Neurophysiology Involved in Neuroplasticity: Mechanisms of Forgetting

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Anáhuac University
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Chapter

Neurophysiology Involved in Neuroplasticity: Mechanisms of Forgetting

Jose Rodrigo Carrillo-Marquez and Jose Damian Carrillo-Ruiz

"You appear to be astonished," he said, smiling at my expression of surprise. "Now that I do know it, I shall do my best to forget it."

"To forget it!"

"You see," he explained, "I consider that a man's brain originally is like a little empty attic, and you must stock it with such furniture as you choose. Now the skillful worker is incredibly careful indeed as to what he takes into his brain-attic. He will have nothing but the tools which may help him in doing his work, but of these, he has a large assortment and all in the most perfect order. It is a mistake to think that little room has elastic walls and can distend to any extent. Depending upon it there comes a time when for every addition of knowledge, you forget something that you knew before. It is of the highest importance, therefore, not to have useless facts elbowing out the useful ones."

The Science of Deduction in A Study in Scarlet.

Sir Arthur Conan Doyle, 1887.

Abstract

Neuroplasticity is the brain's ability to adapt to new stimuli, with the objective to overcome and learn how to deal with novel situations. In this chapter, it will be explained the new neurophysiological mechanism that entitles the processes of brains' plasticity. The intriguing phenomena that surround cognitive mechanisms will be described on a morphological and molecular scale, aiming to understand some of the brains' functions. The principal objective is to clarify and explain that neuroplasticity can take place in different complex tasks such as adaptative behaviors, memory, learning, and automatic conducts. Also, the evolutionary advantage of forgetting will be deeply discussed. The work will describe the functioning of the brain when adapting to new circumstances that affect the procedures of memory. It will be explained why applying biotechnology and neurobioethics is crucial for merging basic and clinical sciences.

Keywords: pruning, forgetting, forgetfulness, neuroplasticity, sprouting

1. Introduction

Forgetting or forgetfulness is not only a passive activity of neurons but also an active process, in which, specific brain areas play role in the neural circuits of temporal and frontal lobes to eliminate information that does not need to be stored in memory. Its importance is sustained by the fact of avoiding saturation of the neural circuitry; knowledge that could be irrelevant or shallow for the diary living activities or in its case, accumulation of chronic unnecessary skills.

This chapter is constructed on the basic principles of neuroplasticity and memory, in order to understand how the information is obtained from the senses and then the perception that might be needed to be kept in the brain, depending on its modality. After this point, which is the molecular and cellular mechanism used by the neurons to filter the relevant juxtaposing the purposeless. It is being added to the clinical feature of neurological illness to distinguish amnesia from forgetting. It will be expressed the future of treating patients that need to ameliorate forgetfulness in their daily life.

Although many new areas are being researched, others are kept apart from the interest of professionals. That is why this book chapter is presented, aiming to inform the new physiological mechanisms that have been described in the forgetting process, so as its relationship with neuroplasticity. Also, there will be an in-depth explanation of some pathologies and affections that trigger this neurophysiological response.

2. Why science takes a fundamental role in neuroplasticity?

Understanding part of the physiology of the nervous system has been one of the most outstanding achievements of the 20th century. It is indisputable that these achievements could not have happened if there was no research involved, so as the interest of the scientific community to try to explain the mechanisms of the brain. The decade from 1990 to 2000 was established by the American Academy of Neurology (AAN) as the "decade of the brain" [1], and it was a transition between elemental bases of neuroscience to a more specific so-called era. It is important to mention that in the 21st century, the growing curiosity to investigate and explain neurophysiology has reached unprecedented milestones due to emerging technologies that have been crucial for research and clinical practice. Topics such as memory, neuroplasticity, neurobiochemistry, neuronal tracts, sprouting, and neuroimmunology are reaching new horizons because of the molecular approach [2]. This is the reason why it should be investigated the neuroplasticity and forgetting. Not just as a new trend, but rather as fields of neuroscience that must be discussed by the community in order to achieve progress. Without the new biotechnology, and in this case neurobiotechnology; discovering and knowing the molecular mechanisms of plasticity, memory, and forgetting would be impossible.

3. Neuroplasticity

3.1 An approach from neuroembryology

To fully understand neuroplasticity, it is first necessary to classify and define what this concept stands for. Several authors have tried to state a formal definition,

yet many of them have not taken into consideration this phenomenon over time. Neuroplasticity is a complex process that starts in the embryo neurogenesis, beginning with neurulation. It is important to state that the closure of the neural tube happens between the 21st and 25th day [3]. From the formation of the neural tube until the moment in which the fetus has a complete morphological nervous system many molecular signals initiate and finish the growth, connectivity, and cellular differentiation within the brain and the rest of the nervous system. Between the 8th week of pregnancy (time by which every human system is formed) to the moment of labor, the nervous system shifts drastically [4].

3.2 The notch pathway and neuroplasticity

One of the most important mechanisms of these changes is the Notch differentiation which is a gene-mediated regulatory cascade also known as the "notch signaling pathway". Its importance comes from its direct participation in cell proliferation and fate, so as differentiation and apoptotic mechanisms. This process assures the development and distinction of the nervous system from small animals (*i.e., Drosophila melanogaster*) to humans [5, 6].

Although this process elucidates how neuroblasts tend to differentiate into neurons and both glial cells, it should be said that the whole process is more complex than the intervention between the "Hes family (1, 5 & 6)", RBPJ and the ligands with Jagged and DII [7]. What can be said is that an incorrect step in the process might change future physiological functions within the nervous system, opening the possibility of mental illnesses and congenital neurological diseases which are not going to be described in this manuscript. Information regarding the topic has been published, but the reality is that studies just explain the correlation between multiple genes, transcripts, and proteins that take part in the complex process of neurological plasticity [8].

Also, epigenetic factors can alter the expression of this mechanism that takes place in embryogenesis and after-birth processes. Lasky states that memory and learning are two of the most important and multifactorial processes that involve a relationship with Notch, so as diverse pathologies that may arise from this process in postnatal development [9]. This evidence has also been restated a few years ago by Engler, adding the participation of NOTCH1 and NOTCH2 in this phenomenon, as well as adding a description of how all these factors take place in adults [10].

3.3 Fresh perspectives regarding neuroplasticity

The reality is that younger individuals have a better capacity than older ones to form neuronal connections, learn and perform new tasks, due to the capacity of younger neurons to arborize and form new circuits [11]. Adult neurogenesis, and thus neuroplasticity, is possible to occur in the hippocampus. This theory has been deeply discussed, but the reality is that more research and more substantial medical evidence should be published in order to get to a consensus [12]. Despite age, individuals that make exercise tend to have an increase in neurotrophic factors (*i.e.,* Brain-Derived Neurotrophic Factor, Nerve Growth Factor, and Glial Cell line-derived Factor) that brings a more efficient functionality in comparison with those who do not exercise [13]. The relationship between oxytocin and the increase of pro-social behaviors, neuronal excitability, and plasticity has been described by Froemke [14]. It is important to acknowledge that the research made by this group determined that mammals

use oxytocinergic modulation in the process of maternal care and social bonding. It is a prolific contribution to the field because of the hormonal and neurological modulation involved in physiological and pathophysiological processes.

3.4 A new proposal in defining neuroplasticity

As said before, neuroplasticity is one of the most intriguing, and yet not fully known mechanisms that occur within the nervous system. It has been said that neuroplasticity consists of changes in a morphological, biochemical, and pharmacological adaptation in neuronal networks. The main objective of this physiological process is the adaptative response of the brain to diverse stimuli. Moreover, neuroplasticity and its physiology are fundamental concepts when approaching the pathophysiology of several neurologic illnesses, based on the ideas proposed by de Olveira in 2020 [15]. Understanding neuroplasticity as a process that relates directly to behavioral patterns and pharmacology, so as the interaction of these fields with pathology.

As a contribution to this field, it is being proposed to define neuroplasticity as a temporal and active mechanism related to neurogenesis and nervous cell apoptosis, starting in the neurulation, and finished until the subject's death, having characteristics of neurochemical and morphological changes that can be altered by other substances and environmental factors. This definition is based upon neurobioethics in order to understand this phenomenon not just at a basic and scientific level but comprehending these neural occurrences in a medical and anthropological way.

It will be described how neuroplasticity is related to memory formation, forgetfulness, and the differentiation between a physiological and pathological operation (**Figure 1**).

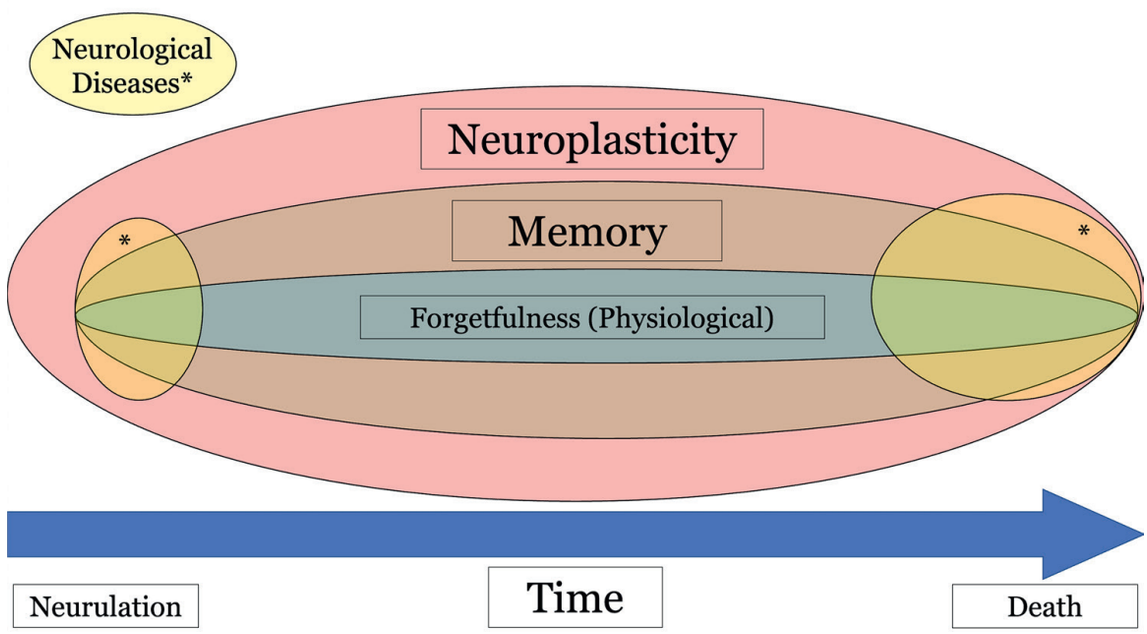

Figure 1.
This graphic represents the relationship between memory and forgetfulness, involved in all the process, the neuroplasticity. This is evident from the formation of the nervous system in neurulation and continues through the time to the moment of the subject's death. Also, the presence of neurological illness modifies both functions.
** = sporadic diseases during lifetime.*

4. Into the memory

Memory as well known is a neurophysiological mechanism that is complex and subdivided into many different subclassifications. The aim of this document is not to discuss nor describe exhaustively each category [16], but rather to mention them and comprehend how memories are formed. Also, this will help to establish in the following pages the criteria to understand what the concept of forgetfulness really means (**Figure 2**).

4.1 Mechanisms of memory formation

According to human physiology, memory is a phenomenon that takes place in the following structures: the hippocampus and the cortex (specifically the neocortex) [17]. Moreover, memory cannot be described as an isolated phenomenon since the cortex and limbic system takes place in memory consolidation. The amygdala plays a fundamental role in emotional response linked with memory being fear, one of the principal factors for plasticity and neurochemical activities in that anatomic region [18, 19]. It is important to state that the relationship between the amygdala and hippocampus balances the encoding processes of memory [20]. Also, it has been determined that the cingulate cortex is involved in action-outcome learning, and it also is an important place of brain connectivity [21].

It is important to mention that memory has also a neurophylogenetic component. Chittka described that many animals such as wasps, bees, and cockroaches have the ability of spatial learning for surviving [22]. Decapod crustaceans have the same ability as well, it has been published that crabs can adapt and be conditioned to solve mazes having an improvement in comparison with those who did not have time to explore the trial [23]. Krichbaum reported that dogs have the capability of episodic memory for accomplishing tasks, even though seven out of ten dogs tested positive in conduct

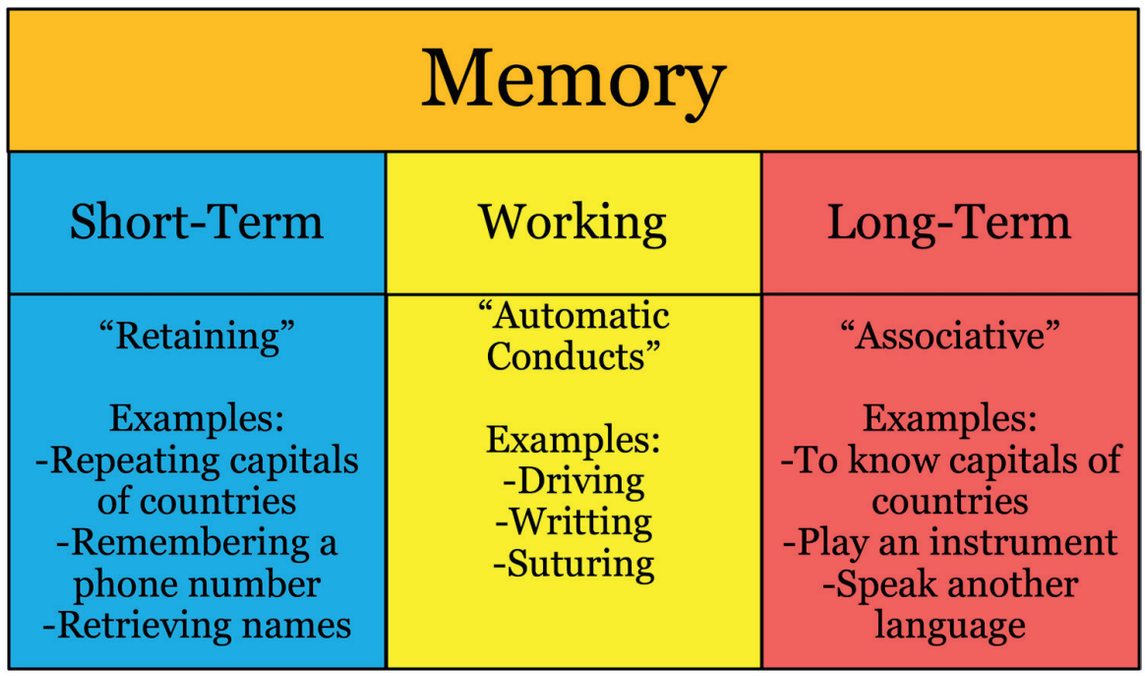

Figure 2.
It is demonstrated the memory function: short-term, working memory and long-term with its main characteristics and examples of each subtype.

experiments, more research should be done to clarify this proposal [24]. According to scientific literature, monkeys can retrieve information from short to medium periods of time, use working memory, and have a limited self-perception when answering cognitive tests [25]. Humans are at top of this evolutionary scale due to their complex brain structure and functional morphology, that no other species own.

It might sound coherent to the fact that the cortex is involved in decoding the diverse stimuli that pass through the senses (*i.e.,* sight, touch, smell, taste, hearing, cognitive estimation, and reasoning). Memory is determined by several factors such as chemicals, hormones, neurotrophic factors, neurotransmitters, external stimuli, and sleep.

Regarding sleep, Klinzing determined that Long-Term Memory is formed during slow-wave sleep in the hippocampus of rodents, so as in humans [26]. Speaking about hormones, it has been described by Acosta that the circadian rhythm plays an important role in starting and stopping the gene and cellular structures that are regulated by an extensive number of hormones (*i.e.,* Cortisol, Digestive Hormones) [27]. Also, the relationship between hormone regulation and the gut-brain axis (GBA) has a fundamental role with the hypothalamus in maintaining a healthy metabolism and a correct function of glutamatergic, cholinergic, calcium-calmodulin, mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinases (ERK's), phosphoinositide 3-kinase (PI3K), ghrelin, leptin, insulin, and glucagon signaling [28].

Also, one of the most recent studies has determined that smoking cannabis containing the active molecule of tetrahydrocannabinol (THC) disrupts short memory, but unclear evidence of neurogenesis in the hippocampus also has been reported [29]. Alcohol abuse in big quantities can prevent the brain from forming new memories, and after the withdrawal, incapacity to remember correctly what happened when drunk. Also, it has other metabolic consequences [30].

Moreover, the hippocampus builds coherent long-lasting memories, merging exploratory visual exploration and memory formation [31]. Adding that also the other senses can take place in this process. The reality is that the theory of engrams "basic biological unit of memory" has been merged with neuroplasticity to understand the physiological mechanism of forming memories [32]. As it has been stated, reducing complex processes: in this case, a "memory to an engram" also can bring detrimental consequences for scientific research.

5. Concept of forgetting or forgetfulness

Forgetting is defined as the loss of memory or the failure of the brain to remember. It is the fact that something concrete or a special person, is not present in the mind of a subject. Although he or she might have known them well previously. It is interesting that forgetfulness is a synonym for forgetting in a colloquial or scientific language, based on the ideas of Della Sala and Cubelli [33]. Nevertheless, forgetting could be more punctual to the "fact of forget", and forgetfulness is the process and state of not remembering [34].

5.1 Objectives of forgetting

It is relevant for the brain and the mind to experience forgetfulness. In the same way a person could be memorizing events, skills, situations, and circumstances in a

natural process; it is necessary for a similar path to forget all the things that are not essential in the activity's life. Indeed, one cannot exist if the other one is abolished. It erases the shallow and specific things dispensable to work. This allows the new experience or knowledge, even though opening the gate for creativity or innovation, inclusively, it could be considered a paradoxical effect because one person forgets insignificant information and could store an important one [35, 36].

Furthermore, forgetting helps to ameliorate traumatic or anxious situations that could be dangerous to mental health. This indicates a capability to grow and promote personality maturation coupled with emotional intelligence.

5.2 Microglia and macroglia in forgetting

The microglia cells are the caregivers of the neurons because they support, nourish, and attack the estrange and harmful cells. This last activity is based on the activation of the complement system: for the attack including C1q, C3, and CR3; and for the cell, preservation uses CD47 (cluster of differentiation 47), SIRPα (signal-regulatory protein), and CX3CR (chemokine receptor 1). Indeed, these components of complement resting the microglia to prune synapsis during neural activity and plasticity [37]. Neuroplasticity involves the stability of the long-term potential (LTP), a neural mechanism based on the dependent- Ca++ gates to produce the learning and memory phenomena [38]. It is in the same direction the memory needs the microglia to consolidate that the use of complement in the inverse sense to get forgetting, undoubtedly with the use of microglia. In a double mechanism with gradual and activity-dependent, the retraction of synapsis mediated by the glia contributes to forgetting [39] (**Figure 3**).

Although there is no substantial evidence of the participation of macroglia (*i.e.,* oligodendrocytes and astrocytes) in forgetting mechanisms [40, 41], further investigation must be required. Based on the proposition that astrocytes play an important role in neurotransmission uptake and neural guidance, so as their immunological properties as cells [42].

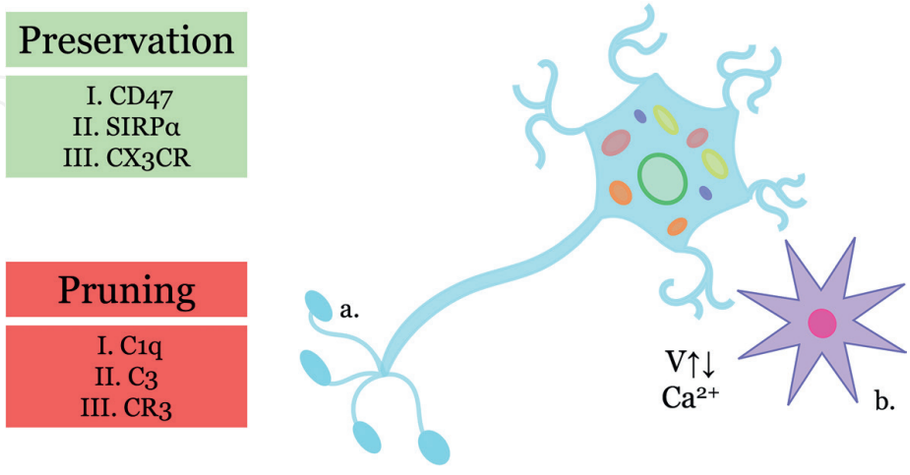

Figure 3.
It is shown the cellular mechanism of forgetting. Preservation and pruning in the neuron (a) and the micro/macroglia (b). V↑↓ Ca^{2+} = Regulation in voltage-gated calcium channels; CD47 = Cluster of Differentiation 47, SIRPα = Signal-Regulatory Protein Alpha, CX3CR = Chemokine Receptor 1; C1q = Complement component 1q, C3 = Complement component 3, CR3 = Complement receptor 3 [37].

6. Neurological diseases

6.1 Amnesia or forgetting?

The first point to consider is determining if exists amnesia or forgetting: It is not the same. Although in both circumstances it shows the absence of retrieval of the elements lived by the person and how they get stored in the brain, the amnesia is produced by a real element damaging the neurons of the memory circuit. There are several conditions that could be presented in different illnesses that produced amnesia [43]. The next are the most common causes to produce it (**Table 1**):

There is much information about each one of the neurologic diseases, but this is not the discussion matter of this chapter. Those have been mentioned to show the difference between amnesia and forgetfulness.

On the other hand, forgetting is the absence of reuptake of the skills or memory elements without lesion to the brain neurons, and neuronal circuitry is intact. Sometimes normal forgetting is considered like a pathological memory problem, and this is not the real image of what exactly happens. An example could be a geriatric patient with failures in memory that could be attributed to incipient dementia. The process of forgetting is explained due to perception and/or attention alteration. Indeed, the simple past of the time could produce a diminution of the capability to retain the information entered into the brain [44, 45].

Some of the concrete neurologic problems are described below (**Table 2**).

6.2 Aging

It is well known that neuroplasticity is produced during the initial stages of the human being after-birth, when the brain is immature. It is needed for establishing

I.	Moderate to severe cranial-brain trauma
II.	Chronic and evolutive dementia (*e.g.*, Alzheimer or Parkinson Disease)
III.	Cardiac and brain stroke
IV.	Nutritional deficiency (*e.g.*, Korsakoff Disease)
V	Brain tumors
VI.	Seizures and epilepsy
VII.	Cerebral infections
VIII.	Thyroid hormones alterations (*i.e.*, hypothyroidism and hyperthyroidism).
IX.	Psychotropic drugs (*e.g.*, antidepressants, antiepileptic, antipsychotic...).
X.	Poisoning interfering central nervous system
	Carbon monoxide (CO)
	Animal or vegetal substances
	Alcohol
	Cannabinoids
	Hard drugs

Table 1.
Amnesia and its causes.

I.	Aging	
II.	Sleep deprivation	
III.	Hypermnesia	
IV.	Severe mental stress	
	Anxiety	Depression

Table 2.
Concrete neurologic problems affecting memory.

connections and making neural circuits that could regulate basic and important levels of diverse functions in the Central Nervous System (CNS) [46]. In this sense, the neuroplasticity of a newborn, and infant, and inclusive an adolescent is more relevant compared to the neuroplasticity of adult and geriatric subjects and patients. The person develops forgetting when the lifetime is passing through his eyes. It is the expected, so it is an important event, but not only the oldest people experiment it. As it has been stated, forgetting is necessary to leave irrelevant knowledge, learn and memorize new ones in each stage of his life [36, 47].

6.3 Sleep deprivation

Patient with moderate-to-severe problems of sleep with different etiologies could present more frequent number of forgetting memories compared to normal subjects. The presence of insomnia is a determinant factor for the lack of concentration because it affects the attention and a correct state of consciousness. It is important the state of anatomical and functional integrities of the Reticular Ascendent Activating System (RAAS), which takes part in several neurotransmitters involved in the arousal-sleep cycle. In this matter, the orexin-neuron groups are involved in this regulation, according to what Chambers stated in 2017 [48]. To consolidate the knowledge, the hippocampus needs to have the presence of a neurophysiological plateau with the intervention of calcium (Ca++) to produce the hippocampal delta waves. Such manifestations demonstrate the consolidation of a set of skills. This is mediate by acetylcholine. It is possible that forgetting could use the same anatomical point, with the performance of inhibitory neurotransmitters like GABA or glycine [49].

6.4 Hypermnesia

One of the most interesting situations of medicine is the presence of photographic memory. It is rare to find people with this extraordinary capability. For the person who had this gift could be used in a social and economic success [50, 51]. The person with this "excess of memory" has an enormous advantage to learn and to extract information from their neuronal circuits. It demonstrated that it exists a hyper-connectivity and optimization of the function of neurotransmitters like noradrenaline, as described by Hurlemann [52]. Nevertheless, when a subject has this situation, it could be difficult to destroy superficial information, and every single moment could be remembered, everything from the big picture to the small details, depending on the individual's capability. This illness does not allow the use of forgetting, so in this person, this could give birth to a paradoxical and noxious psychological effect [53].

6.5 Severe mental stress

One of the most important defense mechanisms against brutal stress is the presence of forgetfulness when some life events, like rape or war survival, could have been lived. This produces a tremendous shock in subjects or in patients, opening the possibility of being diagnosed with "post-traumatic stress disorder" (PTSD). For lucky individuals who forget what happened, the brain uses these psychological mechanisms, described by psychologist and psychiatrist, to bury the unpleasant experience in the unconsciousness or to delete it completely from the memory [54]. It is certainly that powerful inhibitory system in the limbic and memory circuits that had been involved including dopamine, as reported by Sabanda in 2021 [55]. Patients with this trauma had mild to severe anxiety and depression [56]. These add a motive to avoid remembering painful events and could potentiate forgetting. Some studies with war veterans are performed with PET or functional MRI to know what happened in the brain lobes with stress.

7. Therapeutic aspects

Nowadays, there is not an effective treatment for exclusively the absence or the excess of forgetting. There are two possibilities for therapeutic goals: using drugs and not using them. In the first one, all the strategies to avoid forgetting. At this point, it can be used all the drugs involved in the treatment of dementia. Although how it was explained, the mechanism of action is not the same, because in amnesia there is clear damage to neurons, in forgetting not. All the cholinesterase inhibitors like donepezil [57], rivastigmine, or galantamine [58]; glutamate regulators like memantine [59]; or more recently, with the use of monoclonal antibodies treatment like aducanumab could be considered [60], all the studies published in 2022. It is desirable the use of cognitive-behavioral psychotherapy using strategies and exercises to promote memory.

It exists also the use of neuromodulation to promote memory in patients with Alzheimer's disease (AD) [61]. It is still an experimental tool for this proposal. The main target is Deep Brain Stimulation (DBS) to avoid amnesia. The use of DBS could improve the fall of memory centered in the fornix of patients with AD [62, 63]. Not forgetting (how it is considered in this chapter) has already been evaluated.

On the other hand, there are no punctual drugs to increment forgetting. In patients with depression or anxiety, the treatment is focused on its disease, like antidepressants or anxiolytics. Insomnia patients could use anxiolytics. Also, specific medications, like suvorexant, a drug that acts in the orexin neurotransmitter in the hypothalamus to regulate the sleep-arousal cycle, according to Rahman in 2022 [64].

There is no choice to improve forgetfulness in a precise manner, as DBS does with AD patients. It must be explored this area, thinking in a brain surgical target: a list of possible targets is each part of the verbal memory, like the hippocampus, fornix, or amygdala. It could be considered, and indeed, they are used with DBS in patients with epilepsy, aggressiveness, or AD.

Depressive or anxious patients could be treated with Transcranial Magnetic Stimulation (TMS) to diminish the symptoms [65, 66]. Also, it is possible for future protocols to evaluate forgetfulness.

8. Conclusions

Forgetting or forgetfulness is a neurologic active state in which the subject or the patient has an impossibility to obtain old information stored in their memory. Neuroplasticity is a fundamental concept when approaching forgetfulness. Macroscopically, the neuronal circuitry is not damaged, although its molecular scene changes the opportunity to retrieve the information. It is important to mention the existence of drugs that improve amnesia (which is not the same as forgetting), and it is possible to act over forgetfulness. There are no medications to help forget, in cases of sleepiness, mental trauma, or aging. The use of DBS or TMS could be a possibility to increase or decrease, in other words, neuromodulate forgetting.

Conflict of interest

The authors declare no conflict of interest.

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Author details

Jose Rodrigo Carrillo-Marquez[1,2*] and Jose Damian Carrillo-Ruiz[1,3]

1 Faculty of Health Sciences, Anahuac Mexico University, Mexico City, Mexico

2 Alpha Health Sciences Leadership Program, Mexico Anahuac University, Mexico City, Mexico

3 Stetereotactic and Functional Neurosurgery, Mexico General Hospital, Mexico

*Address all correspondence to: carrillomarquezjr@gmail.com

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