

THE SCIENCE OF NEUROLEARNING FROM NEUROBIOLOGY TO EDUCATION



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Seren Gülşen GÜRGEN

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The Science of Neurolearning from Neurobiology to Education

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PREFACE

Dear Readers,

This book brings together the latest research in neuroscience, neurolearning, and neurotoxicity, featuring 17 chapters contributed by scholars from diverse disciplines. Our goal is to explore the effects of various methodologies and environmental factors on neurolearning and the brain-memory relationship from multiple perspectives, while presenting the most recent scientific advancements in the field.

This book is the result of the dedication and expertise of distinguished academics in both basic and applied sciences. In addition to highlighting contemporary studies in basic medical sciences, it also offers valuable insights into clinical sciences. By blending theoretical knowledge with practical applications, we aim to provide a comprehensive and integrated perspective.

We hope this book will serve as a valuable resource for academics, professionals, and all those with an interest in science. It is intended to be a key reference for researchers, clinicians, and students who seek to stay informed about the latest developments in the field.

We extend our heartfelt thanks to all the contributing authors, reviewers, and the publisher for their invaluable contributions to this book. We hope the information and data presented here will contribute meaningfully to the scientific community.

With our best regards

Prof. Dr. Seren Gülşen Gürgen
Asst. Prof. Dr. Hasan Kazdağılı

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CHAPTER I

NEUROPHYSIOLOGY OF ACUTE AND CHRONIC STRESS ON LEARNING AND MEMORY

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1. Introduction

The term “stress” is derived from the Latin words “strictus” and “stringere,” which mean tightness and narrowness, respectively. Initially, the term was used in engineering to denote mechanical strain. Today, “stress” frequently refers to the psychological pressure experienced by individuals. In contrast, ‘physiological stress’ describes a broader situation and, contrary to popular belief, can be beneficial in certain circumstances. Walter Cannon and Hans Selye defined stress as a physiological response. Cannon described stress as a fight-or-flight response that disrupts homeostasis, while Selye defined it as the non-specific consequences of any demand on the body (e.g., rapid heartbeat or insomnia) and proposed a three-stage general adaptation syndrome of stress: alarm reaction, resistance phase, and exhaustion phase (1,2).

In response to stress, two primary systems are engaged: the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis. The ANS rapidly releases catecholamines (adrenaline, noradrenaline, and dopamine), increasing short-term excitability. In contrast, the HPA axis releases corticosteroid hormones (cortisol in humans) during the stress response, which produces longer-lasting effects (3). The timing and severity of the stress response can affect memory processes in various ways. Stress experienced before or after learning can positively or negatively affect memory, whereas stress experienced

during learning usually has a negative effect. High cortisol levels can lead to the suppression of synaptic plasticity and a reduction in the processing of new information. Stress plays a dual role in the learning process, exhibiting both positive and negative effects. Stress during learning can reduce performance by disrupting attentional processes and inhibiting memory encoding. In a study conducted by Schwabe and Wolf (2010), it was discovered that learning under conditions of stress resulted in a decrease in both free recall and recognition performance. However, the timing and context of the stress are also crucial in determining these effects. When stress occurs concurrently with learning and is relevant to the material, it can enhance memory. However, in the absence of this contextual fit, stress can have a detrimental impact on learning outcomes (4). The findings indicate that stress negatively impacts memory during the learning process, affecting both emotional and neutral information (4).

Another study examined the impact of stress on learning strategies, revealing that stress promotes the utilization of straightforward stimulus-response strategies over more intricate cognitive strategies (5). This finding suggests that stress may be an adaptive response influencing learning performance. Moreover, Joëls et al. (2006) put forth a model of how stress affects learning and memory processes. According to this model, stress hormones (especially cortisol) exert their effects through fast and slow pathways. Fast effects enhance attention and information encoding, whereas slow effects impede the processing of new information. This model posits that stress enhances memory when experienced in the context and timing of learning but impairs memory when experienced outside the learning context (3). The effects of stress on learning are complex and multifaceted. Stress can have both positive and negative effects, and these effects vary depending on the type, severity, duration, and context of stress. Future research should focus on more detailed and controlled studies to better understand these complex effects of stress (6,7). Studies on how stress management strategies affect learning and memory processes could lead to important applications in education and health. Research on the effects of stress on learning and memory provides an in-depth understanding of the role of stress in education and mental health (8). This chapter aims to overview current research on the neurobiological basis of stress, its effects on learning processes, and the factors influencing these processes.

2. Stress: Theoretical Background

Stress is a critical area of research worth examining for its effects on general health due to the allostatic load it causes under extreme conditions. Chronic

stress is associated with health problems such as cardiovascular diseases, diabetes, immune system dysfunction, depression and anxiety. Research on this subject is important for developing prevention and treatment strategies that directly impact public health (9). However, stress significantly affects cognitive functions. It affects the brain's ability to reorganize itself by forming new neural connections, which is defined as neuroplasticity. Stress can cause both adaptive and maladaptive changes. For example, acute stress can improve memory and cognitive function, while chronic stress can impair these functions. Research suggests that the mechanisms involved in these processes are structural changes in the hippocampus, amygdala and prefrontal cortex (10–12). It is noteworthy that these regions are both emotional and cognitive centers, especially related to memory. Stress affects behavior and psychological states. It can exacerbate or contribute to the development of mental health disorders. For example, dysregulation of stress responses is an important feature in the pathology of depression and anxiety disorders. Understanding stress responses can inform the development of therapeutic interventions aimed at restoring normal functioning (13–15).

Stress affects individuals differently depending on their developmental stage. Early life stress, including prenatal stress, can have long-lasting effects on an individual's stress response systems and overall health. Research has shown that stress during critical periods of brain development can lead to permanent changes in brain structure and function, emphasizing the importance of early intervention (16). From an evolutionary perspective, stress responses are crucial for survival. They enable organisms to respond quickly to threats and challenges. In modern life, however, the same responses can be triggered by non-life-threatening stressors and can lead to health problems. Understanding this balance between adaptive and maladaptive stress responses is essential for promoting health and well-being (17).

2.1. Stress Hormones and Cognitive Processes

Catecholamines and Glucocorticoids: Research has shown that stress hormones such as catecholamines (e.g., adrenaline) and glucocorticoids (e.g., cortisol) are associated with memory and learning processes. The effects of these hormones occur in key brain regions, including the hippocampus, which is essential for memory formation, and the prefrontal cortex, which is crucial for executive functions and working memory. While high levels of these hormones during acute stress can enhance memory consolidation, chronic stress often impairs memory recall and working memory performance (14). Stress

affects memory processes in two ways. Acute stress can facilitate memory consolidation through the rapid activation of stress hormones. In contrast, chronic stress, characterized by prolonged exposure to glucocorticoids, is associated with hippocampal atrophy, leading to impairments in memory and learning abilities (18).

Anxiety, on the other hand, is the result of chronic stress and is a common side effect of modern urban life. Stressful situations can increase the level of anxiety in individuals and a generalized state of anxiety can develop over time. This process can lead to the individual feeling more anxious in the face of stressful events and perceiving these situations as a constant threat. Anxiety, often caused by uncertain future situations, can significantly impair working memory by consuming the cognitive resources needed to process and store information. High levels of anxiety have been linked to reduced working memory performance, especially in tasks that require simultaneous processing and storage of information (19).

The effects of acute and chronic stress on cognitive functioning are important research themes. Acute stress is known to improve cognitive functions such as increased awareness and improved memory consolidation. These effects are usually temporary and related to the context in which the stressor occurs. Chronic stress, on the other hand, is defined as prolonged exposure to stress. In this case, impairing effects such as impaired memory recall, decreased cognitive flexibility and diminished problem-solving ability occur. The striking reason behind these effects of chronic stress is structural changes such as decreased volumes of the prefrontal cortex and hippocampus, regions associated with cognitive functions (20).

Educational environments, by their very nature, are undoubtedly the settings where the consequences of changes in memory and learning processes can occur most rapidly. In these environments, stress has profound effects on both students and educators. For students, chronic stress can lead to lower academic performance, reduced motivation, and increased dropout rates. Teachers who experience prolonged high stress levels may face burnout, which can negatively impact their teaching effectiveness and overall well-being. Implementing effective stress management strategies in educational settings is crucial for improving student outcomes and teacher satisfaction (21).

2.2 Neurophysiology of Stress and the HPA Axis

The HPA axis is a critical neuroendocrine system that regulates the body's stress response and ensures homeostasis. This system functions through a

complex network of interactions between the hypothalamus, pituitary gland, and adrenal glands and regulates the release of hormones such as cortisol. The main components of the HPA axis are the hypothalamus, pituitary gland, and adrenal glands. This system starts with corticotropin-releasing hormone (CRH) released from the hypothalamus. CRH stimulates the release of adrenocorticotrophic hormone (ACTH) from the pituitary gland. ACTH, in turn, triggers the production of cortisol in the adrenal glands (22–24).

The functioning of the HPA axis begins when CRH, released from the paraventricular nucleus (PVN) of the hypothalamus, stimulates corticotrophic cells in the pituitary gland, triggering the release of ACTH. ACTH stimulates the production and release of cortisol in the adrenal cortex (23). Cortisol mobilizes the body's energy resources and increases its ability to cope with stress. Furthermore, cortisol contributes to the regulation of the HPA axis by inhibiting the release of CRH and ACTH through feedback mechanisms (24, 25).

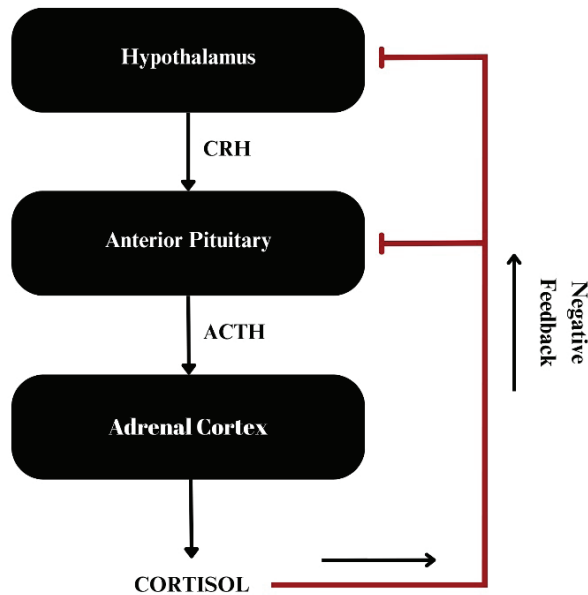


Figure 1: The hypothalamic-pituitary-adrenal (HPA) axis and its stress response: The hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to secrete adrenocorticotrophic hormone (ACTH). ACTH then prompts the adrenal cortex to produce cortisol. The release of cortisol provides negative feedback to both the hypothalamus and the anterior pituitary, regulating the stress response.

The hippocampus also has an important role in the regulation of the HPA axis. Glucocorticoid receptors in the hippocampus sense cortisol levels and regulate CRH release by sending feedback signals to the hypothalamus. This mechanism plays a critical role in maintaining the homeostatic balance of the HPA axis. Furthermore, limbic structures such as the amygdala and prefrontal cortex are also involved in the regulation of the HPA axis and modulate the emotional and cognitive components of stress responses (23,26).

Chronic stress can disrupt the functioning of the HPA axis and lead to various health problems. For example, sustained activation of the HPA axis under chronic stress can lead to persistently high cortisol levels, with negative effects on the metabolic, cardiovascular, and immune systems (27). Furthermore, dysfunction of the HPA axis has been associated with psychiatric disorders such as depression, anxiety, and posttraumatic stress disorder (28,29).

Cortisol plays a critical role in the stress response and its release shows a distinct circadian rhythm. Cortisol levels reach their highest levels during the day for humans and at night for animals that are active during the night. This rhythm is characterized by rapid ultradian releases from the adrenal glands. These daily fluctuations in cortisol levels play a critical role in regulating the body's energy balance and metabolic processes (30–32). High cortisol levels in the morning provide alertness and increased energy, while low levels in the evening facilitate rest and the transition to sleep (33–35).

The circadian rhythm of cortisol is controlled by the hypothalamic-pituitary-adrenal (HPA) axis, which prepares the brain, autonomic nervous system, heart, and blood vessels for optimal cardiovascular function (30). Cortisol peaks in the morning, allowing individuals to reach peak levels at the moment of awakening, which is associated with increased energy and a feeling of alertness (33,34). In the evening, cortisol levels decrease, facilitating the transition to rest and sleep (35). The circadian rhythm of cortisol also has important effects on the immune system. The increase in cortisol levels throughout the day regulates the distribution and function of immune cells. For example, elevated cortisol levels in the morning hours promote the redistribution of T cells to the bone marrow, while increased catecholamines encourage the mobilization of effector CD8⁺ T cells (35). The circadian rhythm of cortisol is also influenced by factors such as age and gender. Cortisol levels tend to increase with aging, which may play a role in the etiology of sleep disorders in older individuals. Additionally, cortisol levels may be lower in women than in men during the pre-menopausal period, but this difference decreases in the post-menopausal period (31).

The functioning of the HPA axis is also influenced by sex hormones. Androgens increase HPA activity, while estrogens decrease it. These differences play important roles in stress responses and disease development between men and women. For example, during periods of high estrogen levels in women, HPA axis responses may be suppressed, whereas in men with high androgen levels, this axis may be more active. These hormonal differences may be decisive in the prevalence and severity of stress-related diseases between the sexes (36,37). Hyperactivity of the HPA axis has been observed in women, especially those with visceral obesity. This is characterized by an excessive hormone response to the combination of corticotropin-releasing factor (CRF) and arginine-vasopressin (AVP). In these women, marked increases in pulse rate have been observed during stress tests (38). It has also been found that early life stressors in women lead to sex differences in the programming of the HPA axis, resulting in higher HPA axis reactivity in women. In men, the HPA axis is more activated by androgens, which increases stress responses. For example, studies on California mice have found that this species has high basal corticosterone levels and shows higher hormone responses to stressors (39). In older individuals, it has been reported that the sensitivity of the HPA axis decreases and this is associated with aging, but does not show gender differences (40).

The HPA axis plays a critical role in maintaining wakefulness and modulating sleep patterns. Dysfunctions of this axis can lead to sleep disorders. Especially in insomnia, overactivity of the HPA axis may be one of the causes of the clinical syndrome. Overactivity of the HPA axis causes high cortisol levels during the night, negatively affecting falling asleep and sleep quality. In the long term, this can lead to chronic insomnia and other sleep disorders (27,41,42). Dysfunctions of the HPA axis have been observed not only in insomnia, but also in other sleep disorders such as obstructive sleep apnea. In individuals with obstructive sleep apnea, overactivity of the HPA axis may contribute to insulin resistance, hypertension, depression and insomnia (41). Furthermore, sleep deprivation can increase the activity of the HPA axis, raising the level of central arousal, which can lead to sleep disturbances (43). Studies in children have shown that poor sleep quality is associated with increased cortisol secretion (27). This is also linked to behavioral and emotional difficulties in children. The effects of chronic stress on the HPA axis are also noteworthy; while hormonal activity increases at the onset of stress, it may decrease over time (25).

Dysfunction of the HPA axis has been associated with various psychiatric disorders. Overactivity of the HPA axis has been observed in depression and

anxiety disorders. Elevated cortisol levels can increase the severity of depressive symptoms and negatively affect cognitive function. Regulation of the HPA axis in patients with depression may be an important target in the treatment process. Similarly in anxiety disorders, overactivity of the HPA axis may increase anxiety levels and affect the severity and duration of the disease (44–46). Dysfunction of the HPA axis may also be influenced by genetic factors. Polymorphisms in the glucocorticoid receptor (GR) gene may affect the function of the HPA axis and play a role in the development of disorders such as depression. In addition, co-chaperone genes that regulate the HPA axis, such as the FKBP5 gene, may also influence the response to antidepressants. Dysfunction of the HPA axis is not limited to depression and anxiety but has also been observed in other serious mental illnesses such as schizophrenia and bipolar disorder. In these diseases, interactions between the gut microbiota and the HPA axis may also play an important role (47).

3. Effects of Stress on Memory

Stress has important effects on memory processes, playing a role in both consolidation and retrieval processes. These effects can vary significantly depending on whether the stress is acute or chronic. This asymmetric behavior is the result of complex interactions between cognitive functions and the duration of exposure of brain regions to stress hormones (48–50).

Acute stress can elicit strengthening or weakening effects on memory, depending on both the timing and context of the stressor. Stress can enhance memory consolidation when it occurs immediately before or after learning. This effect is primarily mediated by rapid activation of the HPA axis, an important neuroendocrine pathway. This activation leads to the release of catecholamines and glucocorticoids (18). Catecholamines released during acute stress increase the encoding and reinforcement of emotional memories. This is particularly evident in the amygdala and hippocampus where these hormones modulate synaptic plasticity and increase long-term potentiation (LTP) (51). Glucocorticoids facilitate memory consolidation by affecting gene expression and protein synthesis in the hippocampus. This process increases the storage of newly acquired information, making memories more resistant to impairment (52).

Chronic stress, on the other hand, often damages memory functions. Prolonged exposure to stress hormones leads to various structural and functional changes in the brain, especially in the hippocampus and prefrontal cortex, which are critical for memory and executive functions. One of the most important of

these changes is hippocampal atrophy(53). Chronic exposure to glucocorticoids causes hippocampal atrophy, characterized by a decrease in the size and number of dendritic spines and death of hippocampal neurons(54). This structural damage impairs the ability of the hippocampus to encode and retrieve memories, leading to impairments in both short-term and long-term memory(55–57). Chronic stress also affects the prefrontal cortex, impairing important functions such as working memory, decision-making and cognitive flexibility. This condition, defined as prefrontal cortex dysfunction, causes difficulties in focusing and planning functions (12).

3.1 Individual Differences in Stress Response

The effects of stress on memory vary from person to person. Factors such as genetic predisposition, early life experiences, and the presence or absence of supportive social networks have a significant impact on cognitive factors. These factors provide the basis for individual differences by exacerbating or mitigating the effects of stress on memory.

3.2 Effects of Genetic and Epigenetic Factors

Genetic predisposition appears to be an important factor in the severity of memory impairments caused by stress to which an individual is exposed. Variations in genes encoding stress hormone receptors, especially glucocorticoid receptors, are one of the factors that dominate the differences between individuals. For example, polymorphisms in the glucocorticoid receptor gene NR3C1 constitute an important factor for cortisol sensitivity (58–60). However, it is important to note that alterations in this gene are associated with extreme psychological stress conditions such as abuse and parental loss. Furthermore, individuals with certain alleles of the FKBP5 gene, which regulates glucocorticoid receptor sensitivity, show more memory impairment when exposed to high stressors (61,62). Early life stress can lead to long-lasting epigenetic changes that affect gene expression and stress reactivity. For example, adverse childhood experiences can lead to methylation of the NR3C1 gene, altered glucocorticoid receptor expression and increased vulnerability to stress-related cognitive disorders. These epigenetic changes may continue into adulthood and affect an individual's ability to cope with stress and memory function (61).

3.3 Social Support, Social Interactions and Resilience

Buffering Effects of Social Support: Strong social support networks significantly buffer the negative effects of stress on memory. Social interactions

and supportive relationships help reduce the impact of stress hormones on brain function, increasing resilience. Studies have shown that individuals with strong social support experience lower cortisol levels in response to stress, which protects against stress-induced cognitive impairments (63–65). Social support not only reduces the physiological response to stress, but also promotes adaptive coping mechanisms. Positive social interactions increase brain plasticity, facilitating the maintenance of better cognitive function and memory even under stress. This resilience is particularly evident in individuals who maintain strong, supportive relationships throughout their lives, emphasizing the importance of social ties in cognitive health (64).

3.4 Stress Affected Memory Stages

Stress can significantly affect different stages of memory, including encoding, consolidation and retrieval. Schwabe and colleagues (2012) conducted a detailed study on the impact of stress on these memory stages and provided valuable insights into how stress affects cognitive processes at each stage (49). Encoding is the initial process of perceiving and learning new information. Stress at this stage can have both reinforcing and disruptive effects, depending on the nature and timing of the stressor.

3.5 Encoding Phase in Acute and Chronic Stress

Acute stress experienced just before or during the encoding phase can enhance the encoding of emotionally salient information. This effect is mediated by rapid activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of stress hormones such as adrenaline and cortisol, which increase attention and focus on stress-related stimuli. The enhancement of memory encoding under acute stress is primarily attributed to the action of catecholamines and glucocorticoids on brain regions involved in attention and perception. Adrenaline, for example, increases arousal and alertness, making it easier for individuals to recognize and encode important details of the stressful event. Cortisol, on the other hand, modulates synaptic plasticity and increases the encoding of information by affecting the amygdala and hippocampus, which are critical for emotion and memory processing (66–68).

But long-term stress can impair encoding by disrupting the function of brain regions involved in learning and memory, such as the hippocampus and prefrontal cortex. Chronic stress leads to structural changes in these regions, reducing their ability to effectively process and encode new information.

Chronic stress causes the sustained release of cortisol, which has detrimental effects on brain structure and function. Prolonged high cortisol levels can cause hippocampal atrophy, characterized by the loss of dendritic spines and synaptic connections. This structural damage impairs the ability of the hippocampus to encode new information. In addition, chronic stress affects the prefrontal cortex, impairing executive functions and working memory and further inhibiting the encoding process (52,69).

3.6 Consolidation Phase in Acute and Chronic Stress

Consolidation is the process by which recently acquired information is stabilized and stored in long-term memory. Stress affects consolidation through its effects on synaptic plasticity and gene expression in the brain. Reinforcement of Emotional Memories: Acute stress can increase the consolidation of emotionally charged memories. This is due to increased glucocorticoids levels in the hippocampus, which facilitate synaptic plasticity and protein synthesis, thereby strengthening the memory trace. The presence of glucocorticoids during the consolidation phase increases the synthesis of proteins required for long-term potentiation (LTP), a process that strengthens synaptic connections. This molecular mechanism allows emotionally significant events to be stored more firmly in memory, making them easier to recall later. The amygdala, which processes emotional information, interacts with the hippocampus to modulate the consolidation of emotional memories (49,52,70).

But chronic stress impairs memory consolidation by causing long-term changes in brain structure and function. Prolonged exposure to high levels of cortisol can lead to hippocampal atrophy, which inhibits the consolidation process and results in poorer memory storage. The detrimental effects of chronic stress on consolidation are due to persistent high levels of cortisol, which interfere with the normal functioning of the hippocampus and prefrontal cortex. Chronic stress reduces the expression of brain-derived neurotrophic factor (BDNF), a protein essential for synaptic plasticity and memory formation. Decreased BDNF levels impair LTP and impair memory (52,69).

3.7 Stress and Memory Retrieval

Acute stress can enhance memory consolidation while impairing memory retrieval. The main reason for this paradoxical effect is high levels of cortisol, which can impair retrieval of stored information in stressful situations. Increased cortisol during stress interferes with the retrieval of stored information, making

it more difficult to access memories when under pressure. The hippocampus is rich in glucocorticoid receptors and high levels of cortisol can affect synaptic plasticity, leading to impaired memory retrieval. This effect is particularly pronounced when the stressor is contextually linked to the recalled memory, leading to recall-induced forgetting. The impairment in memory recall becomes even more pronounced when the stressor is contextually relevant (4) .

Several studies have shown how stress impairs memory retrieval. Research has shown that individuals under acute stress have difficulty retrieving information learned immediately before the stressor. This immediate effect is attributed to the rapid increase in cortisol levels, which impairs hippocampal activity (52). In controlled experiments, participants exposed to stress before a memory recall task performed worse than those not exposed to stress. These findings underline the direct impact of stress hormones on the cognitive processes involved in memory retrieval (71).

This information allows us to draw some practical implications for educational settings and clinical strategies to improve memory retrieval. Students experiencing high levels of stress may find it difficult to retrieve information during exams despite adequate preparation. This points to the need for stress management interventions in educational settings to improve academic performance (20). In a clinical context, patients with chronic stress or anxiety disorders may have impaired memory retrieval skills, which may affect their daily functioning and quality of life. Therapeutic strategies aimed at reducing stress may improve cognitive outcomes in these individuals (23).

4. Stress and Learning

4.1 Neurophysiological Processes of Learning

Research on the neurophysiological basis of learning is based on a series of critical discoveries and studies throughout history. In 1949, Donald Hebb made an important contribution to theories of learning by proposing the principle of “*neurons that fire together, connect together*”, which laid the foundations of synaptic plasticity (72). This theory formed the cornerstone of subsequent neurophysiological research. In 1973, Bliss and Lømo discovered long-term potentiation (LTP) in the hippocampus, emphasizing the importance of synaptic strengthening mechanisms in learning and memory processes (73). Then, in 1978, O’Keefe and Nadel discovered place cells, identifying the role of the hippocampus in spatial memory, and this discovery led to a better understanding of hippocampal functions (74).

In 1986, Collingridge and Bliss provided important insights into the molecular basis of synaptic plasticity by elucidating the critical role of NMDA receptors in the induction of LTP (75). In 1993, Bliss and Collingridge further elaborated on the molecular basis of LTP on synaptic strengthening and memory consolidation (76). In 2000, LeDoux made important contributions to the neurophysiology of emotional memory, detailing the role of the amygdala in emotional learning (77).

In 2002, Lisman et al. helped us better understand cellular learning mechanisms by demonstrating the role of CaMKII in LTP and its importance in synaptic plasticity (78). In 2004, Malenka and Bear explained the role of BDNF in the regulation of synaptic plasticity, emphasizing the importance of neurotrophic factors in learning processes (79). In 2007, Lupien et al. examined the effects of stress hormones on learning and memory, revealing the negative effects of stress on cognitive processes (80). Finally, in 2013, Zovkic et al. elucidated the role of genetic and environmental interactions on synaptic plasticity by investigating the effects of epigenetic modifications on learning and memory (81).

4.2 Synaptic Plasticity and Learning

Learning is a complex and dynamic set of processes that take place in various regions of the nervous system. These processes are based on synaptic plasticity, neurotransmitter release and reorganization of neuronal networks. Various regions of the brain play a prominent role in learning and memory processes; in particular, the hippocampus, prefrontal cortex and amygdala are central to these processes. Synaptic plasticity refers to the changeability of neuronal connections through the strengthening or weakening of synapses and underlies learning. Long-term potentiation (LTP) and long-term depression (LTD) are major mechanisms of synaptic plasticity. LTP is defined as the strengthening of synaptic transmission because of high frequency stimulation, while LTD refers to the weakening of synaptic transmission as a result of low frequency stimulation (76,79). These data suggest that the learning brain undergoes both molecular and cellular changes together, in other words, the system itself changes morphologically.

During learning, the binding of glutamate to AMPA and NMDA receptors results in a rapid depolarization of the postsynaptic cell. This allows more NMDA receptors to open and calcium entry. Calcium promotes synaptic strengthening by activating second messenger pathways. For example, calcium

activation of CAMKII leads to phosphorylation of AMPA receptors and the addition of more AMPA receptors to the membrane, which strengthens synaptic transmission (78).

4.3 Stress and Learning

4.3.1 Acute Stress and Learning

Acute stress, characterized by short duration and specific events or situations, plays an important role in facilitating the organism to respond quickly and effectively to stressors. During acute stress, hormones such as adrenaline and cortisol are released, increasing attention and alertness levels and temporarily improving short-term learning and memory processes. Studies have shown that mild acute stress can improve memory encoding and learning performance. This positive effect of acute stress on learning may be attributed to the rapid and transient effects of glucocorticoids, which increase attention and facilitate information encoding in brain regions such as the hippocampus and amygdala (82).

Glucocorticoids such as cortisol exert rapid effects on brain regions such as the hippocampus and amygdala, enhancing attention and facilitating encoding of information, thereby improving short-term memory performance (83). Activation of the hypothalamic-pituitary-adrenal (HPA) axis and the subsequent release of stress hormones such as glucocorticoids are crucial physiological components in response to fear-evoking stimuli (82). These hormones are involved in modulating fear conditioning and memory consolidation processes (82). In addition, acute stress has been associated with rapid synaptic placement of specific receptors in the hippocampus, facilitating long-term potentiation and memory formation (84).

Furthermore, acute stress has been found to enhance adult hippocampal neurogenesis and the activation of newborn neurons through the secretion of astrocytic fibroblast growth factor 2 (FGF2) (85). The highly conserved stress hormone response particularly affects brain regions such as the hippocampus, which is essential for memory function (85). Moreover, the hippocampus has been identified as a key mediator in glucocorticoid-induced impairment in spatial memory retrieval, and its function depends on interactions with the basolateral amygdala (86). This interaction highlights the complex relationship between stress hormones and memory processes in the brain (86).

Studies have also shown that multiple stress hormones can combine and synergistically mediate persistent memory impairments following acute stress exposure (87). These findings underscore the complex interplay

between different stress hormones and their impact on memory functions (87). In addition, hormonal regulation plays an important role in **AMPA receptor trafficking** and memory formation, further emphasizing the significance of hormonal influences on memory processes (88). The involvement of several neurotransmitters and hormones, including corticotropin-releasing hormone (CRH), in memory deficits and dendritic spine loss following acute stress emphasizes the multifaceted nature of stress-related memory impairments (89).

Chronic exposure to stress hormones such as corticosterone during adolescence has been shown to enhance certain types of learning in adulthood, suggesting long-lasting effects of stress on cognitive functions (90). The differential effect of stress on the cognitive memory functions of the hippocampus and the habit memory functions of brain regions such as the dorsolateral striatum underscores the region-specific effects of stress on memory processes (90). Moreover, the molecular biology of glucocorticoid signaling elucidates the complex mechanisms by which glucocorticoids regulate gene expression and contribute to experience-based allostasis (91).

Acute stress exerts complex effects on learning and memory processes through the rapid effects of stress hormones on brain regions involved in attention, information encoding and memory consolidation. The interplay between different stress hormones, neurotransmitters and brain regions underlines the multifaceted nature of stress-related memory impairments and emphasizes the importance of understanding the molecular and neural mechanisms underlying these processes.

4.3.2 Chronic Stress and Learning

Chronic stress, characterized by prolonged and continuous exposure to stress, is often associated with negative effects. The impact of chronic stress on learning and memory processes can be explained by the structural and functional changes it causes in the brain. Chronic stress can impair the function of brain regions involved in learning and memory, such as the hippocampus and prefrontal cortex, preventing the effective processing and encoding of new information. Structural changes in these regions may reduce the ability to effectively process and encode new information (92).

The long-term effects of glucocorticoids modulate synaptic plasticity in a two-step manner, leading to changes in dendritic structure that can last for weeks. These changes can have lasting effects on learning and memory processes (93). Chronic stress can affect neuroplasticity by altering connections and

communication between nerve cells in the brain, potentially reducing learning capacity (94).

Furthermore, chronic stress can lead to changes in the immune system and disruptions in homeostasis, affecting the body's defense mechanisms and potentially impairing learning processes (95). The effects of chronic stress on the hypothalamic-pituitary-adrenal (HPA) axis can cause disruptions in hormonal regulation and alterations in reproductive functions (96).

Furthermore, chronic stress can impair spatial learning and memory, and several studies suggest that stress can lead to significant cognitive deficits (97). Stress can also alter learning strategies, shifting from flexible cognitive strategies to more rigid, habit-based responses (4). Chronic stress has detrimental effects on learning and memory processes through its impact on structural and functional changes in the brain. These changes, including disruptions in neuronal communication and changes in hormonal regulation, may contribute to reduced learning capacity and impaired memory performance.

4.4 Yerkes-Dodson Law

High levels of stress and anxiety can lead to fear and anger, limited awareness and erratic behavior. The relationship between arousal and cognition was illustrated by an experiment conducted by Yerkes and Dodson in 1908 (98). Yerkes and Dodson varied electric shock levels to condition rats to learn three different luminance discriminations. At the largest luminance difference, the easiest discrimination, the rats' performance improved as the intensity of the shock increased, and they learned it with fewer trials. However, when discriminations were made more difficult by decreasing the luminance difference, mice required more trials and exhibited an inverted U-shaped relationship between shock intensity and performance (98). Yerkes and Dodson argued that in all tasks except the easiest discrimination tasks, performance improved when arousal levels reached the optimum level and deteriorated at higher arousal levels. They also stated that the optimum arousal level depends on the difficulty of the task, with more difficult tasks having lower optimum arousal levels (98).

During the century since Yerkes and Dodson, a more sophisticated understanding has been developed about the response alternatives of organisms and the influence of interactions between brain mechanisms regulating attention and arousal on decision-making processes. Successful decision making requires cognitive processing of relevant information, prediction of relationships between actions and possible outcomes, and optimization of performance by executive

functions. Converging evidence suggests that decision making is associated with parallel pathways connecting the frontal cortex to the striatum, pallidum and thalamus (99–101). Sensorimotor areas of the frontal cortex and dorsolateral striatum/putamen play a critical role in relatively automatic or habitual stimulus-guided actions (102). The prefrontal cortex and dorsomedial striatum/caudate, on the other hand, play an important role in flexible, goal-directed actions guided by working memory, representing information in the brain in the absence of external sensory information (103,104).

Inverted-U Shape

The inverted-U-shaped relationship can be explained by the influence of different neurophysiological processes in different parts of the brain (Figure 2). The hippocampus rapidly switches from “configurational/cognitive map” mode to “flash memory” mode under high emotional arousal. This transition explains the long-lasting but fragmented nature of traumatic events (105). Neurotransmitters also play an important role in this process. For example, neurotransmitters such as noradrenaline and dopamine improve attention and memory processes by increasing arousal at certain levels, while excessive levels of neurotransmitter release can impair synaptic function and reduce performance (4).

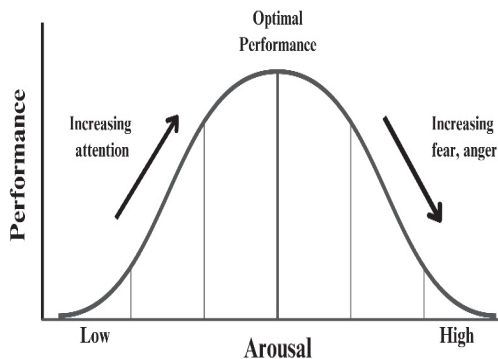


Figure 2. The illustration of the inverted U-shaped curve of the Yerkes-Dodson Law. The curve shows the relationship between performance and arousal.

Recent research has made significant advances towards the neurophysiological underpinnings of the Yerkes-Dodson Law. Fallor and colleagues (2019) have shown that it is possible to improve performance by regulating arousal levels using electroencephalography (EEG)-based feedback

(106). This study showed that arousal levels can be dynamically adjusted using brain-computer interfaces (BCI), thereby enhancing performance by shifting from a high arousal state to a lower arousal state on the right side of the Yerkes-Dodson curve.

The Yerkes-Dodson Law has been recognized as an important psychological principle that explains the effect of arousal levels on performance. However, this law has been subjected to many criticisms from both theoretical and practical perspectives. Methodological limitations are pointed out by the fact that the original study was conducted on rats and generalizing these findings to other species, including humans, is problematic. Furthermore, the universal validity and theoretical underpinnings of the law are also questioned; some research has shown that the relationship between arousal and performance is not an inverted-U curve in all cases. It has been suggested that this relationship may be more complex, especially in situations with complex and variable performance criteria, such as creative tasks or social interactions. The lack of detailed explanations about the biological and psychological mechanisms of the law weakens its scientific validity. Recent research has shown that different types of stress (acute vs. chronic stress) and factors such as individuals' coping mechanisms may influence the relationship between arousal and performance. These criticisms suggest that Yerkes-Dodson's Law requires further research and investigation and that we need to recognize that the relationship between arousal and performance is more complex and multidimensional (4,98,107,108).

The Yerkes-Dodson Law is an important psychological principle that describes the effect of arousal levels on performance. The neurophysiological basis of this law can be explained through the effects of glucocorticoids and neurotransmitters on the brain. Recent research has made significant strides towards understanding the biological basis of this law and has contributed to a better understanding of the effects of stress on cognitive processes.

5. Conclusion

This chapter reviews the effects of stress on learning and memory. In light of the existing literature and experimental studies, it has been observed that stress has a significant effect on both learning and memory processes. The effect of stress on learning is closely related to the intensity and timing of the stress. Stress experienced during learning negatively affects memory encoding processes and decreases both free recall and recognition performance. In this context, it has been determined that individuals under stress recall the information they learn

less effectively and have difficulty recognizing it. In addition, it has been found that the effects of stress on learning may differ between genders; however, in general, women show better recall performance than men even under stress. Recent research suggests that the negative effects of stress on memory formation are closely related to the severity of stress experienced during learning and the individual's coping strategies. In educational and professional fields, the development and implementation of methods to minimize stress in learning processes are of great importance for improving memory performance. Future research may contribute to the development of stress management strategies and the improvement of learning environments by examining the neurobiological mechanisms of stress in greater depth.

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CHAPTER II

MUSIC AND THE BRAIN: THE ROLE OF MUSIC ON COGNITIVE SKILLS

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1. Introduction

There are various views on the association between the brain and the mind, which is more complex than it seems. The most widely accepted view is the computer analogy. According to this view, the mind and brain are like a computer processor and the software that runs on it. Advances in neuroscience studies allow us to map the brain and learn the location of some cognitive processes in the brain. The mind is a concrete representation of our emotions, thoughts, beliefs and desires, while the brain is made up of cells, water, chemicals and blood vessels inside the skull. Just as different programs can work with the same computer hardware, different mental structures can emerge from similar brains. Networks of interconnected neurons process the information received and combine the data to form thoughts, decisions, perceptions and consciousness. Today, it is accepted that the mind and the brain are the same thing, that is, thought is nothing more than brain activity (1,2).

Francis Crick, in his book *The Astonishing Hypothesis*, points out that we can liken the brain to a computer, but when this is taken too far, there is a danger of some unrealistic theories emerging. He lists the differences between the working principle of the brain and the computer as follows: the processing speed of computers is many times higher than the normal firing rate of a neuron. In other words, computers work faster than the brain. The processes in the computer are sequential, while the order in the brain is parallel. For example, millions of axons transmitting visual information from the eye to the brain work

at the same time. Losing a few neurons in the brain does not noticeably change the behavior of the brain, but when a small part of the computer is damaged, or there is a bug in the software, it shows noticeable degradation. The average neuron has 1,000 to 10,000 inputs and as many outputs. Computers have only a few inputs and outputs. Information is stored somewhere in the computer's memory and used when needed. There is no such precise process in the brain. The exact order in which information moves in the brain is not known (3). In line with Crick's thoughts, Pinker, an evolutionary psychologist, argues that the despised computer metaphor should not be confused with the computational theory of mind. The computational theory of mind, which began with the mathematician Alan Turing, addresses the mind-body problem and connects the world of meaning in our mental lives with the brain as a physical piece of matter. According to Pinker, our mind, like our instincts and drives, is a product of evolution and is made up of mental modules rather than a single organ (4). Pinker's thoughts on learning are that it is a part of human intelligence, but that it is only possible because of an innate mechanism designed to do so. He argues that we now need new ways of thinking to understand learning (4).

The real power of the brain is not in the number of neurons but in their connections. The brain can work on many things simultaneously in parallel. Not all neurons are active at the same time. Certain networks of neurons can activate other groups of neurons. For example, when we hear a sound, the sound waves hitting our eardrums cause electrical signals to be sent to our auditory cortex. Neurons in our auditory cortex first analyze the pitch of the sound. Another group of neurons is activated to locate the sound. We turn towards the sound source to see what is making the noise or jump backwards if we think there is danger. This triggers neurons in the amygdala, our emotional center, which in turn activates neurons in the motor cortex (1).

Considering that even the curiosity to understand the neural basis of thought is very recent in the history of science, it is not surprising that the questions we ask about musical activity have not yet been satisfactorily answered. Musical activity involves almost all parts of the brain that we know of and almost all neural subsystems. Different elements of music are handled by different neural regions. The brain first analyzes them and then creates a coherent representation. Following a familiar piece of music, accompanying it, performing music, reading musical notation, listening to and remembering lyrics requires the use of different parts of the brain. Even when listening to music alone, different processes such as distinguishing pitches and timbres, naming them, creating

and identifying melody and rhythm patterns, and emotionally processing and appreciating them activate neural networks in completely different parts of the brain.

2. Effects of Music on Cognitive Skills

From birth, a child is involved in music in various ways, either formally or informally. The common belief is that talent is innate. However, the environment in which a person lives, in other words environmental factors, are more important. Many studies have been conducted in this field emphasizing the importance of environmental factors while acknowledging the role of genetic factors. In these studies, it has been determined that the key factor is to provide the person with the appropriate environment and resources, and that the desire, motivation and effort to acquire musical skills are related to good musicianship (5).

When it comes to the effects of music on cognitive skills, It should be noted that the word “music” covers a wide range of areas such as listening to music, studying music, performing music, and creating music as well as musical talent. As mentioned earlier, according to the prevailing school of thought, it is not necessary to have an innate musical talent to make music. Instead, it is assumed that anyone who starts early enough and works hard enough can achieve an expert level of musicianship.

Musical talent as a distinct ability from other cognitive abilities is closely related to modularity and Gardner’s theory of multiple intelligences. Gardner identified seven different intelligences in his theory: *bodily-kinesthetic*, *interpersonal*, *intrapersonal*, *linguistic*, *logical-mathematical*, *spatial* and, most importantly, *musical*. He later added *natural intelligence* to these (6).

The concept of modularity suggests that 1) the brain has specialized modules for processing different types of information, 2) domain-specific information (language, faces, music, etc.) is automatically processed by the appropriate module, and 3) each module functions independently of the other modules (7). The question arises whether there are regions unique to music. In practice, it can be difficult to determine with certainty whether there are fixed connections between brain structures and behavioral functions. Neuroscientists’ views on which brain regions are specialized for language have changed over time (2). From the perspective of modularity or multiple intelligences, musical ability may be considered different from other cognitive abilities.

2.1. The Mozart Effect: Does Listening to Music Improve Cognitive Skills?

The background of the “classical music improves intelligence” discourse, which is a widespread view that originated in the USA and even influenced the policies of some states, begins with an article published in *Nature* in 1993. The title of the article was *Music and spatial task performance*. In this study conducted by Rauscher, Shaw and Ky, university students were listened to a 10-minute Mozart sonata (K.448), then relax and did nothing, and then the part of the Stanford-Binet intelligence test that includes drawing, folding and cutting paper was administered. As a result, the group who listened to Mozart scored 8-9 points higher on the test than the students who followed the instructions to relax and did nothing. Thus, the “Mozart Effect” was born, which started a significant debate in academia. It even goes so far that it is reported on media in the US and the UK that any piece of classical music improves intelligence and other cognitive skills in young children, and the governor of Georgia even made a statement on the subject. Hospitals give free classical music CDs to new mothers. Books, toys and CDs for this purpose start to be sold. Creating its own industry, the *Mozart Effect* soon became popular unlike any previous music research had ever been. However, it was not met with the same enthusiasm in the scientific world. With similar studies conducted later on, the findings of Rauscher and his colleagues were viewed with skepticism. Later, other studies showed that playing music with young children improved spatial intelligence more than listening to music, and that mice exposed to Mozart had improved orientation skills. However, the study finding is limited to the spatial part of intelligence, which includes mental imagery and temporal ordering skills. Nevertheless, as the author himself states, this led to the belief that Mozart improves intelligence (8).

Later research revealed that the correlation between test performance and listening to music was most likely due to the positive effect of listening to music on the participants’ mood, and not because the music played was Mozart. As studies on the relationship between music and cognition have increased, research has shifted to examine not only the effects of music on listeners, but especially the effects of music education.

2. 2. Music Education and Cognitive Development

The field of music and cognition has attracted the attention of fields other than social sciences such as neuroscience, neuropsychology and neuroanatomy from time to time. Studies have been conducted in this field without ignoring

the cultural importance of music. However, it is an observed fact that systematic studies are relatively late. According to Peretz and Zatorre (2003), it is noteworthy that the relationship between music and cognition has been neglected despite its importance in neuroscience. Because music has similarities and differences with language. Considering musical activities only as a cultural product has been insufficient to answer the question of how the biological foundations of the field interact with culture. However, music can play a key role in understanding the biology of human cognitive functions (9).

Wan and Schlaug (2013) examine the effects of music education on the cognitive development of young children under the title of behavioral studies. In many studies, it is seen that children who get music education have better auditory and motor skill levels such as pitch and rhythm discrimination, melodic perception and finger speed than those who do not. There are also studies showing that music education is effective in skills in different fields. For example, a study based on the similarity between music and language found a relationship between pitch perception and reading ability (10).

While it is not surprising that music improves auditory and motor abilities, findings on its effectiveness on academic achievement are inconsistent even when socio-economic status and family education are accounted for. Long-term music training may alter some multifunctional areas of the brain (intra parietal sulcus). For example, this area is also effective in numerical representations and interference. Accordingly, It suggests that music may also enhance mathematics achievement, but the number of studies in this field needs to be increased in order to say something clear (10).

Long-term studies can better control external factors such as family support and socio-economic status. There are studies showing that music education increases IQ, reading skills, and language use. In one study, one group of children was given painting lessons, and the other group was given music lessons for 6 months. As a result of pre- and post-tests, significant improvements were found in the reading and language perception capacities of the children given music lessons, but no improvement was observed in those given painting lessons (11).

Although there is a positive correlation between music education and cognitive skills in many studies, there are also many studies in which no correlation was found. Some researchers suggest that the reason for this is that they were conducted on adults for whom the effect of music education was thought to have disappeared. Therefore, music education may temporarily enhance the development of various cognitive functions. It has also been

suggested that the link between music education and success in cognitive skills can be explained by improvements in executive functions such as attention and working memory. On the other hand, some studies have found that the positive correlation between music education and working memory, processing speed, and reasoning persists into adulthood, even after accounting for the influence of age, gender, time, parental education, and hobbies (12). Thus, there is still considerable uncertainty regarding the nature and development of the presumed effects of music education on cognition.

3. The Brain of Musicians

In recent decades, there has been an increase in the number of studies on music perception and performance and their connection to the human brain. One of the reasons for this increase is that a wide variety of sensory-motor systems can be studied because there are many ways of making music. These different forms of musical expression allow interesting comparisons to be made between systems (9).

Musicians perform complex physical and mental operations such as translating musical symbols into complex motor processes, performing independent movements of the fingers and hands, remembering long musical phrases, improvising music, and naming and identifying music without a reference sound. The neural substrates of these processes have not yet been fully elucidated. However it is a fact that music changes the brain.

Unfortunately, the differences between the right and left hemispheres of the brain, which are often encountered in the popular press, are overgeneralized. The system called *lateralization of function* refers to the level of right or left dominance, of the brain in which a behavioural trait is affected. The opposite term is *bilateral*, i.e. it is administered equally by the left and right hemispheres. Between the two hemispheres there is a cellular network called the *corpus callosum* (2).

Early neuroscience studies on music focused on whether pitch processing is lateralized in the left hemisphere, just like language. This is important to understand that language and music experience work through similar mechanisms. If music is most strongly lateralized on the right rather than left, this would imply that language and music were independent.

Before the development of techniques like PET (positron emission tomography) and fMRI (functional magnetic resonance imaging), it was commonly suggested that non-musicians process pitch in the right hemisphere

and musicians in the left. However, the finding that the left hemisphere is effective in absolute pitch particularly in the part of the brain related to hearing in the planum temporale shows that this is due to a lack of cells in the right hemisphere, i.e. there is no cell increase on the left. According to this result, skill acquisition does not always enlarge the relevant area of the brain or increase the activity in that area, it simply means that that area of the brain is used more effectively than other areas.

Rather than focusing on specific music-related regions of the brain or studying the left and right hemispheres of musicians and non-musicians, subsequent studies have focused on variation in brain activation during music perception and performance. For example, finding out how music is processed in the brain when people listen to music, play an instrument or learn the genre (2).

3.1. Effects of Music on the Brain: Brain Imaging Studies

Structural change in the brain is the enlargement of the cortical area related to increased activity or the shrinkage of areas that receive no activity, and functional change is when a part of the brain is damaged and healthy cells invade the damaged area and take over its function.

Music education in childhood is effective in both the structural and functional organization of the brain. Studies conducted in the nineties show that the larger anterior corpus callosum in the brains of musicians is different from non-musicians. It was found that the corpus callosum of children who started music education in the early period (7 years and younger) was thicker than those who started later. (13,14) A similar finding was observed in motor regions. The primary motor cortex was found to be large in both hemispheres, but more prominent in the right hemisphere in musicians than in non-musicians (10). This is probably because musicians use their non-dominant hand for years. As observed for the corpus callosum, there was a positive correlation between the size of the primary motor cortex and the onset of instrumental music training (used as a proxy for the intensity and duration of training). Additionally, a positive correlation was observed between the size of the primary motor cortex and the onset of musical instrument training (10).

Structural changes in the brain vary according to the instrument played. For example, it has been observed that precentral gyrus omega signals (the region responsible for hand and finger movement representations) predominate in the left brain in piano players and in the right brain in violin players. In absolute

pitch, asymmetry was found in the planum temporale. All these structural differences seem to be more pronounced in musicians who start training at an early age and practice more intensively (10).

The common point of most fMRI studies is that the posterior superior temporal gyrus regions are activated during music. This region is effective in auditory motor transformation. In a study conducted in 2012, the left superior temporal region was associated with music training (15).

DTI (diffusion tensor imaging), a relatively new technique, measures white matter microstructures. The more hours worked in childhood, the greater the FA (water diffusivity) in the corpus callosum and superior longitudinal fasciculus.

Playing a musical instrument is a complex sensorimotor activity that engages multiple brain regions simultaneously. In particular, interactions between auditory and motor brain regions are important not only for music learning, but also for speech learning. Whether you are learning how to play a note or how to pronounce a word, both tasks involve associating sounds with expressive actions and auditory feedback. It has been observed that when a melody is listened to by someone who knows how to play the piano, motor (inferior frontal) and auditory regions interact and are activated, but when non-players listen, the motor region is not activated (10).

These studies show that long-term music training can be a powerful stimulus for changes in the brain. These changes appear to occur in both the developing and adult brain and affect white gray matter as well as cortical and subcortical structures. Active engagement in music leads to strong perception and action connectivity mediated by sensory, motor and multimodal brain regions, and such activity affects important sound transmission stations in the brainstem and thalamus (10).

In studies on functional differences in the brain, the most prominent differences between musicians and non-musicians were found in the perisylvian regions, which are involved in music listening, pitch discrimination and perceptual tasks related to pitch memory, harmony, melody and rhythm. In these studies, it was observed that musicians process music differently and that left hemispheric activation increased as the complexity of the music increased. The reason for this is unclear. Explanations that non-musicians approach music more holistically and emotionally while educated people approach music more analytically are too reductionist. However, it is difficult to say that music is dominant in the right or left hemisphere. Because there may be aspects of music that can be processed more in the right or left hemisphere by both musicians and non-musicians (16).

In an MRI study showing that musicians may have different hemispheric dominance compared to non-musicians, it was observed that the planum temporale asymmetry in musicians with absolute pitch showed an increase on the left side (16). *Absolute pitch* is defined as naming or creating a given sound without any reference sound. Those with absolute pitch can name musical notes easily and quickly, just like naming colors, usually without any specific training. Very few people have this ability. It is very rare in Western countries and relatively more common in Asian countries where tonal languages are spoken. How it occurs is unclear. However, there are study findings that prove that genetic factors as well as the country of residence and language are effective (17).

To summarize, the realization of the language ability that we acquire in very early periods in a tonal language, the association of words and pitch, with the support of the left brain, enables the acquisition of other features of language and serves for absolute hearing. People who do not have the opportunity to acquire this word-pitch relationship early on find it difficult to acquire absolute pitch later on. While researchers do not exclude the genetic role from the equation, they point out that there is a critical learning period alongside spoken language. One of the best generalizations that can be made about the absolute pitch is that people with this characteristic begin their musical education or participation at an early age (before the age of 6-7). An adult, no matter how hard he or she tries, cannot acquire this characteristic later. At least this is what Schlaug et al. found in their study. It is also true that having an absolute pitch is not a prerequisite for being a good and successful musician. Therefore, it seems doubtful to directly associate this very special condition with musical potential or musical success.

Another musical characteristic is *congenital amusia*, also referred to as “tone deafness”. Defined as a musical disorder, amusia is associated with reduced connectivity between the right auditory and inferior frontal cortices. The main functional cause is a pitch processing disorder. It is not associated with any brain damage, speech delay, language impairment or musical deprivation (18). According to Peretz (2013), the anomaly observed in the behavioral dimension can be traced backwards, first to cognitive processes, then to brain development and finally to genes and environment. Since abnormal behavior also affects the environment, this effect creates a kind of circularity. For example, someone who is amusic may avoid complex musical situations and create a musically weaker environment for themselves. Or the opposite is possible, where children with amusia are educated to compensate for this deficit and the problem is not

noticeable in adulthood. In both cases, amusia may have an impact on the brain and cognition (19).

In a study conducted with 20,000 participants in 2017, Peretz and Vuvan found that amusia is found in 1.5% of the population and more in women than men, is seen in 46% of first-degree relatives of amusic people, is not alleviated by music education, and occurs in isolation from other cognitive disorders other than spatial orientation. Therefore, they suggest that it is caused by genetic variations (20).

Apart from absolute pitch, amusia is not associated with language. It suggests that music may have specialized neural connections independent of language, suggesting that any individual may be born with the potential to be musically competent. The study of this disorder related with music, which is undoubtedly so widely listened to and loved by the majority of people, is a unique opportunity to explore the causal links between music, the brain and genes.

4. Conclusion

The underlying mental mechanisms of musical activities have attracted the interest of many disciplines. Musical activities involve many actions, from listening to playing and creating music. Before brain imaging techniques were developed, it was argued that music might be specific to only one part of the brain. However, developments over the next century proved that music activates many different parts of the brain. Instead of focusing on these specific regions of the brain that are related to music, research has shifted toward answering questions about whether music changes the brain or how music is processed in the brain.

There is a great deal of research in education, psychology, neuroscience, and other related fields on the effects of music on many cognitive skills such as language, intelligence and social communication. The brain activity of musicians and non-musicians is studied, and for example, musicians can perform very difficult tasks such as transcribing what they hear, performing what they see, remembering long musical passages and creating original music. Despite numerous research studies on what goes on in their minds during these activities, the mystery remains. However, researchers agree that music education changes the brain, and musicians have different brain structures and connections than non-musicians.

If we think of musical potential as a broad spectrum, two traits at the two extremes of this spectrum, *absolute pitch* and *amusia*, which are associated

with genetic factors, can provide important data on the neurobiological underpinnings of music. These are not traits that can be enhanced or diminished by environmental factors. This suggests that there are neural connections in the brain specifically dedicated to music, which are independent of other cognitive functions.

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CHAPTER III

MENSTRUAL CYCLE AND MEMORY

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1. Introduction

Memory and learning, as part of the brain's cognitive functions, hold a significant place in human life. Understanding the neurophysiological foundations of memory and the factors influencing these processes is critical for the optimal utilization of cognitive functions. Various cognitive and motor abilities exhibit gender differences, attributed to the influence of sex hormones. In this context, the effects of the menstrual cycle and ovarian steroids on cognitive function, behavior, and mood in healthy women have been researched for years (1-2). The menstrual cycle, representing monthly hormonal fluctuations during the reproductive period, consists of three main phases: the follicular phase, the ovulation phase, and the luteal phase. These phases involve hormonal changes, particularly in levels of ovarian steroid hormones such as estrogen and progesterone, which significantly impact the central nervous system. Brain regions associated with memory and learning, like the hippocampus and prefrontal cortex, are particularly influenced by these hormones (3). Estrogen's neurophysiological effects include enhancing synaptic plasticity, promoting neurogenesis, and supporting anti-inflammatory processes. These effects are notably prominent in the hippocampus, underscoring estrogen's vital role in learning and memory (4). Conversely, progesterone generally exhibits neuroprotective effects and modulates synaptic plasticity, although the underlying mechanisms remain under investigation (5). The fluctuations of neuroactive steroids, like estrogen and progesterone during the menstrual cycle

significantly affect learning and memory. For instance, during the high-estrogen follicular phase, women tend to perform better on verbal memory and spatial learning tasks, while cognitive performance and mood changes are observed during the progesterone-dominant luteal phase (6-7-8). Years of research have demonstrated that fluctuations in hormone levels throughout the menstrual cycle can significantly impact cognitive functions, with these effects varying among individuals. Therefore, taking hormonal cycles into account when evaluating women's cognitive performance can lead to more comprehensive and accurate results.

2. Hormonal Effects on Brain Functions

2.1. The Role of Hormones in Regulating Brain Activity

Hormones influence the brain through receptors located in various cellular sites, including both nuclear and non-nuclear receptors. The effects of sex steroid hormones, thyroid hormones, and stress hormones on cognitive function, mood, and motor functions are well-documented. However, there is ongoing debate regarding whether these hormones affect the entire brain (9). During women's reproductive years, fluctuating levels of estrogen and progesterone throughout the menstrual cycle influence the brain's structure, chemistry, and function by affecting neuronal networks, synaptic plasticity, and neurotransmitter systems (10).

2.1.1. Sex Steroid Hormones

- **Estrogen:** Estrogen (E2) is a neuroactive steroid with receptors in various brain regions, including the cerebral cortex, hypothalamus, pituitary, amygdala, and hippocampus, all of which play crucial roles in memory. Estrogens promote neuronal growth, differentiation, and synaptic formation. Gender differences in cognitive and motor abilities are believed to arise from the influence of sex hormones. For instance, men generally excel in spatial and quantitative abilities, as well as gross motor skills, while women tend to outperform men in verbal abilities, perceptual speed-accuracy, and fine motor skills (11). Estrogen enhances cholinergic function by increasing the synthesis of acetylcholine through the enzyme choline acetyltransferase (CHAT), a function that is deficient in Alzheimer's Disease. Administering exogenous estrogen to older women has demonstrated significant cognitive improvements, suggesting this hormone positively impacts the central nervous system. In one study, 75-year-old women

treated with estrogen showed significantly higher IQ scores compared to those receiving a placebo, indicating its beneficial effects on visual-spatial abilities and memory (11). In addition to its direct effects on neurons, estrogen indirectly stimulates nerve cell growth through neurotrophins. Estrogen and neurotrophin receptors are co-expressed in neurons within the forebrain, hippocampus, and cortex—regions critical for maintaining neuronal processes. Furthermore, estrogen acts as an antioxidant, offering protection against neurotoxins that promote free radical production, and it helps reduce neuronal beta-amyloid formation, a key factor in neurodegenerative conditions (12).

- **Progesterone:** Like estrogen, progesterone is a neuroactive steroid with various effects on the central nervous system (CNS). Neurosteroids rapidly cross the blood-brain barrier (BBB) following parenteral administration, allowing them to reach significant concentrations within the CNS. Pregnenolone, whether administered alone or alongside other treatments, has shown potential in treating memory-related issues. Moreover, progesterone influences a wide range of brain functions and mood, including cognitive skills and anxiety, with many of its effects being mediated through the hippocampus (13). Progesterone is considered a “neurosteroid,” and its metabolite, allopregnanolone, actively promotes myelin production in glial cells and slows the progression of Alzheimer’s disease. Progesterone has also been shown to influence cognitive and behavioral functions. For instance, increased postpartum progesterone levels have been linked to reduced aggressive behavior in lactating mice. Additionally, its interaction with non-genomic GABA receptors suggests potential therapeutic use in treating aggressive behavior, depression, and anxiety. In healthy reproductive-aged women, low progesterone levels have been associated with increased aggression and premenstrual syndrome (PMS) symptoms such as fatigue (14).

- **Testosterone:** As an endogenous agent, testosterone crosses the blood-brain barrier in its free form and influences neuronal cells. Testosterone can exert its effects directly as an androgen or indirectly through conversion to estrogen. Some evidence supports the hypothesis that testosterone may have a protective role in neurodegenerative diseases such as Alzheimer’s disease (AD), mild cognitive impairment (MCI), and depression. Androgens are also known to influence the morphology, survival, and axonal regeneration of motor neurons (15). Gender differences in spatial abilities and other cognitive and motor tests are likely attributed to the effects of sex steroids (16). Testosterone is crucial in the sexual differentiation of mammals, including humans, and contributes to

cognitive and behavioral lateralization, accounting for small but consistent sex differences (17). In women, increased testosterone levels are associated with improvements in spatial memory performance. Changes in cognitive abilities are also observed in women due to fluctuations in testosterone levels during the menstrual cycle, particularly during the high-testosterone ovulation phase (18-19). While testosterone is generally linked to enhanced spatial memory, recent studies suggest that spatial memory can vary depending on testosterone levels (19).

3. Menstrual Cycle Phases and Hormonal Changes

The female reproductive system undergoes periodic changes to facilitate fertilization and pregnancy. These regular changes, marked by the shedding of the uterine lining and vaginal bleeding, are known as the menstrual cycle (20). The cycle typically lasts an average of 28 days, although it can range between 21 and 35 days. It spans from the first day of menstruation to the first day of the next menstruation (21). The menstrual cycle is divided into different phases, each characterized by specific hormonal changes and exhibiting various physiological and psychological effects.

3.1. Follicular Phase

- **Early Follicular Phase (Days 1-6):** This phase involves menstruation, characterized by the shedding of the thickened endometrium over 4-6 days. Estrogen and progesterone levels are low, marked by the onset of follicle development in the ovaries and high follicle-stimulating hormone (FSH) levels.

- **Late Follicular Phase (Days 7-12):** Rising estrogen levels thicken the uterine mucosa and mature ovarian follicles, with estrogen peaking 24-36 hours before ovulation, triggering a luteinizing hormone (LH) surge that induces ovulation (22).

3.2. Ovulation Phase (Days 13-16)

LH and FSH surges lead to the release of an egg from the dominant follicle, with estrogen peaking and progesterone production beginning (23).

3.3. Luteal Phase (Days 17-28)

- **Early Luteal Phase (Days 17-22):** Following ovulation, the corpus luteum forms, secreting progesterone and estrogen to prepare the endometrium

for potential implantation. Progesterone levels are high, stabilizing the uterine mucosa to support possible pregnancy (24).

- **Late Luteal Phase (Days 23-31):** If fertilization does not occur, the corpus luteum degenerates, and progesterone and estrogen levels drop, triggering menstruation and initiating a new cycle (25,26).

4. Neurophysiological Changes Across Menstrual Phases

4.1. *Impact on Hippocampus, Prefrontal Cortex, Amygdala*

Sex steroid hormones regulate neuronal plasticity in various brain regions, particularly the hippocampus, prefrontal cortex, and amygdala. Research highlights the significant influence of these hormones on these areas (27).

- **Hippocampus:** Progesterone and estradiol fluctuations modulate neuronal flexibility in the hippocampus, with high hormone levels in the luteal phase reducing hippocampal activity necessary for memory formation compared to the early follicular phase (27).

- **Prefrontal Cortex:** Gonadal hormones can modulate stress sensitivity by affecting the medial prefrontal cortex area. It has been observed that stress sensitivity is at a higher level during the luteal phase compared to the follicular phase (28).

- **Amygdala:** Elevated exogenous progesterone levels in the mid-luteal phase significantly increase amygdala response to emotional stimuli, indicating the influence of progesterone on stress response and emotional memory (29).

4.2. *Functional Connectivity Changes*

Brain activation and connectivity during verbal working memory tasks demonstrate phase-dependent variations in women. In the luteal phase, reduced connectivity between the left striatum and inferior frontal and parietal regions is observed, but increased frontal activity compensates for these changes. High levels of sex steroid hormones, such as estrogen and progesterone, significantly influence brain functional connectivity (30). Furthermore, throughout the menstrual cycle, hippocampal structure and function show measurable changes linked to hormonal fluctuations. During the late follicular phase, bilateral hippocampal volume increases compared to the early follicular phase, and there is stronger functional connectivity between the hippocampus and the bilateral superior parietal lobule during this time (31).

5. Mechanisms of Hormonal Action

5.1. *Modulation of Synaptic Plasticity and Neurotransmitter Systems*

Changes in synaptic structure and function form the cellular basis of behavior and memory. Synaptic plasticity, which involves changes in the number and/or morphology of neuronal synapses, is fundamental to how the nervous system adapts to a changing environment. Sex steroid hormones, particularly estrogens, influence neuroplasticity through both genomic and non-genomic pathways, leading to long-term changes in brain function. The genomic effects of estrogens, mediated by nuclear estrogen receptors (ER α and ER β), unfold over hours and days, inducing sustained changes in neuroplasticity. Additionally, rapid non-genomic effects initiated by estrogens affect epigenetic modifications, which are critical for memory consolidation and synaptic plasticity. Estrogens have been shown to increase the acetylation of histone H3 in target brain genes, influencing gene expression related to memory processes. These hormones also activate the Extracellular Signal-Regulated Kinase (ERK) through rapid signaling pathways, which are vital for both memory consolidation and synaptic plasticity. The existence of brain-localized estrogenic enzymes and the localization of estrogen receptors support the presence of non-genomic effects on synaptic plasticity. Through these rapid pathways, estrogens modulate synaptic connectivity via the Mitogen-Activated Protein Kinase (MAPK) and PI3K-Akt signaling pathways, further emphasizing their role in regulating neuroplasticity (32). Hormones fluctuating during the menstrual cycle also exert various effects on the neurotransmitter system. Estradiol selectively enhances NMDA receptor (NMDAR) expression and transmission. It has been reported that increased synaptic transmission and Long Term Potentiation (LTP) due to the rise in NMDA receptors strengthen learning and memory. Estradiol also increases dendritic spine density by reducing GABAergic inhibition (33). Progesterone, on the other hand, has been suggested to enhance GABAergic inhibition, potentially impacting emotional states and cognitive processes via the amygdala (34). Another study found that estrogen strengthens excitatory synaptic transmission by increasing presynaptic neurotransmitter glutamate release (35). In summary, fluctuating gonadal hormones during the menstrual cycle have significant effects on cognitive function and emotional state by modulating synaptic plasticity and neurotransmitter systems, particularly in brain regions such as the Hippocampus, Amygdala, and Prefrontal Cortex.

6. Effects on Learning and Memory

6.1. Impact of Hormonal Fluctuations on Emotional Memory Consolidation

Estrogen and progesterone may modulate emotional memory consolidation by influencing cellular mechanisms in brain regions involved in the encoding and consolidation of emotionally arousing information. Numerous studies in both animals and humans have demonstrated that these hormones can alter responses to emotional stimuli in critical areas such as the amygdala, hippocampus, and medial prefrontal cortex (mPFC). A positive correlation has been identified between progesterone levels during the mid-luteal phase of the menstrual cycle and the recall of negative images, indicating that higher progesterone may enhance the recall of negative stimuli (27). On the other hand, estrogens are known for their rapid and potent effects on memory in both sexes. They exert influence through mechanisms such as increasing dendritic spine density, modifying the distribution of spine types, and enhancing the presence of postsynaptic density protein 95 (PSD95) and GluA2 (an AMPA receptor subunit) in dendritic spines within the hippocampus and mPFC. These brain regions are crucial for learning and memory processes (36).

6.2. Relationship Between Sleep and Emotional Memory Consolidation

In a study investigating the effects of estrogen on rapid eye movement (REM) sleep, which is considered critical for memory enhancement, it was demonstrated that estrogen improves emotional memory consolidation by increasing slow-wave sleep (37). Sleep spindles, regarded as a biological marker for general cognitive abilities, play a significant role in memory consolidation. Research has shown that women with a normal menstrual cycle in the luteal phase exhibit higher fast sleep spindle density compared to those in the follicular phase. According to these findings, elevated levels of estrogen and progesterone enhance memory consolidation by increasing sleep spindle density (38).

6.3. Variations in Verbal and Visual Working Memory

Working memory, characterized by its ability to retain and process information, facilitates the integration of cognitive and emotional processes. Hormonal fluctuations significantly impact working memory. Studies have reported that working memory performance is higher during menstrual cycle phases with elevated estrogen levels compared to other phases. Estrogen, in

particular, has a positive effect on verbal working memory, although its influence on visual-spatial memory remains uncertain. It has been suggested that further research is needed to elucidate the biological underpinnings of this phenomenon (39)-40).

6.4. Functional Connectivity Patterns and Working Memory Performance

The neuroanatomical basis of working memory includes the frontostriatal regions, where sex steroid hormones exert their effects on memory by targeting this area. During verbal memory tasks, higher levels of estradiol are associated with increased activity in frontal areas. In the striatum, increases in gray matter volumes have been observed in relation to progesterone levels. Additionally, during verbal and spatial tasks in the luteal phase, increased activation has been noted in the right dorsolateral prefrontal cortex and bilateral striatum (30). Fluctuating hormones during the menstrual cycle significantly impact memory regulation through their modulatory effects on brain activation and connectivity patterns.

7. Interaction Between Stress Hormones and Menstrual Cycle Phases

Sex differences and the modulation of sex hormones in learning under stress remain unclear, with research indicating that ovarian hormone levels play a significant role in regulating stress responses in women. A relationship between ovarian hormones and increased glucocorticoid responses during the luteal phase has been reported, affecting memory consolidation and recall (2). Changes in the menstrual cycle phase influence the relationship between cortisol and emotional memory. Specifically, women in the mid-luteal phase (days 18-24) exhibit a positive relationship between cortisol stress response and the recall of threatening stimuli, a relationship not observed in other phases (41).

8. Clinical and Practical Applications

8.1. Academic Performance and Daily Life Impact

Variations in academic achievement levels associated with cognitive performance have been observed throughout the menstrual cycle in women. Changes in exam stress and performance have been noted across different phases of the cycle. According to a recent study comparing the academic performance of women with regular and irregular cycles, women with regular cycles demonstrated higher academic achievement (42). In this context, it is observed that fluctuating sex steroid hormone levels during the menstrual

cycle phases affect cognitive efficiency, along with mood changes reflected in daily life.

8.2. Potential Interventions for Memory-Related Issues

8.2.1. Hormone Therapy

Numerous studies on hormone therapies have been conducted to address memory-related issues arising from hormonal fluctuations during the menstrual cycle. It has been shown that initiating hormone therapy around menopause can have a beneficial effect on prefrontal mechanisms of cognitive control. Hormone therapy has been reported to prevent the emergence of reduced prefrontal cortex activity, a neurophysiological measure observed in both healthy aging and early dementia (43). According to other studies, age is a crucial factor in the administration of hormone therapy, with potential adverse effects. When applied to older women, small, long-term declines in global cognition, working memory, and executive functions have been observed. Therefore, to assess the safety of hormone therapy, it is important to conduct more evaluations with longer-term follow-up in younger women (44-45).

8.2.2. Hormonal Treatments and Cognitive Therapy

Combined hormonal and cognitive therapies may improve cognitive functions and mitigate decline.

- **Hormone Replacement Therapy (HRT):** Two-thirds of Alzheimer's disease (AD) cases are women, and increasing evidence shows that the APOE-ε4 allele, the greatest genetic risk factor for AD, has a stronger association in women compared to men.

- **Timing of Hormone Therapy and Women Without the ApoE ε4 Allele:** The cognitive outcomes of HRT can be beneficial when initiated with proper timing and under specific conditions. Women without the ApoE ε4 allele may experience improved mood and cognitive outcomes with HRT (46). Additionally, the effects of HRT on reducing the risk of Alzheimer's disease may vary depending on the ApoE genotype and the timing of the therapy initiation (47).

- **Cognitive Interventions:**

- **Combination of Cognitive Training and rTMS:** A study conducted on Alzheimer's patients reported that the combination of repetitive transcranial magnetic stimulation (rTMS) and cognitive training could enhance cognitive

functions. This combination may improve memory and daily functions by increasing neuroplasticity (48).

- **Cognitive Stimulation:** Cognitive stimulation in individuals with moderate Alzheimer's disease can provide significant improvements in memory, attention, and executive functions. While these effects may not be long-lasting in some cases, they generally help maintain cognitive functions (49).

- **Long-Term Cognitive Training:** One-year cognitive training for Alzheimer's patients can improve cognitive performance and may be more effective when combined with medication treatments (50).

In conclusion, steroid hormone therapies such as estrogen and progesterone may have cognitive-enhancing effects when considering age and genetic profile. Sex steroid hormones strengthen synaptogenesis and synaptic connections through their receptors. In addition to hormone therapies, cognitive therapies and neurostimulation techniques may also have beneficial effects on memory, particularly in Alzheimer's disease, thereby improving quality of life. However, more extensive and comprehensive studies are needed to fully understand these positive effects and to apply these treatments to a broader population.

9. Conclusion

9.1. Summary of Neurophysiological Mechanisms Between Hormonal Fluctuations and Memory

This chapter reviews the effects of hormonal fluctuations during the menstrual cycle on cognitive functions, learning, and memory in women of reproductive age through various neurophysiological mechanisms.

- **Hippocampus, Amygdala, and Prefrontal Cortex:** Specifically, these three brain regions are targets of estradiol and progesterone hormones in terms of neuroplasticity. It is clear that the hormonal changes observed during various phases of the menstrual cycle play significant roles in emotional memory performance by affecting activity in the hippocampus, amygdala, and prefrontal cortex. Due to its anabolic nature, estradiol generally has positive effects on memory, whereas progesterone can reverse these effects. However, the effects of sex steroids on the brain remain controversial. They may vary in different brain regions; for instance, estradiol increases neural transmission in hippocampal neurons while decreasing neural excitability in amygdala neurons. These

findings underscore the critical role of menstrual cycle hormones in memory enhancement processes (27).

- **Neurotransmitter Systems:** Sex hormones are known to exert their potent neuromodulatory effects in the brain through GABA and glutamate receptors. By modulating the release and plasticity of neurotransmitter substances into the synaptic cleft, they alter synaptic plasticity and thus affect memory processes. Progesterone, which is predominantly secreted during the luteal phase of the menstrual cycle, influences the inhibition system by suppressing glutamate receptors and increasing GABA receptors. This mechanism explains how cognitive functions and memory can be affected by fluctuations in hormone levels (18).

All these mechanisms highlight the complex interaction between hormones and brain function, emphasizing the need for targeted interventions to mitigate cognitive impairments related to hormonal fluctuations.

10. Future Research Directions

10.1. Identifying Research Gaps and Future Studies

Further studies are necessary to understand the relationship between cognitive health and hormonal fluctuations in the menstrual cycle:

- **Longitudinal Studies:** More long-term studies are needed to assess the chronic effects of hormonal changes on lifelong cognitive decline and neurodegenerative diseases.

- **Mechanistic Insights:** Investigating the specific molecular pathways through which hormones affect synaptic plasticity and memory is crucial. Understanding the roles of hormone receptors and signaling pathways can aid in developing targeted therapies.

- **Gender Differences:** Research should continue to explore how hormonal effects on cognition differ between men and women, considering chromosomal and hormonal influences.

- **Pregnancy Process:** Given the significant cognitive and memory impacts of high estrogen and progesterone levels during the luteal phase, more extensive studies involving pregnant women are needed.

In conclusion, there is a need for a deeper understanding of the neurophysiological mechanisms linking hormonal fluctuations during the

menstrual cycle and memory. Future research will allow us to better understand the effectiveness of necessary treatment methods to support and improve cognitive health related to hormonal fluctuations in women and develop individualized treatment plans.

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CHAPTER IV

EXERCISE AND NEUROPLASTICITY

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1. Introduction

Neuroplasticity, which can be defined at the molecular, cellular, systemic and behavioral levels, is the ability to respond to internal, or external stimuli by reshaping the structure, function and connections of the nervous system. With neuroplasticity, increased branching in dendrites, lengthening of their length, formation of new synapses and increased efficiency of existing ones, new neuron creation, survival and increased resistance to deterioration under stress can be achieved (1). The function of neurotrophins, which are effective in the formation of neuroplasticity, is to ensure the growth, development or differentiation of neurons. Therefore, research on neuroplasticity and neurotrophins has increased recently and is believed to be crucial in treating and preventing various neurological and psychological disorders (2).

Human and animal studies indicate that exercise influences neuroplasticity. Physical exercise and learning new activities trigger neural stem cell proliferation, which is essential for the maturation and sustained vitality of newly formed neurons. Results from human and animal studies indicate that increased physical exercise enhances neuroplasticity in certain brain structures, including the hippocampus, leading to improvements in cognitive, emotional, and behavioral functions (3, 4). Physical exercise is neuroprotective and improves brain function by improving cognition, learning, and memory, as well as regulating cellular redox state (5). In addition, exercise regulates and enhances angiogenesis and glial activation, both of which positively contribute to neuroplasticity (6). The

effects of exercise on neuroplasticity have been examined in various studies based on exercise type, frequency, intensity, duration, and whether the exercise is acute or chronic. Research in this area is ongoing.

Understanding how physical exercise affects neuroplasticity and the resulting changes can enhance success in neurorehabilitation and treatment processes by promoting neuroplasticity-based approaches.

2. Neuroplasticity

Until the early 1900s, the prevailing belief was that the brain was a static organ, formed during the fetal or infant period and that the number of neural cells gradually decreased or did not change after birth. It was believed that only specific memory-related areas, such as the hippocampus and dentate gyrus, could undergo changes in the adult brain. Therefore, it was believed that recovery after nervous system damage was minimal (7). Today, research has proven the exact opposite of this view. Research results in animals and humans have shown that brain cells are shaped and differentiated by environmental stimuli (8).

Environmental stimuli can lead to numerous changes in organs and tissues throughout life. These changes are more pronounced in structures with plastic properties, such as the brain and nervous system, which remain sensitive to change throughout life (9). The changes in the neural pathways in the brain tissue, which is a part of the Central Nervous System, their ability to reorganize and the power required for the organism's adaptation to the environment are expressed as "neuroplasticity". The fact that connections between neurons in the brain are not constant but continuously change allows for the reshaping and reorganization of neurons and their connections in new situations or when needed. Neuroplasticity occurs when new skills are acquired, after any damage to the nervous system or sensory areas. Increased synaptic connections stimulated by environmental factors reshape the brain (10).

Neuroplasticity can be explained by two mechanisms: neuronal regeneration and functional reorganization.

Neuronal regeneration

Neuronal regeneration can be explained by synaptic plasticity and neurogenesis.

When changes in the nervous system extend beyond a single neuron and affect synapses, this adaptive response is referred to as 'synaptic plasticity'. Synaptic plasticity is the capability that enables multiple experiences to change future emotions, thoughts and behavior. New information is stored with changes

in synapses for a long time and memories are formed. Synaptic transmission can either increase and decrease neuronal activity. These changes can occur in milliseconds and may continue for days, weeks or even longer (11).

Dendrites, the most adaptable structures in neurons, reflect neuroplasticity through changes in their form. Therefore, changes in their structure are thought to reflect neuroplasticity. Environmental stimuli trigger the release of neurotrophic factors such as Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), Neurotrophin-3 (NT-3), and Neurotrophin-4 (NT-4) (12). These factors help the cell adapt to stimuli while also preventing apoptosis and protecting against atrophy (13). Another key player in neuroplasticity is neural stem cells. Stem cells undergo a series of changes in response to a suitable environment and stimuli, eventually maturing into neurons (14-16). Neuroplastic changes in the central nervous system are illustrated in Figure 1 below.

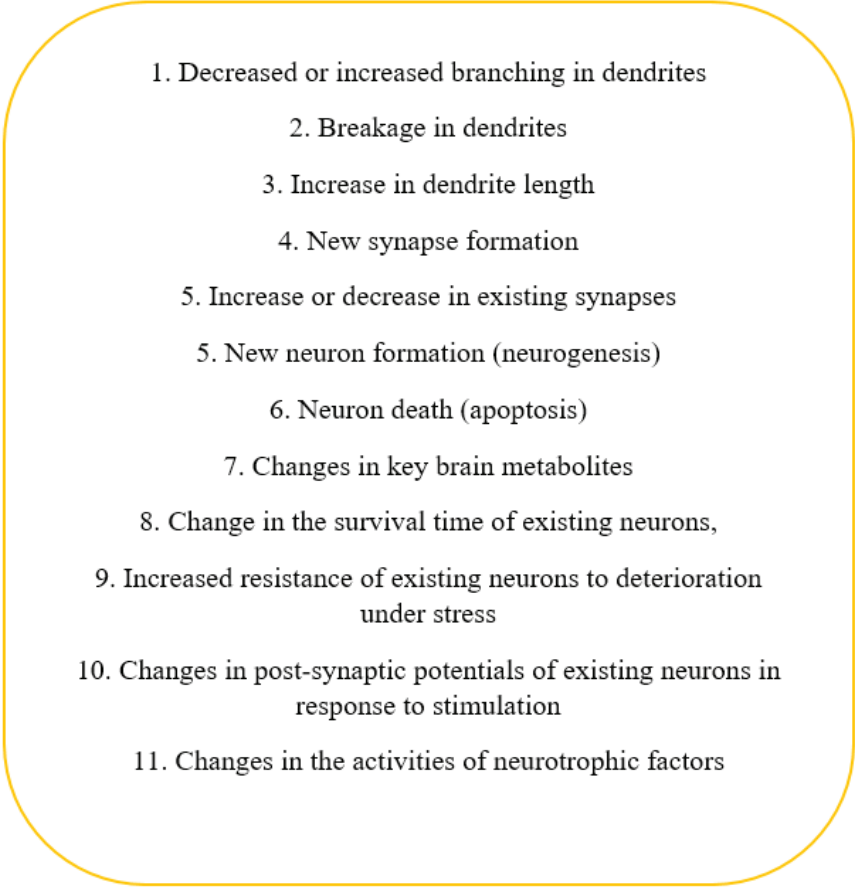
- 
1. Decreased or increased branching in dendrites
 2. Breakage in dendrites
 3. Increase in dendrite length
 4. New synapse formation
 5. Increase or decrease in existing synapses
 5. New neuron formation (neurogenesis)
 6. Neuron death (apoptosis)
 7. Changes in key brain metabolites
 8. Change in the survival time of existing neurons,
 9. Increased resistance of existing neurons to deterioration under stress
 10. Changes in post-synaptic potentials of existing neurons in response to stimulation
 11. Changes in the activities of neurotrophic factors

Figure 1. Changes Related to Neuroplastic Responses

As a result of neuroplastic responses, the effectiveness of synaptic transmission in pre-existing synapses may change or strengthen. Additionally, new synaptic connections may form, existing ones may be pruned, or the excitability of relevant neurons may be regulated (14, 15).

Adaptation to environmental changes can only be achieved through learning. Learning also occurs through synaptic plasticity. Synaptic growth is triggered by an increase in environmental stimuli. For learning to take place, long-term potentiation (LTP), which refers to a sustained increase in synaptic transmission, is necessary (17).

Neurogenesis refers to the creation of functional neurons from neural stem cells, encompassing their division, migration, and differentiation. Neurogenesis continues throughout life in two regions of the adult mammalian brain: the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) in the hippocampus dentate gyrus (DG). Neurotrophic factors play a role in the migration, proliferation and differentiation of neural stem and neural progenitor cells. Additionally, it has been shown that neural stem cells have regulating effects on the restructuring of neural cells, neural plasticity and angiogenesis in damaged tissue. It is known that neurotrophic factor combinations have an important role in adult neurogenesis in the treatment of cerebrovascular, neurodegenerative, oncological diseases and post-traumatic inflammatory damage (18, 19). Neurogenesis has great importance in the formation of neuronal plasticity and the adaptation of organisms to the environment. In addition, it also affects the learning and memory abilities of the living being throughout its life. Neurogenesis slows with age, reducing the potential for learning and repair (20). Neurogenesis is regulated by growth factors and thus new cells begin to develop. During the development of neurons or glial cells, BDNF and other growth factors crucial to the nervous system ensure the survival of these cells (21).

The hippocampus is one of the brain regions with the highest rate of neuroplasticity, and while all kinds of mental exercise increases hippocampal neurogenesis, constant exposure to stress causes a decrease (17). Many factors affect neurogenesis, including growth factors, cytokines, chemokines, neurotrophins, steroids, testosterone, ecdysone, and serotonin. However, physical activity and environmental conditions also affect the proliferation and survival of neurons in vertebrates (22).

In order to understand how neuroplasticity occurs, it is necessary to understand the events that occur inside the cell after neurotransmitters

interact with the receptor on the neuron surface. Chemicals that enable communication between neurons or between a neuron and another cell are called neurotransmitters. In the nervous system, neural signals are transmitted with the help of neurotransmitters. The released neurotransmitters cross the synapse gap and bind to the surface receptors of their target cells. Repetitive neuronal activity consolidates memory by increasing neurotransmitter release at synapses and strengthening neural connections between neuron groups. Neurotransmitters can be excitatory or inhibitory (23). The neurotransmitter released from the presynaptic neuron crosses the synaptic gap and binds to the receptor site on the postsynaptic neuron. Depending on what the neurotransmitter is, it stimulates or inhibits the receiving neuron. Receptors and neurotransmitters act like a key-lock system. A neurotransmitter binds only to a specific receptor. If the neurotransmitter is detected by the receptor site, it triggers changes in the receiving cell. Sometimes neurotransmitters can bind to receptors and cause conduction of the stimulus in the postsynaptic neuron. In some cases, the neurotransmitter may inhibit further signal transmission (24). Depending on the qualitative or quantitative characteristics of the received stimulus, it may cause some changes in neuronal activity and lead to changes in synaptic transmission that will have long-term effects. Frequent and intense stimulation of presynaptic neurons creates action potentials in the postsynaptic neuron. Over time, these synapses become increasingly sensitive and the stimulus is increasingly transmitted to the post-synaptic region. This long-term increase in synaptic transmission is called long term potentiation (LTP). Slow and weak stimulation of neurons also causes changes in the synapses, causing the transmitted stimulus to pass through to the postsynaptic area decreasingly. This change, which is the opposite of LTP, is called long term depression (LTD) (25).

Learning and memory are the most basic and highly specialized functions of the brain. Memory refers to a change in behavior resulting from an experience, while learning is the process by which memory is acquired. Learning is a process in which memory is acquired. The interaction between neurotransmitters and pre- and postsynaptic neurons is crucial for learning and memory formation. Neuroplasticity is important in the formation of long-term memory. Neuromodulators such as acetylcholine (ACh), monoamines, amino acids, lipids, peptides, and neurotrophins play roles in key behavioral processes, including arousal, sleep, motivation, emotions, and memory (23). Learning and memory occur through the interaction of neurotransmitters such as dopamine, acetylcholine, norepinephrine, N-methyl-d-aspartic acid (NMDA), and gamma-

aminobutyric acid. Many cognitive processes depend on the neurotransmitter glutamate, particularly NMDA. Glutamate is a neurotransmitter that generates excitatory postsynaptic signals in the central nervous system (26, 27). Glutamate receptors are of four types. Three of these, called AMPA, NMDA and kainate, are ionotropic receptors. The fourth type is the metabotropic receptor and is called mGluR. Although all glutamate receptor types respond to the same neurotransmitter, they perform distinct functions. Ionotropic glutamate receptors generate excitatory postsynaptic potentials by using their ion channels. Metabotropic glutamate receptors, on the other hand, modulate the nature and intensity of these responses, similar to neuromodulatory effects. Although all types are important for synaptic plasticity, AMPA and NMDA receptors are often considered memory molecules (16, 28).

One of the processes effective in synaptic plasticity is microglial processes. The first microglia to appear during embryogenesis are derived from myeloid progenitors and are the only glial cells of the central nervous system at this stage before both astroglialogenesis and oligodendroglialogenesis (29). Thus, in the absence of astrocytes, microglia play an active role in early embryonic synaptogenesis, while in later stages of pre- and postnatal development, microglia become a key regulator of synaptic pruning, thereby promoting neural connectivity development (30). By clearing and engulfing excitatory circuits involved in the development of neural circuits, microglia shape synapses through a process called ‘pruning’, a process crucial for the promotion of synapse formation and the regulation of neuronal activity and synaptic plasticity (31). Microglia, derived from myeloid progenitors during embryogenesis, are the only glial cells present in the central nervous system before astroglialogenesis and oligodendroglialogenesis occur. Synaptic pruning enhances neural circuits and improves the efficiency of neuronal networks (32). Microglia play a critical role in the modulation of synaptic plasticity, including LTP and LTD (33). In the healthy brain, there is a certain balance between pro-inflammatory and anti-inflammatory markers secreted by microglia, and when this balance is disrupted, synaptic plasticity can be affected (34).

Functional reorganization

When a brain area is damaged, the ability of the corresponding area in the opposite hemisphere to maintain the same function is referred to as ‘equipotentiality’. This concept was redefined when Broca discovered speech loss in unilateral damage to the brain. Broca noted that recovering lost function

due to brain damage is easier in children than in adults. The concept of ‘equipotentiality’ was updated to suggest that the brain has a greater potential to recover lost function when damage occurs early in life (35).

The term ‘replacement’ refers to a brain area taking on a new task unrelated to its original function. Advances in neuroimaging technology have shown that the ‘equipotential’ and ‘substitution’ theories are not entirely accurate (36).

Studies on ‘equipotential’ and ‘replacement’ theories suggest that after hemispherectomy, the motor and sensory areas in the remaining hemisphere reorganize to compensate for lost functions (37). A study in individuals with ischemic stroke showed increased activity in the contralateral premotor cortex (38).

Acute damage to the central nervous system causes a sudden depression of synaptic functions in areas distant from the lesion. This phenomenon is known as ‘diaschisis’ (1). Although diaschisis is believed to result from decreased neuronal activity due to axonal damage, the precise molecular and cellular changes causing cerebral diaschisis remain unknown (39, 40). “Diaschisis” has expanded over time by being divided into different sections as “resting diaschisis”, “functional diaschisis”, “connected diaschisis” and “connectome diaschisis” (41).

3. Exercise and Neuroplasticity

Exercise, defined as planned, repetitive, and structured physical activity, is a simple and widely practiced behavior. It activates molecular and cellular processes that support and maintain brain neuroplasticity (42). After exercise, neurogenesis occurs with increased metabolism and gene expression. At this stage, neuroplasticity is triggered, enabling adaptive changes in the brain. Although it is thought that the nervous system is most plastic in the early periods, it has been determined that this feature is preserved throughout life. In this way, thanks to its ability to adapt to changing conditions, the brain can survive many negative conditions with minimal damage (43). Human and animal research results suggest that increased physical exercise facilitates neuroplasticity of some brain structures and the hippocampus, which in turn supports cognitive functions and emotional and behavioral responses (44).

It is known that physical exercise can reduce many negative health-related conditions and the risk of chronic diseases. Many health organizations recommend exercising most days of the week (45). Physical exercise is associated with an increase in neuroendocrinological changes associated with

neurogenesis, synaptogenesis, angiogenesis and neurotrophin release, as well as improvements in cognitive, sensory and behavioral functions (such as fine motor functions) (46).

3.1 Exercise and Neurotrophins

BDNF is believed to trigger exercise-induced neurogenesis during and after exercise. BDNF, a member of the neurotrophin family, is vital for many functions responsible for neurogenesis, including proliferation, differentiation, maturation and survival. Besides BDNF, signaling pathways like Insulin-Like Growth Factor-1 (IGF-1), Fibroblast Growth Factor-2 (FGF-2), and Vascular-Endothelial Growth Factor (VEGF) are also involved in neuroplasticity and hippocampal neurogenesis. It has been stated that decreased BDNF level is associated with a decrease in functions such as learning, memory and concentration (47).

Besides its primary role in neuroplasticity, BDNF is a neurotrophin involved in metabolism and homeostasis processes (2). BDNF is the most responsive to changes induced by physical exercise, though other neurotrophic factors like NGF, VEGF, and FGF-2 may be transiently affected (48).

Some neurotrophin levels have been investigated in humans after exercise. Peripheral BDNF levels increase after acute physical exercise and return to baseline within minutes to a few hours (2). Endurance training induces changes in BDNF level. There is an increase in IGF-1 level after resistance training (49, 50).

IGF-1 influences the development, differentiation, synaptogenesis, and neurogenesis of brain cells. It has been stated that increased IGF-1 level is associated with improvement in cognitive functions (51).

Physical exercise promotes neurogenesis, while aging and stress have the opposite effect. Increased BDNF, VEGF and IGF-1 levels with exercise promote neurogenesis, but some immunological cells can suppress this process (52).

Long-term exercise in adolescents increases brain tissue oxygenation and nutrition, BDNF level, and causes improvements in memory (53). A dose-response relationship exists between exercise intensity and peripheral BDNF levels following acute exercise (54). BDNF and exercise intensity have a synergistic effect on memory development in the brain during adolescence (55).

Angiogenesis is stimulated by physical exercise and these effects can last for a long time. The neurotrophins that trigger angiogenesis are thought to be IGF-1, BDNF and VEGF. Particularly the hippocampal area is the brain region

most affected by exercise. It is stated that aerobic exercise and resistance training increase hippocampal IGF-1 and BDNF levels (56).

3.2 Exercise, Memory and Cognitive Functions

A sedentary lifestyle leads to numerous health problems. With chronic inactivity and sedentary life, the risk of developing many disorders such as neurodegenerative diseases, cardiovascular problems, musculoskeletal disorders, obesity, metabolic disorders such as diabetes, respiratory problems, aging, neuropsychiatric disorders such as Alzheimer's, depression, and schizophrenia increases significantly (57).

Recent studies show that physically active individuals perform better cognitively and academically compared to sedentary individuals. In these studies, the effects of different age groups, different exercise durations, and different exercise intensities were examined. A 17-year cohort study of middle-aged individuals found that exercise at age 36 slowed memory loss between ages 43 and 53. Memory function declined more in those who quit sports after age 36 than in those who began sports later. Among participants aged 36, 43 and 53 who did physical exercise, the group with the lowest memory loss was the 53-year-old group. Participants aged 36, 43 and 53 who did physical exercise, the group with the lowest memory loss was the 53-year-old group (58). This result confirms the protective effect of regular exercise and having such a habit on cognitive functions. There is a relationship between physical activity in middle age and gray matter volume in later ages (59). It has been found that in middle-aged individuals, those who exercise two or more times a week have higher forebrain gray matter volume compared to those who exercise less (59). This result shows that the frequency of exercise, that is, how many times a week you exercise, is as important as the duration. While exercise is beneficial at all ages, developing exercise habits early in life positively impacts overall health, especially cognitive functions. A look at studies examining all age groups shows that executive functions and memory may benefit the most from the changes that occur with exercise (44). It is known that aerobic exercise has a positive effect on the brain circulatory system, blood flow and blood vessels. Physically active seniors have more small cerebral vessels than less active seniors (60). N-acetylaspartate (NAA), an indicator of neuronal health and survival, is responsible for increasing mitochondrial energy production in neuronal tissues (61). As cardiovascular fitness improves, NAA levels in the frontal cortex increase. As aerobic fitness increases, neuronal losses that occur with aging can

be reduced (62). Chronic aerobic exercise in the elderly people provides greater task-related activation in the prefrontal and parietal brain regions, and executive functions become more effective with decreased anterior cingulate cortex activation (63). Recent research shows that functional connections between brain parts increase with exercise. The part most affected by these connections are the connections between the anterior cingulate cortex and the hippocampus (64). Acute aerobic exercise has a positive effect on memory in young adults. BDNF levels and the number of words held in memory increase after high-intensity acute exercise in young adults (44).

Both physical and cognitive exercises positively affect brain functions. Combining physical and cognitive exercises offers enhanced benefits (65). Regardless of the type of exercise, combining it with cognitive training leads to greater improvement (66).

Functional magnetic resonance imaging (fMRI) is commonly used in human studies to observe structural and functional changes triggered by physical exercise. However, many aspects remain unclear and require further investigation (67).

3.3 Aerobic Exercise and Neuroplasticity

Studies examining the effects of different exercise types on neuroplasticity show that aerobic exercise, known to enhance cardiopulmonary fitness, is highly effective for cerebral neuroplasticity. It is frequently used in the rehabilitation of neurodegenerative and neurological diseases, but no standard exists for the optimal dose, intensity, and duration for enhancing neuroplasticity (68).

The studies explored how both acute and chronic aerobic exercise affect cerebral neuroplasticity. A summary of these studies is described below.

Effects of Acute Aerobic Exercise

In young healthy adults, high-intensity acute aerobic exercise facilitates long-term potentiation-like plasticity in the primary motor cortex, enhances modulation of cerebellar circuits, reduces cerebellar inhibition, and increases catecholamines and neurotrophic substances, indicating an increase in motor cortical plasticity (69). After acute aerobic exercise, a dose-response relationship exists between exercise intensity and peripheral BDNF concentrations (54).

Exercise intensity significantly influences responses after acute aerobic exercise in healthy adults. Similarly, BDNF and cortisol levels, which rise after acute exercise, gradually decline following exercise. In contrast, low-

intensity exercise also contributes to increased neuroplasticity in the motor cortex. Notably, even a single aerobic exercise session promotes motor cortical neuroplasticity in young adults (70).

After a single session of acute aerobic exercise, molecular, functional, and behavioral changes occur. Acute aerobic exercise is unlikely to induce cellular and structural changes like those seen with chronic physical exercise. However, prolonged exercise may enhance cellular stimulation, potentially influencing the structural and functional changes associated with chronic exercise; however, no studies have explored this yet. Table 1 summarizes the possible short-term effects of acute aerobic exercise (71).

Table 1. Short-Term Effects of Acute Aerobic Exercise

Short-Term Effects of Acute Aerobic Exercise		
Molecular	Cellular	Behavioral
BDNF ↑	Cerebellar Blood Flow ↑	Improved Motor and Cognitive Function
VEGF ↑	Glucose and O ₂ Metabolism ↑	
	Neural Activity ↑	
	Receptor Activity ↑	
	Neurotransmitter Concentration ↑	

Effects of Chronic Aerobic Exercise

Numerous studies have examined the effects of long-term aerobic exercise on cerebral neuroplasticity, revealing significant findings. While long-term aerobic exercise is known to increase new neuron formation and synaptic activity through elevated levels of BDNF, IGF-1, and VEGF (68), chronic aerobic exercise appears to have no effect on VEGF levels in elderly individuals (72). This finding indicates that age significantly influences the impact of chronic aerobic exercise on VEGF levels. Increased BDNF and VEGF levels resulting from chronic aerobic exercise are associated with enhanced angiogenesis (68).

A dose-response relationship exists between exercise intensity and peripheral BDNF concentrations, emphasizing the importance of intensity in

maximizing neuroplastic effects. Exercise intensity is important in chronic aerobic exercise responses in school-age children. Research indicates that BDNF levels remain unchanged during low-intensity aerobic exercise. Individuals engaging in high-intensity exercise tend to forget newly learned information less frequently than those in a control group, resulting in improved memory. : Chronic aerobic exercise has been shown to enhance both cognitive and motor skills (53). Long-term exercise training enhances cognitive functions in people with cognitive decline (55). Long-term exercise may reduce the risk of developing Alzheimer's disease due to its inflammation-suppressing properties (73). For elderly individuals at risk of dementia, long-term home exercise can enhance cognitive functions, with benefits persisting for up to a year (74). In aging rats, chronic aerobic exercise improves spatial memory and increases synaptic plasticity proteins in the hippocampus (75).

High-intensity chronic aerobic exercise is perceived as a stressor and triggers the release of central inflammatory cytokines that hinder learning and plasticity. To enhance neurogenesis, it is recommended that exercise be sustained over a long duration and of moderate intensity. Randomized animal studies have shown that while high-intensity interval training improves physical fitness, it does not effectively increase neurogenesis (4).

A study examining the long-term effects of aerobic exercise training conducted twice a week for 6 months included a follow-up that extended 1 year post-intervention. Participants were instructed to continue exercising during the follow-up period and were categorized into high and low fitness groups based on their maximal VO₂ values at follow-up. At the 1-year follow-up, memory performance improved in the high cardiovascular fitness group, while it declined in the low fitness group (76). These results confirm that maintaining the exercise program is crucial for prolonging the benefits gained from aerobic exercise.

Molecular and Cellular Changes Triggered by Chronic Aerobic Exercise

Exercise increases neurotrophic and growth factors in the hippocampus, cerebellum, basal ganglia, cingulate, frontal, and parietal cortices, promoting neurogenesis, synaptogenesis, gliogenesis, and angiogenesis. Increased gliogenesis, neurogenesis, and synaptogenesis contribute to enhanced white and gray matter volume. Increased angiogenesis is critical for supplying the blood needed to nourish neuron development and growth. All these changes contribute positively to neural activity and communication, helping to improve motor and cognitive functions (Table 2) (71).

Table 2. Long-Term Effects of Chronic Aerobic Exercise (71).

Long-Term Effects of Chronic Aerobic Exercise	
Molecular	BDNF, IGF-1, VEGF ↑
Cellular	Gliogenesis, Neurogenesis, Synaptogenesis, Angiogenesis
Structural and Functional	White Matter Volume, Gray Matter Volume, Receptor Activity, Neural Activity, Cerebellar Blood Flow ↑
Behavioral	Improved Motor and Cognitive Functions

3.5 Types of Exercise and Neuroplasticity

A review of the literature reveals that the majority of studies have focused on the effects of aerobic exercise on neuroplasticity. Though limited in number, some studies have explored the effects of resistance, balance, and coordination exercises. There is promising evidence that resistance exercises and coordination training may be effective in protecting and enhancing cognitive functions (77, 78).

In elderly individuals, resistance training has been shown to improve executive functions (79). Suggested: In elderly individuals, resistance exercises trigger an increase in IGF-1 and improve short-term memory and attention (80). Although animal studies are limited, the effects of resistance training in animals mirror those found in humans. Resistance exercises are particularly effective in increasing IGF-1 levels (56).

Despite the small number of studies, one study in elderly individuals found that coordination exercises were more effective in improving visual search tasks compared to relaxation and flexibility exercises. In middle-aged adults, combining stretching-coordination exercises with aerobic exercise leads to a greater improvement in memory and attention scores than aerobic exercise alone (81).

Studies examining the effects of exercise types on neuroplasticity highlight the importance of considering the exercise environment. Is the exercise

performed indoors on a treadmill or bike, or outdoors? Outdoor exercises offer greater sensory stimulation compared to indoor exercises, potentially amplifying the effects of the workout (82).

Taken together, the positive effects of aerobic exercise, resistance, and coordination training on cerebral neuroplasticity and cognitive functions are well-supported by evidence. Regular exercise and physical activity have been shown to benefit executive functions and memory in humans. Sustained cardiovascular fitness and continued exercise are essential for maintaining these benefits over time

4. Conclusion

In conclusion, exercise enhances neuroplasticity and improves cognitive, sensory, and behavioral functions by promoting neurogenesis, angiogenesis, synaptogenesis, and long-term potentiation. First, the increase in neurotrophic factors stimulated by exercise plays a key role in enhancing neuroplasticity and boosting cognitive and behavioral function. Second, exercise induces changes in cerebrovascular function and glial cells, which further support increased neuroplasticity. Lastly, exercise reduces neuronal sensitivity, which may help preserve synaptic function. Exercise may serve as a preventative strategy against neurodegenerative, neuropsychiatric, and cardiovascular diseases, as well as other complications of a sedentary lifestyle, and it may also delay the onset of diseases like Alzheimer's.

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CHAPTER V

MONOSODIUM GLUTAMATE ON BRAIN MEMORY AND LEARNING

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1. Introduction

Food additives are widely utilized in small amounts by the food industry to improve the flavor, color, texture, and appearance of food (1). Among these additives, flavor enhancers are key to providing food with an umami and savory taste (1). One of the most extensively used flavorings in modern times is monosodium glutamate (MSG), which may be found in many commercially packaged foods (such as chips, crackers, bouillon, sauces, etc.) as well as in a lot of home and restaurant recipes. MSG imparts a distinct umami flavor to processed foods, which is Japanese for “savory taste.” Umami is the fifth basic taste, after sweet, sour, salty, and bitter (2). MSG’s umami flavor makes even low-salt foods palatable by enhancing the flavor in low-salt foods, compensating for the reduced salt content. Despite the Food and Drug Administration’s (FDA) position that MSG is safe, animal studies have revealed negative consequences from long-term MSG consumption (3). These negative effects have been connected to a number of illnesses, including asthma, hypertension, obesity, headaches, neurotoxicity, and reproductive organ damage. These effects have been observed in various organs, including the liver, pancreas, thymus, brain, testes, and kidneys (4, 5). The neurotoxic and neurodegenerative effects of this widely used additive, and thus its effects on learning and memory, are among the most extensively studied and debated topics in contemporary research.

2. History of the MSG

Monosodium glutamate (MSG) is a common taste enhancer that is derived from the sodium salt of L-glutamic acid. It is a white, crystalline, odorless compound that dissolves easily in water. L-glutamic acid was first isolated by German chemist Karl Heinrich Ritthausen in 1866. Later, in 1908, Japanese scientist Kikunae Ikeda identified that the predominant taste in the seaweed *Laminaria japonica* was due to its high glutamate content. He established that L-glutamic acid was responsible for this flavor, which is referred to as “umami” (meaning “delicious” in Japanese). Monosodium glutamate, which was first commercially produced in 1909 under the brand name “Ajinomoto,” is now acknowledged as the fifth basic taste in most major cuisines (5). Concerns about the safety of MSG emerged after it became a common kitchen ingredient. Some individuals dining at Chinese restaurants reported experiencing symptoms such as headaches, dizziness, fatigue, and palpitations. These symptoms, initially believed to be linked to MSG, were termed ‘Chinese restaurant syndrome’ in 1968 (5,6). Despite these reports, no clear casual relationship between MSG and these adverse effects has been established. Nonetheless, the safety of MSG has been thoroughly examined by health and food organizations (5,6). In the late 1990s, the FDA classified MSG as Generally Recognized as Safe (GRAS), concluding that there is no evidence to indicating that MSG poses a danger to the public when used within permitted levels (7). Today, MSG continues to be used as one of the most popular flavor enhancers in the food industry.

3. Structure of MSG

MSG is the sodium salt of L-glutamic acid, an amino acid with the chemical formula $C_5H_8NO_4Na$. It consists of 78% glutamic acid, 22% sodium salt and also water (8). MSG, also referred to as Ajinomoto, Chinese salt, and sodium 2-aminopentanedioate (IUPAC nomenclature), is marked E621 in the food industry (8). MSG is a crystalline powder that is white, odorless, and has a melting point of 232 °C. Its molecular mass is 169.11 g/mol. It adds a distinct flavor called umami, which is defined by a taste that is meaty, broth-like, or salty taste. When dissolved in water, MSG breaks down into sodium and glutamate ions. It is also soluble in fats and organic solvents (8,9). The primary reason for using MSG as an additive is its superior and its faster dissolution compared to glutamic acid (8,9).

After consumption, the body breaks down MSG into sodium and glutamate ions. One of the most prevalent amino acids, glutamate is found in large amounts

in the central nervous system (9). It is present in high concentrations in the striatum, cerebral cortex, and dentate gyrus of the hippocampus—regions of the brain that are crucial in mediating cognition. (10). Since MSG does not require enzymatic activity for its breakdown, it is rapidly absorbed by the body, potentially raising glutamate levels in the blood plasma (11). After absorption, glutamate is transported by the amino acid transporter (EAAT-1) and the sodium carboxylate transporter (NaDC-1) in the intestinal lumen before being circulated throughout the body via the bloodstream (11). It is generally acknowledged that almost all of the glutamate that is consumed is broken down in the gut, where the majority of its carbon skeleton is either released as carbon dioxide or utilized to create amino acids including glutathione, alanine, arginine, and lactate. Additionally, the most of its nitrogen is involved in synthesizing glutamine, proline, branched-chain amino acids and urea cycle amino acids (11). In one study, excessive MSG intake (30 mg/kg orally every 20 minutes for 220 minutes) temporarily increased plasma concentrations of glutamate and aspartate for 1-2 hours, but no adverse effects were noted (12). Regularly consuming high amounts of MSG can elevate plasma glutamate levels, which depend on factors like dose, concentration, and age. For instance, in neonatal rats, increasing the MSG concentration from 2% to 10% led to a fivefold increase in plasma glutamate levels (12). It has been observed that MSG doses up to 1 g/kg do not considerably pass the blood-brain barrier (13). Research has shown that glutamate levels in the brains of rats, guinea pigs, and rabbits are significantly higher in the brain than in plasma (11).

4. Effects of MSG

As one of the most popular food additives in the world, MSG is a potent flavor enhancer that is generally regarded as safe by the Food and Drug Administration (FDA), the European Food Safety Authority (EFSA), the Joint Expert Committee on Food Additives (JECFA), a joint agency of the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) (14). Nonetheless, a plethora of research indicates that eating meals high in MSG might result in adverse effects such as headache, migraine, tingling in the face, numbness, perspiration, flushing of the neck and other places, chest pain, heart palpitations, weakness and nausea. These physiological reactions have been referred to as the MSG symptom complex or the Chinese restaurant syndrome (2). Numerous investigations also relate high MSG consumption in food to nephrotoxicity of endocrine disruptors, hyperaggregation of platelets, atrial fibrillation, hypertoxicity, hyperglycemia and the resulting diabetes mellitus,

and obesity (15). Dietary ingestion of MSG has been found to increase platelet count, bleeding and clotting time in rats (16). The administration of MSG (4 mg/g) has also been linked to oxidative stress in the liver tissue of young rats (17). After receiving a single high-dose intraperitoneal injection of MSG, rats' serum levels of the aminotransferases alanine aminotransferase (ALAT) and aspartic aminotransferase (ASAT) were found to be raised, and their hepatocytes showed degenerative alterations (18). Long-term MSG exposure (2 mg/g body weight) has also been linked to hepatocyte damage in albino mice following neonatal exposure (19). In contrast to all these studies, some researchers have reported that MSG does not show any adverse effects when taken with food (20). The most interesting studies on the effects of MSG on many organs are the studies on neurotoxicity related to the nervous system. Numerous recent research have highlighted the fact that oral MSG consumption promotes the production of free radicals, causes DNA damage, and initiates an apoptotic signaling cascade that ultimately results in the necrosis of nerve cells (21). Consequently, it is believed that MSG may set off neurodegenerative illnesses such as multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease and Huntington's disease (22).

5. MSG and Neuron Damage

It is now understood that MSG causes neurotoxicity via elevating LPO, oxidative stress, apoptosis that follows, and cholinergic dysfunction. (23). MSG's constituent glutamate is an essential neurotransmitter, but excessive levels of glutamate are excitotoxic to nervous tissues, causing accumulation in synaptic clefts. This accumulation causes glutamate receptors, especially N-methyl-D-aspartate (NMDA) receptors, to become overstimulated. This activation triggers a number of pathways that harm neurons and affect the functionality of brain tissues (24). Studies have shown that the percentage of damaged neurons increases in all MSG experimental groups, and this effect is dose-dependent. Damaged neurons in these studies were characterized by chromatin condensation and pyknotic nuclei (25). These findings are consistent with other research indicating that MSG can cause nerve damage (26-28). Particularly in the hippocampus's pyramidal neurons, these investigations specifically noted a number of alterations, including widened Virchow-Robin gap and constricted hyperchromatic nuclei (27,28).

An additional investigation revealed that the neuronal damage associated with MSG is most likely due to glutamate excitotoxicity, which is induced by

elevated cytosolic Ca^{2+} levels. This excitotoxicity leads to neuronal death through mechanisms of necrosis and apoptosis (29). Overstimulation of glutamate receptors can initiate several cellular cascades, resulting in cell damage and death. Additionally, MSG may metabotroically activate glutamate receptors, leading to an increased release of Ca^{2+} from the endoplasmic reticulum (29). This release triggers pathways that damage synapses and cause cell death. Consequently, mitochondrial dysfunction, due to the formation of free radicals and the activation of intracellular proteins, results in apoptosis and necrosis (30). According to a research by Onaolapo et al., giving 1 or 1.5 mg/kg of MSG for 14 days resulted in a decline in spatial learning and memory (31). According to a different study, MSG ingestion may have an impact on animal behavior, leading to anxiety and memory loss (32). Research by Akatobi et al. indicated that high doses of MSG were linked to significant chromatin condensation and pyknotic nuclei in neuron cells within the hippocampus, suggesting that MSG may decrease spatial memory, potentially due to its neurotoxic effects (29). MSG administration has also been shown to damage neurons in the hypothalamus of rats, leading to various metabolic abnormalities, including growth disorders, self-mutilation, pseudo-obesity, and hypogonadism (33).

MSG influences both neurons and neuroglial cells in the brain. In the hippocampus, astrocytes derived from neuroglial cells support and shield motor neurons, among other diverse neuronal tasks. On the other hand, motor neuron functions and the morphology of astrocytes are also changed by excessive activation. One common general pathogenic condition is brain astrocyte activation. In this case, there may be dysregulated connection between motor neurons and astrocytes, which accelerates the motor neurons' death (34). Astrocytes regulate the amount of extracellular glutamate. Glutamate is a precursor of GABA and is returned to neurons for GABA synthesis (34). The primary mechanisms by which astrocytes absorb glutamate at synapses are excitatory amino acid transporters (EAATs), also referred to as sodium-dependent glutamate transporters (35). Healthy brains are continuously recycling glutamate between neurons and astrocytes, a process known as the glutamate-glutamine cycle. Glutamate concentrations can rise to 1 mM for a brief period during synaptic activity after which they drop to nanomolar levels. (36). Tonically activated glutamatergic receptors in various cell regions, including dendritic spines and dendrites, are triggered if elevated glutamate concentrations continue to exist in the synaptic cleft (37). Thus, for the purpose of limiting the spatial and temporal extent of neuronal activation, it is imperative

that glutamate be cleared from the extracellular space as soon as possible after neuronal activity (38).

If increased glutamate cannot be cleared, it causes hallmark pathologies such as amyloid- β deposition, tau hyperphosphorylation and neuronal death (29). Therefore, an increase in amyloid and Ki-67 protein expression leads to an increase of astrocyte nuclei in the hippocampus, which in turn regulates the state of processes associated with Alzheimer's disease, with an increase of S-100 and Glial Fibrillary Acidic Protein (GFAP) (39).

6. MSG Learning and Memory

The effects of MSG on the nervous system have been the subject of an intense and ongoing discussion in recent years. Experiments are still being carried out to determine any potential impacts on animals. One of the brain areas most susceptible to glutamate-mediated excitotoxicity is the hippocampus, which is crucial for memory and spatial learning. It has recently been discovered that rats given modest dosages of MSG exhibit symptoms of impaired short-term memory and learning capacity (40). Low dosages of MSG have been shown by Ali et al. to have toxic effects and impair cognitive abilities in young children because the blood-brain barrier is particularly permeable to both large and small molecules at this age (41). Similar results from animal behavioral tests after MSG exposure have been obtained in other investigations. In a different study, rats exposed to MSG experienced memory impairment, which was linked to a decrease in Na⁺,K⁺-ATPase activity in the rats' hippocampal region (43).

Animals that are exposed to artificial taste enhancers, like MSG, may also display symptoms of anxiety, epilepsy, and depression (44). A number of tests can be performed to determine behaviors that are indicative of anxiety, including the forced swim test, raised plus maze test, tail suspension test, open field test, and light/dark transition test (45). The criteria of line crossing, erectness, grooming, and number of defecations are assessed using the open field test (46). MSG injections given to rats during their neonatal period enhanced their locomotor behavior on postnatal days 21 and 65, according to research by Dubovicky et al. (47) Additionally, MSG injections given to newborns have been related to specific hippocampal CA1 pyramidal cell degenerations that have been connected to learning difficulties, according to Ishikawa et al. (48). Rats given MSG injections on postnatal days 1, 3, 5, 7, and 9 exhibited elevated locomotor activity initially, followed by hypoactivity and finally behavioral abnormalities,

according to studies by Kiss et al. (49) and López Pérez et al. (50). The claim that MSG-induced hippocampus degeneration affects behavioral measures is supported by all of the aforementioned findings from earlier research. According to Oliveira de Almeida et al., animals given MSG showed increased hypoactivity. On the 57th day of MSG treatment, they conducted an open field test on rats and found that, following a considerable decline in locomotor activity, the rats were less active in comparison to their original assessed behavior (51). In their investigation, Kardeşler and Başkale put rats through an 8-arm radial maze to test their memory and learning abilities both before and after receiving MSG injections. In order to observe MSG's immediate and long-term effects on rats, the study used eight consecutive administrations. Based on the outcomes of their 8-arm radial maze test, they found that, in comparison to the control group, MSG-injected rats were less likely on day 7 to select the correct arm. Additionally, they believed that the fact that the increase in reaction latency largely happened on the fourteenth day after the MSG injections corroborated the theory that the animals' spatial memory was impaired in some way (52). The density of brain receptors is known to be correlated with spatial learning, as measured by the radial maze test (53). Oliveira de Almeida et al. studied how dopaminergic stimulation affected rats' locomotor activity and how it related to the expression of dopamine D2 receptors (51). They maintained that elevated expression of dopamine receptor D1 rather than receptor D2 was the reason for a decrease in mobilization, which in turn caused a drop in locomotor activity. Other research has reported similar results (54). Schmid and colleagues suggest that the observed decline in learning parameters and GABA levels in the radial maze test results can be accounted for by the positive correlation between GABA receptor density and spatial learning (55). However, it is believed that there is a fundamentally important balance between the amounts of the inhibitory neurotransmitter GABA and the excitatory neurotransmitter glutamate in hippocampal circuits. For every divergence in favor of one of these systems, dysfunctions occurs. According to Bojanic et al., MSG has the ability to overstimulate nerve cells to the point of injury or death, a phenomenon known as "excitotoxicity" (56).

Moreover, the central nervous system (CNS) contains a large number of neuroactive monoamines, including catecholamines and dopamine (57). Both the development of memory and the construction of learning capacities depend critically on catecholamines. One study found that as MSG dosage increased, catecholamine levels dropped (52). Research suggests that learning impairment

and memory loss are related to the drop in catecholamine levels caused by increased MSG dosage.

They came to the conclusion that MSG injections may result in necrosis and immunopathological alterations in the brain's arcuate nucleus and cortex and the hippocampal CA1 region, which may alter an animal's behavior both acutely and over time. Therefore, factors that adversely impact motor sensors and spatial memory include cerebral ischemia and reperfusion (52). Furthermore, it has been shown that MSG causes neuroendocrine abnormalities that result in obesity, insulin resistance, metabolic dysfunctions, altered analgesic responses, glucose intolerance, hypophagia, anxiogenic behaviors, and depressive-like symptoms (58).

7. MSG and Alzheimer's Disease

Apart from its established neurotoxic consequences, some studies have suggested that MSG could be linked to many neurodegenerative illnesses like amyotrophic lateral sclerosis, Alzheimer's and Parkinson's (15, 22). The reduction of different types of memories following MSG administration is consistent with the neurobehavioral alterations seen in animals in animal studies. Semantic, procedural, episodic, and short-term (spatial and working) memories are the most affected by Alzheimer's disease (AD). The thalamus and hippocampal regions are primarily linked to these memories (59). Since locomotor and exploratory behavior are the earliest forms of learning and spatial cognitive abilities, they are the most researched neurobehavioral markers in mice (60). The Morris water maze has been utilized in a number of studies to assess animals' escape latency—an indirect indicator of movement and cognition—after being given MSG (61). Escape latency increased significantly in all of these studies, indicating that MSG impaired learning and spatial cognition (62). Cortes et al., demonstrated that adult mice exposed to MSG during the neonatal stage had reduced spatial information acquisition and memory (42). Specify the research have looked at how MSG affects the noradrenergic pathway (63). Dysfunction of the noradrenergic system plays a significant role in the progression of the disease. This has given rise to the theory that early loss of noradrenergic projections and the resulting drop in noradrenaline levels in the brain cause cognitive impairment and neurodegeneration (64). A few earlier research works have shown how MSG's effects on metabolism can upset the brain's noradrenaline balance. These investigations demonstrated that the brainstem, thalamus, and pons-medulla all had lower noradrenaline levels

following MSG administration (65). Based on the results of these investigations, a hypothesis was made that the pathogenesis of Alzheimer's disease might be linked to MSG-induced noradrenaline dysfunction.

There exists an additional group of ideas that associate problems in intracellular calcium signaling with the pathogenesis of Alzheimer's disease. The pathological features of Alzheimer's disease, including tau hyperphosphorylation, amyloid deposition, and neuronal death, are caused by increased intracellular calcium. Research has indicated elevated levels of calcium signaling, specifically calretinin immunoreactivity and S-100 β , in the spinal ganglia and hippocampal regions of rats treated with MSG. (67). Calcium-binding proteins called S-100 proteins regulate several pathways linked to Alzheimer's disease (68). The development of dystrophic neurites in Alzheimer's disease plaques has been connected to the overexpression of neurite extension factor S-100 beta by activated astrocytes associated with amyloid-containing plaques (69). This demonstrates unequivocally that MSG affects calcium signaling, which could contribute to a pathogenesis similar to Alzheimer's. According to recent research, the astrocytic cytoskeletal protein GFAP is elevated in the blood and cerebrospinal fluid of Alzheimer's disease patients, suggesting that it is a sign of reactive astrogliosis (70, 71). Astrogliosis, a characteristic of AD, is frequently observed around A β plaques (72, 73). Krawczyk et al. further elucidated this theory by showing that the astrocyte nuclei of MSG-treated rats exhibited elevated expression of the proliferation-associated Ki-67 protein (74).

8. Conclusion

MSG is still often utilized as a taste enhancer in a variety of foods. While the FDA typically views this chemical as safe for occasional use, more recent research has shown that large dosages and prolonged use of MSG have unfavorable side effects, raising questions about both its toxicity and safety. Several animal and clinical studies have shown that MSG, particularly at high doses, poses health risks. In dose-dependent manner MSG can raise the quantity of neuronal injury in some areas of the rat hippocampal tissue. Several studies have shown that consuming high doses of this food flavor enhancer over the long term can have neurotoxic effects. These studies suggest that MSG induces neuronal shrinkage, apoptosis, and necrosis through mechanisms such as Ca²⁺ accumulation in the cytosol, overstimulation of NMDA receptors, and astrocyte proliferation around neurons. MSG has been shown to cause memory and learning disorders due to neurotoxicity in experimental animals.

Such behavioral consequences may have emerged as a result of MSG-induced neuronal degeneration in the brain's hippocampus area. MSG has also been hypothesized as a potential trigger for Alzheimer's disease in adulthood. MSG has been shown to cause memory and learning disorders due to neurotoxicity in experimental animals. The consumption of MSG during pregnancy may negatively impact the cognitive development of the child. There is no maximum amount of MSG that can be consumed through food. Initially, MSG's ability to enhance flavor is mostly dose-dependent and self-limiting. MSG typically constitutes 0.2% to 0.8% of the food consumed (75). Higher concentrations damage the flavor characteristics of the food and are therefore not used. More comprehensive behavioral characterization studies over extended periods are needed to investigate the effects of long-term and frequent MSG use on neurotoxicity and neurodegenerative diseases like Alzheimer's. Such research should prioritize long-term exposure rather than solely focusing on high doses.

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CHAPTER VI

THE EFFECT OF WHEY PROTEIN ON BRAIN, MEMORY AND LEARNING

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1. Introduction

In this article, the term “whey protein” (or “whey proteins” in Turkish) is used. However, there is ongoing scientific debate about the accuracy of this term. Some scientists argue that “serum proteins” or “soluble milk proteins” are more precise, as “whey proteins” specifically refer to the proteins found in the whey produced during cheese or casein production. Despite this valid distinction, we have chosen to use “whey proteins” in a broader sense due to its common usage (1).

Proteins can be sourced from a variety of foods, including milk, meat, eggs, soy, and wheat (2). Milk contains two types of proteins: casein and whey protein (3). Whey protein is more soluble and of higher quality than casein and has high bioavailability, making it an excellent choice for bodybuilders seeking a protein supplement. Casein, which makes up 80% of the protein in milk, is generally considered a slow-digesting protein because it takes longer to break down than whey or soy protein (4). Eggs are regarded as one of the healthiest sources of protein for the human body because they contain nearly all essential amino acids. Additionally, since egg protein is free from dairy, it may be a preferred option for individuals with lactose intolerance, despite the availability of low-lactose forms of whey protein (5).

In addition to its biological and structural functions, the nutritional and functional properties of whey are linked to the proteins in its composition. These

properties include a high nutritional value for human health, antimicrobial and antitoxic activity, supporting the growth of beneficial microflora, boosting the immune system, and helping control certain diseases, such as cancer (6).

Dairy products made from processed whey can be added to various foods, such as baked goods, yogurt, ice cream, meat, fish, and baby food, enhancing their nutritional value. Additionally, whey is widely used in a variety of nutritional applications. The use of bioactive whey components is also expanding in both the pharmaceutical industry and the field of nutrition (7).

Whey proteins can be effectively incorporated into the production of infant formulas. The α -lactalbumin and β -lactoglobulins present in whey positively impact normal growth and development because they contain the essential amino acids required for infant nutrition. Pure α -lactalbumin extracted from whey is utilized in infant formula production due to its structural and compositional similarity to the primary protein found in breast milk. Additionally, producing hypoallergenic infant formula through the heat treatment of whey proteins is an effective and straightforward strategy (8).

Whey can be used as an ingredient in sports drinks because it contains high-quality protein. Some studies have shown that whey proteins can benefit athletes involved in various sports. Clinical research indicates that whey proteins in athletes' diets can directly improve performance. Whey protein supplements are rich in essential amino acids, which are necessary for protein synthesis in muscles (8). Since whey proteins are easily soluble in water, they can be readily mixed with other liquids. This solubility facilitates easy consumption by athletes before, during, or after training (8).

2. History of Whey Protein

Approximately 3,000 years ago, whey is believed to have been discovered while using the calf's stomach for transporting and storing milk. It has been observed that the unadulterated milk in the calf's stomach coagulates with the enzyme chymosin (rennet), resulting in the formation of cheese and whey (9). Around 2,500 years ago, Hippocrates (466-377 BC) recommended certain drinks to boost the immune system and enhance the body's muscle strength and growth rate. These early energy drinks were referred to as serums and were rich in lactose, minerals, and fast-absorbing proteins, making them effective at improving physical performance. Later, Galen (131-200 AD), another prominent physician in medical science, also advised his patients about the benefits of whey. Other notable figures, such as İbn-i Sina (980-1037 AD), who conducted

around 200 studies, Hermann Boerhaave (1668-1738), and Thomas Sydenham (1624-1689), whose clinical training methods were widely adopted throughout Europe, also recommended whey to their patients (10).

In the late 16th century, Switzerland witnessed the rediscovery of the importance of whey protein. Farmers observed that pigs fed whey grew faster than those fed other foods, prompting them to start consuming whey themselves. As they experienced improvements in their own health, the benefits of whey quickly became well-known throughout the country (11). Whey was initially an important by-product of cheese production at the first commercial cheese factory in New York City. The factory produced large quantities of whey, which were difficult to dispose of. Consequently, cheesemakers either dumped the excess whey into lakes and rivers or used it for irrigation. Recognizing that whey was being underutilized, farmers began mixing it with barley or grain to create high-protein animal feed (12). Over the past 20 years, whey protein has transformed from a by-product of cheese-making into a highly valuable, nutrient-rich product with significant functional properties (11, 12).

2.1. Whey Protein Supplementation and Brain

An examination of the literature reveals that whey protein concentrate (WPC), a protein complex derived from milk, is associated with numerous health benefits in both humans and rats (13). Whey consists of a diverse mixture of proteins, each with various nutritional, biological, and functional properties (14). Whey protein concentrate (WPC) is specifically processed to preserve the natural form of cysteine-rich proteins, such as serum albumin, lactoferrin, and α -lactalbumin, which serve as cysteine donors in cellular metabolism (15). These proteins exhibit antioxidant activities by stimulating the biosynthesis of glutathione (GSH), which can enhance immune function and help detoxify potential xenobiotics (16). Whey protein concentrate (WPC) is also known for its various nutritional and physiological effects, including antihypertensive, antitumor, hypolipidemic, antiviral, and antibacterial properties, as well as its role as a chelating agent in aging and infant nutrition (17). These benefits contribute to its high value for both animals and humans (18). Additionally, whey protein supplementation has been shown to increase lean mass and strength to varying degrees in older adults (19). During aging, the excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) leads to the synthesis of pro-inflammatory cytokines, such as interleukins (IL-1 β and IL-6) and tumor necrosis factor- α (TNF- α), in the brain. This neuroinflammation

is regarded as a consequence of chronic oxidative stress (20). The protective mechanisms of the aging brain gradually weaken, increasing the risk of neurodegenerative disorders (21). Antioxidants, including those found in whey protein, help neutralize reactive oxygen species (ROS), minimizing cellular damage and maintaining normal cellular function (22). Rich in tryptophan, whey protein can cross the blood-brain barrier, promoting neurogenesis in both rodents and humans (23). Additionally, whey protein has been shown to reduce oxidative stress and enhance mitochondrial activity in the brains of mice (24).

2.2. Effects of Whey Protein on Learning and Memory Performance

Neurodegeneration, a common condition among the elderly, often leads to memory loss or dementia, imposing a significant societal and economic burden. Whey protein hydrolysate, a natural by-product of cheese-making, exhibits strong bioactivity and may provide a potential strategy for slowing neurological aging (25). In 2021, Yu et al. investigated the antioxidant effects of whey protein peptide (WHP) on learning and memory. Their study, which examined the hippocampal tissues of mice, concluded that WHP significantly mitigates declines in spatial exploration, body movement, and both spatial and non-spatial learning and memory abilities associated with aging. The proposed mechanism involves reducing degeneration and apoptosis of hippocampal nerve cells, improving acetylcholinesterase (AChE) activity, decreasing the expression of inflammatory factors (TNF- α and IL-1 β), and alleviating oxidative stress damage in brain tissue. Additionally, WHP was found to enhance the expression of synaptic plasticity proteins, p-CaMKII and BDNF, suggesting that WHP may help alleviate aging-related oxidative stress and cognitive impairment (26). Another study explored the neuroprotective effects of whey protein hydrolysate (WPH) against age-related memory decline and identified its potential mechanisms. The results indicated that WPH is effective in preventing cognitive disorders (27). In research involving diabetic mice, dietary supplementation with whey protein was shown to reduce oxidative stress, protect neurons in the central nervous system, and improve neurological behavior (28). Additionally, a study investigating the combined effects of whey protein hydrolysate (WPH) and treadmill exercise on cognitive decline suggested that both interventions impact the gut microbiome and may be associated with cognitive improvement. This research highlighted that WPH and treadmill exercise are effective strategies for alleviating cognitive impairment and offer promising approaches for treating neurodegenerative diseases (29). Li et al. demonstrated that whey protein powder (PP), derived from bovine milk and rich in milk fat globule

membrane (MFGM), supports neuronal development and cognition in infants. Their study explored PP's role in Alzheimer's disease (AD) and uncovered an unexpected effect on regulating neuroinflammation. They found that PP attenuates neuroinflammation by targeting PPAR γ in the mouse brain. PPAR γ was shown to play a central role in mitigating AD pathology through the PPAR γ -NF- κ B and PPAR γ -mTOR-GSK-3 β pathways (30).

The use of protein supplements is common among athletes, active adults, and military personnel. In a study involving basketball players, Ho CF et al. concluded that consuming a high-protein whey supplement after exercise improved fatigue recovery, which was associated with increased cerebral oxygenation in response to the exercise's difficulty (31). In repeated exercise, reductions in muscle soreness were attributed to the use of protein supplements, which were associated with faster recovery of muscle function due to decreased protein breakdown. The study involving soldiers emphasizes the need for both laboratory and field research to provide evidence-based guidance for selecting protein supplements that enhance soldiers' performance (32).

3. Conclusion

If you read the 'Ingredients' section of a packaged food product in the supermarket, you are likely to encounter the terms 'whey' or 'whey powder.' These ingredients are added to many foods to enhance their nutritional value, and the benefits of whey are numerous. A review of the studies in the literature reveals that whey positively contributes to brain development, memory, and learning.

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CHAPTER VII

THE EFFECT OF NUTRITION TYPES ON ALZHEIMER'S AND LEARNING

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1. Introduction

Dementia is a serious public health problem for older people. Alzheimer's disease (AD), a type of dementia, has become one of the greatest mental burdens. AD, the incidence of which increases with the aging population, is a symptom-oriented disease with no definitive cure. The prevalence of AD in the U.S. population aged 65 and older in 2021 was approximately 11% (1). According to remove the 2022 Turkey Health Survey Report published by TUIK, the prevalence of AD in the Turkish society is 5.5% (2).Currently, AD cannot be treated or prevented with medications, and its prevalence is increasing with the aging population (1).

It is stated that adequate and balanced nutrition supports the development and preservation of cognitive functions by supplying the nutrients necessary for brain health. The relationship between nutrition and learning is complex and influenced by many factors. Various diets may affect cognitive functions in different ways. In general, a diet rich in fruits, vegetables, whole grains and lean proteins and low in processed foods is thought to be best for learning and memory. A healthy and balanced diets can help maintain and improve cognitive function (3).

Insulin plays a key role in brain health. Inadequate and unbalanced nutrition, along with irregular insulin regulation, can lead to neurodegeneration. Insulin is involved in the clearance of amyloid β peptide and in proteostasis

affecting tau phosphorylation. Insulin is a vasoactive hormone. It is involved in regulating both cerebral and peripheral blood flow (3,4). Insulin can also cross into the hypothalamus and the blood-brain barrier (BBB). However, it is negatively affected by conditions such as obesity and inflammation (5). Chronic peripheral hyperinsulinemia reduces the amount of insulin transported to the brain (6). Hyperglycemia can negatively affect brain functions through glucose neurotoxicity, vascular injury, and mechanisms such as the accumulation of glycation end products. Insulin dysregulation can lead to pathological brain aging conditions, including AD and vascular cognitive impairment. Insulin directly affects AD pathology through interactions with A β peptide (7-10). Peripheral insulin sensitivity and hyperinsulinemia have been indicated to decrease in adults with AD (11). It has been reported that dietary restrictions have positive effects on central nervous system (CNS) insulin sensitivity in patients with diabetes (12). In cognitively healthy adults, increased peripheral insulin resistance has been related with lower cognitive scores and more tau concentrations (13). Studies show that adults with AD exhibit dysregulated insulin function in peripheral tissues, along with reduced or mislocalized insulin receptors in the brain and decreased receptor proximity to insulin (14).

Peripheral insulin resistance in Alzheimer's patients has been reported to correlate positively with high A β levels in the brain (15). Peripheral insulin resistance has also been related with increased A β deposition in cognitively healthy adults who are A β -positive compared to those who are A β -negative (16,17). Alzheimer's disease is referred to as a type of insulin resistance or 'type 3 diabetes' in the brain, related to insulin resistance, causing glucose misuse in specific regions of the brain. The literature emphasizes that apolipoprotein E4 (APOE4) is a shared risk factor for AD and type 2 diabetes mellitus (DM). The APOE4 variant has been linked to a form of AD characterized by reduced brain glucose utilization. These biomarkers showed that brain glucose uptake is reduced long before the onset of clinical symptoms of AD (18,19).

Increased inflammation and oxidative stress, dyslipidemia, impaired mitochondrial and synaptic function, and disrupted brain insulin signaling are considered similar pathogenic mechanisms for type 2 DM and AD (20). Tau concentration has been reported to be higher in people with DM compared to non-diabetic, cognitively healthy adults (21). In a study comparing cognitively healthy middle-aged adults with pre-DM/newly diagnosed, untreated type 2 DM, and cognitively healthy adults, using fluorodeoxyglucose (FDG)-positron emission tomography (PET) in areas prone to AD, peripheral insulin resistance

was associated with reduced glucose metabolism (22). Although studies have indicated a relationship between insulin resistance and amyloid accumulation in middle age (23), other studies have not found a link between diabetes and AD pathology (24,25).

Studies propose that diet plays a key role in cognitive health and the development of dementia. A systematic review of studies conducted between 2014 and 2017 reported that dietary interventions were moderately linked to beneficial effects on specific cognitive domains (26). Add “Both” in the beginning supplements and dietary models have been tested in many studies. The Mediterranean diet has emerged as the most effective diet model (27-29).

Nutrition and physical activity are the most beneficial lifestyle changes in peripheral insulin resistance. Adults who consume diets high in simple carbohydrates and saturated fats are more likely to develop AD than those who follow diets rich in lean proteins and polyunsaturated fats. Dietary nutrients, such as vitamins, antioxidants, and fiber, may directly influence cognitive health through their antioxidant, anti-inflammatory, endothelial, and mitochondrial functions (30,31).

1.1. Mediterranean Diet (MedD) and Alzheimer's Relationship

The Mediterranean diet (MedD) is rich in plant foods, grains, fruits, vegetables, legumes, and oilseeds. Research shows that the MedD can help prevent cognitive decline and improve memory. This is due to its richness in brain-beneficial antioxidants and omega-3 fatty acids. One study reported that high fruit and vegetable consumption reduced the risk of cognitive impairment by 26% (32). Another study observed that individuals who consumed one or two servings of green leafy vegetables per day had better cognitive performance than those who did not (33). In a prospective study of 1,640 older adults without dementia, dietary flavonoid intake was associated with improved cognitive function at baseline and a lower risk of cognitive decline at follow-up (34).

Recent studies have reviewed the effect of MedD on β -amyloid and phosphorylated tau tangles. A systematic review and meta-analysis reported that adherence to a MedD-style dietary pattern Was associated with a reduction in β -amyloid and tau tangles, as well as a subsequent reduction in pathology (35). Greater adherence to the MedD over nearly a decade was significantly associated with reduced overall AD pathology and β -amyloid burden. Furthermore, anti-inflammatory, antioxidant and lipid-lowering effects of this dietary pattern have

been reported (36). The MedD was also associated with greater total brain volume, thicker cortex, and fewer white matter hyperintensities (37).

Studies have reported that the MedD, when enriched with olive oil, dairy products, or nuts, improves general cognition, memory, and attention (38-40).

1.2. Dietary Approaches to Stop Hypertension (DASH) and Alzheimer's Relationship

The DASH diet is a program developed to control hypertension. This diet aims to lower blood pressure by reducing salt intake and emphasizing foods rich in potassium, calcium, magnesium, and fiber.

The DASH diet includes nuts, fruit, low-fat dairy products, vegetables, whole grains, fish and poultry. The DASH diet limits fat, red meat, sweets, and sugar-containing drinks. The Dietary Approaches to Stop Hypertension (DASH) diet is similar to the Mediterranean diet (MedD) in its emphasis on vegetables. The DASH diet is reportedly related with improved cognition (41,42). The DASH diet is thought to share characteristics with the Mediterranean diet, in addition to reducing sodium intake, which is associated with improved blood-brain barrier integrity (43). However, some studies report that the DASH diet is not effective in improving cognitive functions. A randomized controlled trial of 79 adults with cognitive impairment found no improvement in general cognitive functions among those who followed the DASH diet (44).

The MedD-DASH Intervention for Neurodegenerative Delay (MIND) diet is designed to protect brain function. The MIND diet, a combination of the MedD and the DASH diet, aims to prevent neuronal damage. The MIND diet limits the intake of foods high in saturated fats and animal products. The MIND diet also includes fruits and green leafy vegetables.

Adherence to the MIND diet is associated with reduced cognitive decline. It also reduces the likelihood of developing AD. When comparing cognitive decline and AD, a stronger inverse association was reported for the MIND diet compared to the MedD and DASH diets (45).

1.3. Vegetarian/Vegan Diets and Alzheimer's Relationship

Vegetarian and vegan diets exclude meat and other animal products. These diets are typically rich in fruits, vegetables, whole grains, legumes, and nuts. These diets are usually rich in fruits, vegetables, whole grains, legumes and nuts. Some studies suggest that vegetarian and vegan diets may help prevent cognitive decline and improve memory. These benefits are attributed to B

vitamins, antioxidants, and nutrients such as dietary fiber, folate, and iron, which support brain health (46-48).

Inflammation plays a significant role in the development of Alzheimer's disease (AD). Elevated levels of inflammatory markers are observed in patients with AD. These markers are also associated with cognitive decline. It has been suggested that a vegan diet may indirectly benefit cognition by promoting a healthy body weight and reducing cardiovascular risk factors (49).

In the context of AD prevention, a vegan diet may contribute to maintaining a healthy blood lipid profile. It also contributes to the hypothesis that quercetin, a natural inhibitor of monoamine oxidase (MAO), may contribute to maintaining mental health and reducing the risk of AD. On the other hand, a vegan diet lacks certain vitamins and micronutrients. Without supplementation, vegans are more prone to deficiencies in vitamin B12, vitamin D, and docosahexaenoic acid (DHA), which are linked to AD (50).

The use of DHA and eicosapentenoic acid (EPA) supplements is recommended in vegan diet. However, a relationship has been demonstrated between increased plasma n-3 polyunsaturated fatty acid (PUFA) levels and prostate cancer (51). Therefore, more research is needed on this topic.

1.4. Ketogenic Diet and Alzheimer's Relationship

The ketogenic diet (KD) is high in fat and low in carbohydrates. KD is recommended as a non-pharmacological treatment for weight loss, increasing fat intake and reducing carbohydrate consumption to provide an alternative energy source for neurons. KD is recommended as a non-pharmacological treatment for weight loss, increasing fat intake and reducing carbohydrate consumption to provide an alternative energy source for neurons. This dietary approach was first developed by Dr. Russell Wilder to treat epilepsy in children. There are variants of the KD model in which the macronutrient ratio varies. The developed KD types are used in the cure of many disorders such as cancer and Alzheimer's disease. The primary mechanism of KD is associated with improved mitochondrial function and reduced oxidative stress. Increased ketone bodies in the blood following KD administration may provide a treatment option by influencing disease mechanisms, either directly or through modulating glutamate activity (52). KD is primarily aimed at achieving weight loss in overweight adults. In older adults or in animal studies, KD interventions are often been associated with significant weight loss. However, this may negatively affect sarcopenia and even contribute to cognitive decline in older adults. Gastrointestinal symptoms

such as vomiting, constipation and diarrhea are the most common side effects. Research suggests that KD may improve cognitive function, particularly memory, and may benefit neurodegenerative diseases.

In a study carried out on mice, it was found that KD decreased amyloid B levels (53). The stage of the disease to which the diet will be applied is important in terms of evaluating the effects of the diet. In patients with advanced AD, KD is recommended alongside medical treatment (54,55). Large studies are needed with cognitive and neuroimaging outcomes to evaluate the effectiveness of KD at different stages of AD and its potential negative effects, particularly in adults with early AD.

1.5. Processed Food-Based Diets (Western Diet) and Alzheimer's Relationship

A diet based on processed foods consists of foods. high in salt, sugar, and fat, and low in nutritional value. This type of diet is known as the Western diet (56). The Western diet is known to negatively affect cognitive functions. Studies indicate that the Western diet is associated with pathological brain aging. Excessive consumption of processed foods is linked to memory loss, difficulty concentrating, and mental decline (57,58).

Consumption of saturated fatty acids and trans fat causes to increased production of amyloid β proteins and increased risk of AD. It is stated that consumption of sugary drinks in particular is also related with cognitive decline. Today, diets rich in glucose, fructose, corn syrup, high glycemic carbohydrates and salt are associated with brain atrophy, neuronal loss and AD2. Elevated blood glucose levels, dehydration and intake of salty foods increase uric acid levels and increase brain fructose levels (59). It is also reported that fructose production and metabolism are increased in regions influenced by AD in patients, including hippocampus entorhinal cortex, middle temporal gyrus, cingulate cortex, sensory and motor cortex and cerebellum (60).

1.6. Intermittent Fasting (IF) Regimes and Alzheimer's Relationship

Intermittent fasting (IF) is a recently popular way of eating. Unlike other types of diets, intermittent fasting is an eating pattern that consists of periods of fasting and periods of unrestricted eating. Intermittent fasting is practiced in several ways. Such as fasting for 24 hours one day a week, limiting daily food intake to a 6-8 hour period, limiting 600-700 calories two days a week. In all types of intermittent fasting, metabolic changes such as blood glucose levels in

the normal range, depletion or decrease in glycogen stores, activation of fatty acids and ketone production, and decrease in circulating leptin are observed (61).

Intermittent fasting is emphasized to have important protective effects against neurodegeneration. IF regimens have also shown promising results in combating cognitive decline. In a study conducted in elderly individuals with mild cognitive impairment (MCI) who regularly practiced IF, changes in antioxidant function, DNA damage, inflammation, insulin and high density lipoprotein (HDL) cholesterol markers and improvements in cognitive functions were reported (62,63). Another study showed that IF improved diabetes-induced cognitive impairment via gut microbiota (64).

The literature emphasizes that intermittent fasting may positively impact on cognitive function in older adults. However, the timing of the eating window and its duration are factors that warrant detailed examination. More studies on IF and β -amyloid deposition and neuroinflammation are needed. The success of future studies is crucial to demonstrate that intermittent fasting is an inexpensive, feasible and powerful preventive tool against AD (65).

2. Conclusion

Increased inflammation and oxidative stress, dyslipidemia, impaired mitochondrial and synaptic function, and impaired brain insulin signaling are considered similar pathogenic mechanisms for Type 2 DM and AD. Since AD pathology is strongly associated with obesity, insulin resistance, and cardiovascular disease, preventive strategies such as nutritional interventions are crucial for reducing AD risk (4,6,15).

Dietary interventions that reduce saturated fats, animal proteins and refined sugars while increasing consumption of polyunsaturated fatty acids, nuts and plant foods are associated with higher peripheral insulin sensitivity, AD, and age-related cognitive decline. Insulin dysregulation may also lead to pathologic brain aging, including AD and vascular cognitive impairment through various mechanisms (25). Further research is required to define the role of insulin in AD and related disorders and to determine the mechanisms of its neuroprotective effects for prevention and treatment. The extent to which the protective effects of nutrition are achieved by enhancing brain insulin function remains a significant research topic.

Healthy dietary patterns and nutritional supplements can improve memory, attention and concentration, executive functions, psychomotor speed, and other

cognitive domains. They can also increase blood perfusion in areas associated with AD. The benefits of the Mediterranean diet, plant foods and protein-rich supplements, certain amino acids and minerals, polyphenols and their combinations, and other dietary supplements are supported by studies (46-49). In conclusion, it can be stated that MedD, MIND, DASH, KD and plant-based dietary patterns are beneficial for brain health.

Dietary interventions, food-based interventions and dietary supplements with antioxidant, and anti-inflammatory effects can help improve inflammation and oxidative damage. Considering the known importance of certain micronutrients, and food metabolites for optimal brain function (e.g. flavonoids, iron and certain vitamins), it is recommended to review dietary recommendations aimed at maintaining adequate nutrient intake to support healthy cognitive function throughout life.

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CHAPTER VIII

EFFECTS OF BREAST MILK INTAKE ON COGNITIVE DEVELOPMENT, LEARNING DISORDERS AND NEURODEVELOPMENTAL DISORDERS

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1. Introduction

Breast milk is an easily accessible nutritional food source that affects children's cognitive, socio-emotional and brain development (1-3). Certain nutrients in breast milk, along with the mother-baby interaction during breastfeeding, contribute to children's brain development (3).

Learning disorders are a set of conditions that affect information processing in children, resulting from impaired brain structure and function. Learning disorders are defined by impairments in understanding or using language, manifested as delays or deficits in reading, writing, listening, speaking, thinking, spelling, mathematical calculation and reasoning (4-6).

Autism spectrum disorder (ASD), a neurodevelopmental disorder, is characterized by difficulties in social interaction, challenges in forming emotional connections, restricted interests and repetitive behaviors, which vary in severity across children. Impairments in autism spectrum disorders include not only severe autistic traits but also deficits in intellectual skills or developmental delays. In this condition, the development and functioning of the brain is affected (5,7).

Another neurodevelopmental disorder affecting learning is attention deficit hyperactivity disorder (ADHD). It is a childhood disorder characterized by symptoms such as decreased attention span, hyperactivity and impulsivity (8,9).

Problems related to learning disorders, neurodevelopmental disorders, and varying learning styles can diminish children's sense of competence at an early age, negatively impacting their academic and social lives (4).

Breast milk intake influences cognitive development (1,10-12) for some learning disorders (13) and autism spectrum disorder (14-16) and attention deficit/hyperactivity disorder, (16-19) which are prevalent in children.

2. Breast Milk and Breastfeeding

Breast milk is the most optimal and nutritious food that supports growth and development. Breastfeeding has positive effects not only during the feeding process but also in later life for the baby to lead a healthy life (11).

The first time a mother breastfeeds her baby after birth, an emotional bond is established between mother and baby (20,21). Skin-to-skin contact between mother and baby reinforces the emotional bond by stimulating the release of oxytocin (21). Through the bond formed between mother and baby during breastfeeding, babies develop a positive psychological relationship (20,21). Establishing a healthy attachment relationship between mother and baby positively affects the baby's life in the long term (22).

Breast milk provides essential nutrients for the developing brain in infants. Breastfeeding plays a key role in significantly improving the cognitive development of infants (14,23).

Within the correct nutrition plan of the baby, breast milk should be exclusively breastfed for the first six months, and after six months, breast milk intake should be continued until 24 months with appropriate and safe additional foods. Proper nutrition is crucial during the 0-2 age period when development is the fastest (20,21,24). If possible, breast milk should be started within the first hour after birth and the mother should be encouraged to feed frequently, at least 8-12 times a day (24). This allows for the intake of colostrum, which contains a large number of bioactive factors produced at the end of pregnancy (14). Colostrum is defined as the newborn baby's first vaccine (24).

Breast milk is highly bioavailable and easily digestible containing essential energy and nutrients needed for the newborn's growth, brain development and immune system strengthening (20). Breast milk contains hormones

(oxytocin, thyroid stimulant hormone, growth hormone, thyroxine, cortisol, insulin), growth factors (epidermal and nerve growth factor, somatomedin-C) neuropeptides (somatostatin, neurotensin, vasoactive peptides) inflammatory and immune regulatory agents (cytokines), hormone precursors that increase lactation (24). It also contains all essential amino acids, lactalbumin, saturated and unsaturated fatty acids, linoleic acid, lactose, various vitamins and minerals (Na, K, Cl, Ca, P, Fe, Vitamin A-D-E-K-C, Riboflavin, Thiamine) and maternal antibodies (25). Breast milk is a perfect blend of substances necessary for the healthy development of a baby's body (26). The composition of breast milk varies from one mother to another and even within the same mother's milk, depending on the age and condition of the infant (11). It has been noted that undernourished mothers may produce breast milk with lower concentrations of certain vitamins and minerals (10).

Breast milk represents the only optimal food with its macro and micronutrients adapted to the needs of the baby (26). "Macronutrients (carbohydrates, lipids and proteins)" and "micronutrients (vitamins and minerals that support normal body processes)" contribute directly to the maturation of the central nervous system and brain development (10).

Breast milk is a unique source of nutrients, containing bioactive factors, hormones and growth factors that support the maturation of the baby's brain (27,28).

3. Effects of Breast Milk on Cognitive Development

Breast milk contains essential nutrients for both neurological and cognitive development. Brain matter is composed of 60% lipids and is influenced by diet. There are positive effects between breastfeeding and cognitive development, with long-term effects into adulthood (1).

Thanks to the essential "long-chain polyunsaturated fatty acids (LCPUFA)" in breast milk, it is believed to contribute to cognitive development by affecting brain development in children (11). Deficiencies such as inadequate breastfeeding in infancy may lead to neurocognitive consequences that persist throughout life (10).

"Polyunsaturated fatty acids (PUFA)" play a critical role in supporting brain development in infants. They uniquely contribute to the development and functioning of the brain by playing important roles in influencing the physical properties of membranes. Other polyunsaturated fatty acids contributing to the

development of the infant nervous system include alpha-linolenic acid (ALA) and linoleic acid (LA) (26).

Breast milk is rich in LCPUFA such as “docosahexaenoic acid” (DHA), a subgroup of omega-3 fatty acids, and “arachidonic acid” (AA), an unsaturated omega-6 fatty acid. These substances are known to support rapid brain development between 6-12 months after birth (29).

Breast milk affects the intelligence score (IQ) of children by providing a nutritional advantage over infant formulas, especially in terms of lipid content. Studies also show that breastfed children score higher on cognitive tests measuring intelligence compared to formula-fed children (12).

Breastfeeding can increase the growth of white matter in the brain by 20% to 30%. It has been reported that babies breastfed during the first 4 months of life are more effective in understanding and solving problems which is important for their learning abilities in the school environment (1).

In a study comparing breastfed and formula-fed infants, it was reported that breastfed infants had better neuro-physiological measurements, better myelination and more mature neuronal development. Although there are more studies in preterm infants, the positive effects of early feeding and breast milk on brain development, especially some nutrients in breast milk have been confirmed to provide optimal development of the brain. It has been shown that the longer the duration of breastfeeding, the better the neurodevelopmental outcomes (29). Studies support that the neurological and mental development of preterm and term infants fed with breast milk is positively affected (3,29).

Intake of essential LCPUFA in breast milk during early development helps improve cognitive function and reduces behavioral problems in children (30).

Breast milk provides optimal nutrients for the developing brain and breastfeeding significantly improves infants' cognitive development. Involved in the development of a healthy brain, sialic acid is a key molecule required for the proper development of gangliosides and is therefore critical for brain development and function. This bioactive component in breast milk cannot be fully replicated in formula (23). There are studies showing that breastfeeding has beneficial effects on IQ test performance compared to formula-fed infants (23,31,32). It is conceivable that sialic acid contributes to this.

Studies provide evidence that breastfeeding, and especially breast milk intake in the first six months, has long-term consequences on performance on intelligence tests (12,30-34).

Isaacs et al. investigated the effect of breast milk on intelligence score, brain volume and white matter development in the brain. For this purpose, a total of 50 children aged 13-19 years were evaluated. It was found that brain development, cognitive abilities and IQ levels of breastfed children were higher. The study suggests that breast milk contributes positively to the cognitive development of children (32).

In a study conducted by Bernard and colleagues in France, the relationship between polyunsaturated fatty acid (PUFA) in breast milk and IQ of children was examined. It was reported that breastfeeding and duration of breastfeeding had a positive effect on intelligence score and increased verbal IQ. Full- scale IQ was higher in children who were breastfed and whose colostrum contained high levels of arachidonic acid (AA) and 3-LC PUFA. Children with low levels of these nutrients had intermediate IQ levels, while those who were never breastfed had the lowest mean IQ (12,33).

In a study conducted in Spain, Boucher et al. observed that longer duration of breastfeeding increased intelligence scores in children. In children aged 5 years, those who were breastfed for 1 year or more had higher intelligence scores than those who were breastfed for 2 months or less (30).

In a study conducted by Rantalainen et al. in Finland, the effects of breast milk intake and duration of breastfeeding on cognitive ability and age-related cognitive change in young adulthood and old age were examined. It was found that those who received breast milk for at least 6 months had higher cognitive ability scores at older ages than those who did not. The neurodevelopmental advantages of breastfeeding continue in advanced ages in case of long-term breastfeeding, and longer breastfeeding may benefit the age-related change especially in verbal reasoning ability (33,34).

Belfort et al. observed that preterm infants (born under 30 weeks) who received more than half of their oral intake as breast milk were associated with larger gray matter and hippocampus volumes than those who did not, with positive associations with neurodevelopmental outcomes at age 7 years. These areas are central to neural function (33,35). Similarly, Ou et al. examined the difference between the gray matter in the brain of breastfed and formula-fed 8-year-old children. Breastfed children had more gray matter in the brain. Higher activation was observed in the perception and language task areas of the brain in breastfed children. Since brain activation is positively correlated with task performance, these findings support the evidence that breastfeeding is associated with performance on intelligence tests (33,36). Numerous studies

show that breast milk intake supports brain development and breastfeeding has a positive effect on intelligence (31,33,37).

Studies have shown that children of mothers who received more docosahexaenoic acid during breastfeeding had better comprehension at the age of three and better verbal and non-verbal intelligence at the age of seven (1,35).

Breast milk, which is a rich source of LCPUFA, insulin-like growth factors (IGF), micro and macronutrients, contributes significantly to brain development by supporting physical growth and brain maturation (38).

4. Learning Disorders and Breast Milk

A learning disorder is defined as a discrepancy between a child's skill level and their performance on academic achievement tests, with severity ranging from significant to severe (4). Learning disorders are neurological disorders that cause children to experience difficulties in learning, cognitive processing and application (8).

Specific learning disorders are classified into four types: reading disorder (dyslexia), mathematics disorder (dyscalculia), written expression disorder (dysgraphia) and unspecified learning disorders (4).

Other disorders included under learning disorders are visual perception disorder, auditory discrimination disorder, dysnomia and pragmatic language disorders (4).

Dyslexia, one of the most common learning disorders, is characterized by difficulty sounding out letters and confusion between similar-sounding words, which hinders the acquisition of basic reading skills. It is a language-based learning disorder (4).

Breast milk intake positively affects the child's language development (22,36,38,39). Receptive language scores at age 3 and verbal intelligence quotients at age 7 have been reported to be higher in children who received long-term breastfeeding (36). In a study conducted by Leventakou et al. in Greece, the relationship between the duration of breastfeeding and language, motor and cognitive development of 18-month-old children was evaluated. The prospective cohort study included 540 mothers and infants. The cognitive, language and motor development of the children were evaluated at 18 months using the "Bayley III developmental scale". As a result, cognitive, receptive and expressive language and motor development scale scores were found to be higher in infants who were breastfed for more than 6 months. In addition, a significant increase was found in the fine motor development scale of children

who were breastfed for more than 6 months compared to those who were never breastfed (11,39).

There is a limited number of studies in the literature examining the relationship between breast milk and learning, conditions affecting learning and learning disorders. In the cohort study conducted by Adams et al. 191,745 school children in Scotland formed the database. In the study comparing exclusively breastfed and formula-fed infants with formula-fed infants, it was reported that exclusively breastfed infants had fewer communication problems, social-emotional-behavioral difficulties, sensory disturbances, and physical motor deficiencies. At the same time, it was observed that the risk of learning disorders decreased in exclusively breastfed and mixed-fed children compared to formula-fed children (13).

There is also evidence in the literature that breastfeeding reduces the risk of some neurodevelopmental diseases known to be associated with learning disorders (14-16,18,19,40). There is evidence in the literature that autism spectrum disorder, (14-16) attention deficit hyperactivity disorder, (16-18) communication problems, (13,36,41,42) mental health problems, (43) behavioral problems and impaired social development (44) and breastfeeding may be associated with higher levels of intelligence in later life (33,37).

Breastfed infants of mothers who were fed high-fat fish once a week also showed better visual and motor skills at age three (1). This may also have an effect on learning disorders such as visual perception disorder.

In a study conducted in Italy in 1130 play children between the ages of 3-5 years, it was reported that babies who were breastfed had better oral development, better speech and better communication with other people (11).

Gorgun and Melekoglu reviewed scientific studies on learning disabilities within Turkish literature from 1972 to 2017. They noted that there were no studies examining the effect of breast milk on learning disorders, highlighting the need for increased scientific research, particularly interdisciplinary studies (6).

There are various studies in the literature on neurodevelopmental disorders such as “autism spectrum disorder” and “attention deficit hyperactivity disorder”, which are not included in the definition of learning disorders but significantly affect learning processes (14-16,18,19,30,40).

5. Neurodevelopmental Disorders and Breast Milk

Neurodevelopmental disorders encompass a range of health issues that arise in early childhood impacting a child’s cognitive, motor and social functions. In

addition to genetic factors, prenatal and postnatal environmental influences play a critical role in the development of these disorders. One of the most significant factors supporting brain development during the postnatal period is breast milk (7,20).

Autism spectrum disorder, a neurodevelopmental disorder, is classified as a pervasive developmental disorder that also influences learning processes (7).

Another neurodevelopmental disorder not categorized as a learning disorder but that significantly impacts learning processes is attention deficit hyperactivity disorder, known to greatly affect the development of cognitive, academic and daily social skills (8,9).

5.1. Autism Spectrum Disorder and Breast Milk

Autism Spectrum Disorder is an early-onset neurodevelopmental disorder that persists throughout life and manifests itself through delays in language and communication skills, impairments in social and cognitive areas, limited interests, stereotypic or repetitive behaviors and limited functionality (14,15). In autism spectrum disorders, serious deficiencies are observed especially in socialization, communication, and fixed repetitive interests and habits (7).

Autism is a disorder directly related to the brain that can be accompanied by intellectual disabilities. The prevalence rate has increased in recent years compared to earlier years. This increase in prevalence is often referred to as the “autism epidemic” (7). Today, there is a consensus that genetic, environmental, familial and anatomical factors contribute to the developmental of ASD (7,20). Factors such as the duration and amount of breast milk intake are considered environmental risk factors for autism (2,16). Some studies suggest a potential relationship between breast milk intake and autism (14,21,38). In a study conducted by Kamasak et al. on children with autism, the condition was associated with lack of or short-term breast milk intake. A significant relationship was found between breast milk intake its duration, and autism. Children who never received breast milk were more frequently observed in the autism group. There are also studies reporting inadequate breast milk intake in children with ASD (15).

Several studies in the literature suggest that inadequate breastfeeding may contribute to ASD (15,21). One study examining the effect of inadequate breast milk intake on the development of autism was conducted in Oman. In this study involving children aged 3 to 14 years, 204 children, including 102 children with autism spectrum disorders and 102 healthy children, were included in the study

and the rate of late initiation of breastfeeding in the autism group was found to be statistically significantly higher using the “Childhood Autism Assessment Scale”. Overall, this study shows that increased risk of autism is associated with inadequate breast milk intake. It has also been argued that decreased colostrum intake with late initiation of breastfeeding may also increase the risk of autism (21).

Some studies have reported that breastfeeding has a protective effect against autism spectrum disorder (30). The need for additional data based on larger samples on the effects of breastfeeding on autism spectrum disorder has been emphasized in more than one study (20,27,31). There are studies showing that longer breastfeeding is independently associated with better cognitive development and fewer autistic traits (30,38).

In a study conducted in China, it was reported that infants who were exclusively breastfed had a lower risk of being diagnosed with ASD compared to infants who were not breastfed for the first six months (38). Similarly, in another recently published study, it was reported that the risk of ASD was low in exclusively breastfed children (14).

In some studies, examining the relation between breastfeeding and autism spectrum disorder, a positive relation was found between longer breastfeeding duration and decreased ASD risk (15,21,30,38). In another study, no significant relationship was found between breast milk intake and ASD. Zhan et al. did not find a significant relationship between breast milk intake and ASD in their study conducted between 2016 and 2020. At the same time, they stated that in the 26 previous studies they analyzed, 15 studies found a positive relation between breastfeeding and ASD, nine did not find any relationship, and two studies reported the opposite effect. Due to these inconsistent data, there is a need for large-scale studies that include new data and better account for confounding factors. Cross-cultural studies have also suggested that breastfeeding practices may be affected by cultural, ethnic and socioeconomic factors (27).

Since there is no known definitive treatment for lifelong autism spectrum disorder, more extensive studies are needed to confirm the role of breast milk intake in the etiology of ASD (38).

5.2. Attention Deficit Hyperactivity Disorder and Breast Milk

Hyperactivity and short attention span in infancy and early childhood are part of healthy development. When children begin to develop impulse control

around the age of four, there is a decrease in hyperactivity and inattentive behavior (9).

ADHD is a disorder that manifests itself with symptoms of hyperactivity, impulsivity and attention deficit starting from childhood and continuing throughout life, leading to cognitive, academic and social problems (8,45). In children, it leads to problems such as impaired school achievement, absent-mindedness, forgetfulness, disorganization, and inability to focus attention for long periods of time (45).

ADHD is a common, chronic neurodevelopmental disorder that is frequently studied in school-age children (8,9). The learning and memory problems seen in this disorder often severely affect the individual's cognitive, academic and social skills as well as their development (8).

In a study conducted by Julvez et al. in Spain, the relationship between the duration of breastfeeding and the social abilities, executive functions, attention deficit and hyperactivity disorders of four-year-old children was evaluated. This study, in which a total of 500 children were followed longitudinally, showed that as the duration of breastfeeding increased, the hyperactivity score at the age of four decreased significantly, while the social ability score increased. This is explained by the important role of LCPUFA in cortical brain development in breast milk. In addition, in this study, it was reported that psychological and physical contact between mother and child supports the development of cortical connections and the limbic system in the infant's brain. Thus, it is said that breastfeeding indirectly affects the neuro-development of the child (19).

Although it is supported that long-term breastfeeding has a protective effect against ADHD symptoms, it cannot be said to have a preventive effect against ADHD (30). The protective effect may be attributed to the possible contribution of nutrients and other bioactive components in breast milk to attentional processes and behavioral regulation.

In a study conducted by Kim and colleagues in Korea, it was reported that breastfeeding for at least the first 4 months reduced the risk of being diagnosed with neurodevelopmental disorders such as ADHD and ASD compared to formula feeding (40). Similarly, another study reported that the likelihood of ADHD was significantly reduced in children who received breast milk for at least 6 months (17).

In another study, the effects of breastfeeding and polymorphisms of the FADS2 gene, which plays a role in fatty acid metabolism, on ADHD were investigated and it was observed that it was associated with increased attention

span at the age of 12 years, less hyperactive behavior at the age of 3 years and a tendency towards higher IQ (46).

In the study by Zeng and colleagues, studies focusing on the relationship between breastfeeding and ADHD in children conducted before 2018 were examined. Evidence suggested that breastfeeding may reduce the risk of ADHD in children (18).

Ozdoner and Er (2023) examined the scientific studies in the Turkish literature between 1991 and 2022 for children with ADHD, but no study on breast milk intake and ADHD was found (45).

More research is needed to analyze whether a specific component of breast milk is protective in the development of neurodevelopmental disorders such as ADHD, or whether the special bonding between mother and infant through breastfeeding plays a role in neurodevelopment (18).

6. Conclusion

It is important that breast milk, accepted by the “World Health Organization” to be the most suitable nutrient for infant growth and development, is given to babies from birth. All babies worldwide have the right to good and adequate nutrition (24). For this purpose, mothers should be encouraged to initiate breastfeeding. The mother should breastfeed her baby within the first hour after birth. Training programs planned in this context will be important for the early initiation of breastfeeding.

Breastfeeding has been associated with better school performance and neurocognitive development in children in numerous studies (17,36,37). There is a growing consensus that breastfed children tend to have higher intelligence scores (37). Therefore, parents should be made aware of the importance of breast milk to increase children’s success and support their cognitive development.

The psychosocial effects of enhanced early mother-infant contact and feeding provided through breastfeeding are thought to be significant for brain development. Since breastfed babies receive more psychosocial stimulation during the feeding process, their brain development will also be positively affected (37).

Comprehensive individual counseling services should be provided to mothers to increase breast milk intake, which contains sufficient nutrients and bioactive components to support infant growth and development and brain development. It will be important to plan activities related to the subject and to

cooperate with healthcare professionals, non-governmental organizations and ministries at this stage to raise social awareness (47).

It is predicted that special education costs can be reduced by promoting breastfeeding for inadequate breast milk intake, which is thought to increase the risk in learning disorders (37).

Large-scale studies measuring the effect of breast milk on disorders affecting learning, which are common in children, are needed.

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CHAPTER IX

THE EFFECT OF TRAUMATIC BRAIN INJURY ON MEMORY

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1. Introduction

Traumatic brain injury (TBI) is the disruption of normal brain functions caused by a blunt injury, such as a blow to the head, impact, concussion, or penetrating head trauma (1). This pathological condition affects millions of people annually, exerting a significant global impact. The clinical management of TBI patients, along with the socioeconomic challenges associated with their care, imposes a heavy burden on healthcare systems and society (2).

TBI significantly increases the risk of emotional, behavioral, and cognitive disorders. Among these, memory impairments are particularly notable, affecting a wide range of memory functions, including working, prospective, semantic, and episodic memory. These memory deficits disrupt daily activities, social interactions, and employment opportunities. The variability in trauma severity and type further complicates prognosis and treatment, making each trauma profile unique.

The uncertainties following TBI have spurred efforts to better understand its clinical manifestations and the complex pathophysiological mechanisms involved. Preclinical studies have utilized animal models to investigate potential therapeutic and rehabilitative interventions. Promising results from animal experiments and early-phase clinical trials have sparked increased interest in these areas. However, due to the complexity of both TBI pathophysiology and

the intricate structure of the human brain, fully understanding these processes and developing effective treatments remains challenging (3).

In this section, we will discuss the epidemiology of TBI, its effects on quality of life, and the pathological processes associated with memory impairments. Additionally, we will explore the brain regions affected by TBI and the mechanisms by which these injuries impact the physiological parameters of memory.

1.1. Prevalence and Epidemiology of TBI

The World Health Organization has estimated that TBI is one of the top three leading causes of death and disability worldwide (4). It is estimated that more than 10 million people globally suffer from TBI each year, including approximately 1.7 million in the United States alone. Of these, about 80% are treated in emergency departments, 16% are admitted as inpatients, and 3% die as a result of their injuries (1). The cost of diagnosing, treating, and caring for TBI patients represents an economic loss of nearly 400 billion dollars annually worldwide (5).

The most common causes of TBI globally are falls (35%) and motor vehicle accidents (17%), followed by injuries from sports and armed conflicts (6). An analysis of hospitalization and mortality rates after TBI shows that the highest rates occur in young children (0-4 years), adolescents and young adults (15-24 years), followed by the elderly population (over 65 years) (7).

1.2. Effects of TBI on quality of life

TBI can negatively affect quality of life in various ways, including cognitive, behavioral, emotional, and physical impairments, as well as interpersonal, social, and occupational functioning. It also impacts families, communities, and the economy as a whole (8). According to the Centers for Disease Control and Prevention, symptoms following TBI can be classified into four overlapping categories: sleep disturbances, physical symptoms (headache, dizziness, fatigue, imbalance, photophobia), cognitive issues (difficulties with attention, concentration, learning, and memory), and emotional symptoms (irritability, depression, and anxiety) (9).

When assessing the quality of life after TBI from a behavioral perspective, conditions such as attention deficits, cognitive impairments, sensory processing issues, communication problems, severe depression, anxiety, personality changes, aggression, and social inappropriateness are often observed in

individuals affected by TBI. These cognitive impairments can arise days, months, or even years after the injury and may persist for a lifetime (8). Additionally, TBI is considered an epigenetic risk factor for the development of neurological diseases, including Alzheimer's, Parkinson's, and depression (10). Epilepsy is another post-traumatic condition that affects quality of life, with its onset often delayed. Early post-traumatic seizures of varying severity occur in 32%–53% of patients with penetrating TBI and approximately 25% of those with brain contusions (8).

These findings underscore the need for more comprehensive information about TBI and the importance of developing strategies to improve quality of life. Such efforts are critical for achieving more favorable outcomes in the prognosis and treatment of traumatic brain injury.

1.3. Classification and Severity of TBI

Although there is no universally accepted method with precisely defined boundaries to classify TBI, some clinical symptoms are considered sufficient for diagnosis. These include acute intracranial damage, neurological deficits, loss of consciousness, amnesia for peritraumatic events, and confusion or altered mental status as seen on typical neuroimaging (11).

In the case of traumatic brain injury, the Glasgow Coma Scale (GCS) is commonly used to assess the patient's level of consciousness. The GCS evaluates three components: eye response, verbal response, and motor response, which are used to classify the severity of head trauma. A GCS score of 13–15 indicates mild brain injury, a score of 9–12 indicates moderate brain injury, and a score of 3–8 indicates severe brain injury (1). The GCS also helps categorize general neurobehavioral outcomes, such as death, vegetative state, severe disability, moderate disability, and good recovery. However, there remains a need for more refined definitions and evaluation criteria to better determine the severity of the injury, guide treatment options, and assess prognosis and functional recovery (8).

2. Pathophysiology of Traumatic Brain Injury

Traumatic brain injury occurs in two distinct phases. The first is the acute (primary/mechanical) injury phase, which results from changes that happen at the time of the trauma. The second is the secondary (delayed/non-mechanical) injury phase.

2.1. Primary Injury

In head trauma, primary injury causes direct tissue damage along with disturbances in cerebral blood flow and brain metabolism (12). The sudden impact of various mechanical forces on the brain may result in two types of primary injuries: focal and diffuse brain injuries (13).

In focal brain injury, damage is characterized by cuts, compression, and concussive forces, including closed head TBI, penetrating TBI, skull fractures, and localized contusions at the site of impact. In the center of the injury site, necrosis of neuronal and glial cells is concentrated, where blood circulation is impaired. As a result, hematomas and epidural, subdural, or intracerebral hemorrhages may occur. A secondary contusion can develop in tissues opposite or surrounding the primary injury site due to the brain rebounding and striking the skull. Depending on the severity, this may lead to cognitive impairments, behavioral changes, and hemiparesis (12, 14).

The main mechanism behind diffuse brain injury is rapid deceleration and acceleration forces, which cause shear and tensile injuries to brain tissues. Strong tensile forces can trigger edema and ischemic processes that damage neuronal axons, oligodendrocytes, and blood vessels. Diffuse TBI often leads to widespread axonal damage in subcortical and deep white matter regions, such as the brainstem and corpus callosum. This axonal damage disrupts axonal transport and the axonal cytoskeleton, potentially leading to delayed secondary pathologies like hemorrhages and brain edema, which can persist for months after TBI (12, 14).

After a primary injury in head trauma, disturbances in cerebral blood flow and brain metabolism are observed. Factors such as hypoxia, hypercapnia, hypotension, increased intracranial pressure, and hyperglycemia arise following the primary injury (see Figure 1). These undesirable factors gradually lead to secondary injury (9, 12). During this stage, lactic acid accumulates, membrane permeability increases, and edema occurs due to anaerobic glycolysis. As ATP stores are depleted, anaerobic glycolysis becomes insufficient to produce the necessary ATP, leading to dysfunction in ATP-dependent ion pumps (10).

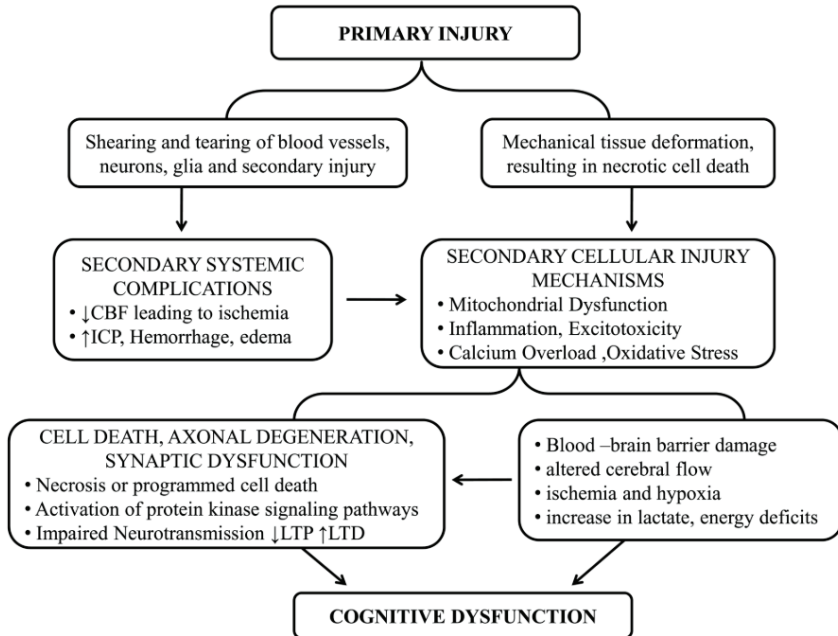


Figure 1: Pathophysiological changes in primary and secondary injury((15).

2.2. Secondary Damage

Secondary damage may occur within hours after the trauma or over a longer period, spanning days to months. This type of injury can lead to mitochondrial dysfunction, ionic imbalances, excessive neurotransmitter release, lipid peroxidation, cell membrane destruction, and neuronal death, following an ischemia-like pattern (16). Excessive release of excitatory neurotransmitters such as glutamate and aspartate can overstimulate NMDA and AMPA receptors, causing excessive excitation of the terminal membrane by activating voltage-dependent Na^+ and Ca^{2+} channels. The continuous intracellular influx of Na^+ and Ca^{2+} triggers a cascade of intracellular events leading to cell death. Simultaneously, uncontrolled chloride (Cl^-), sodium (Na^+), and calcium (Ca^{2+}) entry into the cell may result in acute neuronal swelling (15). A marked increase in intracellular calcium levels activates lipid peroxidases, proteases, and phospholipases, which elevate the concentrations of intracellular free fatty acids and free radicals (10). Activation of enzymes like intracellular translocase and endonuclease can cause necrosis and/or apoptosis by damaging the cell membrane and DNA (see Figure 1) (17).

The brain's inflammatory response to trauma is multifaceted, involving activation of central nervous system immune cells, brain infiltration by peripheral immune cells, and upregulation of inflammatory cytokines, chemokines, and reactive oxygen species (18). These endogenous inflammatory responses are initiated by the migration of monocytes, neutrophils, and lymphocytes toward the blood-brain barrier (BBB). Prostaglandins, proinflammatory cytokines, free radicals, and cell adhesion molecules are all upregulated during this process. TBI also activates astrocytes, which in turn stimulate microglial cells and brain-derived neurotrophic factors. These factors secrete proinflammatory cytokines, support axonal repair, promote cell production, and help sustain neuronal survival by preventing cell death. Additionally, astrocytes reduce glutamate excitotoxicity by regulating extracellular glutamate levels (17, 19).

In head traumas, regions such as the hippocampus, striatum, cerebellum, and pons may be damaged, which can affect neural pathways close to or distant from the cerebral cortex. This may lead to disruptions in the connectivity of corticostriatal, corticohypothalamic, corticopontocerebellar, and cerebellothalamocortical circuits. Moreover, the balance of dopaminergic, noradrenergic, histaminergic, and serotonergic systems may be altered after injury (20).

Deficits in the memory-related brain regions are among the most common neurological symptoms of TBI. The frequent damage to brain regions associated with memory following TBI suggests that memory dysfunction and TBI share common physiological processes.

3. Relationship between Memory and Traumatic Brain Injury (TBI)

Memory is indispensable for all advanced organisms. Memory formation involves a biological transformation process in which sensory, motor, and cognitive experiences are encoded in the brain for future use (21). Memory is a dynamic neural and cognitive progression characterized by three basic processes: encoding, consolidation, and retrieval. These processes occur in different regions of the brain, including the hippocampus, and traumatic brain injury (TBI) can affect each of these processes to varying degrees. The uncontrolled, typically asymmetric nature of the damage following TBI, which is not confined to a specific brain structure, suggests that each trauma will manifest with a unique pattern of loss. Memory impairments are usually graded according to the extent of the lesions caused by the brain injury. Cognitive loss after TBI also depends on the severity of the physical and mechanical forces applied to the brain (22).

In this section, the structure of memory and the effects of TBI on memory will be discussed in detail.

3.1. Basic Processes of Memory

Encoding is the process of transforming an experience into a specific neural representation, known as a memory engram. The hippocampus plays a crucial role in this process, particularly in transforming experiences into long-term memory. Encoding involves receiving information through sensory inputs and forming a neural representation of this information. The hippocampus integrates various sensory inputs and combines them along common pathways with the cortex to create a single memory trace.

Preservation refers to the durability of the engram over time. This process is essential for ensuring that experiences are not forgotten and can be recalled when needed. The storage of information in long-term memory occurs through the strengthening of neural connections and synaptic plasticity. Protein synthesis and neuronal activity are vital in this process, as the synthesis of learning and memory molecules is necessary for reinforcing synaptic connections.

Retrieval is the ability to bring the engram back to consciousness. The hippocampus is also integral to this process, enabling effective recall of memories. During retrieval, stored information is reactivated through neural activity and brought to the level of conscious awareness (21, 23).

There is evidence of similar memory processes in different brain regions. It is believed that similar computations across memory regions may work in concert, supporting various behavioral functions. For example, both the hippocampus and the dorsomedial striatum (DMS) are involved in assessing spatial navigation; the hippocampus processes data from environmental memory, while the DMS supports the use of a goal-directed motor plan within that environment. This example illustrates how different brain regions collaborate to fulfill different steps of the same task. Furthermore, it is noteworthy that various brain regions can perform similar tasks. This redundancy may serve as a backup, providing a compensatory mechanism in case of brain damage that could occur due to various circumstances (20, 23).

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3.3. Basic Types of Memory

In recent years, memory has been categorized as short-term or long-term; however, current research conceptualizes memory traces based on their time dependence, distinguishing between working memory, episodic memory, and semantic memory. Working memory is defined as the cognitive ability associated with the temporary storage, processing, and manipulation of information (24). Episodic memory is less time-dependent and is more focused on the amount of personal experience associated with the memory (25). It involves retrieving and storing information about temporally dated events and the time-space relationships between these events (e.g., “I was sitting in the garden of my house with my mother at 12:00 PM on Saturday last week”). In contrast, semantic memory pertains to retrieving and making sense of facts or events learned without personal experience (e.g., memorizing the names of cities in various countries). The transition from episodic to semantic memory is governed by a hypothetical cognitive process called consolidation (24).

3.4. Physiology of Memory

The events that occur in the brain during memory consolidation consist of two parts: synaptic consolidation and system consolidation. Synaptic consolidation refers to the changes within cells and synapses that take place within minutes after the encoding process ends. In contrast, system consolidation

involves changes in the connections of neuronal networks as a result of synaptic changes, and this process can last for years (26).

Synaptic Consolidation:

In synaptic consolidation, the coding and consolidation processes in brain regions during the acquisition of new information begin with intracellular changes. It is believed that these initial changes lead to structural modifications over time. When examining intracellular changes, one can observe alterations in glutamate receptors, secondary messenger signaling molecules, protein kinases, and changes in the activation of rapidly expressed genes known as immediate early genes (IEGs) (21,27).

The concept of long-term potentiation (LTP) emerges when defining cellular changes, as LTP is observed in many brain regions, particularly in the hippocampus. Neurons stimulated by a strong input (impulse) become capable of responding more quickly to subsequent stimuli due to protein accumulation, receptor level changes, variations in secondary messenger levels, and alterations in gene expression. LTP occurs at synapses and influences both the amount of vesicles released into the synaptic gap and the responses generated in response to stimuli. LTP leads to an increase in thickness known as post-synaptic density (PSD). This thickness consists of receptors, folded proteins, cytoskeletal proteins, adhesion proteins, and numerous signaling proteins. AMPA receptors, NMDA receptors, and glutamate receptors are among the proteins assembled to form this density. A strong input is always required for LTP to occur, but simply increasing frequency is not effective for LTP. The opposite of LTP—weakening synaptic connections and long-term suppression of synaptic activity—is referred to as long-term depression (LTD) (27,28).

System Consolidation:

Research supports the idea that during system consolidation, memory is initially stored in the hippocampus and is subsequently protected (consolidated) against potential damage by being transferred to the neocortex over time. While the hippocampus has a temporary function when encoding semantic memory, the trace theory applies to episodic memory. According to this theory, the hippocampus maintains communication with the cortex, and new connection pathways are established within neuronal networks. Each new experience leads to the formation of a new memory trace between the hippocampus and the

neocortex. This ensures that older experiences are stored more securely than newer ones (24,25). The hippocampus and cortex are the primary brain regions that sustain damage after traumatic brain injury (TBI).

3.4. Damaged Brain Regions and Memory Relationship

The magnitude of the damage to different brain regions is expected to vary depending on the type and severity of the injury. Based on this process, we can infer that memory loss can also be influenced by the severity and exposure to trauma. This section discusses post-traumatic changes in various brain units associated with memory.

Relationship of the Hippocampus with Memory and Trauma:

The hippocampus is a crucial part of a large brain network that interacts to store recent information, retrieve it, and guide actions performed during the memory process. It collects inputs from different cortical regions, which are especially necessary for episodic memory, and obtains spatial or non-spatial information about the environment through projections from the medial entorhinal cortex and the lateral entorhinal cortex, respectively (24). The relational context of episodic memory can be formed through hippocampal functions, such as unifying the elements of an experience into a detailed and integrated framework throughout space and time, and pattern separation (23). Post-traumatic brain injury (TBI) deterioration of the physiological processes of the hippocampal circuits, comprising the dentate gyrus (DG), CA3, and CA1 regions, is believed to be largely responsible for episodic memory impairments (24).

The dentate gyrus (DG), considered an important region in the processing of hippocampal memory, balances cortical inputs with similar patterns in the CA3 region (29). The DG regulates inputs and excitability to the hippocampus, acting as a filter or door guard for cortical stimuli. This filtration capability is supported by the low excitability of the primary cell type known as the granular cell. Granular cells have a very low tendency to generate action potentials due to their properties, combined with strong inhibition from various interneuron populations found in the hilus. The negative effect of TBI here is that the DG structure, which is responsible for monitoring the inhibition mechanism, becomes post-traumatically hyper-stimulated, leading to a deterioration of its filtering capabilities (24).

The CA1 region plays a prominent role in encoding episodic memories and recalling them to consciousness. In contrast to the DG's hyper-stimulating response to injury, post-traumatic CA1 region circulatory activity has been shown to be hypo-stimulated, making it harder to activate due to a high threshold. Therefore, the stimulation of the CA1 circuit decreases even if CA1 pyramidal neurons are activated after injury. This can be partly explained by changes in synaptic inputs to pyramidal cells. Studies using experimental models have shown that synaptic responses recover over time following trauma, but the synaptic strength remains suppressed. Additionally, postsynaptic responses to stimulated glutamatergic events mediated by both AMPA and NMDA receptors have been reduced. The causes of decreased CA1 circuit efficiency reflect imbalances in excitatory and inhibitory synaptic inputs (23). Moreover, even mild TBI can adversely affect the physiological processes of the hippocampal CA1 neurons through NMDA and/or muscarinic receptors, making these neurons more susceptible to secondary ischemic damage. Thus, even mild TBI can produce long-term receptor-intermediate dysfunction that is structurally undetectable without the need for recurring trauma, leading to memory loss (30).

Relationship of the Striatum with Memory and Trauma:

The striatum has traditionally been associated with stimulus-response or habit memory (31). Similar to the hippocampus, the striatum exhibits opposite relationships within the same brain region responsible for memory formation. The dorsomedial striatum (DMS) supports memory processes for flexible, goal-directed behavior (20). Although most of this evidence comes from studies in rats, it is possible to observe these differences in human neurodegenerative systems (23). After a primary cortical injury, there is local destruction of dopaminergic axons linked to the striatal dopaminergic system and disruption of signaling. The striatum serves as the main input core of the basal ganglia and receives motor, oculomotor, executive/personal, and emotional/motivational glutamatergic afferents from various cortical areas. Damage to the striatum, caused both directly and indirectly by TBI, can manifest as a variety of symptoms, including motor dysfunction, motor system memory deficits, cognitive disorders, and behavioral (emotional) changes (20).

Relationship of the Amygdala with Memory and Trauma:

The amygdala is the brain structure involved in classical conditioning that remembers important relationships between fear and reward (24). Different

areas of the amygdala function at varying levels of detail regarding stimuli and their outcomes. This variability serves as a trigger for the formation of different behavioral patterns. In particular, studies have shown that the basolateral amygdala (BLA) has a specific relationship between a stimulus and a particular outcome, while the central amygdala (CeA) supports the formation of the general organization of subsequent emotional states or behavioral processes (23). The amygdala is known to play a significant role in emotional processing. Disorders that may arise from trauma in this context, along with the pathophysiological processes affecting its functioning, are associated with emotional disturbances.

Disturbances in BLA circuits can lead to depression-like behaviors that reflect both cognitive and emotional aspects. In experimental models of depression, increases in post-TBI dendritic atrophy and neural hypertrophy have been observed, along with anhedonia, despair, and cognitive deficits dependent on the prefrontal cortex and hippocampus (32,33). Emotional learning and memory are coordinated with the cognitive aspects of depression transmitted by the BLA through projections to the prefrontal cortex and ventral hippocampus. Post-TBI disturbances in these transmission pathways can lead to deterioration in emotional memory and a tendency toward negative thoughts. Activation of BLA neurons occurs through the strengthening of glutamatergic targets that lead to excitotoxicity, which also affects the hippocampus and other brain regions (34). The BLA also inhibits dopamine release, causing various negative processes, such as decreased motivation through projections to the nucleus accumbens, a tendency toward depression, and increased sensitivity to negative stimuli in individuals with impaired emotional processing during sleep. The BLA also influences the activation of CeA neurons, and post-traumatic anxiety disorders, including emotional states such as anxiety, emerge with systemic disturbances in the CeA region of the amygdala, hippocampus, and prefrontal cortex. Changes in GABA-glutamate levels have been associated with deficiencies in emotional behavior where the amygdala is active (33,35).

Relationship of the Prefrontal Cortex with Memory and Trauma:

The prefrontal cortex (PFC), a cortical region closely connected to the hippocampus, plays a critical role in working memory (WM). WM involves the temporary storage, processing, and manipulation of information, allowing for the performance of complex tasks. WM encompasses encoding information, maintaining conscious awareness of it, and retrieving it to exercise executive control over the information. For effective management tasks in our daily lives,

control by components involved in inhibition, cognitive flexibility, and working memory is essential (36).

While WM is active, various brain regions interact with each other, such as the prefrontal cortex, basal ganglia, thalamus, cerebral cortex, and frontoparietal regions, with increased gamma-band activity noted during information preservation. Any adverse process that affects WM can influence the quality of daily life, leading to difficulties in executive functions (37). Changes in synaptic inputs in the medial prefrontal cortex following post-TBI damage, increased action potential thresholds, and decreased rates of neuron firing have been observed. In a mechanical in vitro model of TBI using cultured cortical neurons, calcium-permeable AMPA receptors in plasma membranes were upregulated, initiating intracellular secondary injury processes (24). Studies on attention and memory processes following TBI have shown that working memory remains lower in patients compared to healthy individuals (38). Animal studies have indicated that the PFC dopaminergic system plays a significant role in the neurochemical basis of WM. The depletion of local dopamine (DA) and/or norepinephrine (NE) in the PFCs of monkeys and rats through the infusion of 6-hydroxydopamine has resulted in deficiencies in spatial WM tasks (36).

3.5. Relationship between Memory and TBI by Type of Injury:

The type of injuries is a crucial parameter influencing the type and severity of memory loss. Focal injuries occasionally affect only the area of the brain where the injury occurs, while diffuse brain damage impacts many brain areas. This condition can reveal the degree of memory impairment in different brain regions, depending on the type of injury. This section discusses the relationship between memory and recurrent trauma, as well as focal and diffuse brain damage, which are two types of primary injury.

Relationship between Focal Brain Injury (Medial Temporal Lobe) and Memory:

The widespread availability of imaging systems, such as diffusion tensor imaging and MRI, offers significant advantages in detecting focal injuries in brain regions after TBI (39). The medial temporal lobe (MTL) memory system comprises the hippocampus, entorhinal cortex, parahippocampal cortex, and amygdala. Structures within the MTL are often damaged during TBI (22). Such injuries can lead to progressive atrophy in brain areas, especially the hippocampus, often thought to result from increased intracranial pressure

and hypoxia (40). Significant MTL damage is believed to be a major cause of permanent or persistent cognitive impairment (22).

Significant bilateral decreases in hippocampal volume have been observed in many individuals after focal injury, affecting both gray and white matter. Decreases in hippocampal volumes, lateral ventricular enlargement, and associated memory impairment can persist even years after the initial injury. Loss of brain volume reflects a poor prognosis for long-term cognitive impairment and memory rehabilitation. In contrast, research has shown that the volume of the amygdala increases with trauma severity and can influence brain development even ten years after TBI. Severe TBI can cause morphological changes in the structures of the temporal lobes, which are believed to be closely associated with memory impairment (22,40).

Diffuse Axonal Injury and Memory Relationship:

Diffuse axonal injury (DAI), or traumatic axonal lesions, is caused by cutting forces induced by rapid acceleration or deceleration of the brain, leading to damage to axons (41). This white matter damage causes widespread disconnections between brain regions. Common locations affected include the corona radiata, corpus callosum, inner capsule, brainstem, and thalamus, and DAI is considered a primary cause of memory problems, even after mild head trauma (35). Post-DAI memory impairment is a complex process that complicates understanding the pathology underlying the injury, which may involve multiple brain regions.

Common brain damage can often be characterized by awareness disorders associated with brain swelling due to axonal and vascular injury following sudden acceleration-deceleration of the head. In DAI, the location of axonal damage or the presence of ongoing focal lesions significantly influences the patient's prognosis (22,41).

Relationship between Recurrent Brain Damage and Memory:

Recurrent brain injuries often occur due to repeated exposure to shock or explosive pressure, particularly in individuals involved in military activities. This exposure can lead to neuropathological changes known as "chronic traumatic encephalopathy" (CTE). These changes include mild neuronal loss in the frontal, parietal, and temporal neocortex, widespread amyloid plaque distribution, rare neurofibrillary tangles, and tau-positive neurofibrillary strands in the neocortex (22).

Athletes have exhibited many signs of CTE in the developing hippocampus, cerebral cortex, basal ganglia, and cerebrospinal nuclei due to recurrent trauma, including both small and large neurofibrillary tangles and tau-positive neural strands. Post-traumatic CTE can extend beyond motor and cognitive symptoms to include emotional disorders (e.g., depression) and behavioral issues (e.g., substance addiction, inhibition deficits, aggression, paranoia) (2). It has been demonstrated that athletes and soldiers exposed to blasts may experience progressive tauopathy.

Memory problems, deficits in planning skills, and disturbances in fine motor skills have been identified. Athletes with a history of concussions have exhibited conditions such as weakened posterior contralateral negativity, poor visual information retention, and impaired visual short-term memory. As the severity and frequency of the concussions increased, deficits in visual and verbal episodic memory, naming, and word retrieval became apparent (22).

3.6. Experimental Animal Models Related to TBI and Memory

TBI animal models play a crucial role in developing potential treatments aimed at reducing or curing oxidative stress, impairments in blood-brain barrier (BBB) permeability, and various other post-TBI biochemical disorders. Each model has distinct procedures and outcomes, designed to adapt to the different circumstances under which individuals suffer from head trauma.

Animal models of TBI are classified into two main categories: open and closed head trauma models. These classifications help us understand the progression of the injury process. Marmarou and Feeney's weight-drop models are examples of closed head injury models, characterized by a rigid skull before impact. This model also leads to BBB deterioration, edema, and temporary changes in neurological conditions. Another closed head trauma model simulates explosion injuries, reflecting pressure waves from an explosive source directed at the head of an anesthetized animal using a shock tube filled with compressed gas.

In contrast, open-head injuries are applied directly to the surface of the skull through craniectomy. Lateral fluid percussion injury (LFPI) and controlled cortical impact (CCI) models are notable examples of this type of injury. The LFPI generates a fluid pressure wave directed at the exposed brain, causing focal and diffuse cortical contusions and injuries at varying severity levels. On the other hand, the CCI creates a focused injury characterized by cortical contusion using a pneumatically driven impact on the exposed cortex. Both

models replicate aspects of human TBI pathology and the cognitive deficits associated with trauma. These experiments allow for comparisons of various degrees of injury severity in humans, ultimately leading to improvements in diagnostic and treatment protocols (24, 42, 43).

In animal studies, memory and behavioral disturbances resulting from TBI can be assessed through various forms of behavioral analysis, including instrumental learning and memory, non-spatial learning and memory, emotional responses, and motor coordination. To measure these effects, several tests related to memory and learning are utilized, such as the Morris Water Maze, Barnes Maze, Radial Arm Maze, Novel Object Recognition, Open Field Test, and Forced Swim Test. Developing animal models to enhance our understanding of the memory process will significantly improve the prognosis of TBI and the development of treatment protocols (24, 42).

3.7. Potential Therapeutic Strategies to Improve Post-TBI Memory Disorder

To date, numerous animal studies have been conducted to mitigate the potential effects of TBI using various interventions, including calcium channel antagonists, steroids, glutamate agonists, NMDA receptor antagonists, oxygen free radical scavengers (antioxidants), immune system modulators (such as IL-1 β , IL-6, TNF- α , and erythropoietin), statins, progesterone, hypothermia, and neurotrophic agents like VEGF, NGF, and BDNF. Many of these interventions have shown promising results. However, it is essential to ensure and support the replication of these studies to advance to Phase III trials (3, 24, 44, 45).

Diet:

Animal model studies have demonstrated that a balanced dietary approach, particularly with branched-chain amino acids, enhances GABA synthesis from glutamate and improves the formation of fear-related memories associated with post-traumatic hippocampal function. These findings suggest that proper nutrition may yield promising outcomes in reducing trauma's effects on memory (24).

Stem Cell Applications:

The differentiation capabilities of various cell types, including bone marrow stromal cells, glia, and neurons, have been observed in both rat and human studies. When administered intravenously to post-TBI rats, bone marrow

stromal cells migrated to the injured cortex and exhibited glial (GFAP) and neuronal (NeuN) phenotypes. These cells promote neurogenesis after TBI and contribute to the formation of new proliferative cells, which is associated with improvements in neurological and motor functions. Mesenchymal stem cell (MSC) cultures reduce neuronal loss by increasing GFAP expression and ACT activity while decreasing inflammatory cytokine levels. Human MSCs have been shown to enhance neurological functions in rats with TBI. Additionally, human fetal stem cell transplantation has been reported to improve motor function and memory while reducing lesion volume and neuronal loss. Fetal stem cells can also differentiate into neurons and astrocytes in the injured hippocampus and cortex (3).

Rehabilitation:

Cognitive rehabilitation is a specialized field focused on improving and compensating for cognitive functions altered by brain damage, particularly in individuals with TBI. A cognitive rehabilitation program can assist individuals in regaining the capacity to process, interpret, and respond effectively to external information (36).

4. Conclusion

Memory impairment after TBI leads to severe decreases in quality of life and significant difficulties in daily functioning. The primary and secondary effects of TBI directly affect memory through synaptic and intracellular changes. Studies on animal models have produced promising results in the development of potential therapeutic strategies. The increased implementation of these strategies to improve post-TBI memory impairment in clinical applications, along with support for research in this area, will enable significant steps to be taken to improve the quality of life of TBI patients. Future research should continue to enhance the effectiveness of these therapeutic approaches and develop personalized treatment plans that can better respond to the individual needs of patients.

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CHAPTER X

RADIOTHERAPY AND NEUROLEARNING: EXPLORING COGNITIVE IMPACTS AND RECOVERY MECHANISMS

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1. Introduction

Radiotherapy is a critical therapeutic approach that significantly contributes to the management of brain tumors and is pivotal in enhancing patient survival outcomes. However, the effect of this therapy on neurocognitive functions has raised significant concerns in the medical community. Neurolearning, which involves the brain's ability to learn and adapt through neuroplasticity, may be negatively affected by the high-energy radiation used in treatment (1). Radiotherapy has been associated with cognitive deficits, including challenges in memory, attention, and executive functions, underscoring the necessity for a comprehensive understanding and development of mitigation strategies (2). The underlying mechanisms of these disorders involve complex interactions between radiation-induced nerve damage, inflammation, and oxidative stress, which together disrupt normal cognitive processes (3). This paper aims to elucidate the cognitive effects of radiotherapy on neurolearning and identify potential interventions to maintain or regain cognitive abilities in the affected individuals. Understanding these mechanisms allows us to develop targeted interventions to improve the well-being of brain tumor patients undergoing radiotherapy (4).

2. General Effects of Radiotherapy

2.1 Beyond the Beam: The Life-Saving Technology of Radiotherapy

Radiotherapy is a crucial treatment modality in oncology, aimed at controlling or eliminating solid tumor masses (5-6). There have been remarkable developments in the discipline of radiation oncology, and continuous innovations have increased the sensitivity of radiation application and enable the development of treatment protocols. These advancements aim to enhance the radiosensitivity of rapidly dividing cancer cells while reducing collateral damage to the neighboring healthy tissues (7-8).

The primary goal of radiotherapy is to minimize radiation exposure of normal tissues while administering the radiation dose precisely to the targeted area. Radiotherapy targets tumor cells, but nearby healthy tissues may also suffer radiation damage. Radiation may cause some side effects in the early or late periods (9-10). Normal tissues must be protected as much as possible to reduce these side effects.

2.2 Radiotherapy Unveiled: Cutting Edge Techniques in Cancer Treatment

Radiotherapy stands as a basic method in the management of oncological patients, complementing surgical interventions and various systemic treatments. Approximately 50% of cancer patients are expected to require radiotherapy at some point in their treatment journey (11). Radiotherapy works by inducing DNA damage in malignant cells that prevents them from replicating or repairing themselves. Beyond the treatment of malignant diseases, radiotherapy is also used in the management of benign conditions such as trigeminal neuralgia, pterygium, keloid scars, heterotopic ossification, acoustic schwannoma and arteriovenous malformations in the brain (12).

In their early stages, early radiotherapy techniques showed less sensitivity and offered limited data on the precise radiation doses administered to the target volumes and nearby critical structures. In this context, advances in technology have also facilitated higher levels of protection of critical organs.

The primary goal and main challenge of radiotherapy is to destroy tumors while preserving the integrity of surrounding healthy tissues and organs. This requires a meticulous balance between delivering a therapeutically effective dose to the tumor while decreasing potential injury to nearby healthy structures (13). The goal has been pursued using a variety of radiotherapy techniques that have evolved over time. Let's explain some of these methods.

2.2.1 Conformal Radiotherapy (CRT)

Rapid technological advances have enabled significant strides in radiotherapy procedures, making it possible to transition from traditional two-dimensional radiotherapy to three-dimensional conformal radiotherapy (3D CRT).

Conformal radiotherapy represents a sophisticated approach within radiation oncology, designed to administer high radiation doses specifically to a well-defined tumor area, while reducing exposure to the surrounding healthy structures. This approach uses advanced imaging and planning technologies to shape radiation beams to fit the three-dimensional (3D) tumor structure, thereby increasing the sensitivity and effectiveness of treatment (14–15).

2.2.2 Intensity Modulated Radiation Therapy (IMRT)

Intensity Modulated Radiotherapy (IMRT) represents a highly advanced version of three-dimensional conformal radiotherapy (3DCRT). Compared to traditional 3DCRT, IMRT offers two significant improvements: the ability to vary dose intensity across individual beams during radiation delivery and the use of computerized inverse planning. The modulation is achieved through the precise movement of multileaf collimators (MLCs) during the radiation process and facilitates the accumulation of the optimal dose distribution within the target region.

IMRT achieves this modulation by creating beams of various sizes, and these beams are shaped by repositioning the MLCs. MLCs are composed of thin leaves that can move independently, and these leaves are used to shape the radiation beam according to the patient's tumor. The continuous repositioning of these leaves ensures that the radiation dose is directed precisely to the target area while minimizing the exposure of surrounding healthy tissues to radiation. In other words, the use of multiple modulated beams allows well-conformed doses applied to target areas while maximizing protection of adjacent healthy tissues from radiation damage. The high sensitivity and compatibility of IMRT allows the dose to be increased to the tumor and protects normal tissues more.

IMRT can be utilized using two distinct methods. The first technique is known as segmental MLC or step and shot technique. In this technique, each beam is divided into multiple segments with different collimator leaf positions and radiation is delivered only when the leaves reach their designated positions. The cumulative effect of these segments creates a modulated intensity field. The second technique is dynamic, where radiation is delivered continuously as the

collimator leaves move. In this case, modulation is provided by changes in the speed and spacing of the leaves (16-17).

2.2.3 Volumetric Modulated Arc Therapy (VMAT)

Ongoing innovations in radiotherapy have enabled the introduction of advanced rotary-based techniques, including Volumetric Modulated Arc Therapy (VMAT) and TomoTherapy. Introduced in 2007, VMAT shares the ability to provide similarly highly conformal dose distributions with Intensity Modulated Radiotherapy (IMRT). However, VMAT distinguishes itself by including three additional changeable parameters in the radiation process.

Unlike IMRT, VMAT allows the gantry to rotate up to 360 degrees and the ability to dynamically adjust the rotation speed. It also allows changes in the displacement of the collimator leaves and the dose rate. This flexibility enables multiple beam entry angles, reducing the overall duration of radiation sessions and the number of monitor units required compared to IMRT (18-19). As a result, VMAT can increase treatment efficiency while maintaining high precision in dose delivery (20).

2.2.4 Image-Guided Radiation Therapy IGRT

Radiotherapy has relied heavily on radiological imaging techniques since its inception. Accurately creating the target volume during radiotherapy has become critically important with the emergence of advanced technologies such as three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT). Visualizing tumor tissue with precision allows higher doses to be delivered to the tumor while better sparing surrounding healthy tissues from radiation. Modern diagnostic imaging methods routinely used today include ultrasound (UZV), magnetic resonance imaging (MRI), computed tomography (CT) and positron emission tomography/computed tomography (PET/CT). Thanks to recent technological advances, some of these diagnostic tools have become more easily integrated with linear accelerators.

New technologies such as cone beam CT (CBCT) increase soft tissue contrast. Over the course of radiotherapy treatment, which usually lasts several weeks, significant changes in patient position and the size and location of target volumes can occur, both between treatment fractions and within a single fraction. Precise patient positioning is essential to ensure the accuracy and repeatability of radiation

Image-guided radiotherapy (IGRT) is critical to detect organ movements between fractions. IGRT helps identify tumor progression using imaging during

radiation therapy, thus protecting patients from unnecessary radiation exposure. IGRT is an indispensable technique in modern radiation oncology and is used in methods such as IMRT, volumetric modulated arc therapy (VMAT), stereotactic ablative radiotherapy (SABR) and particle therapy. However, not every patient is a suitable candidate for IGRT. This method is particularly indicated for tumors located close to radiosensitive organs, situations where a sharp dose gradient is required, abdominal and pelvic tumors where organ occupancy may alter anatomical configurations, or situations where dose escalation is required.

Rational use of IGRT is essential because this technique exposes patients to additional radiation of up to 0.1% to 3% of the total treatment dose (21-22-23). A careful balance must be struck between the benefits of improved targeting and the risks associated with extra radiation exposure.

2.2.5 Stereotactic Body Radiotherapy (SBRT)

Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiotherapy (SBRT), is an advanced, non-invasive treatment modality. Developed by applying the principles of gamma knife technology and stereotactic radiosurgery (SRS), used in the treatment of brain metastases, to external central nervous system tumors, the terms SBRT and SABR are used to describe the treatment of tumors outside the central nervous system. SRS refers to a method for treating lesions in the central nervous system.

SABR is known for using highly coherent, high-dose, and precise beams of radiation to treat small tumors and is performed under imaging guidance that requires extreme caution. Unlike traditional fractionated radiotherapy techniques (such as 3DCRT, IMRT, VMAT and IGRT), SABR delivers higher radiation doses within a limited number of fractions, a process known as hypofractionation.. This treatment approach allows the overall treatment time to be reduced from a few weeks to a few days (23-24).

The development of SABR technology has been facilitated using modern linear accelerators, advanced imaging modalities for real-time radiation guidance, repeatable immobilization systems, and the application of IMRT and VMAT planning techniques. These technological advances enable precise delivery of radio ablative doses to the tumor while minimizing radiation exposure and potential damage to surrounding healthy tissues (25-26).

2.2.6 Proton Therapy

Proton therapy is an advanced form of radiotherapy that uses protons instead of traditional X-rays to treat cancer. This approach allows targeting

tumors more precisely, minimizing radiation-induced damage to surrounding healthy tissues. Proton therapy has become especially important in pediatric oncology because children's developing bodies are more sensitive to radiation.

One of the key benefits of proton therapy lies in its ability to precisely target tumors with high radiation doses, thereby minimizing the potential for long-term side effects and the development of secondary cancers. This makes it an ideal treatment option for pediatric patients, especially those with various types of cancer, such as brain tumors and sarcomas. Proton therapy is particularly crucial for younger patients due to their extended life expectancy, as research shows it is associated with lower rates of secondary cancer compared to conventional photon therapy.

Proton therapy represents a significant advance in the field of pediatric oncology and offers a targeted and less harmful treatment option. Thanks to this innovative approach, the chance of successful treatment increases, and the long-term health and well-being of survivors improves (27-28).

2.3 Innovative Radiotherapy Techniques in Brain Tumor Treatment

In treating brain tumors, radiotherapy holds a key position. It is a method that aims to protect surrounding healthy tissues while delivering radiation doses precisely and effectively. Modern radiotherapy techniques offer new innovations in brain tumor management.

One of the most important techniques is known as Intensity Modulated Radiation Therapy (IMRT). IMRT modulates the radiation beams, providing different intensities in the treatment area. This technique ensures that the radiation is delivered to the tumor in the most appropriate dose and protects the adjacent healthy tissues (29). Research indicates that IMRT can lessen toxicity and enhance the quality of life for patients receiving treatment for tumors. (30).

Another innovative approach is called Stereotactic Radiosurgery (SRS). SRS targets small brain tumors with submillimeter precision using very highly focused beams radiation. SRS, usually given in a single session, is effective in treating of metastatic brain lesions and some benign tumors. Technologies such as Gamma Knife and CyberKnife offer non-invasive treatment options that reduce patient recovery time and hospital stay (31).

Volumetric Modulated Arc Therapy (VMAT) is another innovative method in radiotherapy. VMAT involves continuously rotating the linear accelerator around the patient, allowing to simultaneously adjust the configuration and

strength of the radiation beam. This technique provides superior dose compliance and treatment efficiency with shorter treatment times compared to IMRT (18).

As a novel treatment method, proton therapy offers unique advantages for brain tumor management. Proton therapy uses charged particles and release their maximum energy at a certain depth, sparing normal tissues around the tumor. This feature makes proton therapy especially important for pediatric patients and tumors located near critical structures (32).

TomoTherapy is a form of radiotherapy that combines computed tomography (CT) and intensity modulated radiation therapy (IMRT). This method provides continuous imaging and precise dose delivery, which is critical in the management of complex brain tumors. Clinical studies have shown that TomoTherapy provides excellent tumor control and minimizes neurocognitive side effects by reducing exposure to surrounding healthy brain tissue. This characteristic makes it both a sensitive and efficient radiotherapy option for brain tumors (33-34).

These innovative radiotherapy techniques represent important advances in treating brain tumors, offering effective and less invasive options. Ongoing research and technological advances promise better outcomes for patients in the future.

3. Brain Neuroplasticity and Neurolearning

3.1 Brain Structure and Function

The human brain is a complex organ consisting of many structures and playing important roles in various cognitive functions and physiological processes. The brain is divided into several main regions such as the cerebrum, the cerebellum and the brainstem (35-36).

The cerebrum is the largest part that governs most brain functions. It is responsible for higher-level brain functions such as thought, memory, emotion and sensory processing. It is divided into two hemispheres, and each hemisphere controls the opposite side of the body. The cerebral cortex, the outer layer of the cerebrum, is divided into four lobes: frontal, parietal, temporal and occipital. The frontal lobe plays a role in executive functions, decision making and motor control. The parietal lobe processes sensory information such as temperature, touch and pain. The temporal lobe is important for auditory processing and memory formation. The occipital lobe is related to visual processing (35-36-37).

Found at the rear of the brain, the cerebellum is vital for regulating motor functions, coordination, and balance. It integrates sensory input and refines motor activities, enabling smooth and precise movements. Minor brain damage can cause ataxia, which is a lack of coordination and difficulty maintaining balance (36-38).

The brainstem links the brain to the spinal cord and is composed of three sections: the pons, midbrain and medulla oblongata. It regulates essential functions like breathing, heart rate and blood pressure. Additionally, the brainstem facilitates communication between the brain and the rest of the body. (35-36).

In addition, there are important structures deep in the brain such as the thalamus, hypothalamus and limbic system. The thalamus channels sensory and motor signals to their designated regions in the cerebral cortex. The hypothalamus regulates homeostasis by controlling hunger, body temperature, thirst, and circadian rhythms. The limbic system is essential for emotion, behavior and long-term memory formation. It includes the hippocampus, amygdala and other structures (37-39-40).

Neuroplasticity is a key feature of the brain for restructuring, increasing its ability to form new nerve connections, for learning, memory, and recovery after injury. This feature is important for cognitive development and acquisition of new skills throughout life (35-41).

We said that the brain has a complex structure. Understanding this structure and being able to describe its function is important in advancing medical science and developing treatments for neurological disorders. Research in neuroscience continues to reveal the secrets of this extraordinary organ on our thinking, feeling, and interaction with the world (35-36-39).

3.2 Neuroplasticity, Neurolearning and the Impact of Radiotherapy on These Processes

Neuroplasticity is the name given to the brain's capacity to reorganize itself by creating new nerve connections throughout life. This ability allows the brain to compensate against injury and disease and to adjust its activities in response to new situations or environmental changes.

Neurolearning refers to the brain's ability to learn and acquire new skills through the formation of new neural connections. The formation of new neural connections forms the basis for learning. Neurolearning and neuroplasticity are closely interconnected processes. Evidence suggests that engaging in varied

environments and learning activities can lead to notable structural alterations in the brain.

3.2.1 Mechanisms of Neuroplasticity and Neurolearning

Neuroplasticity works through two main mechanisms: synaptic plasticity and structural plasticity. Synaptic plasticity refers to changes in the strength of connections between neurons. The term structural plasticity describes the brain's ability to modify its physical structure. These processes are facilitated by neurogenesis and synaptogenesis.

Neurolearning, like neuroplasticity, is related to synaptic plasticity and structural plasticity. Synaptic plasticity is related to changing the strength of connections between neurons. It occurs by modulation of chemical and electrical transmission in synapses. Structural plasticity is the physical changes that occur in the dendrites and axons of neurons. This could be due to the creation of new synapses or the enhancement of existing ones. (42).

A study by Merzenich et al. (1984) emphasized the adaptability of the brain by showing that the sensory cortex can reorganized itself after partial nerve damage in adult monkeys (43). Another study further detailed that experiences such as learning and environmental enrichment can lead to significant structural changes in the brain (44).

3.2.2 The Brain's Self-Repair Abilities

The brain has the ability to repair itself. Thanks to this ability, it can regenerate itself after various neural damages such as stroke or traumatic brain injury. After injury, the brain undergoes several repair processes: redirection of nerve pathways, sprouting of new dendrites, and reorganization of cortical maps.

Cramer et al. (2011) reviewed post-stroke recovery mechanisms and emphasized the role of neuroplasticity in functional recovery. They stated that intensive rehabilitation can promote neuroplastic changes and improve motor skills (45).

3.2.3 Effect of Radiotherapy on Neuroplasticity and Neurolearning

Radiotherapy, a common treatment for brain tumors, can significantly affect neuroplasticity and neurolearning. Although effective in controlling tumor growth, radiotherapy can also damage healthy brain tissue, leading to cognitive deficits and impaired neuroplasticity and neurolearning. This

reduction in neurogenesis affects the brain's ability to form new connections. This is especially true of processes such as neurogenesis, where new neurons are formed in the hippocampus, an area crucial for learning and memory.

The extent of the radiotherapy effect is influenced by several factors, with the most significant being the radiation dose administered, the fractionation scheme, the volume of the brain exposed, and the irradiation methods used.

It is possible that radiation-induced neuroinflammation may lead to neuronal damage and disruption of neurogenesis. Monje et al. (2003) highlighted in a study on mice that radiation diminished hippocampus neurogenesis, essential for learning and memory (46). This suggests that radiation may negatively affect the brain's capacity to form new neural connections.

Research further shows that radiotherapy might affect the integrity of the blood-brain barrier, making it more permeable and potentially causing damage to the nervous system. A study by Greene-Schloesser et al. (2012) emphasized that radiotherapy-induced oxidative stress and inflammation contribute to cognitive decline (47).

3.2.4 Strategies to Reduce Radiotherapy-Induced Damage

Different strategies are under investigation to minimize the impact of radiotherapy on neuroplasticity and cognitive learning. Studies are ongoing on neuroprotective agents such as antioxidants and anti-inflammatory drugs for their potential to preserve cognitive function and increase neuroplasticity after radiotherapy.

Interestingly, cognitive rehabilitation and physical exercise promote neuroplasticity and cognitive recovery. Chen et al. (2015) demonstrated that physical exercise could increase hippocampal neurogenesis and improve cognitive function in mice exposed to radiation (48).

Additionally, advanced radiotherapy techniques such as proton therapy and stereotactic radiosurgery enable more precise targeting of tumors, minimizing the exposure of healthy brain tissue to radiation and reducing the risk of cognitive side effects.

Neuroplasticity and neurolearning are essential for cognitive development, adaptation, and the brain's healing process after injury. Although necessary to treat brain tumors, radiotherapy has the disadvantage of potentially damaging healthy brain tissue. Understanding the effect of radiotherapy on neuroplasticity and neurolearning is important for developing strategies to preserve brain function in patients undergoing radiation therapy. Ongoing work on neuroprotective agents,

cognitive rehabilitation, and advanced radiotherapy techniques is exciting to improve outcomes and preserve the brain's extraordinary ability to adapt.

4. The Impact of Radiotherapy on Learning and the Hippocampus

The hippocampus, located in the ventromedial area of the temporal lobes, is a bilateral structure adjacent to the temporal horn of the lateral ventricle. Its main functions include facilitating learning, enhancing memory, and promoting developmental recombination. It also plays a role in decoding new memories (49). Bilateral and single monetary damage to the hippocampus can alter learning and memory formation (50). Therefore, the irradiation of the hippocampus during radiotherapy may significantly affect cognitive processes.

An important study found that exposure of the hippocampus to radiotherapy impairs cognitive functions. In the study assessing the influence of radiation on the neurogenic niche, it was noted that cognitive functions significantly decreased post-radiation (51).

In radiotherapy, particularly in high-dose brain irradiation, it is clear that one of the most crucial factors is the protection of the hippocampus. The amount of radiation dose the hippocampus is exposed to is especially important in young individuals and children. The relevance of hippocampal damage to cognitive dysfunction is significant. However, standardized protocols to predict hippocampal damage and the appropriate dose range for its restriction have not yet been developed. (52).

Although modern local RT techniques have improved tumor control, Whole Brain Radiotherapy (WBRT) -induced cognitive dysfunctions have turned into a concern that cannot be dismissed in current WBRT clinical practice. It is especially important for patients with high survival. There is a significant dose-effect relationship between cognitive decline after RT and the dose received in the hippocampus (53).

Today, radiotherapy aims not only to control tumors and minimize the risk of recurrence but also to maximize patients' quality of life post-treatment. Therefore, patients receiving radiotherapy should have hippocampus protection with appropriate RT techniques.

In studies, children who received radiotherapy were evaluated with neurocognitive studies for up to 5 years after treatment. It has been shown that average doses of 45 Gray (Gy) or higher applied to the left temporal lobes cause significant long-term decreases in IQ (54,55).

Radiation-induced neurological damage is a growing concern for patients who have received radiotherapy for brain cancer. Although survival rates are increasing for many tumors, preserving quality of life remains critically important. Although extensive research has explored the harmful effects of radiation on critical structures like the optic chiasm, brainstem, and white matter, these effects remain poorly understood (56). There are studies showing that the harmful effects of radiation cause neuroinflammation, demyelination and vascular damage, and this may cause a general dysfunction in the form of cognitive decline. Progressive cognitive decline is observed in 50–90% of patients receiving cranial radiotherapy. Radiation-induced cognitive decline reduces quality of life by reducing functional independence and general performance status (1).

WBRT causes a decrease in quality of life and an increased risk of cognitive decline (57). Stereotactic radiosurgery (SRS) is known to provide better permanent local tumor control than WBRT. This has led to less use of WBRT in practice (58). Studies show that patients treated with WBRT have greater cognitive impairment than patients treated using advanced technological treatment methods such as SRS or brachytherapy (59).

Brown et al. 2016 reported that patients with 1–3 brain metastases who underwent SRS alone had less cognitive impairment at 3 months compared to patients who received SRS and WBRT together (60).

In a clinical study published by Palmer et al in 2022, they evaluated long-term outcomes in patients with 1–4 brain metastases who underwent SRS alone or WBRT alone. The study shows that WBRT patients experienced greater cognitive decline than SRS patients at all times assessed. They also added that WBRT patients presented greater intracranial control at one year than SRS patients (61). There are also studies concluding that WBRT + SRS can keep malignancy away for longer. Sustained cognitive decline has been seen in long-term survivors treated with WBRT, and it has been suggested that WBRT may lead to worsening cognitive decline in their patients (62).

In a study conducted by Armstrong et al., patients with low-grade brain tumors were compared with those who received RT and those who did not. A decrease in semantic memory was observed in patients receiving RT (63). This difference in memory may arise from the hippocampus's sensitivity to radiation (64).

Studies investigating cognitive functions in low-grade glial tumors show that cognitive losses are often present in these patients. The cause is the tumor

and treatment with antiepileptics. Very few cases of cognitive decline can be attributed to RT. Those due to radiation are those who received WBRT or were treated with large fractions (65, 66, 67, 68, 69).

Cognitive function losses are multifactorial in high-grade glial tumors. Radiation has little contribution. To prevent cognitive function losses due to radiotherapy, whole brain irradiation should be avoided (70).

In brief, many factors affect cognitive functions, including tumor, anxiety, depression, surgery, chemotherapy, antiepileptics, steroids, immunotherapy, hormone therapy, anemia, hypoxia and paraneoplastic syndromes. To separate the effects of radiation, the effects of low-dose radiation and high-dose radiation on cognitive functions can be examined. In addition, not exceeding the radiation tolerance doses of brain areas related to cognitive functions will improve the quality of life of patients.

5. Conclusion

Radiotherapy is a cornerstone of treating primary and metastatic brain tumors, providing significant benefits for tumor control and patient survival. However, the cognitive side effects of radiotherapy, particularly in the domains of attention, memory, and executive function, present a substantial challenge. The pathophysiological mechanisms underlying these cognitive impairments include direct neuronal damage, vascular injury, neuroinflammation, and disruption of neurogenesis. These factors highlight the complexity of radiotherapy-induced cognitive dysfunction.

Understanding the intricate relationship between brain structure, neuroplasticity, and cognitive function is crucial for developing effective neuroprotective strategies. Innovations in pharmacological interventions, advanced radiotherapy techniques, and cognitive rehabilitation offer promising avenues for preserving cognitive function and enhancing the quality of life for patients undergoing treatment.

Ongoing research and clinical trials are essential for elucidating the mechanisms of radiotherapy-induced cognitive dysfunction and developing targeted interventions to mitigate these effects. By integrating knowledge from neuroscience, oncology, and cognitive rehabilitation, healthcare professionals can better assist patients in managing the cognitive challenges associated with radiotherapy and enhance their overall well-being.

In conclusion, while radiotherapy is a crucial element in combating brain tumors, it is essential to weigh its therapeutic benefits against the potential

cognitive risks. Continued efforts to refine neuroprotective strategies and personalized treatment approaches will be instrumental in achieving this balance, ultimately improving patient outcomes and quality of life.

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CHAPTER XI

THE ROLE OF FMRI IN THE STUDY OF LEARNING AND MEMORY PROCESSES

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1. Introduction

Functional magnetic resonance imaging (fMRI) is a revolutionary tool for studying brain function. Its ability to measure brain activity at high spatial resolution has made this technology indispensable in cognitive neuroscience research and clinical applications. In this chapter, the historical development of fMRI, its use in the study of neurodegenerative diseases and learning processes, model-based fMRI approaches, and potential future applications will be presented in detail.

2. Overview of Functional Magnetic Resonance Imaging (fMRI)

fMRI uses blood flow changes to measure activity in different regions of the brain. This method is based on the magnetic differences between oxygenated and unoxygenated hemoglobin in a magnetic field (1). When brain activity increases, blood flow and oxygenation levels in the regions of interest also increase, which can be detected by fMRI.

2.1. High Field Strength MRI Systems

The use of 7 Tesla and above MRI systems has become widespread. These systems provide higher spatial and temporal resolution (2).

2.2. Multispectral fMRI

This method allows multiple brain slices to be imaged simultaneously. Significantly increases temporal resolution (3).

2.3. Resting State fMRI

It has become an important method for analysing functional connections in the brain. It is used to understand neurological and psychiatric disorders(4).

2.4. Machine Learning and fMRI

The use of machine learning techniques in data analysis and interpretation has increased. In particular, multi-pattern analysis (MVPA) has found widespread use (5).

2.5. Real-Time fMRI

It has started to be used in neurofeedback applications. It plays a role in the development of brain-computer interfaces (6).

2.6. Multimodality Imaging

The use of fMRI in combination with other techniques such as EEG and MEG has become widespread. This approach allows a more comprehensive understanding of brain activity (7).

2.7. Advanced Statistical Methods

Bayesian approaches and other advanced statistical methods are becoming more frequently used in fMRI data analysis (8).

2.8. Long-term fMRI Studies

Long-term fMRI studies have begun to be conducted to examine brain development and aging processes (9).

2.9. Connectome Mapping

The use of fMRI to create detailed maps of brain connections has increased. The Human Connectome Project is an important initiative in this field (10).

2.10. Ethical Issues and Data Sharing

There is a growing awareness of the sharing and ethical use of fMRI data. The creation and sharing of large data sets has become widespread (11).

3. fMRI in Neurodegenerative Disease Research

3.1. The Importance of fMRI in the Study of Alzheimer's Disease

Alzheimer's disease (AD) is a common neurodegenerative disorder that leads to severe impairments in memory and other cognitive functions. Early diagnosis of AD and monitoring of disease progression is critical to improve the effectiveness of treatment strategies. fMRI is an important tool in this process. In particular, changes in activity in brain regions such as the hippocampus and neocortex can be observed during the encoding of new information (12). Decreases in hippocampal activity are evident in the early stages of Alzheimer's disease and correlate strongly with clinical measures of memory (13). This correlation suggests that fMRI plays an important role in the diagnosis of the disease.

3.2. Changes in Hippocampal and Neocortical Activation

In the early stages of AD, decreased activity is observed in hippocampal and neocortical regions during learning and recall of new information (12). These changes are associated with the accumulation of beta-amyloid plaques and tau proteins in brain tissue. By precisely measuring changes in activity in these regions, fMRI can be utilized for early diagnosis of the disease (14).

3.3. Correlation with Clinical Memory Measures

When fMRI is combined with clinical memory tests, it becomes a powerful tool for diagnosing Alzheimer's disease (AD) and monitoring the disease's progression. For instance, in fMRI studies, decreases in hippocampal activity during episodic memory tasks correlate with performance decrements observed in clinical memory tests (13).

3.4. Using fMRI in Clinical Studies

In clinical research, fMRI is used to monitor treatment responses and evaluate treatment efficacy. By visualizing changes in brain activity before and after treatment, fMRI allows for the objective measurement of responses to new pharmacological therapies (15).

3.5 Monitoring Treatment Responses

fMRI can be used to evaluate the effects of pharmacologic agents on the brain in the treatment of AD. For example, the effects of drugs such as

acetylcholinesterase inhibitors on hippocampal and neocortical activity can be monitored by fMRI and thus information about treatment efficacy can be obtained (16).

4. Advanced Imaging Techniques in Learning Studies

4.1. Introduction to Arterial Spin Labeled (ASL) Perfusion Imaging

Arterial spin-labeled (ASL) perfusion imaging is an advanced fMRI technique that directly measures cerebral blood flow. ASL quantitatively assesses blood flow in brain tissue, providing more precise measurements of brain activity compared to conventional BOLD fMRI (Detre et al., 1992). This technique offers significant advantages, particularly in the study of learning and memory processes (17).

4.2. Principles and Practices of ASL

ASL labels water protons in the magnetic field, allowing them to reach the brain tissue. The labeled water protons join the blood flow and reach the brain tissue, where they cause changes in the magnetic resonance signal. These changes are evaluated as quantitative measurements of blood flow (18).

4.3. Advantages over Traditional Imaging Techniques

ASL offers several advantages over conventional BOLD fMRI. In particular, ASL enables quantitative assessment of brain activity, as it provides a direct measurement of cerebral blood flow. Furthermore, ASL can make precise measurements even at low task frequencies, allowing for a more detailed examination of learning and memory processes (17).

4.4. Case Studies: Learning Processes and ASL

The application of ASL to learning processes helps us understand brain activity associated with various cognitive tasks. For example, blood flow changes in the premotor cortex and inferior parietal lobe during a serial response time task correlate with performance improvements (19). Such studies provide important insights into the neurophysiological basis of learning (20).

4.5. Serial Response Time Task Example

The serial response time task is a cognitive task commonly used to study learning and motor control processes. During this task, participants are asked

to make responses that follow a specific pattern. In studies using ASL, blood flow changes in the premotor cortex and inferior parietal lobe were observed during this task and changes were correlated with improvements in task performance (19).

4.6. Blood Flow Changes in the Premotor Cortex and Inferior Parietal Lobes

In studies using ASL, blood flow changes in the premotor cortex and inferior parietal lobes were observed during a serial response time task. These changes correlated with improvements in participants' task performance. These findings reveal the critical role of the premotor cortex and inferior parietal lobe in learning and motor control processes (20).

5. Model-Based fMRI in Cognitive Processes

5.1. Explaining Model-Based fMRI

Model-based fMRI allows for a deeper understanding of cognitive processes. This approach involves combining computational models with fMRI data, thus making it possible to more precisely identify brain regions associated with specific cognitive processes (21). This technique is particularly useful in the study of complex cognitive functions such as reward learning and decision-making processes (22).

5.2. Combining Computational Models with fMRI Data

By combining computational models with fMRI data, model-based fMRI enables more precise identification of brain regions associated with specific cognitive processes. This approach helps us to better understand the neurophysiological underpinnings of cognitive processes and allows us to make more precise measurements of brain activity (21).

5.3. Identification of Brain Regions Associated with Specific Cognitive Processes

Model-based fMRI is particularly useful in the study of complex cognitive functions such as reward learning and decision-making processes. This technique allows us to gain a deeper understanding of the neurophysiological underpinnings of cognitive processes and more precisely identifies brain regions associated with specific cognitive processes (22).

5.4. Reward Learning and Decision Making Applications

Model-based fMRI is an important tool in understanding reward learning and decision-making processes. This technique is used to map cognitive mechanisms and related brain regions (23). For example, interactions between the striatum and prefrontal cortex are associated with reward expectancy and decision-making processes (24). Such studies provide valuable insights in the field of cognitive neuroscience and help us understand the neurological underpinnings of human behavior.

5.5. Case Studies and Key Findings

Case studies using model-based fMRI have provided important insights into reward learning and decision-making processes. For example, one study examined how monetary rewards to participants affected activity in the striatum and prefrontal cortex and found that changes in activity in these regions were associated with reward expectancy and decision-making processes (23).

5.6. Implications for Understanding Cognitive Mechanisms

Such studies help us understand the neurophysiological underpinnings of reward learning and decision-making processes. Interactions between the striatum and prefrontal cortex are associated with reward anticipation and decision-making processes, and changes in activity in these regions reflect the motivational value of reward and decision-making processes (24).

6. Future Directions and Clinical Applications

6.1. The Potential of fMRI in the Development of Novel Therapeutic Approaches

fMRI plays a critical role in the development of new therapeutic approaches for the early diagnosis and treatment of neurodegenerative diseases. This technology can be used to develop treatment strategies tailored to the individual course of the disease, especially in personalized medicine applications (25). Early diagnosis is vital to slow disease progression and improve quality of life (26).

6.2. Early Detection and Intervention Strategies

fMRI is an important tool in the early detection of neurodegenerative diseases and in the development of intervention strategies. By detecting

early changes in the brain, early interventions can be planned to slow disease progression. This is critical in improving patients' quality of life and slowing disease progression (26).

Personalized Medicine in Neurodegenerative Diseases

Personalized medicine involves determining treatment strategies based on the individual biological and genetic characteristics of patients. fMRI is an important tool in developing treatment strategies appropriate to the individual course of the disease. For example, brain activity data obtained with fMRI can be used to monitor patients' responses to treatment and optimize treatment strategies (25).

6.3. Emerging Technologies and Methods

fMRI technology is constantly evolving and its integration with other neuroimaging techniques is increasing. In particular, the combination with techniques such as magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) allows for a more comprehensive assessment of brain function (27). Furthermore, artificial intelligence and machine learning methods in data analysis and interpretation increases the accuracy and applicability of fMRI (28).

6.4. Integration with Other Neuroimaging Techniques

When fMRI is used in combination with other neuroimaging techniques such as MRS and PET, it provides a more comprehensive and detailed assessment of brain function. This integration allows us to study different aspects of brain activity and gain a better understanding of neurophysiological basis of cognitive processes (27).

1. fMRI and EEG (Electroencephalography) Integration:

Basic Principle: Combines the high spatial resolution of fMRI with the high temporal resolution of EEG.

Advantages: Combines millisecond-level temporal information with millimeter-level spatial information. Determines both rapid changes and precise location of neural activity.

Challenges: Elimination of artefacts in EEG signals within the MRI scanner. Development of data fusion and simultaneous analysis methods.

Application Areas: Localisation of epilepsy foci. Sleep studies. Detailed examination of cognitive processes (7).

2. fMRI and MEG (Magnetoencephalography) Integration:

Basic Principle: Combines the high temporal resolution of MEG with the high spatial resolution of fMRI.

Advantages: Requires less head modelling than EEG. It is advantageous in auditory studies due to its silent operation.

Challenges: High cost of MEG equipment. Inability to collect MEG and fMRI data simultaneously (usually performed in separate sessions).

Application Areas: Language processing studies. Sensorimotor integration research (29).

3. fMRI and PET (Positron Emission Tomography) Integration:

Basic Principle: Combines the high temporal and spatial resolution of fMRI with the molecular and metabolic information of PET.

Advantages: Displays both haemodynamic response and specific molecular processes.

Provides information on neurotransmitter activity.

Challenges: Radiation exposure of PET. High cost and complex logistical requirements.

Application Areas: Investigation of neurodegenerative diseases (e.g. Alzheimer's). Drug development and pharmacokinetic studies (30).

4. fMRI and NIRS (Near Infrared Spectroscopy) Integration:

Basic Principle: Combines the whole brain coverage of fMRI with the portability and low cost of NIRS.

Advantages: Allows measurement of brain activity in natural settings. Suitable for studies on children and infants.

Challenges: Limited depth penetration of NIRS. Data fusion and interpretation difficulties.

Application Areas: Developmental neuroscience studies. Social interaction and communication research (31).

5. Multimodal Integration and Future Trends:

Data Fusion Techniques: The use of machine learning and artificial intelligence algorithms is increasing.

Real-time Multimodal Imaging: New hardware and software solutions are being developed for the simultaneous use of multiple techniques.

Big Data Approaches: Integration and analysis of large data sets from different modalities is gaining importance.

Personalised Medicine Applications: Multimodal imaging allows a better understanding of individual brain functions and the development of personalised treatment strategies (32).

6.5. Advances in Data Analysis and Interpretation

The use of artificial intelligence and machine learning methods in fMRI data analysis and interpretation increases the accuracy and applicability of this technology. These methods provide powerful tools for analyzing large and complex data sets, allowing us to make more precise and accurate measurements of brain activity (28).

7. Conclusion

In this chapter, we discuss how fMRI technology is being used to study learning and memory processes and the key findings in this field. fMRI is an indispensable tool in understanding and treating neurodegenerative diseases, studying learning processes and exploring cognitive mechanisms. In the future, further development of fMRI and its integration with other neuroimaging techniques will increase the depth and accuracy of research in cognitive neuroscience.

fMRI has become a crucial tool in the investigation of learning and memory processes, particularly within the field of cognitive neuroscience. Its application has facilitated advances in understanding neural mechanisms and provided valuable insights into neurodegenerative diseases. This technique has revealed the complex interactions between different brain regions and networks, which is crucial for understanding learning and memory at multiple levels, including the fundamental processes of encoding and retrieval. The field is poised for further advancement. If the development of fMRI technology and integration with other neuroimaging techniques and analytical approaches continues, our understanding of the neural mechanisms involved in cognition will continue to deepen. The future of fMRI in the field of learning and memory research lies in its potential to provide more precise and natural measurements of brain function, facilitate early diagnosis of disease, and personalize healthcare. Its applications in the field of cognitive modelling are particularly noteworthy in the

field of medicine. The evolving methodology and analytical techniques of fMRI will undoubtedly have a significant impact on the development of cognitive neuroscience research. Its capacity to enhance both the depth and accuracy of our understanding of human cognition will facilitate the development of novel therapeutic approaches for cognitive disorders.

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CHAPTER XII

NANONEUROTECHNOLOGY: NANOSCIENCE IN LEARNING AND MEMORY

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1. Introduction

Nanomedicine is an emerging branch of medicine that uses nanobiotechnology tools such as nanoparticles and nanopharmaceuticals to prevent, diagnose, treat and monitor diseases. Nanotechnology is a rapidly developing science that has the potential to revolutionize many fields, from biomedical research to materials science. Particularly in neuroscience, nanotechnology-based approaches are of great interest in better understanding the mechanisms of learning and memory and in treating disorders in these areas. Precise interventions at the molecular level are needed to understand the functions of a complex organ such as the brain and to treat diseases that affect these functions. Nanoparticles offer unique properties in this regard and have become promising tools in neuroscience thanks to their ability to interact with brain cells, cross the blood-brain barrier and deliver therapeutic agents directly to target sites. In the future, nanotechnology will bring us one step closer to precision therapy. In other words, we will be able to deliver the right dose, at the right time, in the right place, or achieve maximum effect with minimal damage to adjacent tissue. Compared to conventional therapeutic drugs, nanomedicines are expected to be superior as they will provide higher drug solubility and availability, longer retention time, selective targeting, more effective treatments

and reduced side effects. Nanomedicines will enable us to overcome the major disadvantages of classical drugs (1,2).

Brain diseases and neurological disorders are very common among our population. It is estimated that around 1.5 billion people worldwide suffer from brain disorders. Learning and memory are complex processes that rely on the structural and functional plasticity of the brain. Synaptic plasticity is at the heart of these processes and occurs when connections between brain cells are strengthened or weakened. However, factors such as neurodegenerative diseases, trauma or aging can cause these functions to deteriorate. Nanotechnology offers new and effective approaches to prevent or treat these impairments. In particular, targeted drug delivery systems, neuron protection strategies and neurogenesis-promoting technologies developed through nanoparticles in the treatment of diseases that directly affect learning and memory, such as Alzheimer's and Parkinson's disease. At the same time, the design and development of successful therapies is complicated by the presence of the blood-brain barrier (BBB). This often leads to failures in clinical trials. Further development of nanotechnology is thought to be beneficial for the treatment of brain diseases as it will allow non-invasive, targeted delivery of drugs across the BBB without altering their properties.

1.1. Nanotechnology and Therapeutic Agents

Nanotechnology is a powerful tool with the potential to revolutionize healthcare. Nanoparticles and nanotechnological therapeutic agents offer high sensitivity, efficacy and safety in the diagnosis and treatment of diseases. These innovative technologies have attracted the attention of researchers and studies on the development of more personalized and effective treatment methods in the field of health have gained momentum (3,4).

Nanotechnology is a branch of science and engineering that involves the manipulation and control of materials at the atomic and molecular level. It is a field that studies the physical, chemical and biological properties of materials in sizes ranging from 1 to 1000 nanometers, and at these scales, materials gain new functional properties. Nanotechnology has the potential to revolutionize health, electronics, energy, environment and many other fields. The use of nanotechnology in health offers major innovations in the diagnosis, treatment and prevention of diseases (5). By designing controlled drug delivery systems with nanotechnology, it helps to maintain optimal treatment levels by providing controlled and timed release of drugs. In addition, by binding targeted agents

to nanoparticles, drugs are targeted to specific diseased cells or tissues in the body (6,7) . Thus, targeted therapy increases the efficacy of the drug while minimizing the side effects of the drug. Nanotechnological tools can be developed to provide early diagnosis of diseases with high-precision imaging and sensor systems. Nanoparticles are used as contrast agents in techniques such as magnetic resonance imaging (MRI) and position emission tomography (PET) and fluorescence imaging. Nanoparticles used in techniques such as MRI and PET provide clearer and more detailed visualization of diseases. Nanoparticles can be used for both diagnostic and therapeutic purposes at the same time. These “theranostic” agents can be used for both diagnosis and treatment of disease.

Particles with a diameter between 10-1000 nm are called nanoparticles. Nanoparticles can adsorb many drugs due to their small size and porous structure. They are used as targeted delivery systems for the transport of small and large molecules by altering their pharmacodynamic and pharmacokinetic properties (8,9). Nanoparticles have been researched and formulated for various useful purposes such as drug delivery, tissue targeting, cancer treatment, diagnostic and imaging agent purpose. Therapeutic agents are chemical or biological substances used for the treatment, management or prevention of diseases. These agents can be in various forms such as drugs, biological substances (antibodies, gene therapies), small molecules and nanoparticles. Effective targeting and controlled release of therapeutic agents increases treatment efficacy while minimizing side effects. Hydrophobic drugs are known to exhibit several advantages, such as increased solubility, increased concentration of drug transport at the tumor site and reduced immunogenicity.

1.2. Importance of Nanoparticles in Research on Learning and Memory

Learning and memory rely on dynamic processes of the brain, such as synaptic plasticity and neurogenesis. Synaptic plasticity is the change in the strength and efficiency of synapses, the connections between neurons (10–13). Neurogenesis refers to the formation of new neurons. These processes are the cornerstones of learning and memory formation. Nanotechnology offers innovative ways to target and modulate these processes. Nanoparticles can positively influence synaptic plasticity and neurogenesis by increasing the targeting and bioavailability of drugs to brain tissue. For example, nanotechnological therapeutic agents can be used in the treatment of neurodegenerative diseases such as Alzheimer’s and Parkinson’s, memory and learning disorders. Furthermore, these agents also offer potential treatment strategies in conditions such as traumatic brain injuries

and learning disorders (14–16). The effects of nanotechnological therapeutic agents on learning and memory are being intensively investigated in both animal models and human clinical trials. Nanotechnology offers innovative approaches for targeting and enhancing the efficacy of treatments, while therapeutic agents can positively contribute to learning and memory processes by modulating synaptic plasticity and neurogenesis. This field offers a broad perspective for future research and clinical applications.

2. Neuro-Nanotechnology: A Revolutionary Approach to Neurological Disorders

Neuro-nanotechnology is an innovative multidisciplinary science that deals with the application and utilization of nanotechnology on neurological systems, aiming to develop advanced diagnostic and therapeutic strategies for neurological conditions. This field involves developing nanoscale materials and devices to understand, diagnose and treat the functions of the nervous system. By manipulating materials at near-atomic scales, researchers create nanostructures that can interact with neural circuits and aim to control and repair damaged neural pathways. This approach is critical in the treatment of various neurological disorders. Neuronanotechnology uses nanotechnological tools to study and manipulate neuronal structures such as nerve cells, synapses and neural networks. This technology is used to understand the function of nerve cells and provide innovative solutions for the diagnosis and treatment of neurological diseases. The main goal of neuronanotechnology is to better understand, diagnose and treat neurological diseases. In neuro nanotechnology, these properties are used to create tools and materials that can interact with neural tissues in innovative ways. Neuronanotechnology can be applied in a wide range of fields, from brain-machine interfaces to the treatment of neurodegenerative diseases (17,18).

Furthermore, nanoneuroscience is the intersection of nanotechnology and neuroscience and focuses on how these fields can improve our understanding of the nervous system. This subfield aims to develop new technologies for the diagnosis and treatment of neurological diseases and to explore the complex interactions between neurons and how they form networks. Neuronanotechnology has the potential to revolutionize the treatment of central nervous system (CNS) diseases. Using nanotechnology, researchers can develop tools for the prevention, diagnosis, monitoring and treatment of conditions such as

Alzheimer's, Parkinson's and various neurodevelopmental disorders. Advanced drug delivery systems, improved imaging techniques and neuroprotective materials are making significant impacts in this field (19).

The field of neuronanotechnology explores using nanotools with biomimetic designs to improve interactions with the nervous system. These tools can provide better methods to study brain activity and develop more effective and targeted therapies. For example, the integration of optogenetics with nanotechnology enables precise control of neuronal activity using light and offers new ways to modulate brain function and treat neurological disorders (20).

Neuronanotechnology uses various nanotechnological tools and methods to understand memory and learning processes and to treat disorders in these processes. Studies in this field aim to provide innovative solutions in the treatment of neurological disorders. In this field, there are many studies using various nanoparticles for the diagnosis and treatment of diseases.

3. Nanotechnological Agents Used in Neurological Disorders

Neurodegenerative diseases are defined as diseases that cause the gradual degeneration and death of nerve cells (neurons). These diseases lead to impaired central nervous system function and progressive brain damage. Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis (ALS) are the most common and best known types. Neuronal degeneration causes severe impairments in memory, movement, speech and cognitive functions, which significantly affects patients' activities of daily living and quality of life. Neuro nanotechnology has the potential to revolutionize the treatment of central nervous system (CNS) diseases. Using nanotechnology, researchers can develop tools for the prevention, diagnosis, monitoring and treatment of conditions such as Alzheimer's, Parkinson's and various neurodevelopmental disorders(21,22).

Memory and learning disorders are among the major symptoms of neurodegenerative diseases. Alzheimer's disease, in particular, is characterized by memory loss and declines in cognitive function. Disruption of synaptic plasticity and neurogenesis processes plays a central role in the pathophysiology of these diseases. Decreased synaptic plasticity leads to impaired communication and information storage between neurons, while inhibition of neurogenesis prevents the formation of new neurons. In Parkinson's disease, the loss of dopaminergic neurons leads to impaired cognitive functions as well as motor skills. This directly affects learning and memory processes(21,22).

The aging population is an important factor increasing the prevalence of neurodegenerative diseases. Increasing life expectancy worldwide leads to an increasing proportion of the elderly population. Aging is a process that increases the risk of neuronal degeneration and accelerates the development of neurodegenerative diseases. The incidence of these diseases increases significantly with age; for example, Alzheimer's disease is more common in individuals aged 65 years and older, and the risk increases with age. With an ageing population, health problems and care needs related to neurodegenerative diseases are also increasing. This places a huge burden on healthcare systems and necessitates the development of innovative and effective approaches to the treatment and management of these diseases.

The increasing prevalence of neurodegenerative diseases poses a significant public health challenge. The treatment and management of these diseases requires the development of novel therapeutic strategies to protect nerve cells and promote synaptic plasticity. Nanotechnological therapeutic agents offer promising solutions in this context. By targeting the pathophysiology of neurodegenerative diseases, nanotechnology offers innovative approaches to protect nerve cells and enhance synaptic plasticity. These technologies are considered to have great potential for efficacy and safety in the treatment of neurodegenerative diseases.

One application area of neuronanotechnology is the clearance of amyloid beta plaques, which play an important role in the pathophysiology of Alzheimer's disease. These plaques accumulate in the brains of Alzheimer's patients, disrupting synaptic communication and leading to memory loss. Nanoparticles are used to clear amyloid beta plaques. These nanoparticles target amyloid beta proteins and aim to prevent plaque formation or clear existing plaques. Gold nanoparticles are used to target and clear amyloid beta plaques. The surface of gold nanoparticles can be coated with antibodies or peptides that can bind specifically to amyloid beta proteins (23).

Neuroinflammation is an important mechanism underlying memory and learning disorders. Nanoparticles can be used for targeted delivery of anti-inflammatory drugs to reduce neuroinflammation. Lipid-based nanoparticles can be used for targeted delivery of anti-inflammatory drugs to inflammatory sites in the brain. Reducing neuroinflammation helps protect nerve cells and improve memory processes (24).

Synaptic plasticity underlies learning and memory processes. Nanoparticles can be used to deliver neurotrophic factors or other synaptic modulators to

enhance synaptic plasticity. Polymeric nanoparticles, nanoparticles made from polymers such as polylactic acid (PLA) and poly(lactic-co-glycolic acid) (PLGA), enhance synaptic plasticity by providing controlled release of neurotrophic factors. This helps support learning and memory processes (25).

Neuronanotechnology also plays an important role in neuroprotection and neurogenesis. Neuroprotection protects brain cells from damage. Nanoparticles can be used for the delivery and release of neuroprotective agents. Silica nanoparticles are used for the delivery and controlled release of neuroprotective agents. These nanoparticles help reduce cellular stress in brain tissue. They can also support the formation of new neurons by promoting the process of neurogenesis (26).

Neuronanotechnology also has important applications in the fields of brain-machine interfaces and memory enhancement. Brain-machine interfaces (BMIs) are systems that provide direct communication between the nervous system and external devices. Nanotechnological electrodes and nanosensors are used to record brain signals and interact with external devices. Carbon nanotubes are used in brain-machine interfaces due to their high conductivity and biocompatible properties. These nanotubes communicate directly with nerve cells, allowing modulation of memory and learning processes (27).

3.1 Neuronal Protection Mechanisms of Nanoparticles

Nanoparticles effectively protect neurons through various mechanisms: Controlled release of therapeutics minimizes toxicity and maximizes therapeutic effect by ensuring that drugs are released at the right time and at the right dose. They show antioxidant properties by reducing oxidative stress by neutralizing harmful free radicals. They facilitate the crossing of the blood-brain barrier, allowing therapeutic agents to reach the brain effectively. Support neuronal function. Supports cognitive function by increasing synaptic connections and neuronal signaling. Promote neuronal survival by modulating inflammation in the brain. They provide scaffolds that promote the growth and regeneration of neurons by creating scaffolds for neuronal growth (28).

4. Interaction of Nanoparticles with Brain Cells

The interaction of nanoparticles with brain cells determines their biological activity and therapeutic potential. Nanoparticles can interact directly with brain cells thanks to their surface properties, size and shape. In particular, surface

modifications affect the binding and uptake of nanoparticles into cells. The interaction of nanoparticles with brain cells occurs through cellular mechanisms such as endocytosis and transcytosis. These interactions allow therapeutic agents to be transported into the cell and released in target cells (29,30).

A selective barrier known as the blood-brain barrier (BBB), which protects the central nervous system, prevents many therapeutic agents from reaching the brain. Since many drugs cannot cross the BBB, therapies can be ineffective. Nanoparticles can overcome this barrier and reach brain tissue thanks to their strategy to overcome the BBB. The ability of nanoparticles to cross the BBB can be enhanced by surface modifications and carrier systems (31). For example, polymer-coated nanoparticles can be transported into brain tissue via endocytosis by interacting with receptors on the BBB. Furthermore, nanoparticles with specific ligands attached to their surface can cross into the brain via transport proteins on the BBB. Lipid-based nanoparticles and liposomes are other important delivery systems used to cross the BBB (32). These nanoparticles can easily cross cell membranes thanks to their lipophilic properties .

Strategies to cross the blood-brain barrier also include methods that temporarily increase the permeability of the BBB. Physical methods such as ultrasound and microbubbles temporarily open the BBB, facilitating the passage of nanoparticles into brain tissue. Biochemical methods such as peptide-based carriers and polymeric microcapsules are also among the strategies to overcome the BBB. These methods aim to achieve targeted delivery of nanoparticles to brain tissue and increase the efficacy of therapeutic agents (33) .

The effects of nanotechnological agents on synaptic plasticity and neurogenesis play an important role in improving learning and memory processes. Synaptic plasticity refers to changes in the strength and efficiency of synapses and is the basis of learning and memory processes. Nanoparticles can carry neurotrophic factors and synaptic modulators to enhance synaptic plasticity. For example, nanoparticles carrying brain-derived neurotrophic factor (BDNF) promote the strengthening of synapses and the formation of new synaptic connections (34).

Neurogenesis refers to the formation of new neurons and is an important component of brain plasticity (35). Nanotechnological agents can improve brain function by promoting neurogenesis. Carrier systems such as silica nanoparticles and polymeric nanoparticles support the formation of new neurons by carrying neurogenic factors and other neurotrophic agents. These nanoparticles help reduce cellular stress and promote cell regeneration in brain tissue. Particularly in neurodegenerative diseases such as Alzheimer's and Parkinson's, supporting

the process of neurogenesis is critical for slowing disease progression and preserving brain function.

Nanoparticles interact with brain cells, enabling targeted delivery and release of therapeutic agents. Through their strategy of crossing the blood-brain barrier, nanoparticles reach brain tissue and modulate synaptic plasticity and neurogenesis processes. These effects contribute to the improvement of learning and memory processes and offer innovative solutions in the treatment of neurological diseases. The development and optimization of nanotechnological agents may have promising results in the treatment of neurodegenerative diseases.

5. Use and Importance of Nanoparticle-Based Drug Delivery Systems in Neuronanotechnology

5.1. Ability of Nanoparticles to Cross the Blood-Brain Barrier

Nanoparticles offer revolutionary innovations in the treatment of neurological diseases. Nanoparticles play an important role in drug delivery systems because their ability to cross the Blood-Brain Barrier (BBB) allows drugs to reach directly into brain tissue. The BBB is a selective barrier that protects the central nervous system (CNS) and prevents many therapeutic agents from reaching the brain. This barrier consists of components such as tight junctions between endothelial cells of brain capillaries, the basement membrane and pericytes. The BBB protects brain tissue from harmful substances, while at the same time allowing the passage of essential nutrients (31,36).

The blood-brain barrier is a selective barrier that protects the central nervous system and prevents many therapeutic agents from reaching the brain. Structures such as tight junctions of endothelial cells, astrocyte foot processes and pericytes form the structural components of the BBB. By preventing many macromolecules and drugs from reaching the brain, the BBB protects brain tissue from potentially harmful substances in the bloodstream. This structure protects brain tissue from toxins and pathogens, while at the same time allowing the passage of nutrients and essential molecules (28,37).

5.2. Mechanisms by which Nanoparticles Overcome the BBB

Nanoparticles use various mechanisms to cross the BBB. Cellular mechanisms such as endocytosis and transcytosis enable nanoparticles to reach the brain tissue. Furthermore, specific ligands and modifications added to the surfaces of nanoparticles facilitate this passage by increasing the interaction

with transport proteins on the BBB. Biocompatibility and biodegradability of nanoparticles are critical for safe therapeutic applications (29).

Targeting and Bioavailability of Drugs to Brain Tissue is of great importance for the success of therapy. Nanotechnologically targeted delivery systems increase the effective delivery and bioavailability of drugs to brain tissue. These systems increase the stability of drugs, provide controlled release and allow them to accumulate in high concentrations in target cells. For this purpose, nanoparticles can be coated with biocompatible structures such as Poly ethylene glycol (PEG), which increases the stability of the transported drugs by preventing their degradation in the biological environment. Nanoparticles, such as PLGA nanoparticles, can be used for drug delivery, enabling controlled release of the drug and enhancing its therapeutic efficacy (38).

Various types of nanoparticles are used for targeted drug delivery and enhancement of therapeutic efficacy. Polymeric nanoparticles are used as effective carriers to overcome the BBB. Polylactic-co-glycolic acid (PLGA) nanoparticles have shown successful results in drug delivery to brain tissue due to their biocompatibility and biodegradability. Fornaguera et al. (2015) demonstrated that PLGA nanoparticles are effective in the treatment of brain tumors (36,39). Recent research has revealed that nanoparticles made with natural polymeric nanoparticles, alginate, are successfully transported into the brain. For example, it has been shown that alginate-cholesterol micelles coated with lactoferrin can transport a neuroprotective steroid into the brain, and alginate nanomaterials cross-linked with chitosan can enhance the transport of an antidepressant into the brain (40). In addition, doxorubicin-alginate nanocomplexes containing chitosan frameworks have shown increased absorption in the rabbit brain (41).

Chitosan, a cationic linear polysaccharide, is one of the most widely used natural polymeric nanomaterials for drug delivery due to its affordability, biodegradability and accessibility to a variety of molecular weights (42). Due to their positive charge, which enhances cell absorption and makes them suitable for pairing with negatively charged therapies, these natural nanomaterials show promise for delivery to the brain. For example, PEG-chitosan nanomaterials modified with antibodies have shown high brain absorption, which researchers believe is due to the complementarity between the antibody and the positively charged chitosan (43).

Polymeric micelles have recently attracted the attention of researchers as a potential drug delivery route to the CNS (44). Polymeric micelles are thought to be more durable than non-polymeric micelles because they have a

long duration of action and good biodistribution. Micelles have a core-shell structural architecture, ranging from 10 to 100 nm in diameter, consisting of an outer hydrophilic environment, usually composed of PEG, and an inner hydrophobic core, such as fatty acids, phospho lipids, polypropylene glycols, polycaprolactone (45); The outer hydrophilic coating gives the micelles durability throughout the aqueous environment, prolongs the time they travel in the bloodstream, and protects them from the reticulo-endothelial system (RES). The category of pluronic (Poloxamers) block copolymers is of particular interest due to their ability to suppress drug efflux transporters, P-gp efflux transporters abundantly expressed in the BBB, and enhance drug delivery to the CNS. In addition, they have been found to increase the stability and solubility of the drug in plasma, which facilitates the transport of low-molecular drugs integrated into them to the brain (46).

Carbon-based nanomaterials play an important role in neuroscience projects. In particular, carbon nanotubes (CNTs) and graphene (GR) interact effectively with neurons, enhancing nerve cell growth and synaptic plasticity (47,48). CNTs have been found to promote the proliferation and survival of hippocampal neuron cells, as well as potentiate glutamate and glutamate and γ -aminobutyric acid (GABA) synaptogenesis. The potential of CNTs and other carbon-based nanomaterials to improve memory and learning processes is associated with their ability to promote synaptic plasticity(49). The strengthening of synaptic connections and the creation of new synaptic pathways increase the efficiency of learning and memory processes. By increasing the functionality of neurons and regulating synaptic activity, these nanomaterials may contribute to the improvement of cognitive functions. Carbon nanofiber-based (CNF) nanoelectrodes have also been developed in collaboration with the Mayo Clinic as a neurochemical monitoring and stimulation tool. These ultra-small CNFs (50 nm in size) were fabricated using the chemical vapor deposition method (PECVD). These electrodes can be used to measure neurochemical concentration levels. CNTs and CNF-based nanoelectrodes thus offer new solutions for the monitoring and treatment of neurological functions (50).

Gold nanoparticles have been used in the treatment of neurological diseases by enhancing their ability to cross the CNF with surface modifications. Shi et al. (2017) reported that gold nanoparticles were used in the treatment of brain tumors by crossing the BBB thanks to ligands added to their surfaces (51). There are studies on increasing the survival rate of motor neurons and nerve regeneration with gold nanoparticles (52). In addition, targeted magnetic

nanoparticles have been directed into brain tissue using a magnetic field and there are many studies reporting that they can be used in the treatment of neurological diseases (53). For brain progenitor cell (C17.2) MR imaging Lu Zhang et al. developed fluorescent mesoporous silica coated superparamagnetic iron oxide nanoparticles for magnetic resonance (MR) imaging of brain progenitor cells (54). The magnetic core size of these nanoparticles is about 10 nm and the size of the coating layer is about 20 nm. These nanomaterials could be monitored using a clinical MRI scanner after being injected into the brains of mice after stroke. It was also observed that the labeled cells were directed towards the ischemic region even when administered intravenously. Histo-logical examinations of brain tissues confirmed the findings of the MRI scans (54). This suggests that they have a high potential to cross the blood-brain barrier and can be used effectively in cellular imaging.

Liposomes are effective in drug transport as they have a similar structure to biological membranes, enabling controlled drug release into brain tissue. Loeb et al. showed that liposomes that encapsulate and transport neurotransmitters such as GABA are effective in reducing epileptic activity, which increases the passage of GABA across the BBB. Liposomes may control inflammation by reducing microglial reactivity. Liposomes containing phosphatidylserine contribute to the protection of neurons by inhibiting proinflammatory responses in microglial cells. These liposomes bind preferentially by microglia and provide suppression of inflammatory responses through phosphatidylserine receptors. These properties offer great potential for the use of liposomes in the treatment of neurodegenerative diseases (55–57). Silica nanoparticles are used as drug carriers thanks to their high surface area and porous structure. Silica Nanoparticles promote the growth and development of nerve cells by providing prolonged release of brain-derived neurotrophic factors (BDNF) (58).

Brain imaging is a critical technique in the study of central nervous system (CNS) diseases and provides important clues for novel therapeutic interventions. Whole brain scans play an important role in understanding the clinical progression of neurodegenerative and psychiatric diseases by recording functional and structural changes of neural communication in the nervous system. However, current whole brain imaging methods face limitations such as lack of sensitivity to specific biomarkers, short half-life following intravenous injection and poor blood-brain barrier (BBB) crossing (59–62).

Molecular imaging techniques are very useful in exploring mechanisms of neuronal activity arising from synaptic processes. In particular, in vivo optical

fluorescence microscopy offers great advantages in revealing the process steps of disease pathology at neuronal resolution and in evaluating the outcomes of experimental therapeutic approaches. However, current neuroimaging methods have limitations such as artifact interference caused by fluorescence probe instability and phototoxicity (63–65). To overcome these challenges, nanostructures with diverse surface chemistries and excellent optical properties have been developed. (66,67).

In the context of therapeutic strategies, nanotechnology applications aim to limit and reverse neurological diseases (68). PLLA scaffolds, with a superstructure composed of shaped Poly-(l-lactic) acid (PLLA) fibers with dimensions of 50–350 nm and porosity of 20–85%, are an example of nano-engineered systems developed from such research. PLLA scaffolds and nanofiber networks enable rapid and persistent differentiation of neuronal progenitor cells. They promote neuronal regeneration and reduce glial scarring. In nanofiber networks, neural progenitor cells encapsulated from the cortex of an embryonic mouse led to rapid and persistent neuronal differentiation (69–71). Nanotechnology has been used to mitigate this threat by reducing the negative impact of injury-induced free radicals, an important neuropathological mechanism that causes neurotrauma, ischemia and degenerative diseases (72,73).

6. Neurodegenerative Diseases

6.1. Use of Nanotechnology in Neurodegenerative Diseases

Alzheimer's Disease: Alzheimer's disease is a progressive neurodegenerative disease characterised by the death of brain cells and deterioration of brain tissue. The disease is primarily characterised by memory impairments and, as it progresses, affects a person's ability to think and perform activities of daily living. The main symptoms of Alzheimer's disease include forgetfulness, difficulty remembering recent events, reduced decision-making and problem-solving ability, and problems with language use. Traditional treatments include medications such as cholinesterase inhibitors and memantine. These medications aim to relieve symptoms and slow the progression of the disease. Innovative treatments include nanotechnological drug delivery systems, gene therapy and immunotherapy methods that target the accumulation of beta-amyloid plaques and tau proteins (74,75).

Parkinson's Disease: Parkinson's disease is a chronic and progressive neurodegenerative disorder characterised by the loss of dopamine-producing

neurons. The disease leads to memory and learning disorders as well as motor symptoms. About 40 per cent of people with Parkinson's develop cognitive impairments and dementia. Symptoms include tremors, muscle stiffness, slowing of movements and postural instability. Memory and learning impairments are particularly pronounced in executive functions and working memory. Traditional treatments aim to control motor symptoms with drugs such as dopamine agonists and levodopa, while cholinesterase inhibitors can be used for cognitive symptoms. Innovative treatments include deep brain stimulation, gene therapy and nanotechnological drug delivery systems (17,76).

Memory and learning disorders are an important component of neurodegenerative diseases and both traditional and innovative approaches are used in the treatment of these disorders. Nanotechnological therapies offer promising results in this field, especially thanks to their ability to cross the blood-brain barrier and their targeted drug delivery capacity.

6.2 Nanotechnological Therapeutic Agents in Alzheimer's Disease

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder affecting the central nervous system with a high prevalence in the elderly population. Deposition of amyloid-beta ($A\beta$) plaques and formation of neurofibrillary tangles (NFTs) play fundamental roles in the pathophysiology of AD. In this disease, oxidative stress triggers neuronal damage by leading to $A\beta$ and NFT accumulation. In this context, natural antioxidant molecules exert neuroprotective effects by reducing oxidative stress, inhibiting the formation of $A\beta$ plaques and reducing tau tangle formation. For example, encapsulation of flavonoids such as curcumin, quercetin and resveratrol in nanoparticles has been used to enhance brain targeting and bioavailability of these compounds. Amyloid plaques are formed by the accumulation of $A\beta$ peptides in the brain and neurofibrillary tangles are the result of abnormal phosphorylation of tau proteins. Nanoparticle-based therapies aim to prevent $A\beta$ accumulation and reduce the phosphorylation of tau proteins by targeting these pathological processes. For example, metal nanoparticles and antioxidant molecules provide neuroprotective effect by preventing the formation of $A\beta$ aggregates. Acetylcholinesterase Inhibitors (AChEI), which are widely used in Alzheimer's treatment, are limited by low bioavailability and difficulties in crossing the blood-brain barrier. However, delivery of these drugs by nanoparticles may improve brain targeting and reduce peripheral side effects (77).

Lipid nanocarriers are effective in the treatment of AD by enabling the transport of antioxidants and other neuroprotective molecules to the brain. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) show high efficacy especially in brain-targeted drug delivery. These nanocarriers can reach high concentrations in brain tissue thanks to their ability to cross the BBB (78). In addition, nanocelators that degrade A β plaques can prevent the formation of A β aggregates through chelation of metal ions (77).

Metal nanoparticles also have an important place in the treatment and imaging of Alzheimer's disease. For example, gold nanoparticles have shown therapeutic potential by targeting amyloid beta (A β) plaques and enabling them to dissolve (78). In addition, magnetic nanoparticles, such as iron oxide nanoparticles, can be used in the diagnosis of the disease, allowing imaging of brain tissue. Imaging techniques used in Alzheimer's disease include molecular imaging methods such as magnetic resonance imaging (MRI), positron emission tomography (PET) and fluorescence imaging. These methods are important in early diagnosis of the disease and monitoring the effectiveness of treatment. Nanoparticles can be used as contrast agents, particularly for the detection of amyloid plaques and tau protein (15).

6.3 Nanotechnological Therapeutic Agents in Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder characterised by the degeneration of neurons, particularly those that produce dopamine. Dopamine deficiency is a key pathophysiological factor in Parkinson's disease. This leads to symptoms such as motor disorders, tremors, muscle rigidity and bradykinesia. The protection and repair of dopaminergic neurons is critical in slowing the progression of the disease (79,80). Nanoparticles can improve treatment efficacy by enabling efficient transport of dopamine, dopamine agonists and neuroprotective agents to targeted brain regions. In particular, polymeric nanoparticles and lipid-based carriers are used as dopamine transport systems, optimising drug delivery to brain tissue. Dopamine-loaded polymeric nanoparticles have been reported to have the potential to improve motor disorders with less toxicity than conventional treatment methods. Metal nanoparticles may show neuroprotective effect in Parkinson's disease. These nanoparticles, which protect neurons by reducing oxidative stress, also support neuronal repair processes (77).

Nanoparticles also play an important role in diagnosing Parkinson's disease and monitoring disease progression. Advanced molecular imaging techniques

such as PET and SPECT can detect α -synuclein and other disease markers. Superparamagnetic iron oxide nanoparticles used for magnetic resonance imaging (MRI) can detect pathological changes in brain tissue more accurately and earlier. The progression of the disease plays an important role in monitoring the treatment process (81).

7. Memory and Learning

7.1. Basic Characteristics of Memory and Learning Disorders

Memory and learning disorders occur as a result of impairments in brain function and adversely affect a person's ability to acquire, store and recall information. These disorders are often associated with structural or functional changes in areas of the brain such as the hippocampus, prefrontal cortex and amygdala. Memory disorders can affect various types of memory, such as short-term memory, long-term memory and working memory. Learning disorders are characterised by difficulties in the acquisition and application of new knowledge (82).

7.2. Nanoneurotechnological Advances in Memory and Learning Disorders in Neurodegenerative Diseases

Nanotechnology is making significant advances in addressing memory and learning impairments associated with neurodegenerative diseases such as Alzheimer's and Parkinson's. Nanoparticle-based drug delivery systems enable targeted drug delivery to brain regions by crossing the blood-brain barrier, thereby improving treatment efficacy. Research shows that nanoparticles can increase the efficacy of drugs targeting amyloid-beta proteins in Alzheimer's disease and improve cognitive functions in mouse models. Furthermore, nanoparticles with neuroprotective properties can improve motor functions by protecting neurons from damage in Parkinson's disease (68,83). Furthermore, nanotechnological methods such as nanoemulsions and polymeric carriers enable drugs to reach the brain effectively. In addition, magnetic nanoparticles and carbon nanotubes can be used as contrast agents in neuroimaging techniques, allowing better visualisation of brain structures. Such nanotechnological approaches offer innovative strategies to address memory and learning disorders, and these technologies have great potential to improve cognitive function and quality of life. Experimental studies on nanotechnological treatments are evaluating the efficacy of these treatment methods. Animal models are used to test the

neuroprotective and neurogenesis-promoting effects of nanoparticles on the brain (84,85).

7.3. Memory Reinforcement and Retrieval in Learning Disorders: Nanotechnological Interventions

Nanotechnological interventions offer innovative approaches in the treatment of learning disorders. Nanoparticles increase synaptic plasticity by carrying neurotrophic factors and promote the formation of new synaptic connections. This provides a significant advantage in the treatment of learning disorders. Furthermore, nanotechnology can treat genetic causes of learning disorders by providing carrier systems for gene therapy (86).

Nanotechnological approaches play an important role in memory strengthening and retrieval processes. Nanoparticles improve memory functions by stimulating the formation of new neurons. This contributes to the improvement of learning and memory processes. Furthermore, nanotechnological agents used in reducing the accumulation of amyloid plaques in conditions such as Alzheimer's disease may have promising results in the treatment of neurological diseases (32,74,87).

7.4. Nanotechnological Interventions on Dyslexia and other Learning Disorders

Nanotechnological approaches in the treatment of learning disorders such as dyslexia attract attention. In the treatment of learning disorders such as dyslexia, nanoparticles offer targeted treatment approaches. Since dyslexia is caused by specific neurological differences in the brain, nanoparticles can be designed to act directly on these regions. For example, neurotrophic factors or drugs can be delivered to brain tissue with the help of nanoparticles, which contributes to improving brain function. Research in the treatment of dyslexia generally focuses on polymeric nanoparticles and lipid-based nanoparticles. These nanoparticles offer more effective treatment by enabling the transport of drugs to the target site. In individuals with learning disorders, neurotransmitter balance may be disturbed. In this context, metal nanoparticles and magnetic nanoparticles can regulate synaptic functions by providing a more balanced release of neurotransmitters, thereby improving learning processes. For example, magnetic nanoparticles regulate neurotransmitter release and increase synaptic plasticity by directing a magnetic field to specific brain regions (81,88,89).

Nanotechnology offers revolutionary innovations in the treatment of learning disorders. The opportunities offered by this technology have great potential to improve learning processes and develop individualised approaches in education. The use of nanoparticles in education and treatment may become more widespread in the future, significantly improving the quality of life of individuals with learning disorders.

8. Possible Side Effects of Neuronanotechnology

Although nanotechnology offers important innovations in the field of neuroscience, it faces several challenges due to the complexity of the nervous system. The structural and functional complexity of the brain makes it difficult to apply nanoparticles *in vivo*. Integrating nanotechnology into the nervous system should be considered with caution given factors such as the vulnerable nature of the central nervous system to damage and the difficulties in crossing the blood-brain barrier. The potential for the use of nanoparticles in targeted therapies in brain structures offers promising solutions for the treatment of neurodegenerative diseases and other neurological disorders. However, this process requires careful planning and research to prevent unforeseen side effects (18).

Nanoparticles are widely used in medical applications. However, there are concerns about the effects of these particles on brain functions and potential side effects. Some nanoparticles may cause neurotoxicity, especially with prolonged exposure. Nanoparticles containing cadmium and lead are known for their neurotoxic effects and can cause damage to nerve cells. Such nanoparticles can trigger harmful processes such as oxidative stress and apoptosis (programmed cell death), which impair memory and learning functions. They can also trigger an inflammatory response in brain tissue. In particular, during long-term use of metal oxide nanoparticles, neurological complications resulting from their accumulation should not be ruled out. Magnetic nanoparticles such as iron oxide nanoparticles (Fe_3O_4) can cause over-activation of microglial cells in the brain. These cells can lead to inflammation in brain tissue, which can damage memory and learning processes. Some nanoparticles are not biodegradable and can accumulate in the body over time. This bioaccumulation can lead to long-term organ damage and impaired brain function. Bioaccumulation of nanoparticles such as titanium dioxide (TiO_2) can lead to adverse effects on neural functions. Exposure to TiO_2 nanoparticles can cause memory and learning impairments in

offspring, both during pregnancy and lactation. Nanoparticles containing heavy metals such as cadmium and lead are generally not used in memory and learning studies because they have highly toxic effects on the nervous system. Systemic exposure to silver nanoparticles (AgNPs) may cause impairments in memory and learning functions and should therefore be used with caution. Copper oxide nanoparticles (CuO-NPs) may lead to minor changes in memory and learning performance and increased anxiety levels. Sulphur-based nanoparticles and some organic nanoparticles may overstimulate the immune system and cause neuroinflammation. Such nanoparticles are also among those that should be avoided. Although nanotechnology has great potential in memory and learning research, the biocompatibility, toxicity profile and long-term effects of the nanoparticles used should be carefully evaluated. In particular, controlling side effects such as neurotoxicity, inflammation and bioaccumulation is critical for the development of safe and effective treatments in this field (90–92).

9. Conclusion

Researchers have already seen significant effects of the application of nanotechnology to neuroscience and these effects are expected to continue in the near future. The possibilities offered by nanotechnology in neuroscience open new horizons in the understanding and treatment of neurological disorders related to learning and memory processes. The development of targeted drug delivery systems, the use of nanomaterials with neuroprotective properties and nanotechnological interventions that can regulate synaptic plasticity offer promising approaches, especially in the management of neurodegenerative diseases such as Alzheimer's and Parkinson's. Furthermore, the integration of nanoparticles with brain-computer interfaces and advanced imaging techniques allows for more precise control of neuronal activity and more in-depth analysis of brain functions. However, the full integration of these technologies into clinical applications requires answering important questions regarding their long-term biocompatibility, toxicity and safety profiles. Further research is needed on the mechanisms by which nanoparticles cross the blood-brain barrier and the long-term effects of these processes. In the light of all these developments, nanotechnology stands out as a key technology that will shape the future of general neurological research and clinical applications, as well as treatments for learning and memory disorders. Future research is expected to further deepen this field and pave the way for more effective, personalised treatment methods in

neuroscience. However, although technically and theoretically complex, these applications can play a major role in the advancement of clinical neuroscience. While much of this research is valuable, much remains to be done.

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CHAPTER XIII

EFFECTS OF NEW GENERATION EDUCATIONAL TECHNOLOGIES ON LEARNING EFFICIENCY

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1. Introduction

In recent decades, the field of education has witnessed a significant transformation with the integration of technology. What began as basic tools like projectors and digital presentations has evolved into sophisticated systems powered by artificial intelligence, augmented reality, and adaptive learning platforms (1). These new-generation educational technologies have reshaped how students learn, engage, and process information. From personalized learning paths to virtual classrooms that simulate real-world scenarios, the modern educational landscape is radically different from the traditional classroom setting (2).

As technological advancements continue to accelerate, the potential for enhancing learning outcomes has grown exponentially. Tools such as AI-driven tutoring systems, immersive virtual simulations, and mobile learning platforms are not only increasing accessibility but also creating more dynamic, interactive, and efficient ways of learning. This chapter will cover how these tools are shaping the educational environment, with a specific focus on improving learning efficiency (3).

Learning efficiency refers to the ability of learners to process and retain information in a way that maximizes the educational outcomes with minimal

effort (4). In an age where knowledge is rapidly expanding and time is often constrained, improving learning efficiency has become a priority for educators and institutions alike. New-generation technologies offer a promising avenue to address these challenges by streamlining learning processes, reducing cognitive load, and catering to individual learning needs (5).

The central question of this chapter revolves around the extent to which these new technologies influence learning efficiency. Are they truly optimizing how students learn, or are they simply adding another layer of complexity? To answer this, we will explore the types of technologies currently in use, the metrics by which we can measure their effectiveness, and real-world examples where these innovations have either succeeded or fallen short. Through this, we will better understand how to harness the potential of new-generation technologies to create more effective and engaging learning experiences.

2. Historical Evolution of Educational Technologies

2.1. From Chalkboards to Digital Classrooms

The history of educational technology is one of continuous evolution, marked by key innovations that have transformed teaching and learning methods (6). In the early 19th century, the use of the chalkboard revolutionized classrooms, allowing teachers to visually present lessons to larger groups of students (7,8). This relatively simple tool remained a staple of education for over a century, but the landscape began to shift dramatically with the advent of digital technologies in the latter half of the 20th century (9).

The introduction of the personal computer in the 1980s marked a significant turning point, offering students and educators access to powerful new learning tools. Word processors replaced handwritten assignments, while educational software and CD-ROMs provided interactive learning experiences previously unattainable with traditional methods. By the late 1990s and early 2000s, the rise of the internet brought with it an unprecedented access to information and resources. Online research, distance learning, and collaborative platforms became integral parts of the educational process, leading to the first wave of digitally enhanced classrooms (9).

As schools and universities embraced these technologies, the shift toward digital learning gained momentum, culminating in the emergence of e-learning platforms, video lectures, and online degrees. This period laid the foundation for the more sophisticated, data-driven technologies that we see today.

2.2. Emergence of New-Generation Technologies

In the last two decades, the educational technology landscape has evolved even further with the emergence of new-generation tools. These innovations are defined by their ability to personalize learning experiences, adapt to individual student needs, and provide immersive, interactive environments that go beyond traditional teaching methods (10).

One of the most transformative technologies in education is artificial intelligence (AI). AI-powered adaptive learning systems analyze vast amounts of student data to tailor educational content in real-time, offering personalized learning paths that optimize for efficiency (2). This level of customization was previously unimaginable with earlier technologies and has revolutionized how educators approach teaching and learning.

Augmented reality (AR) and virtual reality (VR) have also emerged as powerful tools, particularly in fields like medicine, engineering, and the sciences, where hands-on experience is crucial. These technologies allow students to engage in simulated environments, providing experiential learning without the constraints of physical resources (11). For example, medical students can practice surgical procedures in virtual environments, while engineering students can interact with complex machinery through AR simulations (12).

Gamification and interactive learning platforms are further examples of how new-generation technologies have shifted the educational paradigm. By incorporating elements of game design into learning, these platforms increase student engagement, motivation, and retention of knowledge (13). This approach recognizes that learning does not have to be a rigid, passive experience but can be dynamic and fun, fostering a deeper connection to the material.

As we move further into the 21st century, mobile learning and cloud-based platforms have expanded access to education like never before. Students can now learn from anywhere, at any time, using their smartphones or tablets. This flexibility not only enhances learning efficiency but also democratizes education, making it more accessible to a broader range of learners across the globe (14).

In summary, the evolution of educational technologies from simple chalkboards to immersive digital classrooms has been marked by rapid innovation. New-generation technologies are at the forefront of this transformation, offering unprecedented opportunities to enhance learning efficiency through personalization, interaction, and flexibility. As these tools continue to develop, they hold the potential to further revolutionize education, making learning more effective and engaging than ever before.

3. Core New-Generation Educational Technologies

3.1. *Artificial Intelligence and Adaptive Learning*

Artificial intelligence (AI) is perhaps the most transformative technology reshaping education today. In the context of learning, AI serves as a powerful tool to personalize and optimize the educational experience. Adaptive learning platforms powered by AI analyze data from individual students—such as their performance, learning style, and engagement—to adjust content dynamically. This level of personalization was previously impossible with traditional teaching methods, where all students received the same instruction, regardless of their individual needs (2).

AI-driven platforms provide real-time feedback, enabling students to progress at their own pace. For example, if a student struggles with a specific concept, the system can offer additional resources, practice problems, or a different explanation tailored to that student's needs. Conversely, students who excel can be presented with more challenging material to ensure they remain engaged. This creates a highly efficient learning process, minimizing wasted time on areas the student has already mastered (15).

Augmented reality (AR) and virtual reality (VR) are among the most exciting developments in educational technology. These immersive technologies allow students to experience learning in ways that were previously only theoretical. For example, AR can overlay interactive visuals onto physical spaces, enabling students to explore complex concepts in a more hands-on manner. In biology, AR can transform a simple textbook diagram of the human body into a fully interactive model that students can manipulate in real time, exploring each organ or system in detail (16).

Similarly, VR takes this a step further by immersing students in entirely virtual environments. This is particularly useful for subjects requiring practical experience, such as medicine, engineering, and the sciences. VR allows students to perform virtual surgeries, engage in mechanical repairs, or conduct scientific experiments in a risk-free environment (17). The ability to practice and repeat these experiences is invaluable for building both confidence and competency before applying these skills in the real world.

The use of AR and VR also has the potential to revolutionize fields like history and geography. Students can “travel” to ancient civilizations, explore famous landmarks, or experience important historical events firsthand, creating a deep and memorable connection to the material (18).

3.2. Gamification and Interactive Learning Platforms

Gamification refers to the application of game-design elements—such as points, badges, and leaderboards—into learning environments to boost engagement and motivation. By turning learning into a more interactive and enjoyable process, gamification addresses a common challenge in education: keeping students motivated and involved.

Interactive learning platforms like Kahoot!, Duolingo, and Quizlet employ gamification principles to foster a sense of achievement and progression (19–21). These platforms often allow students to compete against themselves or others in real-time quizzes, games, or exercises. This competitive element taps into intrinsic motivators, pushing students to engage with the material more thoroughly (19).

Gamified learning also enhances retention. Studies show that students are more likely to remember information learned in an enjoyable and interactive way compared to passive learning methods (22). Additionally, these platforms often offer immediate feedback, helping students correct mistakes on the spot and reinforcing learning as they progress. Gamification isn't limited to academic quizzes; it extends to simulations that teach real-world skills (23). For instance, management students may participate in business simulation games where they make decisions that impact a virtual company's success, providing practical experience in a controlled environment (24).

3.3. Mobile and E-Learning Platforms

The rise of mobile technology and cloud-based learning has fundamentally changed how students access education (25). With mobile learning, students can engage with content on the go, using their smartphones or tablets to access lessons, watch instructional videos, or participate in discussion forums. This increased accessibility is especially beneficial for non-traditional learners who may not have the flexibility to attend scheduled classes (26).

E-learning platforms like Coursera, Udemy, and Khan Academy have made quality education available to anyone with an internet connection. These platforms provide courses from prestigious institutions on a wide range of subjects, often at little or no cost (27–29). The flexibility to learn at one's own pace, coupled with the ability to choose from a global catalog of courses, has empowered lifelong learning and upskilling in an ever-changing job market.

Mobile and e-learning platforms have also democratized education by reaching underserved populations, such as learners in remote or developing areas where access to formal education is limited. By removing geographical and temporal barriers, these platforms ensure that education is more inclusive, accessible, and flexible (30).

3.4. The Synergy of New-Generation Technologies

These core new-generation educational technologies do not exist in isolation. Instead, they often work in synergy, creating a comprehensive learning ecosystem that amplifies efficiency. AI might power an adaptive learning platform, while immersive VR experiences supplement traditional learning materials, and gamified elements keep students engaged throughout. This convergence of technologies offers a holistic approach to modern education, equipping students with the skills, knowledge, and experiences needed to thrive in a rapidly evolving world (31).

The introduction of these tools has opened doors to new learning possibilities, making education more personalized, engaging, and effective. As they continue to evolve, the question is no longer if they improve learning efficiency but how effectively they can be integrated into various educational systems to maximize their potential.

4. Measuring Learning Efficiency

Measuring learning efficiency with new-generation educational technologies involves assessing key metrics such as learning speed, retention rates, and student engagement. One significant approach to improving learning efficiency is through feature selection, particularly in high-dimensional data contexts. emphasizes that effective feature selection can enhance learning efficiency by employing various methods such as filters, wrappers, and embedded techniques, which can significantly reduce the complexity of the data and improve model performance (32). This is particularly relevant in machine learning applications where the dimensionality of data can impede the learning process, thereby necessitating efficient feature selection strategies.

Moreover, the active learning paradigm has been shown to influence learning efficiency significantly. Tavassoli et al. (2022) discussed how different types of queries, such as membership and equivalence queries, can impact the efficiency of model learning in variability-intensive systems (33). The efficiency of learning in such contexts is crucial, as it determines how quickly and effectively a model can adapt to new information. This is echoed in the work

of , Gabillon et al. (2014) demonstrate that high-quality policies can be learned in a sample-efficient manner through the use of submodular functions, which are prevalent in active learning scenarios (34).

In the realm of cognitive psychology, Zerr et al. (2018) provided empirical evidence that individuals exhibit varying degrees of learning efficiency, which can be reliably measured through specific tasks (35). Their findings underscore the importance of understanding individual differences in learning rates and retention, which can inform tailored educational strategies that enhance overall learning efficiency. This is further supported by the work of , who proposes a method for evaluating English learning efficiency that incorporates ecological classroom theory and data envelopment analysis, thereby providing a structured approach to assessing educational effectiveness (36).

Additionally, the integration of technology in education, particularly through online platforms, has been shown to enhance learning efficiency. highlight the role of collaborative annotating and data mining in formative assessments, which can significantly elevate learning efficiency by providing immediate feedback and fostering engagement among learners (37). This aligns with the findings of , who employs a data envelopment analysis model to evaluate the efficiency of English learning in vocational education, emphasizing the importance of considering both input and output factors in the learning process (38).

Furthermore, the development of recommendation algorithms tailored to individual learning styles has been shown to improve learning efficiency in online environments. discuss a personalized learning resource recommendation algorithm that enhances students' learning efficiency by aligning resources with their specific learning needs (39). This approach is vital in promoting active participation and exploration among learners, thereby fostering a more efficient learning environment.

Measuring learning efficiency involves a comprehensive understanding of various methodologies, individual differences, and technological advancements. By integrating insights from feature selection, active learning, cognitive psychology, and technological applications, educators and researchers can develop more effective strategies to enhance learning outcomes.

5. Case Studies: Success Stories and Challenges

5.1. Success Story: AI-Powered Adaptive Learning in Higher Education

A standout success story in the realm of educational technologies comes from Arizona State University (ASU), which implemented AI-powered adaptive

learning platforms to improve student outcomes in large, introductory-level math courses. Using a system called ALEKS (Assessment and Learning in Knowledge Spaces), the university tailored course material to each student's needs, providing personalized learning paths and real-time feedback (40).

Before using the platform, many students struggled with traditional, lecture-based teaching methods, leading to high failure and dropout rates. After implementing ALEKS, ASU saw a 20% increase in pass rates, as well as a significant reduction in the time students spent mastering core concepts (40). The technology's ability to adjust to each learner's pace and provide targeted support transformed the course into an efficient, student-centered learning experience.

However, the success of this adaptive learning platform also highlighted challenges. Some students initially found the system overwhelming, especially those unfamiliar with self-paced, technology-driven learning. Additionally, some faculty members expressed concern about the over-reliance on automated systems, which, they felt, could depersonalize education. Overcoming these challenges required a blended approach, where human instructors provided supplementary support and guidance, creating a balanced integration of technology and traditional teaching (40).

5.2. Success Story: Gamification in K-12 Education

Gamification has been particularly effective in engaging younger learners. A prime example is the use of Classcraft, a gamified platform that transforms the classroom into a role-playing game where students earn points and rewards for academic achievements and positive behavior. In schools across the United States and Canada, Classcraft has been credited with increasing student engagement, particularly among middle and high school students who struggled with motivation in traditional settings (41).

In one study conducted in Chili, teachers reported that using Classcraft led to improved attendance, increased participation, and a greater sense of collaboration among students. The platform encouraged students to take ownership of their learning, motivating them to complete assignments and engage with the material more actively. Teachers also found that students were more likely to help each other, fostering a cooperative learning environment that extended beyond the game (42).

Challenges emerged, particularly around maintaining long-term engagement. While the initial novelty of the gamified platform was effective, some students began to lose interest after the novelty wore off (43). Additionally, the competitive elements of the game sometimes created friction between

students, requiring careful moderation by educators to ensure a positive and inclusive environment (43).

5.3. Success Story: VR in Medical Training

Virtual reality (VR) has made significant strides in medical education, providing an immersive, hands-on learning environment for students to practice complex procedures. At Stanford University's School of Medicine, VR is used to teach anatomy, surgical techniques, and clinical decision-making (44,45). One of the most notable applications is the use of VR for surgical simulation. Medical students can practice procedures such as brain surgery in a virtual environment, giving them the opportunity to make decisions, manipulate tools, and learn from mistakes without any real-world consequences (45).

This approach has led to measurable improvements in both learning efficiency and student confidence. In a controlled study, students using VR simulations to learn anatomy performed better on assessments compared to those using traditional textbook-based methods. They also reported feeling more prepared and confident when transitioning to real-life surgical practice (46).

Despite its advantages, VR faces challenges related to cost and accessibility. High-quality VR equipment can be expensive, limiting its widespread adoption in some institutions (47). Additionally, prolonged use of VR can cause discomfort, such as motion sickness, which affects a small percentage of users (48). Overcoming these challenges requires continued investment in affordable, accessible VR solutions and ensuring that the technology is integrated in ways that complement, rather than replace, traditional medical training.

6. Barriers to Implementing Educational Technologies

While new-generation educational technologies have the potential to revolutionize learning, several barriers hinder their widespread adoption. These barriers are multifaceted, including issues related to cost, infrastructure, training, and resistance to change. Addressing these challenges is critical to ensuring that educational technologies can be fully integrated into classrooms and other learning environments.

6.1. Cost and Infrastructure Limitations

One of the most significant barriers to implementing advanced educational technologies is the high cost of acquisition and maintenance. Tools like virtual reality (VR) headsets, augmented reality (AR) systems, and AI-powered

adaptive learning platforms often come with hefty price tags (47). Schools, especially those in underfunded areas or developing countries, may struggle to afford the necessary equipment and software. Even when initial funding is available, the ongoing costs of maintenance, software updates, and technical support can create financial strain.

In addition to cost, infrastructure limitations, particularly in remote or rural areas, pose a significant barrier. Many educational technologies require high-speed internet, reliable power supplies, and advanced technical infrastructure that are not universally available (49). Without these foundational elements, students and educators cannot fully utilize technology, perpetuating the digital divide.

6.2. Teacher Training and Digital Literacy

The successful integration of technology in education depends not only on the availability of tools but also on the competency of educators in using them (50). Lack of adequate training is a common barrier to implementing new-generation technologies. Many teachers feel unprepared to use advanced tools like AI-driven platforms, VR simulations, or gamification systems in their classrooms. This lack of digital literacy can lead to underutilization or misuse of the technologies, reducing their potential impact on learning efficiency (51).

Providing educators with continuous professional development opportunities is essential for overcoming this barrier. Schools and institutions must invest in training programs that not only teach the technical skills required but also how to effectively incorporate these tools into lesson plans and classroom activities (52). Without proper support, even the most innovative technologies may fail to produce the desired outcomes.

6.3. Resistance to Change

Resistance to change is a common psychological and organizational barrier to the adoption of new educational technologies. Teachers, administrators, and even students may be hesitant to shift away from traditional methods of teaching and learning, particularly if they have been successful in the past. This resistance is often rooted in fear of the unknown, concerns about job displacement (especially with AI-driven tools), or simply the discomfort associated with learning new systems (53).

To overcome resistance, it's essential to create a culture of openness and experimentation within educational institutions. Stakeholders should be involved

in the decision-making process, and the benefits of technology adoption should be clearly communicated. Incremental implementation strategies—starting with small pilot programs before full-scale rollouts—can also help ease the transition and build confidence in new tools (54).

6.4. Equity and Accessibility Issues

Educational technologies can inadvertently widen the gap between privileged and underprivileged students (55). While tech-savvy schools may have access to the latest tools, students in underserved areas may be left behind due to lack of resources, digital infrastructure, or technological literacy. Additionally, students with disabilities may face challenges if the technology is not designed with accessibility in mind (56).

Addressing these equity issues requires a commitment to inclusive design and policy. Educational technologies must be developed with diverse learners in mind, ensuring that platforms are accessible to all students, regardless of their physical, economic, or geographic circumstances. Governments and organizations can play a critical role in funding initiatives that bridge the digital divide, ensuring that all students have access to the same learning opportunities (57).

7. Conclusion

The integration of new-generation educational technologies has significantly improved learning efficiency, offering personalized, immersive, and engaging experiences for students worldwide. From AI-driven adaptive learning platforms to AR/VR simulations, these tools have transformed traditional methods of education, addressing diverse learning needs and enhancing outcomes. However, challenges such as cost, digital infrastructure, teacher training, and access inequalities must be addressed to ensure that all students benefit from these advancements.

The future holds great promise as technologies like AI, immersive learning, and blockchain continue to evolve. These innovations will likely reshape the educational landscape, offering new opportunities for both students and educators. By embracing these technologies thoughtfully and addressing potential barriers, we can move toward a more equitable, efficient, and effective educational system that prepares learners for the demands of the 21st century.

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CHAPTER XIV

LEARNING, LEARNING STYLES, AND LEARNING STRATEGIES

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1. Introduction

Learning is a concept that emerges and is emphasized together with the concepts of information age and information society. Effective learning is one of the dimensions aimed to be developed in individuals. The concept of learning and learning to learn means that students recognize their own learning characteristics, know the strategies used in learning, and choose and apply appropriate strategies. In short, the process of learning to learn is related to both the learning styles and learning strategies of individuals. This section aims to summarize the defined concepts of learning and the categorized learning styles and strategies identified by various researchers from the past to the present.

2. Learning

Over the years, significant changes have occurred regarding the concepts of learning and teaching. Therefore, a wealth of information has been presented to consider the differences in how learners perceive, process, and organize information, solve problems, and design learning-teaching processes. Learning is a dynamic process that continues throughout life and represents a permanent change in behavior or the capacity to behave in a particular way based on practice and other life experiences (1, 2). Additionally, learning is a behavior

that occurs as a result of repetition and experience, and continuity is necessary for learning to occur (3).

Conversely, learning has been defined in different ways by many researchers and theoreticians from past to present. According to the behavioral approach, learning is the individual's response to certain stimuli through specific behaviors and the changes that may occur in those behaviors (4). According to this approach, changes in behavior, shaping of behavior, and reinforcement are the three main components of the learning process (4, 5). According to the cognitive approach, learning consists of internal mental concepts that can be inferred from what individuals say and do. This approach acknowledges the impact of environmental conditions on learning and emphasizes that individuals' thoughts, beliefs, attitudes and values also influence their learning (6). According to the constructivist approach, learning develops as a result of making connections between previous knowledge and newly acquired knowledge, with a focus on the process of learning (6).

The behaviorist understanding of learning and teaching does not take the human mind into account in the learning process and explained learning as an action-reaction bond. Cognitive understanding takes into account individual differences in learning and argues that learning is an active mental process (7). Psychological and educational understandings that emerged especially in the 1900s and 2000s emphasized that individuals have different characteristics from each other and that these characteristics should be taken into account in the learning and teaching process. As the constructivist understanding gained importance in the learning and teaching process over time, the idea that learning is an individual activity and that there are individual differences in the acquisition and organization of information and the meaning attached to information has begun to be accepted (7). Views of behaviourist, cognitive and constructivist approaches to learning and teaching are presented in Table 1 (7, 8).

Table 1. Views of Behaviourist, Cognitive and Constructivist Understanding on Learning and Teaching

	Behaviorist Understanding	Cognitive Understanding	Constructivist Understanding
Quality of Information	Based on objective reality, independent of the knower	Based on objective reality, dependent on the prior knowledge of the person who knows	Based on subjective reality that is individually and socially constructed
Instructive's Role	Transfer information	Managing the information acquisition process	Helping students to cooperate
Learner's Role	Passive	Semi-active	Active
Learning	Change in overt behavior as a result of conditioning	Processing information	Individual discovery and structuring of knowledge
Teaching Type	Separation, generalization, association, chaining	Processing information in short-term memory and storing it in long-term memory	Problem solving based on real situations
Teaching Type	Inductive	Inductive	Deductive
Teaching Strategies	Presenting information, practicing, giving feedback	Activating the student's cognitive learning strategies	Active, self-controlled, intrinsically motivated investigative learning
Educational Environments	Various traditional environments (programmed teaching, computer-assisted teaching, etc.)	Instructor and computer-based instruction	Interactive environments that require the student to show physical/mental reactions to progress
Evaluation	Separate from the teaching process and criterion-based	Separate from the teaching process and criterion-based	Within the learning process and independent of criteria

3. Learning Styles

Learning style is characterized by a combination of cognitive, emotional, and physiological characteristics that indicate how the student perceives and responds to the learning environment (9, 10). It is not just an ability, but a preferred way that individuals use their abilities (11). Individuals' learning styles vary in terms of their natural, habitual, and preferred ways of assimilating, processing, and retaining new information and skills (12). Therefore, learning styles can evolve over time (13). Moreover, learning styles are not fixed behavior

patterns and can change depending on different situations and tasks (14). The various learning styles identified by different researchers are summarized below.

3.1. Gregorc's Learning Styles

Gregorc defined four different learning styles such as concrete sequential, concrete random, abstract sequential and abstract random (15).

3.1.1. Concrete Sequential Learning Style

Individuals with this learning style prefer direct instruction, manual activities, the tactile method, step-by-step gradual teaching, and real-life examples (7, 15).

3.1.2. Concrete Random Learning Style

Individuals who adopt this learning style prefer a trial-and-error approach, enjoy environments rich in stimuli, are good at competitions, are implementers of change, do not like structured things, think quickly and take risks, and produce unusual and creative ideas (7, 15).

3.1.3. Abstract Sequential Learning Style

Individuals with this learning style prefer a logical, analytical, and verbal approach based on intelligence and well-organized materials (7, 15).

3.1.4. Abstract Random Learning Style

Individuals who adopt this learning style like to focus on relationships and their emotions, respond more positively to visual teaching, and appreciate time for group work and reflection (7, 15).

3.2. Kolb's Learning Styles

According to Kolb, there are four different learning styles such as diverging, assimilating, convergent, and adapting (16).

3.2.1. Diverging Learning Style

Individuals with this learning style review concrete situations from many perspectives, organize relationships in a meaningful way, make patient, objective and careful judgments during the learning process, but do not take action and prioritize their own feelings and thoughts while shaping their thoughts (7, 16).

3.2.2. Assimilating Learning Style

Creating conceptual models is the most distinctive characteristics of individuals who adopt this learning style. These individuals focus on abstract

concepts and ideas when learning and need opportunities to process information (7, 16).

3.2.3. Converging Learning Style

Problem solving, decision-making, logical analysis of ideas and systematic planning are the most distinctive characteristics of individuals who adopt this learning style (7, 16).

3.2.4. Accommodating Learning Style

Individuals with this learning style are open-minded in the learning environment, adapt to changes easily, prefer to learn by applying and feeling, and need opportunities to apply learned concepts to new problems (7, 16).

3.3. Felder And Silvermann's Learning Styles

Felder and Silvermann mentioned four different learning styles such as sensing - intuitive, visual and auditory, active - reflective, and sequential and global (17).

3.3.1. Sensing - Intuitive Learning Style

This learning style is based on the Theory of Psychological Types and is closely related to the nature of the information preferred in the learning process and the personality characteristics of the learner (17).

3.3.2. Visual and Auditory Learning Style

This learning style is related to the receiving/perception phase of the learning process. According to this learning style, it is thought that individuals learn more when visual and auditory forms of information are presented together (17).

3.3.3. Active - Reflective Learning Style

This learning style is associated with two active mental processes: active experience and reflective observation. While active experience involves doing something in the outside world with information, reflective observation involves examining and manipulating information through introspection (17).

3.3.4. Sequential and Global Learning Style

According to this learning style, the organization and arrangement of information in the brain can occur in sequential and global modes. The sequential learner uses successive, related, small, linear steps when receiving and understanding information (17, 18).

3.4. Fleming And Mills's VARK Learning Styles

Fleming and Mills categorized learning styles as visual, auditory, reading/writing and kinesthetic (19).

3.4.1. Visual Learning Style

This learning style requires using visual materials such as demonstrations, movies, pictures, and diagrams. Individuals who adopt this learning style learn best when information is presented visually and in written form (19, 20).

3.4.2. Auditory Learning Style

Individuals who adopt this learning style learn best when information is presented verbally, learn in a classroom environment by listening to lectures and participating in group discussions, and also learn by re-listening to information recorded on audio tapes or CDs (19, 20).

3.4.3. Reading/Writing Learning Style

Individuals who adopt this learning style enjoy lists, dictionaries, textbooks, lecture notes or navigating, drafting lecture notes, paraphrasing class notes, and reviewing multiple-choice exam questions, take notes, and study better with notes from lectures or difficult reading material (19-21).

3.4.4. Kinesthetic Learning Style

This learning style includes physical experiences (experiences gained through touching, feeling, holding, doing and applying). Individuals who adopt this learning style, when they do an activity physically where they use and experiment with materials in the classroom environment. In order to learn, they need to actively participate in classroom activities (19, 20).

3.5. Reinert's Learning Styles

Reinert emphasized four different learning styles: visual, auditory, verbal-symbol, and movement-based (22).

3.5.1. Visual Learning Style

Individuals who adopt this learning style prefer to learn by frequently using their sense of sight, remember details and colors well, and enjoy watching demonstrations, reading, and writing while learning (20, 22).

3.5.2. Auditory Learning Style

Individuals with this learning style prefer to learn through the sense of hearing, learning by listening and participating in group discussions.

They are successful in oral exams and speak fluently and articulately (20, 22).

3.5.3. Learning Style with Verbal Symbols

Individuals who adopt this learning style prefer verbal elements in learning, attach great importance to words, favor verbal symbols more, learn something by repeating, and use words functionally (20, 22).

3.5.4. Movement-Based Learning Style

Individuals with this learning style benefit more from the sense of touch in learning, find it difficult to listen for long periods, may interrupt others, and rewrite the notes they take at home (20, 22).

3.6. Grasha's Learning Styles

Grasha defined six different learning styles such as competitive, collaborative, avoidant, participant, dependent, and independent (23, 24).

3.6.1. Competitive Learning Style

Individuals who adopt this learning style strive to perform better than others in the learning environment, enjoy being noticed and attracting attention due to their success, and believe that they need to compete to achieve the reward at the end of the learning process (23, 24).

3.6.2. Collaborative Learning Style

Individuals with this learning style enjoy sharing their talents and ideas with others. The advantages of this style include enhanced teamwork and collaboration skills (23, 24).

3.6.3. Avoidant Learning Style

Individuals who adopt this learning style do not participate in instructors, other learners, and do not care about what is happening in the classroom. Their performance is often low and they are not productive in achieving their goals (23, 24).

3.6.4. Participant Learning Style

Individuals with this learning style enjoy attending classes and take care to complete compulsory and optional assignments. However, they tend to prioritize the needs of other learners over their own (23, 24).

3.6.5. Dependent Learning Style

Individuals who adopt this learning style only learn compulsorily, have little intellectual curiosity, see all kinds of authority instructions as what needs to be done, and see their instructors and classmates as a part of the educational framework (23, 24).

3.6.6. Independent Learning Style

Individuals with this learning style are confident in their learning abilities and prefer to focus on subjects they consider important, studying independently rather than covering all subjects (23, 24).

3.7. McCarthy's 4MAT Learning Styles

McCarthy mentioned four different learning styles such as imaginative, analytical, prudent, and dynamic (25).

3.7.1. Imaginative Learning Style

Individuals who adopt this learning style prefer to learn by feeling and observing, integrating their experiences with their own insights. They learn by listening and sharing, receive information concretely, and process it reflectively (20, 25).

3.7.2. Analytical Learning Style

Individuals with this learning style attach importance to sequential learning, seek continuity, want to learn whatever is accepted knowledge, learn best through traditional methods, rely on their mental abilities to understand, and prefer the information that is validated or proven by experts (20, 25).

3.7.3. Prudent Learning Style

Individuals who adopt this learning style combine theory and practice, test ideas with common sense and experimentation, and seek to understand the reasons behind phenomena. They receive information abstractly, actively process it, evaluate the usefulness of what they encounter, learn by thinking and testing theories, and focus on achieving practical results (20, 25).

3.7.4. *Dynamic Learning Style*

Individuals with this learning style prefer to learn by feeling and doing, enjoy exploring independently, and appreciate trial-and-error approaches. They receive information concretely, actively process it, learn through trial and error, are adaptable to changes, and can easily communicate with others (20, 25). Researchers and the learning styles they define are presented in Table 2.

Table 2. Researchers and the learning styles they define.

Researchers	Learning styles they define
Gregorc, 1984	Concrete Sequential Learning Style Concrete Random Learning Style Abstract Sequential Learning Style Abstract Random Learning Style
Kolb, 2007	Diverging Learning Style Assimilating Learning Style Converging Learning Style Accommodating Learning Style
Felder & Silvermann, 1996	Sensing - Intuitive Learning Style Visual and Auditory Learning Style Active - Reflective Learning Style Sequential and Global Learning Style
Fleming & Mills, 1992	Visual Learning Style Auditory Learning Style Reading/Writing Learning Style Kinesthetic Learning Style
Reinert, 1976	Visual Learning Style Auditory Learning Style Learning Style with Verbal Symbols Movement-Based Learning Style
Grasha, 2000	Competitive Learning Style Collaborative Learning Style Avoidant Learning Style Participant Learning Style Dependent Learning Style Independent Learning Style
McCarthy, 1990	Imaginative Learning Style Analytical Learning Style Prudent Learning Style Dynamic Learning Style

As can be seen, different researchers from past to present have defined a wide variety of learning styles in line with their own perspectives. The common goal of all defined learning styles is to help individuals experience an effective learning process and access information in the shortest and most accurate way. However, all learning styles differ from each other in practical application. This is undoubtedly due to individual differences. Therefore, in order to facilitate the learning processes of individuals, it is very important to determine the personal characteristics of individuals, to reveal the learning styles they adopt with different scales, and to raise awareness in individuals on this issue. Furthermore, instructors who determine the commonly preferred learning styles of their students and adapt their teaching methods accordingly will make the learning process more efficient and enjoyable, thereby strengthening the relationship between learners and instructors.

4. Learning Strategies

Learning styles and strategies are closely related and share similar foundational concepts. Learning strategies are not self-formed but are directly linked to individuals' innate learning styles and personality traits. Moreover, individuals' success largely depends on their awareness of their learning styles, which has led to the development of diverse learning strategies. Moreover, individuals' success largely depends on their awareness of learning styles. This situation has caused individuals to develop different learning strategies. Although it is known that the learning strategies preferred during learning are an important criterion for success, there is no clear consensus in the literature regarding the definition and classification of learning strategies. This situation has led to a wide variety of definitions regarding learning strategies by researchers (26, 27, 28). In the most general terms, learning strategies are the learner's efforts or actions to make sense of, appropriate or internalize the information necessary to learn by passing it through her mental processes (29). Consequently, the purpose of the learning strategies employed during the learning process is to influence the learner's affective state and facilitate the selection, organization, and integration of new information (30, 31).

Weinstein & Mayer (1983) defined eight different learning strategies such as basic learning repetition, complex learning repetition, basic sense-making, complex sense-making, basic organizing, complex organizing, comprehension monitoring, and affective strategies (Table 3) (26). This classification has since

been revised to identify five distinct learning strategies: repetition/iteration, sense-making, organizing, comprehension monitoring, and affective strategies (Table 3) (32).

Table 3. Learning Strategies

Researchers	Learning Strategies
Weinstein & Mayer, 1983	Basic Learning Repitition Strategies Complex Learning Repetition Strategies Basic Sense-Making Strategies Complex Sense-Making Strategies Basic Organizing Strategies Complex Organizing Strategies Comprehension Monitoring Strategies Affective Strategies
Özer, 2002	Repetition/Iteration Strategies Sense-Making Strategies Organizing Strategies Comprehension Monitoring Strategies Affective Strategies

4.1. Repetition/Iteration Strategies

Mental repetition serves as the foundation for repetition/iteration strategies, which are effective in learning information intended to be retained as it is; therefore, this strategy is utilized for fundamental learning within the learning process. Additionally, the repetition/iteration learning strategy involves learners effectively naming or ordering the content presented to them sequentially during the learning process. Examples of these strategies include underlining words in the text, taking notes verbatim, and writing without modification. These strategies effectively facilitate two essential learning attributes: selection and acquisition (30, 31).

4.2. Sense-Making Strategies

These strategies rely on the principle of associating information in short-term memory, or newly acquired knowledge, with existing information to facilitate its transfer to long-term memory. This strategy aims to enhance the meaningfulness of new information by establishing connections between units of information, thereby promoting meaningful learning. Examples of sense-making strategies include constructing sentences, expressing verbal information

in various ways, answering questions, taking notes, creating mental images, simulating scenarios, and summarizing (30, 31, 33).

4.3. Organizing Strategies

These strategies simplify learning by rearranging and structuring the information to be learned and are often used alongside meaning-making strategies. These strategies encompass tools that assist learners in preparing for the subject matter and systematically comprehending both previously and newly acquired information. Organizing strategies may involve grouping terms or ideas, dividing them into smaller subsections, identifying key concepts, or extracting main ideas from larger bodies of information. Examples of these strategies include outlining, creating informational diagrams, and tabulating (30, 31, 33).

4.4. Comprehension Monitoring Strategies

These strategies help learners organize, manage, and control their own learning processes. The things that learners adopt in this strategy are certain learning ability to use strategies and reflection on their own thinking. Additionally, these strategies consist of two basic elements such as knowledge about cognition and monitoring cognition. Examples of these learning strategies include identifying and addressing problems, focusing attention and directing responses, self-reinforcement and evaluation, as well as correcting mistakes and generating solutions (30, 31).

4.5. Affective Strategies

Individuals may encounter various difficulties arising from emotional factors during the learning process. To overcome these challenges, individuals need to employ strategies that motivate them. Affective strategies are used to eliminate obstacles to learning caused by affective or motivational factors. These strategies typically foster the creation and maintenance of suitable external and internal conditions for effective learning. Moreover, these strategies encompass skills such as remaining alert and relaxed to stimuli, maintaining concentration, focusing carefully, determining priority issues, selecting a quiet workspace, developing positive attitudes, reducing anxiety, and providing positive self-reinforcement (26). Examples of these strategies include concentrating attention, developing positive attitudes, enhancing motivation, and reducing anxiety. In this context, individuals engaging in negative self-talk can overcome this by making positive affirmations, developing positive attitudes towards learning

by identifying the roots of their negativity, reconciling new information with existing knowledge and previously learned ideas, and alleviating excessive anxiety through regular practice, achieving success, and enhancing self-confidence.

5. Conclusion

This section has summarized learning, learning styles, and learning strategies. Learning is a dynamic process that continues throughout life. Consequently, individuals continue to learn in every aspect of life at all times. In the learning process, individuals adopt different learning styles and strategies. A diverse range of learning styles and strategies has been defined by researchers throughout history. These learning styles and strategies, defined by various authors, appear to be closely related and grounded in similar foundational concepts. However, preferred learning styles and strategies may vary depending on individuals' cognitive and personal characteristics. Furthermore, an individual's ability to learn effectively and achieve success hinges on utilizing the most suitable learning styles and strategies. Thus, raising awareness about learning styles and strategies from an early age is essential.

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CHAPTER XV

NEURO LINGUISTIC PROGRAMMING AND LEARNING

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1. Introduction

Neuro-Linguistic Programming (NLP) is described as a set of communication techniques that work together to support personal development, adaptation, and learning strategies. It was developed in the early 1970s at the University of Santa Cruz in California (1). NLP emerged from the research of Richard Bandler and John Grinder, who studied the characteristics that contribute to the exceptional success of individuals (2). NLP is an approach aimed at teaching people how to use their brains more effectively. By learning to program their brains, individuals become aware of their latent potential. NLP helps individuals become more successful by reducing stress and anxiety, increasing self-confidence, and motivating them toward success. NLP views learning from a positive perspective, linking thoughts, words, and behaviors to goals in order to enhance effectiveness and success (3).

2. Neuro Linguistic Programming (NLP)

NLP is considered a way to codify and replicate excellence, helping people achieve their desired goals (4). It is also a method that allows people to use their brains more effectively and productively (5,6). NLP applies techniques to organize the nervous system to achieve goals (7). According to O'Connor, NLP focuses on the high-level use of intelligence and how we structure our experiences. NLP is not just a set of techniques but also a way of thinking (8). It

is a field of study that examines individuals' cognitive, linguistic, and behavioral structures, teaching and implementing their effective use (9).

NLP enables individuals to enhance creativity, develop free behavior, set goals, and create opportunities to achieve those goals successfully (10). It analyzes the strategies employed by successful individuals and puts them into practice to achieve personal goals. It connects thoughts, language, and behavioral patterns learned through experience with specific outcomes (1). NLP is also an educational method that teaches how to apply these relationships in education, work, communication, and therapy. Since our minds work through programs, we need to program them to change emotions, thoughts, and behaviors and to improve performance (11). Without changing our mental programming, we may struggle to achieve desired results. Proper programming improves brain performance, which is why it's essential to work on enhancing it rather than setting limits (12).

NLP combines three core areas:

- *Neuro*: How do the brain and thoughts function? Neuro refers to how we mentally organize our lives. It involves our perception of the external world through our sensory organs, such as sight, smell, hearing, touch, and taste, and the neurological processes related to these perceptions. The way a person's brain processes sensory information is crucial. The nervous system, acting as the body's electrical system, spans the entire body and mind, and each person's system is unique in its abilities (8,13,1). Neuro describes how people experience the world through their senses, translating these experiences into conscious and unconscious thought processes, which in turn activate the neurological system (14).

- *Linguistics*: This domain of NLP concerns the use of verbal and non-verbal language systems through which individuals communicate both internally and externally. How do we interpret our experiences and assign meaning to them? Changes in language can lead to physiological and neurological shifts. It explains how language use impacts both the individual and those around them (13,1).

- *Programming*: How do we organize our actions to achieve a goal? Programming refers to how we train the mind by analyzing behavioral and linguistic patterns to increase attention and accomplish set goals (15). It focuses on how people encode or mentally represent their experiences and applies learning theory. Programming encompasses the processes and

strategies individuals use to think, learn, make decisions, solve problems, evaluate, and achieve results (8,13,16). NLP reflects how we organize thoughts and actions (15).

NLP shows individuals how to organize their internal programming and recode experiences to achieve desired outcomes (16). The essence of NLP is to create a positive, well-structured individual capable of setting and pursuing goals that benefit themselves and others. In this context, NLP enhances effective communication, personal development, mental control, and overall life quality (10).

While NLP focuses on personal development and change, achieving these requires the individual to believe in the process and be willing to engage in it. Goal orientation and determination are key to success. Furthermore, individuals must establish relationships based on learning and interaction, planning and structuring their goals accordingly (8). NLP is noted for helping people overcome fears, anxieties, prejudices, beliefs, and limitations. However, it also enables individuals to achieve much more (17).

2.1. Principles of NLP

NLP, which offers important techniques for personal development and achieving excellence, is based on the following fundamental elements (results, rapport, sensory acuity, flexibility) (5, 8, 4):

Results: The central question NLP seeks to answer is “What do you want?” Knowing what one wants is essential for success. Once an individual identifies their desired result, they can begin their journey. This principle consists of five steps:

- Evaluating the goal as important and highly desirable.
- Focusing on the goal and channeling the mind toward it.
- Visualizing the goal, creating a clear mental image.
- Concentrating on the process and evaluating all necessary resources.
- Taking action to achieve the goal.

Success requires clarity and focus on one’s goals.

Rapport: Essential for effective communication, rapport involves making an effort to understand and respect the other person. Being able to view things from their perspective is crucial. NLP provides the skills needed to build

relationships based on understanding and respect. Over time, rapport can develop into trust.

Sensory acuity: This refers to individuals' awareness of their surroundings and events by using their senses. Paying attention to how others communicate—listening, making eye contact, and observing—helps understand their values. The more sensory acuity one develops, the greater their awareness of subtle changes.

Flexibility: If ongoing actions aren't yielding results, flexibility is necessary. This means being open to trying new methods and approaching tasks differently.

3. NLP and Learning

Our brain is like a network woven with nerve cells, and these nerve cells (neurons) act as communication hubs. Neurons receive signals from other cells, process them, and transmit them to other cells through synapses. This electrochemical process forms the basis of human behavior. Every time we think, speak, or move, electrical and chemical communication takes place between tens of thousands of neurons. We process all incoming information through these networks, and previously stored information influences how and what we learn. Learning new information, combining it with prior knowledge, and recalling information we thought we had forgotten are all functions of this network. No two human brains are alike (18). Learning is a mental activity, and every learning experience results in an increase in synaptic connections in the brain. These connections strengthen and develop with use. In this sense, stimulating the brain with experience and information is vital for its development. All experiences, even those before birth, contribute to brain development (19).

Learning is considered a concept that explains personal development. We learn to act, feel, and think in various ways. During the learning process, levels of consciousness vary depending on different learning stages, which consist of four stages (8,20):

Unconscious Incompetence: At this level, the individual is unaware of what they do not know or what they could achieve with knowledge.

Conscious Incompetence: The individual is aware of their lack of competence in a subject and realizes how much more there is to learn.

Conscious Competence: The individual has acquired a skill but it has not yet become a habit; this stage is satisfactory but progress may slow.

Unconscious Competence: The skill becomes automatic, requiring no conscious thought, allowing the individual to focus on other tasks.

According to O’Connor, a fifth stage, Mastery, should be added. Mastery is more than just conscious competence; it reflects a state where the person works effortlessly, often experiencing a “flow” state (8). The learning process is a mental activity, and for learning to be effective and lasting, it is essential to use brain functions actively (19).

Learning takes time, no matter the level. Receiving a good education is crucial for effective learning. In a successful learning process, a good teacher breaks down complex tasks into manageable steps, maintains interest, and ensures motivation and mood remain positive. Good teachers don’t just impart knowledge—they also teach effective learning strategies (8). It has been stated that using NLP in classrooms enhances relationships, facilitates teaching, and improves learning (13).

NLP provides individuals with skills, strategies, and techniques to overcome mental challenges encountered throughout life. This model helps people understand how their brain functions and prepares it to work toward their goals. It utilizes many conceptual ideas and techniques to achieve this. Through these techniques, individuals improve their internal learning processes (21).

In the teaching and learning process, NLP emphasizes the importance of communication. NLP supports effective communication through various strategies and techniques to help achieve academic success (22). NLP ensures that no student is left behind in the learning process, recognizing that every student learns differently. Different techniques can be employed for effective learning; otherwise, the process may suffer. Therefore, it is important for educators to understand how their students learn most effectively. Achieving this requires effective communication between educators and students. NLP plays a vital role in developing students’ communication skills, improving their learning processes, and enhancing achievement (23).

The emotional state of the learner is critical in the learning process. Learning occurs through emotions such as curiosity, interest, excitement, and engagement. If these emotions are absent, learning becomes more challenging. The information that a person needs should align with what is being presented to achieve a shared goal. When this alignment happens, individuals are more willing to learn voluntarily. For this reason, teachers strive to foster positive emotional states in their students (8,24).

Teaching is a dynamic process. In this sense, teaching is not simply about ‘imparting information,’ but rather about equipping students with the skills they need to effectively and efficiently manage their own learning processes. Students should be able to take initiative in their learning without relying on others. This is where the concept of “learning to learn” becomes important (25).

Learning to learn means understanding how one learns best. It also means being consciously involved in the learning process. With this awareness, individuals experience a more efficient and enjoyable learning process. When a person learns to learn, they strive to create a mental map that reflects external reality as accurately as possible (26).

It is essential for individuals to understand their brain’s capabilities, their potential, and their abilities for successful learning. Becoming more independent, creative, critical, and constructive, as well as developing problem-solving skills, are vital components of learning to learn (27). NLP helps individuals better understand and manage their mental processes. It plays a key role in solving problems encountered in learning and increasing motivation. By using NLP techniques, students can discover their own learning styles, manage negative emotions, and experience a more successful learning process.

4. Improving Learning Skills with NLP Techniques

NLP is a collection of techniques that provide insight into how individuals think, how they communicate with themselves and others, and how this communication creates different behavioral patterns. Accordingly, NLP aims to eliminate fears, desires, and mental or emotional obstacles that may hinder learning, using techniques that seek to transform behavioral patterns from negative to positive and from failure to success. It refers to a holistic and flexible approach, taking into account individual needs and desires (28,29). In this context, NLP techniques that impact the learning process are outlined below.

4.1. Representation Systems

Everyone has a unique worldview. People experience the world through their senses, but they do not all use their senses in the same way; thus, everyone tends to have their own system of representation. We collect and learn information through our five senses. The more we engage our sense organs in the learning process, the better we remember that information. For example, when we see, hear, and practice how something is done, it becomes harder to forget. The more

we activate our neurological system, the faster and more effectively we learn. Information and experiences are stored in the conscious and subconscious mind through the five senses, but we process our internal and external experiences through three primary channels. When we access information, we rely on one of these channels—visual, auditory, or kinesthetic. We learn most effectively through our dominant channel. While everyone uses all their senses, one typically predominates. NLP emphasizes that individuals can create effective and powerful internal representations. The more visual, auditory, and kinesthetic information included in these representations, the stronger and more memorable the experience becomes (12,13).

Visual learners tend to use their imagination more and find it easier to learn by seeing. Their learning is most effective when they can watch or read. For them, tools like maps, posters, presentations, and diagrams are particularly beneficial. Through visualization, a transformation occurs in the conscious mind, which activates the representational system (21). Auditory learners, in contrast, learn best when information is delivered verbally and through discussions. These learners excel at listening and enjoy engaging in conversations (30, 31). Kinesthetic learners benefit more from hands-on experiences; they learn best by touching, applying, and moving. Participating in activities and practice-based learning is crucial for them (12). Flexibility and a recognition of individual differences are central to NLP (5). By understanding individuals' representational systems and how they are applied, we can adopt more effective approaches to influencing others (32). Knowing how students' minds work is key to understanding them (33). If educators apply techniques that align with students' learning preferences, they can facilitate learning more easily, quickly, and naturally.

4.2. Creating Harmony

Harmony is considered a quality relationship based on interaction and respect between two people. Adaptation is essential for strong communication. NLP supports the development of the necessary skills to form relationships grounded in mutual respect and understanding. Without good relationships, harmony cannot be expected to emerge. Adaptation is crucial for the success of learning processes, as harmony fosters a positive learning environment. It enhances learning effectiveness and motivation by creating a sense of community, unity, focus, and participation (8,34). NLP emphasizes the importance of understanding individuals' preferred learning styles and uses various concepts

to empower them, showing that they have the ability to overcome obstacles and take control of their work (35). Harmony also helps establish a bond of mutual understanding. Building a relationship between teachers and students enhances the overall learning experience for students (36).

4.3. Modeling

Another important application of NLP is modeling, which involves observing and applying the behaviors and strategies of successful people (37). In modeling, how a task is accomplished is key. It is viewed as the discovery of excellence, where what institutions or individuals achieve independently is considered a form of perfection (4). Success can be modeled and taught to others. By identifying the strategies of successful individuals, students can develop suitable strategies for themselves to reach their goals. However, modeling does not imply copying someone exactly; rather, it focuses on replicating the process or method employed by successful people (8,38). Modeling is about achieving conscious competence and mastery over acquired skills. With practice, these skills become habits—a way of thinking. NLP helps individuals learn not only how to learn but also how to be successful (39).

4.4. Reframing

People assign meaning to events based on their values, beliefs, and experiences. Reframing involves changing a person's perception of an event, thus altering its meaning. If the meaning changes, their reactions and behaviors also shift (8,4). Reframing encourages looking at negative events from different perspectives, fostering self-improvement, creativity, and mental flexibility. By interpreting events in a more positive light, motivation increases. The reframing technique involves reinterpreting a situation or event from a different perspective, thereby changing its emotional impact.

4.5. Meta Model

In NLP, the Meta Model is used to clarify and make language more understandable. It focuses on how thoughts are transformed into words, aiming to reveal the limiting elements in communication. The Meta Model addresses linguistic patterns that cause uncertainty, using questions to refine these patterns (8,21). For instance, when someone claims, "I'm a failure," the statement may stem from past experiences that shaped this belief. The Meta Model aims to dismantle such self-imposed limitations, encouraging a more positive

thought process. According to Meta Modeling, three basic elements hinder communication: generalizations, distortions, and deletions. By identifying and clarifying these linguistic ambiguities, the Meta Model promotes more accurate and efficient communication, minimizing misunderstandings and conflicts (12,38,29).

The Meta Model helps individuals break out of stereotyped or prejudiced thinking, fostering analytical and critical thought. This leads to healthier communication and more open learning environments.

4.6. Anchoring

Anchoring is an NLP technique that trains the mind to associate specific stimuli with positive emotions. For instance, when a particular sound, sight, or sensation consistently evokes the same response, this is called anchoring. Anchoring helps students shift into a relaxed or confident state when feeling anxious or upset (21).

4.7. Metaphor

Metaphors in NLP are tools like stories, comparisons, or analogies that explain complex concepts. Metaphors facilitate the understanding of abstract ideas, sparking creativity and enabling individuals to express themselves more freely (8,40). They enhance narratives and improve learning by linking new information to known experiences (41).

5. Studies on NLP and Learning

In a study conducted by Lashkariana and Sayadiana in 2015, the effect of using NLP techniques on the learning development and motivation levels of Iranian English students was evaluated. It has been observed that English learners show a significant improvement in their English proficiency after taking NLP techniques, as well as an increase in their motivation levels. Establishing more effective communication with students during the learning process with NLP techniques is very important in terms of strengthening the learning environment and increasing academic success (34).

In the study conducted by Manana et al. (2024) with Lebanese children aged 6-11, the effect of NLP techniques on the intellectual capacity of children was evaluated. It has been stated that there is a significant increase in the academic success of students trained with NLP, and that it increases the cognitive development of children over the age of 8 (42).

In the study by Rumawan et al. (2018), it was stated that there was a significant difference between students who learned to write narrative text through Neurolinguistic Programming and students who learned to write narrative text using the traditional method, and that the average scores of students who learned using the NLP method were higher (43).

In the study conducted by Rustan (2017), the situation of high school students in learning creative writing and the effectiveness of the NLP model in learning creative writing were evaluated. As a result of the data obtained from the study, it was seen that the average scores of students who learned creative writing with the NLP model were higher than those who learned with the traditional method. It has been stated that learning to write short stories with NLP's creative learning-based learning model improves students' creative writing skills more effectively than traditional learning (44).

In Pratama et al.'s (2019) study, it was evaluated whether the training provided using NLP techniques had an effect on students' text writing skills and self-efficacy. According to the study, it was stated that NLP techniques were effective in increasing students' vocabulary knowledge, developing writing skills and self-efficacy, and also increased students' motivation to practice writing on their own (45).

In the study conducted by Taşpınar et al. (2007) with students of the faculty of education, an experimental and control group was formed from students taking "Introduction to the Teaching Profession" and "Development and Learning" courses. Students in the experimental groups were given training in which NLP principles and their effects were explained with examples. As a result of the research, it was observed that the students used the concepts of "success" and "goodwill", which are among the concepts that constitute NLP principles. Additionally, it has been observed that students who received this explanation increased their success in their courses (46).

In Acaralı's (2009) study titled "NLP Techniques in Acquiring Basic Skills in Violin Education", the effect of students' NLP techniques on education was evaluated. In the study, it was stated that studies were carried out to increase communication and interaction in the classroom by adapting NLP techniques, and activities were developed for students' representation systems. As a result of the study, it was emphasized that there was a significant positive effect on the violin playing performance of students to whom NLP techniques were applied (47).

In the study conducted by Işık in 2019, the effect of painting education supported by NLP on students' painting studies was evaluated. Activities were

organized for students' representation systems, and story and music activities were carried out to change students' negative beliefs about painting. As a result of the study, it was stated that NLP-supported education had a positive impact on the students and that they gained different perspectives in the paintings they made (48).

In his study, Gülten (2012) examined the effects of classroom activities prepared according to NLP techniques on the foreign language learning process in children. While one group was taught vocabulary using traditional methods, the other group was trained using songs and activities prepared with NLP techniques. As a result of the analysis, it was seen that students who received training according to NLP techniques were able to remember the words taught more easily. At the same time, the use of songs and NLP activities in education increased class participation and motivation (49).

In the study conducted by Abbassy et al. (2018), the effectiveness of NLP techniques in improving the English oral communication skills of university students learning English for special purposes was evaluated. Participants in the current study were randomly divided into two equal groups. Both groups were taught by the same instructor, and the experimental group was taught through Neuro Linguistic Programming. The control group was given normal type of training. It has been stated that the verbal communication skills of students using NLP techniques have improved more than other students. With the data obtained, it can be concluded that Neurolinguistic Programming is effective in improving students' English oral communication skills (50).

6. Conclusion

NLP consists of techniques designed to use the human brain more efficiently. The way people perceive the world and the way they think is completely unique to them. A person's peace, good relationships and success in life can be created by programming the mindset. NLP allows the mind to work more productively. According to NLP, when a person knows what he wants, he can take action towards the goal and achieve success. In addition, it is of great importance for a person to establish good communication with those around him and to maintain his relationships with respect and understanding. NLP is used in many areas such as working life, personal development, education and training, and sports. It states that people should be aware of their own powers and use these powers when they need them. NLP helps people become aware of these powers. It suggests strategies and techniques on how to solve the problems you encounter. It gives guidance on how a person can use his brain better during

the learning process and what kind of work he should do. Studies have shown that NLP is effective in helping people achieve more successful results in the learning process.

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CHAPTER XVI

EFFECTS OF LEARNING SIGN LANGUAGE ON LANGUAGE ABILITY AND COGNITIVE PROCESSING

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1. Introduction

Sign language is a linguistic system that addresses the communication needs of the deaf individuals and relies on visual and kinesthetic elements. Understanding the effects of sign language on linguistic and cognitive processes raises significant scientific questions not only for deaf individuals but also for general language learning and brain functions. Sign language offers a visual-kinesthetic mode of expression, distinct from traditional auditory-verbal languages, and this provides various opportunities to investigate its effects on language learning processes and cognitive functions.

The impact of sign language on linguistic abilities has been explored through extensive research on language comprehension, production, and processing. Sign language includes unique phonological, morphological, and syntactic structures, which enable learners to develop advanced linguistic skills. “For example, Padden ve Humphries (2005) examined how the grammatical structures of sign language contribute to the development of individuals’ language abilities. Liddell ve Johnson (1989) investigated how the acquisition of sign language, particularly during childhood, affects language development and highlighted its impact on verbal language skills (2).

The effects on cognitive processing are crucial for understanding the impact of sign language on cognitive functions. The visual and kinesthetic nature of

sign language is important for studying how it affects spatial thinking, attention, and memory processes. Emmorey (2002) explored how learning sign language enhances spatial reasoning skills and the implications of these improvements for overall cognitive functioning (3). Additionally, the visual analysis and motor skills required by sign language may positively impact attentional processes. Another study conducted by Bavelier (2001) examined how sign language improves individuals' attention and visual processing capacities, suggesting that these improvements may lead to cognitive advantages (4).

Memory and problem-solving abilities are also areas significantly affected by learning sign language. The need to process sign language structures rapidly can enhance individuals' memory capacities and problem-solving strategies (5).

Neurologically, learning sign language is associated with specific adaptations in the brain's auditory and visual-motor regions. For deaf individuals, learning sign language involves the activation of the visual and motor cortices instead of the auditory cortex. One study by Neville et al. (1998) investigated how these changes in brain structures resulting from sign language influence individuals' cognitive and linguistic functions (6).

In this context, understanding the effects of sign language on linguistic abilities and cognitive processes contributes to our comprehension of the role of this language in learning and brain functions from both linguistic and neuroscience perspectives.

2. Concept of Sign Language and Linguistic Features

Sign language is a mode of communication used by deaf and hard-of-hearing individuals, involving the use of the hands, fingers, facial expressions, and body movements instead of spoken words (7). Sign languages are visual and kinesthetic systems that convey meaning and are recognized natural languages in their own right. These languages serve as an integral part of the cultural and social identity of deaf communities (8).

Visual-Kinesthetic Communication: Unlike spoken languages, sign languages utilize visual and kinesthetic communication channels. The formation and understanding of signs depend on a combination of hand movements, finger placements, facial expressions, and body language. This characteristic makes sign language an effective communication tool for individuals with visual-kinesthetic learning preferences (3).

Grammar and Syntax: Sign languages are independent linguistic systems with their own grammatical structures. In these languages, the ordering of signs, grammatical categories (nouns, verbs, adjectives, etc.), and sentence structures play a crucial role in meaning creation. The grammar and syntax rules in sign languages determine their ability to produce and express meaning (10).

Cultural and Social Context: Sign languages are shaped by the cultural and social contexts of specific communities. The evolution of the language, vocabulary, and meaning production develops according to cultural references and social norms (9). This context reveals the relationship between sign language and societal and cultural structures.

Language Diversity: There are many different sign languages worldwide, varying according to geographic, cultural, and historical differences. For example, American Sign Language (ASL) and Turkish Sign Language (TİD) are based on different linguistic families and cultural backgrounds (1). This diversity reflects the linguistic independence and specificity of sign languages.

Evolutionary Dynamism: Sign languages evolve dynamically due to factors such as social changes, technological innovations, and cultural transformations (3). This process demonstrates their ability to adapt to innovations and modern concepts, thus highlighting the ongoing development and adaptation of sign languages.

3. Importance of Sign Language

Sign language is a crucial communication tool for deaf individuals. Sign language replaces spoken language and operates as a visual-gestural system that enables deaf individuals to express themselves and communicate effectively with others. The significance of sign language can be summarized under several key headings:

Communication and Understanding: Sign language allows deaf individuals to communicate effectively. Visual and kinesthetic signs, which replace spoken words, enable deaf individuals to express themselves and interact effectively with others. This aspect of sign language helps overcome communication barriers and enables deaf individuals to actively participate in social life (1). For instance, sign language assists deaf individuals in better managing challenges they face in daily life and strengthening their social connections (7).

Cultural Identity and Social Belonging: Sign language is a crucial element in reinforcing the cultural identity and sense of belonging of deaf

communities. It reflects the cultural values, traditions, and social norms of these communities and aiding in the preservation of their cultural heritage (8). Sign language creates a strong cultural bond among deaf individuals and strengthens their sense of social belonging (10). Moreover, the use of sign language enriches cultural expressions and social relationships within deaf communities.

Education and Access to Information: In education, sign language significantly enhances deaf individuals' access to academic knowledge and learning processes. Educational materials and teaching strategies based on sign language enable deaf students to develop their linguistic and academic skills. Education through sign language enhances students' academic performance and promotes educational equity (12). The role of sign language in education improves students' academic achievements and social skills (1).

Social Integration and Rights: Recognizing and supporting of sign language promote the social integration of deaf individuals and their access to equal rights. The use of sign language increases participation in social life and upholds the principles of accessibility and equality for deaf individuals (3). The impact of sign language on social integration facilitates deaf individuals' access to social and economic opportunities and promotes social justice (14).

4. Applications of Sign Language

Education: Sign language has a wide range of applications in special education institutions and mainstream education systems. In education, sign language enhances the academic success of deaf individuals and facilitates their access to educational materials. Education through sign language aids students in developing their linguistic and academic skills (1). Moreover, sign language-supported teaching strategies enhance the learning processes of deaf students (12).

Healthcare Services: In healthcare settings, sign language ensures that deaf individuals can access health information and communicate effectively with healthcare professionals. Sign language interpreters and sign language-supported health services contribute to the safeguarding of patient rights and the enhancement of healthcare quality (8). The role of sign language in the healthcare sector supports the accessibility of health services and effective communication (15).

Legal and Public Services: In the fields of law and public services, sign language facilitates deaf individuals' access to legal processes and public

services. Sign language interpreters in judicial proceedings and public services safeguard the rights of deaf individuals and contribute to the administration of justice (9). The use of sign language in legal and public services supports social equality and accessibility (16).

Media and Entertainment: In media and entertainment, sign language is used in television programs, films, and other media content to provide deaf individuals access to cultural content. Sign language subtitles and interpretations enhance media content accessibility content and support equal access to cultural and entertainment materials for deaf individuals. (3-17). Sign language applications in media and entertainment promote social integration and cultural access.

Social Events and Interactions: The use of sign language in social events and interactions allows deaf individuals to participate effectively in society. The application of sign language in social events fosters social diversity and inclusivity, aiding deaf individuals in establishing social connections (8-18). Sign language promotes equal participation and social bonds in community activities.

5. Effects of Sign Language on Linguistic Abilities: A Comprehensive Scientific Review

Sign language is a visual-kinesthetic linguistic system designed for deaf individuals. The effects of this language system on linguistic abilities encompass a broad area of research regarding language development and cognitive functions. Understanding the impact of sign language on linguistic abilities provides insights into both the language development of deaf individuals and the broader theories of language and cognitive sciences. Presented below is a comprehensive examination of the effects of sign language on linguistic abilities.

5.1. Effects of Sign Language on Language Development

Language Development and Structural Similarities: Sign language plays a crucial role in the language development process of deaf individuals. The process of learning sign language in children shows similarities to the learning processes in spoken languages. Children learning sign language go through universal stages of language development and acquire the grammatical structures vocabulary, and sign systems of the language (1). Deaf children learning sign language experience similar developmental stages as hearing

children and develop their linguistic abilities through this process. The role of sign language in this language development process facilitates the learning of structural features and grammatical rules of the language (7).

Cognitive Functions and the Impact of Sign Language: The impact of sign language on cognitive functions includes the development of visual and kinesthetic processing skills. Individuals communicating through sign language may develop strong skills in processing visual-spatial information. Sign language users often exhibit significant improvements in visual-spatial processing abilities and memory capacities (3). The effects of sign language on cognitive functions suggest that deaf individuals process visual and kinesthetic information more effectively than auditory or spoken information (10). This development aids in understanding how linguistic and cognitive processes integrate, highlighting the positive effects of sign language on cognitive functions.

Bilingual Competence and Sign Language Use: Sign language offers an opportunity for deaf individuals to develop bilingual competence. Bilingual individuals develop the ability to switch between two languages, enhancing their language skills (9). Bilingual individuals' learning of both languages' grammatical and structural features enhances their language abilities and cognitive skills (11). Understanding how sign language supports bilingual competence and how individuals transition between two languages is crucial for integrating language development and cognitive functions.

Social and Effective Communication Skills: One of the effects of sign language on linguistic abilities is the development of social and effective communication skills. Sign language serves as an effective communication tool in social interactions, strengthening individuals' social bonds. This indicates the potential of sign language to enhance social communication skills and empathy. The effect of sign language on social communication skills enhances the role of deaf individuals in societal relationships and interaction capabilities.

Linguistic Creativity and the Uniqueness of Sign Language: Another effect of sign language on linguistic abilities is the promotion of linguistic creativity. Sign language allows individuals to develop originality in linguistic expressions and supports linguistic creativity (9). This capacity for originality in sign language enhances the diversity of linguistic expressions and aids in the development of individuals' language skills. The uniqueness of sign language fosters linguistic creativity and diversity in expressions, aiding in the understanding of how linguistic abilities develop.

6. Effects of Sign Language on Cognitive Processing

Sign language is a communication mode for deaf individuals, serving as an alternative to auditory communication and relying on visual-kinesthetic signs. The effects of sign language on cognitive processing are significant for language learning, cognitive functions, and overall mental health. Understanding the impact of sign language on cognitive processing deepens our comprehension of both the cognitive development of deaf individuals and broader theories in cognitive science and language. Below, we discuss the effects of sign language on cognitive processing in detail.

7. Effects of Sign Language on Cognitive Processing

Visual-Spatial Processing Abilities: Sign language has a significant impact on developing visual-spatial processing abilities. Sign language users must visually encode and interpret the meanings and structures of signs. This process can enhance sign language users' visual-spatial processing abilities (3). Research shows that individuals who use sign language perform better on visual-spatial tasks, and these skills play an important role in daily life (21). The impact of sign language on visual-spatial processing helps us understand how these abilities develop and how they relate to mental processing.

Memory and Information Processing: Sign language may also influence memory and information processing. Sign language users must retain signs and their meanings in memory, applying this information when necessary (3). Understanding the effects of sign language on memory and information processing is key to exploring how the memory capacities and processing strategies of deaf individuals might differ (10). These effects of sign language can aid in understanding how linguistic and cognitive processing integrate.

Linguistic and Cognitive Flexibility: Sign language may promote linguistic and cognitive flexibility. Sign language users may switch between two distinct language systems (sign and spoken language), potentially enhancing their cognitive flexibility (9). Bilingual individuals develop linguistic and cognitive flexibility by switching between language systems. The ability to transition between sign and spoken languages may increase linguistic and cognitive flexibility (11). This aids in understanding the role of sign language in cognitive flexibility and its impact on mental processing.

Empathy and Social Cognition: Sign language may further influence empathy and social cognition. Individuals using sign language often develop

heightened empathy and sensitivity in social interactions (1). Exploring this effect of sign language provides insight into the development of social cognitive skills in deaf individuals and the promotion of empathy.” “Sign language’s role in social interactions can enhance individuals’ social bonds and communication skills.”

Cognitive Investment: Sign language may also influence cognitive investment. Learning sign language demands cognitive and linguistic investment, potentially enhancing cognitive skills (9). The process of acquiring and using sign language can improve cognitive and linguistic abilities, clarifying its overall impact on mental processing.

8. Effects of Sign Language on Neurological Adaptations and Brain Structures

Sign language, primarily used by deaf individuals, is a language system based on visual-kinesthetic signs. Understanding how sign language influences neurological adaptations and brain structures is vital for grasping how language learning and usage are represented and processed in the brain. Sign language’s impact on brain structures offers deeper insights into the cognitive and neurological traits of deaf individuals. The following section will detail the effects of sign language on neurological adaptations and brain structures.

8.1. Effects of Sign Language on Neurological Adaptations

Functional Adaptation of Brain Hemispheres: The use of sign language induces to significant changes in the functional organization of brain hemispheres. In deaf individuals, however hearing and language processing are typically concentrated in the left hemisphere, sign language may enhance the involvement of the right hemisphere in visual-spatial processing and motor control. Emmorey (2002) and other studies show that sign language users exhibit heightened activity in the left hemisphere related to linguistic functions, while the right hemisphere plays a crucial role in visual and motor processing (3). This highlights how sign language influences functional adaptations and organizational changes in brain structures (1-20).

Plastic Changes in Visual-Motor Processing and Brain Structures: Learning sign language can induce plastic changes in brain structures associated with visual and motor processing. For sign language users, the interactions between the visual cortex and motor cortex are enhanced (20). Research

conducted by Corina et al (2002) demonstrates that sign language users actively engage both the visual cortex and motor cortex in recognizing and interpreting signs (20). Additionally, neuroplasticity has been observed in brain regions linked to sign language, reflecting both structural and functional changes in the brain during sign language learning (4).

Changes in Linguistic and Cognitive Processing Areas: Sign language causes significant changes in linguistic and cognitive processing areas. The use of sign language can lead to alterations in the Broca and Wernicke areas, which are involved in language processing. Petitto et al. (2000) found that sign language users experience functional changes in these brain regions associated with linguistic processing and develop distinct neural representations related to sign language (22). These findings are important for understanding the linguistic and cognitive effects of sign language on brain structures.

Neuroplasticity and Brain Adaptations to Sign Language: The learning of sign language promotes neuroplastic changes in brain structures. Neuroplasticity refers to the brain's ability to undergo structural and functional changes in response to learning and environmental stimuli. Bavelier et. al (2001) investigated how sign language learning stimulates neuroplasticity and affects brain adaptations (4). Observed neuroplastic changes during sign language learning help understand how brain regions adapt to the functions associated with sign language and the impact of these adaptations on cognitive processing.

Integration of Auditory and Visual Cortices: Sign language creates an integrated functional connection between auditory and visual cortices, supporting multisensory processing. Corina et al. examined how sign language users might involve the auditory cortex in processing visual information to extract the meaning of signs, demonstrating how this integration supports brain regions' functional connectivity (20). This type of integration is critical for understanding the effects of sign language on brain structures and how multisensory processing operates.

9. Sign Language and Structural Changes in Brain Structures

Reorganization of the Visual Cortex: Sign language leads to significant changes in the structural organization of the visual cortex. The activity of the visual cortex increases for the recognition and processing of signs. Studies by (4) observed expansions and increased activity in the visual cortices of sign language users. These changes demonstrate how the brain's visual processing

capabilities adapts during sign language learning. The reorganization of the visual cortex reflects the effects of sign language on visual-spatial processing processes in the brain.

Motor Cortex and Sign Language: The motor cortex plays a critical role in the production of sign language. Physically performing signs requires greater functional activation of the motor cortex. Research by (27) showed that sign language users experience structural changes and expansions in their motor cortices. These findings reveal that learning sign language promotes neuroplastic adaptations in brain structures related to motor skills. The reorganization of the motor cortex is important for understanding the relationship between sign language production and motor control.

Changes in Broca and Wernicke Areas: Broca and Wernicke areas are brain regions associated with language processing. Sign language can also cause changes in these areas. The Broca area is related to language production, while the Wernicke area is related to language comprehension. Functional changes in these areas have been observed during sign language learning. Pettito et al (2000) reported heightened activity in the Broca area and variations in language processing within the Wernicke area among sign language users (22). These changes are critical for understanding the effects of sign language on the brain's language processing regions.

10. Sign Language and Functional Adaptations

Sensory and Motor Integration: Sign language promotes integration between sensory and motor regions of the brain. The extraction of meaning from signs and the production of signs require coordinated functioning of the visual and motor cortices. Sign language users utilize both visual and motor information processing to derive meaning from signs. This integration enhances connectivity between brain regions and underscores the role of neuroplasticity (27).

Neuroplasticity and Long-term Adaptations Neuroplasticity supports long-term structural and functional adaptations during sign language learning. Research conducted by Bavelier (2001) examined the effects of sign language acquisition on neuroplasticity and the brain's long-term adaptation processes. Adaptations occurring in various brain regions during sign language learning are important for understanding how cognitive functions related to sign language are reorganized and their effects on cognitive processing.

10. 1. Brain Functions in Deaf Individuals: Neurological and Cognitive Adaptations

Comprehending brain functions in deaf individuals is essential for understanding neurological and cognitive adaptations. This section will comprehensively examine changes in brain functions among deaf individuals, neuroplasticity, and cognitive adaptations associated with hearing impairment.

Structural and Functional Changes in the Auditory Cortex: In deaf individuals, changes in the functional and structural properties of the auditory cortex are important for understanding how the brain responds to hearing loss. The auditory cortex typically processes auditory information. However, in the case of hearing loss, the auditory cortex shifts from auditory functions to processing other sensory information. Bavelier D et. al (2001) observed that in deaf individuals, the auditory cortex's capacity for processing visual and somatosensory information increased (4). Such neuroplastic changes reflect the brain's ability to adapt to environmental stimuli and the effects of hearing loss on brain structures.

Sensory and Motor Integration: Hearing loss influences the integration between sensory and motor systems in the brain. Deaf individuals often exhibit heightened use and development of alternative sensory modalities, such as visual and somatosensory. Saito et. al (2005) reported showed structural changes in the motor cortices and increased activity in the visual cortices of deaf individuals (27). Hearing loss may enhance the integration of visual and motor regions in the brain and support learning alternative communication methods like sign language. These adaptations affect the brain's ability to process sensory information and develop motor skills.

Changes in Cognitive Functions: Hearing loss can also result in significant changes in cognitive functions. Deaf individuals may show differences in visual attention, spatial awareness, and cognitive control. Research on deaf individuals has revealed that visual attention and spatial processing abilities are often more developed (3). However, hearing loss can create challenges in social interaction and language processing. Difficulties in linguistic and social skills may encourage deaf individuals to develop cognitive strategies and enhance other cognitive abilities.

Neuroplasticity and Structural Adaptations: Neuroplasticity refers to the brain's ability to undergo structural and functional changes in response to environmental changes, learning processes, and experiences. In deaf individuals,

neuroplasticity supports long-term adaptations in brain structures. Observations of expansions in the visual and motor cortices, along with an increased capacity of the auditory cortex to process alternative sensory information, have been documented in the context of hearing loss (20). Neuroplasticity is an important mechanism for understanding adaptations in sensory and cognitive processes in deaf individuals.

Sign Language and Brain Functions: Sign language, as a common communication method among deaf individuals, affects brain functions. Acquiring and utilizing sign language can notably enhance the functionality of the visual and motor cortices. Petitto et al. (2002) found increased activity in the motor and visual cortices of sign language users (22). The heightened activation of the motor and visual cortices during sign recognition and production represents a significant finding for understanding the effects of sign language on brain functions and its relationship with neuroplasticity.

Sensory-Motor Integration and Cognitive Development: Alterations in brain functions in deaf individuals are a result of sensory-motor integration processes and cognitive development. Despite the limitations imposed by hearing loss, deaf individuals may show development in other sensory modalities and cognitive functions. Sensory-motor integration processes enhance connectivity between various brain regions, aiding individuals in adapting to environmental stimuli. Cognitive development is supported by developing strategies to balance the effects of hearing loss.

11. Supporting Research on the Effects of Sign Language on Language Ability and Mental Processing

Sign language serves as an essential communication medium for deaf individuals, significantly influencing brain functions, language abilities, and cognitive processing. The use of sign language leads to structural and functional changes in various brain regions, resulting in noticeable adaptations in language processing and cognitive processes. This section comprehensively addresses research supporting the effects of sign language on language ability and mental processing, detailing the neurological, linguistic, and cognitive dimensions of these effects.

11.1. Effects of Sign Language on Language Ability: Sign language plays an important role in the development of language ability. “It serves as a foundational tool for acquiring and enhancing linguistic skills among

deaf individuals.” “Users of sign language broaden their linguistic capabilities by understanding both the meanings of signs and their structural configurations.”

a. **Linguistic Structures and Sign Language:** Emmorey et. al (2002) examined the effects of sign language on language ability, revealing how sign language users process linguistic structures (3). Studies show that sign language users place significant importance on the visual and motor aspects of signs in their language processing. Sign language may reorganize brain regions conventionally associated with auditory language processing, resulting in heightened activity in the visual and motor cortices. These adaptations may create significant changes in language processing and lead to the development of different strategies related to linguistic structures.

b. **Sign Language and Language Development** Research by Pyers et. al (2009) investigated the role of sign language in children’s language development (28). The studies demonstrated that children who learn sign language exhibit significant language development in both sign and spoken languages, with sign language proving particularly effective for vocabulary acquisition and understanding linguistic structures. These findings support the role of sign language in linguistic learning processes and the relationship between sign language and language development.

11.2. Effects of Sign Language on Cognitive Processing: The effects of sign language on mental processing can create significant changes in cognitive processes and brain functions. Sign language users experience adaptations in cognitive processes and use different strategies in language processing and communication.

a. **Visual Attention and Sign Language:** Studies by Bavelier et. al (2001) demonstrated that sign language users gain advantages in visual processing and attention skills (4). Learning sign language allows sign language users to process environmental visual information more effectively and enhance their visual attention. The advancement of motor skills and visual processing capabilities associated with sign language offers valuable insights into the impact on these cognitive processes.

b. **Cognitive Strategies and Neurological Adaptations** Research by Corina et al (2007) detailed the brain functions and neurological adaptations of sign language users (20). Increased activity in the motor and visual cortices was observed during sign recognition and production. Such neurological adaptations

are important for understanding how sign language interacts with brain functions and the impact of sign language use on cognitive strategies (20).

12. Neurological Adaptations and Brain Functions

Sign language can lead to neurological adaptations in brain functions, resulting in structural and functional reorganization. These neurological adaptations occurring during sign language learning facilitate functional changes in brain regions and adjustments in cognitive processes.

a. Changes in Brain Structures

Petito et. Al (2000) Reported changes in brain activity observed during sign language learning. Increased activity in the motor and visual cortices of sign language users was noted (22). These findings provide significant data for understanding the effects of sign language on brain functions and neurological adaptations.

b. Sign Language and Neuroplasticity

Marschark et al. (1996) Revealed structural changes in the motor and visual cortices of individuals learning sign language (21). These neuroplastic changes occurring in various brain regions during the learning and use of sign language establish a critical foundation for understanding the effects of sign language.

13. Applied Areas of Sign Language Learning

Sign language learning has significant impacts in various applied areas, enhancing social integration and functionality for individuals with hearing impairments. In the educational field, sign language greatly improves communication and learning processes for students with hearing impairments. Research by Scherer (2006) indicates that the use of sign language enhances learning efficiency in educational settings and positively influences academic success for individuals with hearing impairments (23). Sign language enables teachers to communicate more effectively with students and increases the accessibility of educational materials, providing an equitable educational environment (24).

In professional environments, sign language facilitates the integration of individuals with hearing impairments into the workforce and promotes effective communication within workplaces. Employees who have received sign language training can communicate more effectively with their hearing-impaired colleagues and improve productivity in work processes (25). Sign

language helps individuals with hearing impairments develop their professional skills and enhances their access to career opportunities (26).

In health and social services, the use of sign language improves access to healthcare services and the effectiveness of social support for individuals with hearing impairments. Health professionals' proficiency in sign language facilitates patient-doctor communication, enhances the quality of healthcare services, and improves the treatment process (29). Social service professionals' knowledge of sign language ensures that individuals with hearing impairments can access social services and support programs more effectively (10).

In societal and cultural contexts, sign language learning supports the social integration of individuals with hearing impairments and contributes to the preservation of cultural values. Sign language enables hearing-impaired communities to maintain their forms of cultural expression and pass their cultural heritage to future generations (30). In this context, sign language plays a crucial role in promoting social equality and inclusivity (31).

13.1. Educational and Instructional Methods: Strategies for Learning and Applying Sign Language

Sign language education employs various teaching methods and strategies to support effective communication and social integration for individuals with hearing impairments. Traditional classroom instruction remains the most prevalent approach in sign language teaching, where educators systematically instruct students in sign language rules, grammar, and vocabulary. This method involves using textbooks, visual materials, and interactive activities to ensure structured learning of sign language (32). Another approach, known as immersion, offers students the opportunity to learn sign language in a natural environment. This method encourages students to be in communities where sign language is spoken or to use the language in their daily lives, allowing their language skills to develop in real-life contexts (33).

The integration of technology plays a pivotal role in sign language education. Online courses, video lessons, and sign language applications offer students the ability to learn at their own pace, while providing instructors with opportunities to monitor progress and offer feedback (13). Additionally, virtual reality (VR) and augmented reality (AR) technologies emerge as innovative methods for enhancing sign language learning. These technologies help students develop their sign language skills in an interactive and immersive environment, simulating real-world scenarios for practice (34).

13.2. Clinical and Psychological Applications: Sign Language and Psychological Health

Sign language plays a critical role as a communication tool in clinical and psychological applications for individuals with hearing impairments. In psychological counseling and therapeutic processes, sign language empowers individuals with hearing impairments to establish therapeutic relationships and express their emotional states more effectively. Therapists who know sign language can better understand the emotional and psychological needs of their clients, thereby increasing the effectiveness of the therapy process. In crisis situations, sign language is essential in emergency assistance and support processes (36). The capability of crisis intervention teams to utilize sign language ensures rapid and effective communication with individuals with hearing impairments during emergencies, thereby enhancing the accessibility and efficiency of emergency services (37). Additionally, the use of sign language in support groups strengthens social connections for individuals with hearing impairments and reduces social isolation. These support groups bolster individuals' psychological well-being and foster their social integration (24). Training in sign language for clinical and psychological health professionals is also crucial; such training cultivates professionals' sensitivity to the unique needs of individuals with hearing impairments and enables them to adapt their services accordingly (24). In summary, sign language offers effective communication and support in clinical and psychological applications, positively impacting the overall psychological health and quality of life for individuals with hearing impairments.

13.3. Social and Societal Impacts: Sign Language and Its Role in Society

Sign language has a significant impact on the social integration and societal interactions of individuals with hearing impairments. In terms of social relationships, sign language facilitates the formation of social networks and connections for individuals with hearing impairments. Challenges encountered by those unfamiliar with sign language can exacerbate social isolation while learning and utilizing sign language enhances these individuals' active roles within the community (35). In this context, sign language not only enhances family communication but also deepens friendships, improves social interactions for individuals with hearing impairments, and enables more active participation in societal activities (26).

Concerning societal acceptance and discrimination, sign language generates significant social impacts. Widespread knowledge of sign language can improve understanding and acceptance of individuals with hearing impairments. A lack of familiarity or misconceptions about sign language can perpetuate discrimination and stigmatization (30). Thus, sign language education and awareness initiatives contribute to diminishing societal discrimination and enhancing the social acceptance of individuals with hearing impairments.

Educational and awareness programs have the capacity to amplify the societal impacts of sign language. Expanding sign language education within society heightens awareness of the rights and needs of individuals with hearing impairments, thereby promoting social equality and inclusivity (24). Such programs facilitate both the active participation of individuals with hearing impairments in social life and the increased sensitivity of society towards sign language and individuals with hearing impairments.

From the perspective of cultural identity, sign language enables individuals with hearing impairments to preserve and express the cultural values of their communities. Sign language enables these communities to maintain their traditions and play an active role in cultural activities (1). This situation strengthens the sense of belonging and increases social participation for individuals with hearing impairments.

In conclusion, sign language profoundly impacts the social integration and societal interactions of individuals with hearing impairments. It offers a broad range of impacts from social relationships to societal acceptance and discrimination, education and awareness, and cultural identity and participation. Strengthening the societal impacts of sign language enhances the quality of life for individuals with hearing impairments and supports social equality.

14. Conclusion

Sign language has a comprehensive impact on the social integration, psychological well-being, and social interactions of individuals with hearing impairments. Research indicates that sign language significantly improves individuals' social interactions and societal experiences. The role of sign language in increasing societal acceptance, strengthening social relationships, and providing effective communication in psychological support processes is clearly evident. Educational and teaching methods that support sign language promote more effective participation in social life, while the use of sign

language in psychological counseling and therapy processes allows for a better understanding of clients' emotional and psychological needs (36). In crisis situations, sign language enhances the effectiveness of emergency services and ensures the safety of individuals with hearing impairments (37). Furthermore, the role of sign language education and awareness programs in combating societal acceptance and discrimination increases the social acceptance of individuals with hearing impairments (30).

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CHAPTER XVII

NEUROENTREPRENEURSHIP AND ITS EFFECTS ON LEARNING

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1. Introduction:

Neuropreneurship is the process of commercialising advanced research and technological innovations in the field of neuroscience to create economic and social benefits. This discipline involves the use of in-depth knowledge about the functioning of the brain, the functions of the nervous system, and their effects on human behavior to develop practical applications and products (1). Neuropreneurship requires a multidisciplinary approach; it lies at the intersection of various fields such as neuroscience, psychology, engineering, information technology, and business.

Neuropreneurship offers innovative solutions in a wide range of fields, from biotechnology and medical devices to educational technologies, marketing strategies, mental health, and rehabilitation services. For example, developments such as brain-machine interfaces, neurostimulation devices, cognitive performance-enhancing applications, and neural data analytics can be included in the product portfolio of neuroentrepreneurship (2).

Entrepreneurs in this field shape and optimize neuroscientific research and technologies in line with market needs. This process involves creating new business models, finding investment sources, and complying with legal requirements. It also emphasizes the importance of ethical issues and data privacy, taking care to develop neurotechnologies in a way that is compatible with human rights and societal values. In conclusion, neuroentrepreneurship is

an approach to business development based on innovative thinking and scientific knowledge in the process of commercializing neuroscientific findings. This process requires the integration of both scientific and commercial perspectives and produces solutions aimed at improving the general welfare of society (3).

Neupreneurship differs significantly from traditional entrepreneurship, and these differences are evident at both the theoretical and practical levels. Firstly, neupreneurship is closely related to basic scientific research. Neupreneurs seek to translate the results of advanced research on the brain and nervous system into commercialisable products and services (4). This process requires following the latest discoveries and technological innovations in neuroscience and transforming this knowledge into practical solutions. Traditional entrepreneurship develops new business models and products based on existing market needs. Traditional entrepreneurs can operate in a variety of sectors, and their innovation processes are often based on market trends and consumer demands rather than scientific research.

Secondly, neupreneurship requires a multidisciplinary approach. Neupreneurs work at the intersection of disciplines such as neuroscience, engineering, psychology, information technology, and business. This means that neupreneurship processes are complex and require the integration of different fields of knowledge. Traditional entrepreneurship can also be multidisciplinary, but the depth of scientific and technical knowledge in neupreneurship is greater. Third, neupreneurship is subject to significant regulatory and ethical requirements. Neuroscientific applications often involve sensitive issues related to health and safety, so neuroentrepreneurs must work closely with regulatory agencies and ensure compliance with ethical standards. Human rights and data privacy issues are of great importance, especially in applications such as brain-machine interfaces and neurostimulation devices (5).

Neupreneurship has the motivation to develop solutions aimed at increasing social benefit. Neupreneurs aim to increase the general welfare of society by providing innovative solutions in areas such as health, education, and mental health. This is one of the overlapping aspects of neupreneurship with social entrepreneurship. Traditional entrepreneurship can also provide social benefits, but economic gain is usually at the forefront (1,6,7).

Neupreneurship and neuroscience-based interventions can provide significant benefits in education. Neuroscience education facilitates understanding of cognitive processes and improves educational outcomes by increasing self-efficacy and autonomy. Neuroeducation influences pedagogical

approaches and student knowledge. The proliferation of neurointerventions in educational settings and the availability of accurate information to educators underline the important role of the learning process..

2. History of Neuropreneurship and Studies

Global entrepreneurship research has increased in many disciplines (8,9). Entrepreneurship plays a crucial role in the economic and social development of nations (8); entrepreneurial activities not only stimulate economic growth and innovations in the market but also increase employment levels by providing jobs (9). Entrepreneurship, or certain aspects of entrepreneurship, can be taught, and the entrepreneurial spirit can be created through learning (10). With the increase in entrepreneurial activities, entrepreneurship education is constantly evolving. This trend has been generally recognised by academics focusing on entrepreneurship, which has become a rapidly developing area of research (11). However, researchers have approached this issue from various angles, particularly with regard to the factors that contribute to entrepreneurial behaviour (12,13,14,15).

Several studies have been conducted in different regions and sectors, using survey analysis, experiments, and interviews for data collection and discussion of entrepreneurial behaviour. Turulja et al. (2020) examined the impact of entrepreneurial intention and informal support ; their results showed that family and friends had a significant positive effect on entrepreneurial intention (16). Lopes et al. (2020) investigated environmental factors related to entrepreneurship ; their results showed that students from metropolitan areas or large cities had higher levels of entrepreneurial intentions than students from small cities (17). Authors (18,19) used functional magnetic resonance imaging (fMRI) to analyse decision-making tasks and found that entrepreneurs are more effective in decision-making than managers; entrepreneurs make quick decisions in a shorter time. In addition, another study (20) used functional neuroimaging to examine the decision-making behaviour of entrepreneurs.

In this study, we observed that neuroscience and entrepreneurship have a clear relationship; therefore, it is crucial to discuss common methodologies and trends underlying neuroentrepreneurship research. Two research directions are examined in this study. First, we explored the concept of neuropreneurship and the study of neuropreneurship using scientific research methods. Second, we created a roadmap for entrepreneurial researchers interested in conducting

research on neuropreneurship. Through a summary of key studies, an analysis of co-citation networks, research trends at different points in time, and a summary of neuropreneurship research methods, we provide a guide to neuropreneurship research for entrepreneurs and researchers.

3. Importance of Neuropreneurship Studies

Neuropreneurship refers to the process of transforming neuroscientific findings and technological innovations into commercial products and services. The importance of studies in this field can be evaluated in many aspects, such as the integration of various disciplines, increasing social welfare, revolutionising health services, and accelerating innovation processes (21). While addressing the importance of neuroentrepreneurship at the academic level, it is necessary to consider the opportunities offered by this field and the challenges it faces. The first and most obvious importance of neuroentrepreneurship studies lies in the transformation of neuroscientific research for the benefit of society. Neuroscience provides in-depth knowledge about the brain and the nervous system, enabling this knowledge to be utilised in health, education, and technological developments. For example, neurostimulation devices developed through neuropreneurship have led to significant advances in the treatment of neurological and psychiatric diseases such as Parkinson's disease and depression (22). Such devices have accelerated the process of integration into clinical applications, thanks to the innovative approaches of neuropreneurs (9).

Another important contribution of neuropreneurship is the development of personalised healthcare services. Neurotechnologies enable the creation of personalised treatment and rehabilitation programmes by monitoring the brain activity of individuals. This can be used not only in the treatment of diseases but also in improving the cognitive and emotional capacities of healthy individuals. For example, neurofeedback technologies help individuals control their own brain activity, contributing to stress management and improving focusing skills (23).

Neuroentrepreneurship studies are also of great importance in the field of education. Neuroscientific research contributes to the development of educational technologies by providing a better understanding of learning processes. Using this knowledge, neuroentrepreneurs can create innovative educational tools and platforms that individualise and optimise learning experiences. For example, neuro-educational applications can increase educational success by providing

dynamic learning programmes that can be tailored to students' learning styles and speeds (24).

Neuropreneurship also has important effects on mental health and well-being. The use of neuroscientific findings enables a more accurate assessment of individuals' mental health conditions and the development of effective interventions. Initiatives in this field offer innovative solutions for the early diagnosis and prevention of psychological problems, stress management, and emotional stabilisation. For example, neurotechnological solutions offered through mobile applications and wearable devices help users monitor and manage their mental health (25).

Another important dimension of neuroentrepreneurship is the economic and commercial opportunities it offers. Neuroscience and neurotechnologies make significant contributions to the economy by offering high value-added products and services. By commercialising innovative ideas, neuropreneurs create new jobs and contribute to economic growth. This also encourages academic and industrial collaboration by funding scientific research. Neuropreneurship thus demonstrates the potential of scientific knowledge to create economic value.

Another factor that increases the importance of neuroentrepreneurship is its approach that prioritises social benefit. Neuropreneurs aim to increase the general welfare of society by providing neuroscientific solutions to social problems. This is an aspect that overlaps with social entrepreneurship and enables neuroentrepreneurship to develop solutions that are compatible with values such as human rights, ethics, and sustainability. For example, the ethical use of neurotechnologies requires the protection of individuals' privacy rights and the development of technologies in accordance with human rights (26).

Neuropreneurship refers to the process of the commercialisation of neuroscientific findings and technological innovations. This field is based on a multidisciplinary approach that requires in-depth scientific knowledge about the functioning of the brain and nervous system and strategic business development skills to transform this knowledge into economic and social benefits.

The goals of research in the field of neuroentrepreneurship are wide-ranging and include the development of neurotechnologies, improvement of healthcare, innovation in education, and enhancement of social welfare. We will examine the main goals of neuroentrepreneurship research in detail..

4. Development and Commercialisation of Neurotechnologies

One of the main goals of neuropreneurship research is the development and commercialisation of neurotechnologies. Neurotechnologies include devices and applications used to monitor, modulate, or enhance brain and nervous system functions. This includes innovative technologies such as brain-machine interfaces (BMI), neurostimulation devices, neurofeedback systems, and neuroproteomics tools. It aims to evaluate the efficacy, safety, and feasibility of these technologies and make them suitable for clinical and commercial use. Cost-effectiveness and accessibility of these devices are also important research topics (22, 27, 28, 29).

Neuropreneurship also plays an important role in the development of personalised healthcare services. Neurotechnologies enable the creation of personalised treatment and rehabilitation programmes by monitoring the brain activities of individuals (27). In this context, neuroentrepreneurship research aims to develop personalised health solutions based on genetic, epigenetic, and neurophysiological profiles of individuals. Personalised approaches, especially in the treatment of neurological and psychiatric diseases, can improve the quality of life of patients by increasing treatment efficacy (30).

One of the important goals of neuroentrepreneurship research is to improve mental health and well-being. The use of neuroscientific findings enables a more accurate assessment of the mental health status of individuals and the development of effective interventions. Initiatives in this field offer innovative solutions for early detection and prevention of psychological problems, stress management, and emotional stabilisation. For example, neurotechnological solutions offered through mobile applications and wearable devices help users monitor and manage their mental health. Such applications encourage individuals to manage their own health more consciously and proactively (31).

The field of neuropreneurship in education employs neuroscientific findings to enhance learning processes and provide tailored learning experiences. Neuropreneurs engage in research to comprehend the neural mechanisms underlying the learning process and utilise this understanding to develop innovative educational technologies. This enables the creation of dynamic learning programs that can be adapted to align with students' learning styles and rates. For instance, neuro-educational applications can bolster educational outcomes by optimising students' learning potential.

A further key objective of neuroentrepreneurship research is to deliver social and economic advantages. The field of neuroscience and the development

of neurotechnologies have the potential to significantly contribute to economic growth by providing products and services that offer high value-added benefits. The commercialisation of innovative ideas by neuropreneurs results in the creation of new employment opportunities and contributes to economic growth. Furthermore, this encourages collaboration between academic and industrial partners, with funding provided for scientific research. Neuropreneurship illustrates the capacity of scientific knowledge to generate economic value.

Furthermore, the objective is to enhance the general welfare of society by providing neuroscientific solutions to social issues. Neuropreneurship research strives to adhere to the highest standards of regulatory and ethical conduct. Given the sensitive nature of neuroscientific applications and their potential implications for health and safety, neuropreneurs must collaborate closely with regulatory bodies to ensure compliance with ethical norms. This is particularly crucial in the context of brain-machine interfaces and neurostimulation devices, where human rights and data privacy concerns are paramount. In this regard, neuropreneurship research offers invaluable guidance on the ethical utilisation of neurotechnologies and adherence to regulatory frameworks.

5. Modern approaches to Neuroentrepreneurship

The principal methodologies and approaches employed in neuropreneurship research at present comprise neuroscientific research techniques, data analytics, user-centred design, clinical research, and business development strategies. The field of neuropreneurship employs a range of neuroscientific research techniques with the objective of gaining insight into the functioning of the brain and nervous system. Such techniques include magnetic resonance imaging (MRI), electroencephalography (EEG), positron emission tomography (PET), and functional MRI (fMRI). These tools facilitate the creation of comprehensive maps of brain activity, thereby enabling neuroentrepreneurs to gain insight into the functions of specific brain regions and neurological processes.

Furthermore, neuroscientific research techniques are employed to assess the efficacy and safety of neurotechnologies. Data analytics and artificial intelligence assume a pivotal role in neuropreneurship research. The examination of extensive data sets pertaining to the brain and nervous system facilitates a more profound comprehension of neuroscientific findings. Machine learning algorithms and artificial intelligence are utilized to process brain signals, discern patterns, and generate individualized brain activity profiles. These methodologies empower

neurotechnologies to become more effective in personalized healthcare and neurofeedback applications.

User-centred design and user experience (UX) methodologies are of great importance in neuropreneurship research. As neurotechnologies interact directly with the brain activity and behavior of individuals, the user experience needs to be optimized. The user-centred design process enables the development of products and services by focusing on the needs and feedback of users. In this process, methods such as surveys, focus groups, usability tests, and prototyping are employed. User experience research increases the acceptability and adoption of neurotechnologies (32, 33).

Clinical trials are critical for evaluating the efficacy and safety of neurotechnologies developed in the field of neurointerventionalism. Randomised controlled trials (RCTs) are widely used to establish the effectiveness of devices and treatment protocols. These studies provide scientific evidence supporting the use of neurotechnologies in clinical practice. Furthermore, long-term monitoring and safety assessments help identify possible side effects and risks associated with neurotechnologies. Neuropreneurship research involves the process of commercialising scientific findings and creating economic value. In this context, business development strategies and commercialisation approaches are of great importance. Activities such as market analysis, competitive analysis, formulation of business plans, and provision of financing support the successful commercialisation of neurotechnologies. Protecting intellectual property rights and meeting regulatory requirements are also important components of this process.

The methodologies and approaches used in neuropreneurship research are shaped by a comprehensive framework that includes neuroscientific research techniques, data analytics, user-centred design, clinical trials, and business development strategies. These methodologies play a critical role in the development of neurotechnologies, the evaluation of their efficacy and safety, the provision of products and services that meet the needs of users, and the commercialisation of scientific findings. Through these interdisciplinary approaches, neuropreneurship enables the transformation of scientific knowledge into economic and social benefits.

Neuropreneurship involves neuroscientific research methodologies that aim to gain an in-depth understanding of the functioning of the brain and nervous system. One of the main methodologies used in this field is neuroimaging techniques. Neuroimaging plays a critical role in the development and evaluation

of neurotechnologies by visualising brain activity and structure. Furthermore, experimental and systematic reviews are used to test the efficacy and reliability of these techniques (34, 35, 36, 37).

Neuroimaging techniques use advanced imaging tools to study the anatomical and functional structure of the brain. These techniques include magnetic resonance imaging (MRI), functional MRI (fMRI), electroencephalography (EEG), and positron emission tomography (PET).

- **Magnetic Resonance Imaging (MRI):** MRI provides information on anatomical details by visualising the structural features of the brain at high resolution. This technique helps neuroentrepreneurs detect abnormalities in brain structure and develop devices for diagnosing neurological diseases (38).

- **Functional MRI (fMRI):** fMRI measures brain activity by monitoring blood flow and oxygen utilization in the brain, identifying regions that are active during specific tasks or stimuli. In neuropreneurship, fMRI is used to evaluate the effects of neurotechnologies on the brain and understand cognitive processes (39).

- **Electroencephalography (EEG):** EEG records the electrical activity of the brain, allowing for monitoring of brain waves at the millisecond level due to its high temporal resolution. EEG is widely used in developing neurotechnologies such as neurofeedback applications and brain-computer interfaces (40, 41).

- **Positron Emission Tomography (PET):** PET measures brain metabolism and neurotransmitter activity, visualising brain functions and chemical processes using radioactive isotopes. PET is particularly important in neuroinformatics for early diagnosis and treatment monitoring of neurological diseases (38, 42).

Experimental and systematic reviews are used to evaluate the efficacy and reliability of neuroimaging techniques and neurotechnologies. Experimental reviews provide controlled environments to test specific hypotheses. Randomised controlled trials (RCTs) are among the most frequently used methods in this context, being tightly controlled studies in which participants are randomised into groups to evaluate the clinical efficacy and side effects of neurotechnologies (43). Systematic reviews and meta-analyses evaluate the overall effectiveness and application areas of neuroimaging techniques and neurotechnologies by thoroughly analysing the existing literature. These reviews help neuroentrepreneurs make decisions based on scientific evidence by synthesising research findings (44).

Neuroimaging techniques and experimental and systematic investigations are important methodological tools in neuropsychiatry. Neuroimaging contributes to the development and evaluation of neurotechnologies by analysing brain activity and structure in detail. Experimental and systematic reviews scientifically test the effectiveness and reliability of these techniques and technologies. These methodologies enable neuroentrepreneurs to develop innovative and effective neurotechnologies, accelerating progress in this field (45).

Neuropsychiatry can be defined as the transformation of neuroscientific knowledge and technologies into commercial opportunities. This field of study aims to develop innovative and creative solutions by examining the neuroscientific foundations of entrepreneurial processes and decision-making mechanisms. Furthermore, it has the potential to positively influence educational and learning processes from an early age, enabling the identification of useful pathways.

6. Emotional and Cognitive Processes in Neuropsychiatry:

Neuropsychiatry offers important contributions especially in the areas of cognitive processes, decision making, opportunity recognition, creativity and innovation. Neuropsychiatry aims to understand the cognitive mechanisms underlying these processes by examining the decision-making processes of entrepreneurs from a neuroscientific perspective. The prefrontal cortex of the brain plays a critical role in decision-making processes. This region is responsible for high-level cognitive functions such as risk assessment, problem solving and strategic planning. Neuropsychiatry research uses brain imaging techniques (fMRI and EEG) to identify factors that influence entrepreneurs' decision-making processes. This research reveals how entrepreneurs make decisions under uncertainty and the neurobiological basis of these decisions. This makes it possible to develop more effective decision-making strategies (46).

Opportunity recognition is one of the key components of the entrepreneurial process, and neuroentrepreneurship provides important findings by examining the neuroscientific underpinnings of this process. Opportunity recognition often occurs in environments of uncertainty and complexity, and the brain has specialised mechanisms for perceiving novel and potentially lucrative opportunities in such environments (47). In particular, regions of the brain such as the ventral striatum and amygdala play critical roles in reward and emotional processing (48). By studying the activities of these regions, neuropsychiatry

seeks to understand how entrepreneurs recognise and take advantage of new opportunities. This understanding contributes to the development of entrepreneurship education and support programmes.

7. Creativity and innovation in neuropsychiatry:

These are two important elements at the centre of neuroentrepreneurship. The prefrontal cortex and the region of the brain known as the default mode network (DMN) play an important role in creative thinking processes. Creative thinking requires efficient information exchange between different regions of the brain. Neuropsychiatry research aims to increase the ability of entrepreneurs to develop innovative solutions by examining the neuroscientific basis of creative processes (49). It uses neuroimaging techniques and cognitive tests to determine how to optimise creative processes and promote innovative thinking.

Neuropsychiatry makes important contributions to the entrepreneurship ecosystem by providing in-depth insights into cognitive processes, decision-making, opportunity recognition, creativity and innovation. Research in this field enables entrepreneurs to better understand brain functions and develop more effective strategies. Neuropsychiatry plays a critical role in transforming scientific knowledge into practical applications and encourages the development of innovative and creative solutions in the world of entrepreneurship (50, 51).

8. How Neurointerventions Can Improve Memory and Learning

A review of the literature on neurointervention research in the field of learning and memory performance indicates that a range of techniques and methods have demonstrated efficacy in this domain. The following sub-headings present a synthesis of the most significant findings on this topic:

8.1. Brain Stimulation and Memory Performance:

Brain stimulation, especially repeated transcranial magnetic stimulation (rTMS), may be effective in improving memory performance. A study in the literature showed that rTMS applied to the left prefrontal cortex can improve verbal learning. TMS reversibly alters brain activity using magnetic pulses. It is possible to modulate an important cognitive activity such as memory by magnetic stimulation of various cortical areas. Although memory performance

has been reported to be ‘enhanced by TMS’ in various pathological conditions, more research is still needed in healthy individuals (52). Neuroinitiatives that will emerge in the field of TMS may use the current technique to improve memory, especially in pathological conditions. In addition, the use of this technique in healthy individuals has a significant R&D potential.

8.2. Neurofeedback and Cognitive Performance:

Neurofeedback, a biological feedback method, can improve cognitive performance by providing participants with real-time feedback gains from controlled EEG activities. Training to increase the activity of SMR (sensorimotor rhythm), the brain region that combines sensory and motor information, has led to improvements in focused attention processing and semantic processing. In addition to improvements in various pathological conditions, behavioural and electrocortical measurements have been associated with attention processing and have been found to benefit individuals, except that they can provide control in healthy individuals (53). In addition, an increase in short-term memory performance has been observed with neurofeedback training (54). Neurofeedback can be used as an important method that can be used in neuroinitiatives in the field of Neurofeedback and Cognitive Performance. Improvement can be observed in various pathological conditions and benefits can be provided on behaviour and attention in normal individuals.

8.3. Physical Exercise and Neurogenesis:

Physical exercise positively affects the hippocampus, which is responsible for the learning and memory processes of the brain, neurogenesis, which is the formation of new neurons, and memory functions. Controlled and voluntary exercises increased learning and strengthened the memory process. Studies have also shown that the number of hippocampal neurons, which are important for learning, increased with increased intensity of physical exercise, running, aerobic exercises. In addition, the increase in functional functions between physical exercise and the brain reveals a protective effect against cognitive aging and pathological conditions (55, 56).

Regular and sustained physical exercise has been demonstrated to enhance the formation of new neurons and facilitate learning. This underscores the potential value of incorporating physical exercise into neuro-entrepreneurship studies. Furthermore, research and development initiatives tailored to individual needs can be pursued.

8.4. Neuropharmacological Approaches:

Neuropharmacological interventions can improve learning and memory processes through various neurotransmitter systems. Especially recently, the nervous system, memory, memory and learning have been studied by utilising neuroanatomy, molecular terminology and physiology. Various efforts are being made to integrate the findings obtained in learning and memory with the system and cells to reveal nutrients, drugs and lifestyles. Substances such as dopamine, glutamate and adenosine receptor modulators can be used for attention and encoding processes, while serotonin neurotransmission is important for recall processes. The basic principles related to memory and learning are the recognition and acquisition of new stimuli, making the learned information permanent and retrieval of the remembered information (57). The utilisation of neuropharmacological techniques and diverse methodologies within the domain of neuroentrepreneurship can facilitate enhancements in the ease of learning, memory fortification, memory augmentation and long-term, enduring learning.

8.5. Intermittent Learning and Neurogenesis:

Presenting information intermittently over time increases learning and the survival of new neurons, making it longer and more permanent. Spaced learning creates a more permanent memory and increases the number of new cells in the hippocampus. In line with the studies, intermittent training has achieved higher performance than collective training and better memory has been observed (58). The utilisation of intermittent learning as a pedagogical approach has the potential to enhance the neuroentrepreneurship capabilities of individuals. This is achieved through the implementation of structured training programmes that are conducted over specific time intervals and durations.

The results demonstrate the potential of diverse neurointerventions to enhance learning acquisition, memory performance, and retention. Each method possesses distinctive methodologies and outcomes, offering avenues for future research to flourish in diverse avenues.

9. Conclusion

The field of neuropreneurship makes a significant contribution to the advancement of knowledge. By studying the structural and functional characteristics of the brain in entrepreneurs, researchers can analyze learning and information processing patterns and subsequently optimize them. This body of

knowledge provides the foundation for developing entrepreneurship education programs. For instance, neuropsychiatry research can identify the knowledge capacities and learning styles of entrepreneurs, enabling the development of bespoke training programs that facilitate enhanced learning and retention.

One of the most significant contributions of neuropsychiatry is enhancing the objectivity and data-driven nature of entrepreneurs' decision-making processes. Neuroscientific research elucidates the underlying mechanisms of decision-making, the factors that influence these processes, and the neural correlates involved. This information enables entrepreneurs to make well-informed decisions and mitigate the risks of unforeseen situations.

Furthermore, neuropsychiatry significantly contributes to the advancement of innovation and creative thinking processes. Analyzing brain activity in the context of creative thinking can enhance entrepreneurs' capacity to generate novel ideas and identify original solutions to existing problems. This constitutes a substantial advantage, particularly in rapidly developing and intensely competitive sectors.

Additionally, neuropsychiatry represents a novel and promising field of study with considerable potential for application in contemporary business practice. The objective of this field is to enhance the efficacy of entrepreneurial processes by integrating insights from neuroscience, enabling entrepreneurs to make more informed, creative, and effective decisions. A more profound comprehension of cerebral functionality and cognitive processes can assist entrepreneurs in achieving enhanced success in risk management, strategic planning, and innovation.

Moreover, neuroentrepreneurship plays a pivotal role in fostering the growth of leadership competencies. Utilizing neuroscientific methodologies allows leaders to enhance communication with employees, motivation, and team cohesion, positively influencing the overall performance of the organization. The application of neuroscientific methods can facilitate the development of leadership skills such as empathy, emotional intelligence, and stress management.

Neuropsychiatry has the potential to transform the entrepreneurial ecosystem. By integrating neuroscientific knowledge into business processes, entrepreneurs can become more innovative, effective, and successful. Further research and application of this discipline could lead to radical transformations in the business world, establishing it as a key discipline in the future landscape of business.

The field of neurointerventions has recently emerged as a promising avenue for enhancing memory and learning processes. Technologies such as brain-machine interfaces, neurological stimulation techniques, and AI-assisted neural connections have the potential to optimize cognitive processes by providing direct access to brain functions. Such technologies offer effective solutions, particularly for individuals experiencing memory loss and learning difficulties. The formation of memory is dependent upon the brain's neural circuits, which can be modified through neuroplasticity. Neurointerventions can enhance memory function by modulating these neural circuits. The application of mild electrical stimulation to the brain has been demonstrated to facilitate the learning process, promoting deeper learning and enhanced retention of information. For instance, techniques such as deep brain stimulation and transcranial magnetic stimulation have been shown to enhance memory formation by augmenting neural activity in designated regions of the brain.

Furthermore, neurointerventions offer novel avenues for treating neurological disorders that transcend the limitations of individual learning capacities. In the context of memory disorders such as Alzheimer's disease, neurological stimulation technologies have demonstrated encouraging outcomes in maintaining and enhancing patients' cognitive function. Additionally, neurointerventions are instrumental in addressing memory loss resulting from brain injuries and traumas.

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