulthood as it is constantly stimulated by internal physiology and environmental conditions. The hippocampus is one of the few areas in the brain where neurogenesis persists throughout adulthood, supporting learning and memory and potentially contributing to brain repair [1, 4]. While the regenerative potential of stem cell niches in the brain is still a topic of debate, an increasing body of evidence suggests that in the hippocampus, newborn neurons integrate into existing circuits and play a critical role in learning, memory, and neurological disorders [4].

Understanding hippocampal neurogenesis is therefore of utmost importance, due to its crucial role in cognition and regulation of emotions, as new neurons are integrated rapidly into its network, providing a certain level of cellular flexibility to the brain [3].

2.1.2 Types of neuroplasticity

Neuroplasticity, the ability of the brain to change and adapt with input and repetitive use, is an extraordinary tool that allows the mature brain to adjust to

environmental changes, to learn, and to repair itself after lesions or disease. This capacity is divided into two categories: structural and functional plasticity.

Structural plasticity involves the expansion or retraction of the synaptic area through the remodeling of spines, dendrites, and/or axons. It involves dendritic formation and spine development, which are regulated through various cellular factors including microtubule regulatory proteins, neurotransmitters, glucocorticoids, and growth factors. Dendritic spines, which represent an important component of the synapses between hippocampal neurons, undergo structural plasticity in terms of formation, shedding, expansion, and atrophy. The potentiation or depression of synaptic activity, modifications in the synaptic function or number of synapses, and the generation of new dendritic spines facilitate the integration of neurons into networks [4, 6].

Functional plasticity refers to the regulation of neurotransmission, the reorganization of synaptic components and receptors, and the regulation of the strength or efficiency of synaptic transmission. Synaptic plasticity can manifest as the growth of new synaptic connections or pruning of existing ones, as changes in the strength or efficacy of synaptic transmission, and as modulated excitability of existing synapses. There are many forms of synaptic plasticity, such as post-tetanic potentiation (PTP), long-term potentiation (LTP), and long-term depression (LTD) [4].

The interaction of structural and functional plasticity is evidenced by synaptic plasticity leading to structural modifications in dendritic spines. The cellular basis of these adaptations is thought to be synaptic plasticity leading to changes in the functional connectivity of neuronal networks in the brain. The remodeling of synaptic connections can be measured both at the functional and at the morphological level. The function of synapses can be evaluated through electrophysiological recordings of spontaneous activity and can involve the release of neurotransmitters. The morphology of synapses refers to the number and shape of contacts between neurons. These changes can be accompanied by variations in the shape, number, and function of the other cells that surround the neurons, including glia, endothelial cells, and resident immune cells such as microglia and perivascular circulating macrophages [7].

2.2 Modulation of plasticity

Neuromodulation controls synaptic plasticity at different levels: at the network level by directing the flow of information, at the circuit level through changes in the balance of excitation and inhibition, and at the synaptic level through the modulation of intracellular signaling cascades [6]. The modulation of structural plasticity is influenced by various molecular, physiological, or external factors.

Molecules such as vascular endothelial growth factor (VEGF) can promote neurogenesis, and hormones and peptides involved in glucose homeostasis also support neurogenesis by influencing the proliferation, differentiation, and survival of NSCs. Physical activity, exposure to an environment rich in sensory stimulation, learning (especially task-specific learning), exploration, and social interactions have all been shown to significantly facilitate neurogenesis. However, neurogenesis declines dramatically with age or under intense stress. Antidepressant treatment, on the other hand, can improve hippocampal neurogenesis through its positive effects on mood and cognition [2, 3].

2.2.1 The role of glucose metabolism in the modulation of hippocampal plasticity

The activity of neural circuits in the hippocampus is influenced by metabolic stimuli and energy supply. Hormones and peptides involved in glucose homeostasis,

such as insulin, glucagon-like peptide-1 (GLP-1), insulin-like growth factor-I (IGF-I), and ghrelin, are thought to play a role in neural plasticity, including synaptic plasticity (i.e., synapse potentiation and depression), structural plasticity (i.e., dynamics of dendritic spines), and adult neurogenesis, thus, impacting cognitive performance. For example, insulin and IGF-I activate the phosphatidylinositol trisphosphate kinase (PI3K)/Akt and Ras-mitogen-activated protein kinase (Ras/MAPK-ERK) pathways, which affect gene expression and have a significant impact on NSC proliferation and neuronal activity. GLP-1, secreted by the gut in response to satiation, helps to regulate glucose homeostasis by enhancing insulin release from pancreatic β-cells and increasing glucose sensitivity. In contrast, ghrelin, secreted by the stomach, stimulates feeding behavior and counteracts the effects of insulin.

However, it's important to note that chronic hyperstimulation of insulin/IGF-I effectors can lead to a premature decrease in the NSC pool, thus insulin may exert either beneficial or detrimental effects on NSCs depending on the timing and duration of stimulation [4].

2.2.2 The role of physical exercise and particularly running in hippocampal plasticity

The hippocampus demonstrates significant functional plasticity in response to exercise. Specifically, running increases neurogenesis in the DG of the hippocampus, leading to improved synaptic plasticity and memory function, particularly in spatial memory and pattern separation. Neurotrophins, neurotransmitters, and other peripheral components, such as myokines, hepatokines, and adipokines, may mediate these changes in neural plasticity in response to physical exercise [8].

The process of establishing connections between developing neurons and various brain areas involves multiple neurotransmitters. Glutamate and gamma-aminobutyric acid (GABA) serve as the primary excitatory and inhibitory neurotransmitters, respectively, in the brain. Both play a role in regulating the integration and survival of new neurons. Glutamate is particularly important for exercise-induced changes in DG synaptic plasticity, as running enhances DG LTP, a form of synaptic plasticity that is thought to be a cellular model for learning and memory [5].

Neurotrophins, such as brain-derived neurotrophic factor (BDNF), play a significant role in brain plasticity. BDNF expression levels in the hippocampus are increased by running in animal models, leading to improved hippocampal plasticity, spatial memory, and object recognition. In humans, exercise-induced increases in BDNF serum levels have been linked to changes in hippocampal volume, while reduced BDNF levels are associated with age-related decline in hippocampal volume. BDNF promotes synaptic plasticity through downstream targets such as cAMP-response element binding (CREB) protein, synapsin I, and synaptophysin, while simultaneously increasing its own messenger RNA (mRNA) and its receptor tyrosine kinase B (TrkB) [5].

Exercise also modulates cerebrovasculature, leading to better perfusion and delivery of oxygen, nutrients, neurotrophins, and other factors that promote brain function. Walking and running increase cerebral blood flow (CBF) in multiple regions within the brain, including the hippocampus. Additionally, skeletal muscle releases myokines that appear to play a role in neural plasticity as well [5].

2.2.3 The role of rich environments in neural plasticity

The impact of the living environment on both overall health and brain plasticity is significant. Prolonged stress can increase the risk of various diseases, including

cardiovascular diseases, cancers, neuropsychiatric disorders, and neurodegenerative diseases. In contrast, a stimulating environment can contribute to improved health and behavioral performance by optimizing brain plasticity. In depressed individuals, a decrease in hippocampal volume has been observed. Conversely, a stimulating environment, such as high-level spatial orientation training, has been associated with an increase in hippocampal volume [8].

The ability of an enriched environment to stimulate hippocampal growth can be explained by an increase in the density of dendritic arborization, the length and volume of myelinated fibers, and the number of dendritic spines in the hippocampus [7]. At the molecular level, an environment rich in social interaction, learning, exploration, and sensory stimulation promotes the expression of neurotrophic factors in the hippocampus. These factors, including BDNF, IGF-1, and NGF, can affect neurogenesis and synaptic plasticity by exerting their influence on various cell types. In astrocytes, they regulate metabolism, recycle, and eliminate metabolites, promote myelination in oligodendrocytes, regulate synaptic pruning in microglia, and enhance angiogenesis in endothelial cells. Increased neuronal activity intensifies the release of neurotrophic factors, which in turn, boosts neurogenesis and synaptogenesis, encouraging further neuronal activity [7]. The immune system plays a role in normal behavioral processes and circulating T cells have a supportive role in brain function, cognitive abilities, and hippocampus neurogenesis, although the mechanisms of their involvement in hippocampal plasticity are still not fully understood [7].

In nonpathological conditions, T cells do not have direct access to the brain parenchyma, but a small number of T cells are present in the brain's blood vessels, in the choroid plexus, and in the meninges. T cells are thought to interact directly with endothelial or epithelial cells of the choroid plexus or contribute indirectly to the release of factors such as cytokines or chemokines in the blood or cerebrospinal fluid. Alternatively, T cells could also participate in the functioning of hormonal systems that regulate brain plasticity [7, 8].

2.2.4 The effects of stress on neuroplasticity

Transient mild stress can enhance learning and memory, but chronic or severe stress leads to the disruption of hippocampus-dependent memory. Extended or high-dose treatment with glucocorticoids seems to have a similar effect, as patients treated with glucocorticoids have presented impairments in hippocampus-dependent memory [9]. The hippocampus can be damaged at the level of morphological neuroplasticity by sustained levels of stress or glucocorticoids due to the atrophy and retraction of the apical dendrites of hippocampal pyramidal cells. Prolonged intake of corticosterone in higher doses than are typically achieved in vivo can even result in the death of hippocampal pyramidal cells [8].

Many forms of synaptic potentiation are triggered by increases in synaptic calcium influx and the local concentration of the second messenger molecule cyclic AMP (cAMP). Local calcium influx is activated only when presynaptic and postsynaptic cells are depolarized simultaneously, while cAMP is regulated by many modulatory neurotransmitters, including serotonin, dopamine, and norepinephrine, as well as by calcium. Local elevations in calcium and cAMP induce events required for short-term synaptic plasticity. Inducible transcription factors and cAMP- CREB turn on effector genes that contribute to the stabilization of synaptic plasticity [10]. Brain-derived neurotrophic factor (BDNF) influences synaptic plasticity in both the presynaptic and postsynaptic cells. Other growth factors have also been demonstrated to influence

LTP, including the VEGF. This has been implicated in the actions of stress and antidepressant treatments, like BDNF. Acute and chronic stress lead to reductions in hippocampal BDNF mRNA levels, suggesting an impairment of some of the mechanisms of neuroplasticity [10].

Other growth factors are regulated by stress, nerve growth factor (NGF) is upregulated by chronic stress, while VEGF is suppressed by chronic stress. Similarly, the angiogenic actions of VEGF are impaired by glucocorticoid treatment. The involvement of trophic factors beyond BDNF suggests that a multifaceted apparatus of neuronal support may be undermined by stress and, possibly, enhanced by antidepressant therapies [10, 11]. Chronic stress or elevations in glucocorticoids can lead to neuronal atrophy, especially dendritic retraction in cells of the CA3 cell field. Glucocorticoid excess increases glutamate release in the CA1 region of the hippocampus, and chronic behavioral stress increases extracellular levels of glutamate in the CA3 region. Glutamate antagonists can attenuate or block some of the effects of chronic glucocorticoid excess on dendritic morphology in the hippocampus [11].

2.2.5 The role of antidepressants in the modulation of neuroplasticity

When depression leads to a deficit in neuroplasticity, then antidepressant treatments may enhance neuroplasticity and even reverse deficits produced during the symptomatic period. In addition to enhancing functional neuroplasticity, antidepressants produce structural plasticity. This is observed at several different levels, including the numbers of synapses, spines, dendrites, and even the number of cells themselves.

Synaptic potentiation and other forms of neuroplasticity are controlled by both positive and negative regulatory mechanisms. Under certain circumstances, LTD may provide a homeostatic counterbalance to excessive synaptic potentiation. Inhibitors of the signal transduction cascades that contribute to synaptic potentiation also provide a counterbalancing influence. Examples include phosphatases such as calcineurin, which can antagonize signaling through the MAPK cascade, and phosphodiesterases, which break down cAMP and thus attenuate PKA (protein kinase A) mediated signaling and other cAMP-dependent processes [10, 12].

Understanding the properties of adult neurogenesis may contribute to enhancing hippocampal functions. However, it is unknown whether increasing adult hippocampal neurogenesis is sufficient to improve cognition and mood. Furthermore, the stimulation of adult hippocampal neurogenesis, when combined with an intervention such as voluntary exercise, produces a robust increase in exploratory behavior. In contrast, increasing adult hippocampal neurogenesis on its own does not produce an anxiolytic or antidepressant-like behavioral response [13].

As mentioned before, the DG subregion of the hippocampus is a substrate for both cognition and mood regulation. Evidence from neuroanatomical, computational, electrophysiological, behavioral, and human brain imaging studies converges to suggest the crucial role of the DG in the formation of new episodic memories by transforming similar experiences or events into discrete, non-overlapping representations, a process known as "pattern separation." Consistent with these DG functions, the ablation of adult hippocampal neurogenesis impairs pattern separation and blocks some of the behavioral effects of antidepressants. In sharp contrast, the impact of selectively increasing adult hippocampal neurogenesis on cognition and mood is not known. Addressing these questions has proven difficult owing to a lack of strategies that selectively increase adult neurogenesis [14].

3. Connectivity

The hippocampus is a complex structure of the brain responsible for multiple functions, such as learning, memory, and emotion, all of which we rely heavily on and value greatly in our daily lives. Understanding its role in the organization of the entire brain and especially the dynamic relation of its different subregions with the cerebral cortex is of utmost importance to discern the mechanisms of brain disorders, such as Alzheimer's disease (AD), temporal lobe epilepsy, and schizophrenia.

The capacity to store memories is established during infancy and is related to sleep, specifically slow-wave activity (SWA). This supports the brain's processing of information in two ways. First, information encoded during wakefulness is mediated through sleep, renewing the brain's capacity to store new information. Second, sleep supports the creation and strengthening of long-term memory [15]. These functions rely on the circuits that connect the hippocampus and the prefrontal cortical networks, helping to store experienced events into new memories. These effects are observed primarily during deep, non-rapid eye movement sleep (NREM) and, specifically, slow-wave sleep (SWS), a deep form of NREM.

Unlike adults, infants and children have a greater need for sleep, spending almost half of their life sleeping in a disorganized manner at first, with periods of daytime sleep, gradually shifting to less, but more organized night sleep, with established slow oscillations (SOs). Studies have shown that sleep disturbances in children are associated with learning difficulties [16]. This highlights the critical nature of this period in brain development. Practically, sleep time decreases gradually with growth, but sleep patterns change, with deep sleep defined by an increase in SWA, comprising 75% of total sleep time by the age of 2–3, compared to the first post-natal months, when there is an equal distribution between REM (the so-called "active sleep" because of the presence of muscle impulses) and NREM (also known as "quiet sleep"). Spindle activity, defined as NREM oscillations resulting from waxing and waning patterns in neuronal firing, is also relevant for cerebral development and follows the same course as SWA, showing a significant increase during childhood and puberty and reaching a plateau during adolescence. The consistent increase in SWA and the reaching of optimal spindle density, which occurs until the onset of puberty, promote a significant enhancement of synaptic network connectivity. It is important to keep in mind that the inherent maturation of synaptic connectivity that comes with age must be further sustained by utilizing the network; the network connectivity grows stronger with encoding information [15].

The episodic representation of events in time and space is based on the activity of the hippocampus and the prefrontal cortex. On the other hand, semantic and procedural memories like recalling memorized facts or how to ride a bike, for example, processes that involve repeated training, do not necessarily involve hippocampal function. The postnatal hippocampus reveals a complex dynamic as it attains a number and density of synapses like those in adults as early as first six months of life. However, infants present limited memory capacity, with hippocampus-dependent episodic memory performance increasing slowly over time. This leads to a higher rate of forgetting in children compared to adults, and it could explain the absence of autobiographical memories before three years old. Following this initial three-year period, there is a relevant increase in SWA and a shift of sleep activity toward more frontal cerebral areas during childhood, gradually enhancing the ability to store more information for a longer time, thus consistently expanding the episodic memory capacity up until the early stages of puberty. Inside this time window, the synaptic

connectivity within the cortical networks undergoes significant transformation, leading to an overall evolution in memory capacity and, together with it, an intensified synaptic plasticity [15].

Once the transition to adolescence begins, the human brain develops new abilities and progressively reorganizes itself over time, increasing cognitive functioning and memory performance. Puberty and adolescence bring a reduction of sleep time and sleep pressure during wakefulness, together with the stabilization in SWA. If a first stream of gonadal hormones initiates the definition and the structure of neuronal networks during childhood, a second stream of the same hormones is set to completely grow and trigger those networks during puberty [17]. It is in this period when the different regions of the brain work in increasing synchrony, and the brain becomes a system within which all its constituent elements (brain areas) impact and influence one another, in a functional interaction that can be evaluated in terms of functionality and effectiveness. Functional connectivity is characterized by temporal correlations between spatially dispersed neurophysiological incidents [18]. Of course, effective connectivity is the one offering a more complex overview of the interconnection and exchange within the cerebral network [19]. Research on this topic revealed that there is a remarkable development of memory processing capacity provided by maturation, that memory performance is enriched with age, evolving from neuronal connections based on elementary visual processing to connections governed by multi-modal processing on a higher level. During adolescence, there is a great development in white matter pathways, an essential element for efficient connectivity within the cerebral network, gradually translating into more substantial, more resilient, and more efficient structural connectivity [19].

During adolescence, the brain undergoes significant development and reorganization. One aspect of this development is the increased influence of sex on cerebral processes and changes within the hippocampal network. Research has shown that adolescent girls reach peak brain volumes earlier than boys, while testosterone is associated with a greater increase in white matter in boys [20, 21].

As individuals transition into adulthood, cognitive processes become more complex and problem-solving becomes increasingly reliant on memory. Additionally, there is a notable improvement in pattern separation, creativity, conceptualization, higher-order self-observation, perspective, future thinking, and risk-taking. These abilities are all connected to cerebral mechanisms that control emotion and motivation. Emotion can also play a role in functional connectivity and decision-making, with trait anxiety found to impact decision-making and risk-taking. Research has also revealed that when people are faced with risky situations, two functions are activated in decision-making: evaluation and choice. The first involves assessing various possibilities, while the latter involves preferring one option over others for reasons deemed pertinent to the situation [22, 23].

A crucial aspect of decision-making is weighing the potential consequences of a choice. The anticipation of negative consequences, such as loss or a negative perception of risk, generates aversion as a behavioral predisposition. Studies have found that aversion to loss and risk triggers activity in cerebral areas related to motivation and emotion, including the amygdala and the prefrontal cortex [24]. Trait anxiety has been shown to undermine decision-making in risky situations by impacting episodic future thinking and episodic memory, cognitive processes related to the hippocampus. It is also associated with contextual fear learning [25] and is thought to be a part of contextualization and episodic prospective memory. Individuals affected by trait anxiety show a deficit in attentional control, tending to focus on negative outcomes,

which can lead to a reduction in rational cognitive function that relies on executive control. This can result in a preference for instant rewards over delayed, greater gratification, which suggests how trait anxiety interferes with the functional connectivity between the hippocampus and other cerebral areas. Conversely, when not disturbed by impairments such as anxiety or cognitive bias, the functional connectivity between the hippocampus and connected cerebral regions can enable creativity. Connectivity of the hippocampus with the medial temporal lobe leads to the creation of new associations starting from familiar concepts, while the connectivity of the middle temporal gyrus (MTG) with the hippocampus enables the construction of new concepts or categories and its connectivity with the executive control system promotes breaking the limits of the old concepts and patterns.

Low-quality sleep has been associated with depression and its detrimental effects. Studies have revealed that the lateral orbitofrontal cortex is affected by depression, being sensitive to the areas triggered by the failure to attain anticipated rewards. The functional connectivity between this cortical area and the precuneus, a cerebral area related to the perception of self, generates low self-esteem by linking this self-representation with the previously mentioned lack of rewarding, activating depression symptoms and causing distressing incessant thinking which has a heavy, negative impact on sleep [26].

With age, significant changes take place in the hippocampus and its subfields, with relevant effects on memory, cognitive and functional connectivity. Studies have shown that certain hippocampal regions function differently depending on the type of information being processed and the cognitive processes involved. For example, retrieval-based mental operations that process visual, spatial, or neutral information appear to rely on the hippocampal posterior regions, whereas encoding- and association-based mental operations that process emotional or motivating information appear to depend on the hippocampal anterior regions [27]. Additionally, volumetric declines in the DG/CA3 and CA1 regions have been reported in several studies [28].

Aging seems to make the functional dissociation between the anterior and posterior hippocampus more pronounced in terms of how each contributes to memory processing. Studies have also observed a gradual shift from one to the other over time. Some research has shown an increasing dominance of the connectivity involving the posterior hippocampus in aging individuals, suggesting that the brain undergoes a reorganization of cerebral networks and their connections as a means of sustaining cognitive processes. This may be an adaptation to the fact that the anterior hippocampus is the first to suffer from atrophy [29]. However, other studies have found that the volume and proportions of the anterior and posterior hippocampus regions were not significantly different in aging subjects compared to young individuals. However, a general decrease in the functional connectivity between the hippocampus and the rest of the brain as people age is typically observed, with several cerebral areas developing further functional connectivity to the posterior hippocampus. This may be related to the additional effort made by an aging brain to maintain normal memory function [29, 30].

The brain is a highly complex network, with a wide range of subregions, each of them essential for normal cognitive functioning. Connectivity, the continuous flow of information and influence of one subsystem (a cerebral area) on others, is vital for sustaining the brain's complex capacity for memory and learning, the very foundation of human consciousness. Connectivity is formed during infancy and defined by continuous adjustments throughout life, undergoing changes specific to each life stage, and finally adapting to aging and related cognitive decline.

4. Pharmacological interventions

Although the hippocampus is the most widely recognized brain region linked to memory and learning, it is a vulnerable, plastic structure that can be affected by a wide range of triggers and stimuli, such as pharmaceutical elements. Due to its fairly straightforward structural connectivity and its different roles and functions, the hippocampus is an ideal model for pharmacological research. Numerous medications from several pharmaceutical classes have been demonstrated to have favorable effects on its function, while others were shown to elicit harm.

4.1 Prescription medication

4.1.1 Lithium

In addition to its well-known therapeutic effects on bipolar disorder and depression, lithium has neuroprotective effects on neurodegenerative diseases like traumatic brain injury (TBI) [31]. Lithium has also been shown to have neuroprotective properties. A wide range of neurotrophic effects is displayed by lithium. For instance, lithium enhances LTP and hippocampal neurogenesis, and elevates cytoprotective B-cell lymphoma protein-2 (bcl-2) levels in a number of rodent brain regions and in cultured cells [32–34]. Due to this, neuroprotective and antiapoptotic properties are produced. In people with bipolar disorder, lithium builds up in the brain's neurogenic regions and has a positive impact on hippocampal volume [35]. However, prolonged use of lithium, especially at low doses, results in decreased neurogenesis and hippocampal atrophy [31].

4.1.2 Estrogens

Beyond their role in regulating reproductive function, estrogens have numerous additional effects on the nervous system. According to reports, they have an impact on verbal fluency, verbal memory tests, spatial task performance, fine motor skills, signs of Parkinson's disease, and tardive dyskinesia [36]. The neuroprotective properties of estrogens are well known. Sex hormones have the hippocampal region as a target, and large amounts of estrogen are produced by hippocampal neurons [37]. It has been established that ovarian estrogens affect neurogenesis in the DG. Also, estrogen has a variable impact on inflammatory markers and a considerable impact on thrombosis and thrombolysis. It also leads to higher CBF, glucose transport, and glucose metabolism [38]. However, a few of the effects of estrogen may be negative. Some estrogens' prothrombotic properties may have harmful effects on the cerebral vasculature, and proinflammatory effects may be damaging [39].

4.1.3 Sodium valproate

After more than 40 years of use, sodium valproate has a good safety profile. Its broad activity against both generalized and partial seizures, ability to stabilize mood in bipolar disorder, and effectiveness in treating migraines make it unusual among anti-convulsants. When compared to other anticonvulsants, it has comparatively few side effects and is frequently used by epileptic patients, sometimes with great success for decades [40]. Sodium valproate has neuroprotective properties. It enhances cytoprotective protein bcl-2 in the central nervous system, encourages neurite outgrowth,

and activates the extracellular signal-regulated erk pathway, a signaling pathway used by numerous endogenous neurotrophic factors to control neurogenesis, neurite outgrowth, and neuronal survival [41]. Additionally, in the DG of the hippocampus, valproate stimulates neurogenesis possibly via the ERK pathway and guards against excitotoxicity [42].

4.1.4 Fluoxetine

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) with therapeutic indications for bulimia nervosa, posttraumatic stress disorder, anxiety disorders, and major depressive disorder [43]. One of the biological mechanisms of fluoxetine in the treatment of depressive disorders is suggested to be the way it regulates dendrite atrophy of hippocampal neurons caused by NOS overexpression, by halting the overexpression of nitric oxide synthase [44]. Moreover, it overturns cell proliferation in response to unavoidable stress [45]. It has been discovered that an increment in hippocampal S100beta content is the cause of fluoxetine's neurotrophic action [46]. The stimulation of neurogenesis in the hippocampus may serve as a bridge between the behavioral effects of ongoing antidepressant therapy, such as fluoxetine [47]. In depressed rats, fluoxetine can boost the number of hippocampal neurons, enhance the stereology of synaptic structures, and restore the structure and functionality of the hippocampus [48].

4.1.5 Phenytoin

Phenytoin is an anti-seizure medication that has been studied in clinical trials for nearly eight decades. It is mostly used to treat tonic-clonic and partial seizures [49]. The motor region of the cerebral cortex is subject to a highly selective inhibitory effect from phenytoin. Phenytoin extends the neuronal refractory period by binding to the inactivated state of the Na+ channel as its mode of action [50]. Phenytoin prevents neurodegeneration by blocking the effects of chronic stress on the number of pyramidal neurons in the hippocampal CA3 area and the length of all their apical dendrites [51]. It also prevents dendritic atrophy and inhibits glutamate release [52]. Phenytoin has several additional advantageous neuroprotective properties, for instance, increases right brain volume by 6% in PTSD and has antiseizure properties [53, 54].

4.1.6 Cerebrolysin

Cerebrolysin, an amino acid and peptide blend, mimics the biological effects of neurotrophic factors and has been shown to have positive effects when given to patients who have experienced an ischemic stroke while exhibiting a benign safety profile [55]. The mechanism of action of Cerebrolysin is multi-faceted and has been demonstrated in a range of studies, including animal and *in vitro* studies. One of the key mechanisms of action of Cerebrolysin is its impact on the hippocampus, which is a crucial area for learning and memory. By regulating the growth of synapses and promoting neuroplasticity in the hippocampus, Cerebrolysin has been shown to improve memory and cognitive function in patients with ischemic stroke [55]. Additionally, Cerebrolysin activates the Sonic Hedgehog pathway, which boosts neurogenesis and oligodendrogenesis in the hippocampus, contributing to the development and structuring of the brain [56]. Cerebrolysin has been shown to reduce the production of free radicals and programmed cell death, control the inflammatory response,

and reduce the toxic effects of neurotransmitters (excitotoxicity) [55]. Cerebrolysin promotes neuroplasticity, neurogenesis, and oligodendrogenesis in the hippocampus, and reducing oxidative stress and inflammation to promote neuroprotection and neurorecovery. The biological agent, therefore, has the potential to improve cognitive function and reduce the risk of damage after brain lesions.

4.2 Drug use

Prescription medication used for diverse purposes can impact the hippocampus in varied ways, but it is also important to look at the way addictive substances affect it. Drug abuse and addiction are major global health issues, and both are frequently associated with various types of neurological impairment. Due to the hippocampus' high level of plasticity and its capacity to support declarative and contextual memories, drugs may cause changes in hippocampal function that have a significant impact on behavior. Drug-induced changes to hippocampus-dependent learning and memory appear to play a significant role in the emergence and maintenance of drug addiction, according to a large body of human and animal studies [57].

4.2.1 Cocaine

Cocaine use is typically characterized by compulsive behavior and obsessive drug seeking. It is a highly addictive psychostimulant derived from the leaf of the Erythroxylon coca plant [58]. It is the most prevalent illegal substance among patients who seek emergency care and has detrimental effects on the heart, lungs, and mind [59–61]. Cocaine directly affects several brain areas in the mesolimbic circuit, including reward-related areas such as the nucleus accumbens and ventral tegmental area, as well as areas that govern cognition like the prefrontal cortex and hippocampus [62]. Given its involvement in learning and memory, as well as reward, the hippocampus may be a key area for the rewarding effects of cocaine [58, 63]. Research has shown that the ventral hippocampus mediates cue-induced and cocaine-primed reinstatement of cocaine self-administration, in contrast to the dorsal hippocampus [64, 65]. Additionally, the dorsal and ventral hippocampus may play different roles in stress-related relapse to cocaine seeking. Studies have shown that stress has opposing effects on these regions' synaptic plasticity, with stress increasing ventral hippocampal synaptic plasticity while decreasing synaptic plasticity in the dorsal hippocampus [66]. Therefore, during a time of high stress such as cocaine withdrawal, the ventral hippocampus may play a larger role in the resumption of cocaine-seeking behavior. Furthermore, cocaine CPP has been found to increase the phosphorylation of hippocampal cAMP-response element binding protein (CREB), a transcription factor that is crucial for the formation of long-term memory and synaptic plasticity [67, 68].

4.2.2 Amphetamine

Racemic a-methylphenethylamine (amphetamine, also known as "speed") was first discovered in 1910. It was later synthesized and sold under the trade name Benzedrine to treat a variety of ailments, including narcolepsy, depression, Parkinson's disease, and pulmonary dysfunction [69]. However, the euphoric effects of amphetamine were quickly recognized, leading to its abuse for its pleasurable effects, such as feelings of self-confidence, energy, and alertness [70].

Research soon showed that amphetamine and its derivatives, such as dextroamphetamine, have procognitive effects, including improved intelligence, concentration, and intellectual performance [71, 72]. These effects were later supported by studies that showed that amphetamine and its derivatives enhance memory consolidation [73], memory recall [74], attention, and psychomotor performance [75, 76], information processing [77], and logical reasoning [75].

Amphetamine was initially used to treat ADHD due to its attention-enhancing properties, but later, medications with fewer psychoactive side effects replaced it [78]. However, despite its acute procognitive effects, amphetamine and methamphetamine use has detrimental consequences for cognition, including impaired memory, attention, flexibility, inhibition, and decision-making. Additionally, its toxic impact leads to the degeneration of neuronal apoptosis and monoaminergic terminals [79].

4.2.3 Cannabis

Cannabis, a plant that has been used for therapeutic, recreational, and commercial purposes for many years, has several products derived from it, such as hemp oil and hemp fiber. Hashish and marijuana are examples of recreational drugs made from cannabis subspecies that have been selectively bred to produce a high yield of D9-tetrahydrocannabinol (THC), the plant's primary psychoactive component. Studies have shown that the administration of THC and cannabidiol impairs contextual fear conditioning and hippocampus-dependent spatial learning in the Morris water maze and radial arm maze [80, 81]. This is similar to the effects of opiates but different from the effects of cocaine and amphetamine [82]. Cannabinoids have been shown to impair all phases of memory processing, including encoding, consolidation, and retrieval. The amnestic effects of cannabinoids have been attributed to several mechanisms, including effects on LTP and LTD, as well as the suppression of neurotransmitter (GABA, glutamate, acetyl choline, and dopamine) release [83]. Hippocampal plasticity deficits from acute cannabis use may be the cause of the disruption of hippocampus-dependent learning. For instance, in the hippocampus, acute THC decreased the amplitude of both spontaneous and conditioned stimulus-evoked potentials [84].

4.2.4 Opiates

Opiates are a group of psychoactive substances that are either synthetically made or naturally derived from the opium poppy. They include morphine, diacetylmorphine (also known as heroin or diamorphine), codeine, oxycodone, and methadone. Patients may receive a legal prescription for opiates such as oxycodone for pain relief. However, as tolerance grows, these legally prescribed opiates may lose their analgesic effects, which can lead to drug dependence as users attempt to increase their effectiveness or prevent withdrawal effects [57]. The consequences of opioid exposure on hippocampus anatomy and hippocampus-dependent learning and memory imply that some of the cognitive dysfunction seen in opiate abusers may be related to altered hippocampal function. Despite this, several studies have suggested that opiate abuse-related cognitive decline may also be linked to compromised frontal lobe function [85, 86]. For example, opioids have been shown to reduce adult neurogenesis in the hippocampus [87] and alter clathrin, a protein that is linked to the density of synapses in the hippocampal nucleus [88]. Furthermore, there is evidence that chronic use of heroin and morphine harms hippocampus-dependent spatial learning in the Morris water maze, radial arm maze, and Y-maze [89].

5. Non-pharmacological interventions

5.1 The importance of sleep

The strong connection between sleep and neurological health is well-established, and interest in this subject is increasing. The natural process of aging brings about alterations in sleep patterns, which can further lead to neurodegenerative disorders. Finding viable solutions for confronting cognitive impairment has been a growing interest among researchers in recent years; as a result, focusing on sleep enhancement methods has become an important path to be followed in order to achieve this goal.

It has been observed that older adults are commonly affected by sleep fragmentation and a significant reduction in SWS [90], together with a reduction in SWA and sleep slow oscillations (SOs). These factors have a negative impact on sleep-mediated memory retention [91]. These factors are relevant for approaching neurodegenerative disorders because early intervention in sleep-wake calibration has been suggested as a potential factor in delaying or alleviating such conditions, such as Alzheimer's disease (AD), where the focus is increasingly shifting to the early stages [92], using neuromodulation as a strategy for delaying the disease progression as much as possible [93].

Memory consolidation depends on neuronal processes that take place during sleep when information related to declarative memories (the ones linked to remembering facts and events, and not skills) is transferred from the hippocampus to the neocortex and integrated into long-term existing information [94]; the synchronization of different networks within the neuronal system during three essential waveforms (hippocampal sharp-wave ripples, SOs, and spindles) of SWS is what the consolidation of sleep-dependent memory relies on [95]. Therefore, the solution for ensuring high-level functioning memory and cognition is represented by different interventions developed for enhancing sleep, especially SWS and SWA.

5.2 Transcranial electrical stimulation (TES)

Transcranial electrical stimulation (TES) is a non-invasive method that modulates neuronal activity through the application of moderate electrical current via scalp electrodes [96]. Studies have focused on both short-term and long-term stimulation (transcranial direct current stimulation—tDCS) during wake, nap, or nighttime sleep in healthy individuals and older adults with conditions such as mild cognitive impairment (MCI), Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis, and stroke. Positive effects have also been observed in the treatment of psychiatric conditions such as schizophrenia and depression [97]. The impact of tDCS on the nervous system is related to its ability to modulate neuronal excitability in polar coordinate systems. Anodal tDCS has been shown to increase excitability, while cathodal tDCS reduces it, producing lasting effects on the subjects' motor cortex. This type of system has also been suggested to affect synaptic plasticity in the hippocampus, specifically related to LTP and LTD. However, the data indicate that the effects of tDCS on hippocampus plasticity are highly dependent on current polarity and the specific subregion studied. While the results are not homogenous and linear, the primary advantage of nap studies is that tDCS has been observed to enhance sleep, and as a result, sleep-mediated declarative memory.

More research is needed to understand the effects of tDCS during nighttime sleep and wakefulness [98]. Anodal tDCS has been shown to enhance memory through molecular adjustments in the hippocampal synaptic system. When applied before the

acquisition step, tDCS is thought to increase proteins that enable glutamate signaling and ion channel activity, thereby strengthening memory performance [99].

5.3 Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a technique that uses a magnetic field to send electrical current pulses into the cerebral cortex, modulating cortical plasticity in both human and animal models [100]. Repetitive TMS (rTMS) has been shown to produce significant benefits for memory function in healthy young adults and to enhance cognitive functions and memory in patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI). rTMS performed during sleep or immediately before sleep has been observed to increase sleep spindle-associated oscillations (SOs), positively impacting sleep-mediated memory [101]. Studies have also revealed the benefits of rTMS in enhancing spatial memory, due to its ability to calibrate and sustain hippocampal synaptic plasticity. Low-intensity magnetic stimulation (LIMS) has been shown to enhance synaptic activity and stimulate nerve regeneration and cell morphology maintenance, while high-intensity magnetic stimulation (HIMS) is thought to reduce synaptic plasticity [102]. The most common areas targeted for rTMS are the ones related to the frontal association (dorsolateral prefrontal cortex—DLPFC), for its impact on several cognitive functions such as working memory, its important role in treating psychiatric conditions like severe depression and for being widely considered a safe region for performing rTMS. Left and right DLPFC seems to respond differently to rTMS. In previous research, rTMS to the left DLPFC has been linked to enhanced memory function, by increasing resting-state functional connectivity and brain activation patterns during encoding and retrieval in memory tasks [102]. That may be due to the prefrontal-mesiotemporal lobe circuitry potentiation and hippocampal synaptic multiplications [103]. The angular gyrus (AG) is also targeted less frequently, for its high functional and structural connectivity to the brain areas that support declarative memory functions. Both areas are viable targets for rTMS due to their optimal location directly under the skull, within the typical TMS structures [102]. Most procedures involving rTMS have focused on a single brain area at a time, but there have also been studies in which rTMS targeted multiple brain regions, and this type of stimulation has also been proven to be beneficial in modulating neuronal activity, suggesting a high potential for cognitive improvement. Research involving multitarget stimulation, in which several focal points in both frontal and parietal regions of the brain were simultaneously stimulated five days a week over a six-week period, showed significant improvements in AD patients regarding cognitive performance, lasting for up to 12 weeks, providing very encouraging results in the field and suggesting persistent modulation of the functional neuronal system [104].

5.4 Sensory stimulation

Sensory stimulation is a commonly used method for enhancing sleep and is represented by various techniques such as vestibular stimulation (induced through slow, gentle rocking, which has been observed to enhance SWA and the density of spindles in naps), olfactory stimulation (which is effective, especially when dealing with targeted memory reactivation), or auditory stimulation. Among these techniques, acoustic stimulation [105] has been found to be the most efficient. It is a safe, non-invasive method that can be applied even in a familiar environment by

the beneficiaries themselves, but it is limited to those without any associated hearing impairment. The delivery of acoustic stimulation has been suggested to increase SWA and SOs, to show relevant effects on enhancing memory, and to also generate benefits beyond memory consolidation, such as improvements in cardiovascular and immune systems. Even if SOs originate in cortical and thalamic regions, they mirror global synchronous neural activity, that spreads throughout the neocortex and also in subcortical structures, like the hippocampus [106]. In addition to their involvement in synaptic downscaling and homeostasis, SOs are causal in the consolidation of memory. The coordination of fast-spindle activity (12–15 Hz) and hippocampus ripples to the up-depolarizing state appears to be crucial for this consolidating function, contributing, in this manner, to hippocampal plasticity [107]. The acoustic stimuli can be provided through headphones or even bone conduction. Some researchers have pointed out that unilateral stimulation can be as effective as bilateral stimulation in increasing SOs for both cerebral hemispheres. The most commonly used stimulus type in acoustic stimulation is pink noise, defined as one of the most prevalent noises in nature, which has a wide range of sound frequencies transferred in a 1/f distribution, with lower frequencies offering a more significant contribution [100]. Numerous studies have shown that acoustic stimulation using pink noise contributes to a lower complexity in neuronal activity during sleep, ensuring an increased balance in the sleep state resulting from optimal coordination of brain waves [100]. The methodology used for acoustic stimulation during sleep is also important because there is a fine line between beneficial stimulation for promoting slow waves and generating sleep fragmentation or arousal. This is why the search for optimal calibration of the stimulation is a continuous process, involving constant monitoring and adjustment. This calibration regards the intensity of sounds (the range present in most studies is 20–65 dB, either at a fixed or at a varied volume within these limits), timing (it has been observed that arbitrary acoustic stimulation or immediate delivery of stimulation following SOs lowest level stage do not contribute to SOs or sleep-mediated memory enhancement, but coordinating stimulation with the high levels of SOs); so a particular endogenous SOs time window, with the help of EEG monitoring during sleep, is shown to be essential for obtaining these benefits [106].

5.5 Physical exercise and diet

Physical exercise has been observed to be an effective means of preserving overall health and promoting optimal function of the nervous and cardiovascular systems. Additionally, it has been identified as a non-pharmacological intervention for hippocampal modulation, as it has been shown to have significant beneficial effects on cognitive and metabolic functions, as well as on cerebral plasticity. This is achieved through the reduction of metabolic-related disorders and inflammation in adipose tissue, as well as by contributing to the balance of insulin resistance [108]. In particular, for aging individuals who are susceptible to a decline in cognitive and memory performance, an active lifestyle and regular exercise routine can have a significant impact, including a reduction in the risk of dementia, which is expected to become a major public health concern in the coming decade [109]. Many studies, including those involving both healthy adults and those with neurodegenerative disorders, have reported significant cognitive benefits from regular physical exercise. The minimal frequency for achieving these benefits is suggested to be at least 30 minutes per session, three times a week, for a minimum of 16–24 weeks [110].

There have been several attempts to correlate the intensity of exercise to cognitive performance, but the measurement of memory capacity is too complex for a linear and clear cause-effect model to be identified. Most studies have revealed that different intensity levels in exercises engage and enhance different memory processes, and a determinant factor in cognitive performance is optimal recovery post-exercise. High-intensity physical exercise has been observed to affect cognitive processes and complex assignments during training or immediately after it, difficulties in verbal acquisition and focus have been noted, but can have beneficial effects on working memory enhancement after proper rest when fatigue does not weigh in the equation of cognitive performance. There are outcomes pointing to both aerobic exercise promoting improvement in executive memory skills and to more moderate exercise boosting overall memory performance, so the optimal approach would be combining and alternating the two [111]. Running has been proven to lower hippocampal basic metabolic panel (BMP) levels, and transgenic mice with decreased BMP signaling showed impressive improvements in hippocampal cognitive function and neurogenesis [112].

The possible mechanisms behind linking memory improvement to exercise are multiple and on varied levels and are yet to be fully identified and assessed. It has been observed that an exercise routine enhances cerebral blood circulation, especially within the hippocampal area, which is mainly associated with memory and learning processes. The assumption is that this enriched blood circulation is a result of lactate, secreted by the skeletal muscles when contraction occurs and then used in different cerebral areas for optimal blood pumping and oxygenation and for boosting cerebral metabolism [111]. Lactate has also been associated with neurogenesis in some studies, being thought to be a contributor to increased cerebral gray matter integrity and reduced atrophy in the hippocampus, with a strong impact on memory and learning capacity [113]. Additionally, contraction of skeletal muscles has been shown to promote mitochondrial function, with a significant direct impact on resistance to oxidative stress, metabolism, cell survival, and proliferation of energy-productive proteins [114], but it was discovered that acute exercise can lead to mitochondria having a negative impact on memory performance by producing reactive oxygen species (ROS). This is why an exercise is a beneficial tool for neuronal processes only when approached regularly, at moderate levels. Furthermore, the contraction of the skeletal muscles during exercise seems to secrete several proteins that generate an increase in neurotrophic factors, which promote and sustain long-term memory and plasticity within the hippocampus [111]. The endocannabinoid system (ECS) is a biological lipids network with an essential role in modulating the nervous system, by enhancing synaptic plasticity, neurogenesis, and other neurophysiological functions. The endocannabinoid (EC) has been revealed as an important factor in lowering cerebral inflammation, anxiety, and oxidative stress, so the fact that its levels are increased by physical exercise is another proof of the great potential exercise has in modulating neuronal plasticity and memory performance. Reduction of insulin resistance is another mechanism that relates physical exercise to improvements in hippocampal plasticity, as it has been observed to elevate the level of enzymes that increases insulin sensitivity and thus prevent neurodegeneration [111].

When it comes to diet, research has shown that it can have a direct and immediate effect on neuronal activity and efficiency. Studies have demonstrated a notable decline in the performance of hippocampus-reliable processes such as learning and memory after only four days of consuming a diet high in saturated fats and added sugars [115]. Recent literature on this subject also indicates that even a week of a

high-fat diet can affect memory and learning capacity, causing difficulty in recognizing objects and leading to mood disruptions and impairments in hippocampal plasticity if this type of diet is continued for more than a week [115].

A high-fat diet can generate chronic inflammation, reducing the density of dendritic spines in granule neurons and altering LTP in the hippocampus. It can also increase the levels of ROS in body fat, triggering a neuroinflammatory response and damaging synaptic plasticity. This can activate metabolic syndromes, disrupting the secretion of inflammatory-regulator cytokines and having a significant impact on both peripheral metabolism and hippocampal microglial activation, resulting in significant damage to plasticity within the hippocampus [116]. Excessive ROS generated by hyperglycemia can also have a damaging effect on mitochondrial DNA and oxidative capacity, leading to a decrease in ATP formation and mitochondrial density within neurons and the emergence of insulin resistance, and reduced exercise endurance in skeletal muscles [117]. Neuronal plasticity can also be suppressed by a significant intake of palmitate, the most saturated fatty acid found in the cerebrospinal fluid and in circulation. Studies have shown that palmitate increases microglial activity, leading to lower insulin sensitivity and resulting in microglial inflammation, which can cause a serious decline in the growth of surrounding neurons and ultimately have damaging effects on learning and memory processes [116].

Caloric restriction has been identified as a feasible solution for cognitive and neurotrophic enhancement. It has the ability to regulate mitochondrial biogenesis, enabling synaptic plasticity within the hippocampus, thus, increasing memory and learning capacity. Intermittent fasting has also been shown to have a beneficial impact on hippocampus-reliant spatial memory function and on reducing seizure rate [116].

5.6 Environmental and lifestyle enrichment

The well-functioning of cerebral processes within the hippocampus can also be enhanced by environmental enrichment, as researchers have found in several studies. The hippocampus is the cerebral area that is most vulnerable to degeneration induced by aging, and its functional integrity and plasticity can be restored and maintained by multiple environmental stimulations on many and varied levels: cognitive, social, motor, and sensory. These stimulations are provided by continuously performing complex and challenging physical and mental activities, which are constituents of the paradigm called enriched environment (EE). In humans, exposure to a complex environment as early as possible is of high importance and has a lifelong impact on cognitive functions. Studies have revealed that people who benefit from elevated education are less likely to be affected by cognitive decline and the associated degenerative disorders [118]. EE was found to trigger certain changes within the hippocampal transcriptome, translating into lowered spatial learning deficits and other cognitive benefits. EE has also been observed to reduce anxiety levels and increase strength, specifically grip strength, as well as enhance muscle performance. The physical exercise performed in an EE is more stimulating and beneficial overall. The various stimuli offered by an EE trigger simultaneous signaling in multiple, different regions of the brain, facilitating learning and enabling the adaptive potential, thus maintaining a high level of cognitive functions and ensuring neuronal plasticity in the hippocampus.

For example, light has been shown to be an important factor that can influence neurogenesis, as it is related to sleep and the circadian rhythm. The body and brain can be negatively affected by the disruption of circadian rhythms, which can be caused by aging, neurodegenerative disorders, or harmful light regimes. Continuous

light can impede hippocampal neurogenesis and cognitive function. Additionally, exposure to low light at night can decrease the expression of hippocampus neurotrophic factors. These findings are highly relevant to the negative effects of nighttime light, such as that emitted by electronic devices, on mental and cognitive function. Light has been proven to be the most effective trigger for synchronizing circadian rhythms with their surroundings. Importantly, rhythmic light and dark cycles regulate psychiatry and behavior even when there is no functional molecular clockwork present. As different suprachiasmatic nucleus (SCN)-dependent and independent pathways deliver different types of light information to the hippocampus, it becomes clear that light exposure and intensity can affect hippocampus-dependent learning and memory. This effect is likely caused by an increase in active p21-activated kinase 1 (PAK1) and an increase in CA1 LTP in the hippocampus. However, it is unclear whether rhythmic light and dark conditions, as opposed to persistently dark conditions that do not change with the circadian cycle, promote neurogenesis [119].

The non-pharmacological factors that have been observed to modulate hippocampal plasticity are non-invasive methods adopted to improve memory and learning processes. Transcranial electrical and magnetic stimulation, which involves the use of scalp electrodes to send moderate electrical impulses to the brain, has been shown to have beneficial effects on sleep-dependent memory enhancement and cognitive function improvement in patients with neurodegenerative disorders. Sensory stimulation is another approach that can be used to enhance memory and learning performances, with acoustic stimulation using pink noise proving to be the most efficient. Adopting a ketogenic diet, practicing intermittent fasting, and engaging in physical exercise have also been shown to be beneficial in promoting learning processes and memory functional enhancement for not only overweight individuals but also for the general population, as long as they are approached in a prudent and balanced manner. An enriched environment is also a contributor to the modulation of hippocampal plasticity, as it enhances cerebral processes through positive pressure to adapt to multiple and diverse environmental stimuli, thus, enabling learning and memory functions.

Nevertheless, the presented non-pharmacological interventions are not intended to represent an exhaustive list of instruments with hippocampal plasticity modulation effects. Studies and findings in this area are ongoing and continuously reveal new ways and means of approaching this sensitive and important matter. At the same time, it has been observed that these interventions have better results when combined in the same protocol. For example, physical exercise alone has beneficial results, but physical exercise in an enriched environment is even more effective in promoting hippocampal plasticity [120] as well as caloric restriction-induced by intermittent fasting merged with physical exercise [116].

6. Conclusions

It is well-established that the optimal functioning and performance of the nervous system and cognitive processes depend on the overall well-being of the body. Imbalanced dietary habits, a sedentary lifestyle, lack of quality sleep, and various environmental conditions and stimuli have been shown in numerous studies on both humans and animals to negatively impact learning and memory. Additionally, the use of prescription drugs for other medical issues or the use of harmful substances like illicit drugs can also have detrimental effects. The hippocampus, a cerebral

region known to be associated with these processes, is characterized by its plasticity. While negative factors can negatively impact its performance, the activity of the hippocampus can also be proved or enhanced by exposure to interventions described in this chapter.

Currently, research on the hippocampus is focused on understanding the underlying mechanisms of various brain disorders, such as Alzheimer's disease, temporal lobe epilepsy, and schizophrenia, as well as the neural basis of memory and emotion. One exciting avenue for future research is the study of the neural circuits connecting the hippocampus and the prefrontal cortex, as this can provide insight into how memories are stored and consolidated. Additionally, research on the role of sleep and SWA in the hippocampus is also gaining traction, as it has been shown to play a critical role in memory formation and consolidation. Another promising area of research is the use of neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), to investigate the dynamics of the hippocampus and its subregions in real-time, which could provide a deeper understanding of the neural processes involved in brain disorders and memory formation. Overall, the hippocampus is a complex and multifaceted structure of the brain, and there is still much to be discovered about its functions and the mechanisms that underlie them.

Conflict of interest

The authors declare no conflict of interest.

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