2 Learning and Memory

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2.1 Introduction

According to the ancient Greek mythology, Mnemosyne was the goddess of memory and the mother of the nine Muses of the arts and science (Dudai and Carruthers 2005). Learning and memory are closely related fundamental higher brain processes that allow individuals to adapt to the environment, create, and widen not only their personal history but also the population culture (Benfenati 2007).

Learning helps people to enquire and encode information making them able to adopt new behaviors. Learning is a whole lifetime process that intervenes in almost all occasions of people's social living. As a result the acquired experiences can alter an individual's behavior (Mazur 2015).

Memory is connected with learning. The initial information is encoded, preserved over time, and used when any need occurs. Any damage in the encoding, the storage, and the retrieval of the information disturbs the process of memory. In fact, memory is the result of learning, but these two procedures are intermingled and essential for the survival of not only humans but also all living creatures (Engel 1999).

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2.2 Learning

Learning is the possession of knowledge and skill through systemic study or through experience and error. There are two types of learning under the interest of psychobiology: associative learning and nonassociative learning. The associative learning is the procedure by which an individual finds out the connection between two stimuli or between an action and an event. The nonassociative learning is a simple form of learning that describes a relatively stable alteration in the power of response to a single stimulus due to repeated exposure to this same type of stimulus (Mazur 2015; Rescorla 2014).

2.2.1 Associative Learning

Some typical forms of associative learning are complex enough, and they are presented as classical conditioning, operant conditioning, and observational learning.

2.2.1.1 Classical Conditioning

In classical conditioning subjects learn to form an association between two events happening in sequence. In particular, a neutral stimulus produces a certain response to another stimulus. In the beginning of the twentieth century, the Russian physiologist Ivan P. Pavlov discovered the classical conditioning accidentally during experiments upon digestion. Pavlov gave food to a dog, and he watched the secretion of saliva, while the dog was consuming the food. In particular, he presented a stimulus like the sound of a metronome (conditioned stimuli), and afterward he supplied the food (unconditioned stimuli). He repeated this procedure a few times, and as a result he noticed that the dog started to salivate in response to the sound of the metronome. Pavlov came up with the conclusion that if a specific stimulus was present while the dog was given food, then that particular stimulus could be connected with food and could provoke salivation on its own. He made the dog to repeat this procedure, and as a result he realized that the dog was able to begin salivating before eating. This particular type of learning was named Pavlovian conditioning or classical conditioning (Pavlov et al. 1929).

Later, Pavlov and his colleagues introduced the terms acquisition, extinction, generalization, and discrimination in an attempt to clarify classical conditioning. They also introduced the rules of temporal contiguity and contingency. According to their studies, acquisition is the initial phase when a dog is trained, for example, to salivate at the sound of a bell. A conditioned stimulus should precede the unconditioned stimulus by several seconds interval (temporal contiguity). Then, a certain behavioral response, the conditioned response is produced. Conditioned stimulus must forecast the unconditioned stimulus (contingency). Extinction is a phenomenon that describes the gradual weakness and fading of conditioned response after the repetitive appliance of conditioned stimulus when the unconditioned stimulus is absent. For example, in extinction when salivation of the dog is the conditioned response, it will gradually decline if the bell is ringing repeatedly without supplying any food (unconditioned event). Generalization is the procedure that an individual already conditioned to a specific event will probably respond to a similar event without the occurrence of training to the new event. For example, if a particular tone makes a dog to salivate, tones of higher and lower frequency will also lead to salivation. On the other hand, during discrimination the dog is taught to salivate in a different way to two different stimuli tones.

Classical conditioning was postulated to be related with some clinical presentations like phobias, but it was also used to treat some certain pathological behaviors like addiction (Mackintosh 1983).

2.2.1.2 Operant Conditioning

Edward L. Thorndike and B. F. Skinner are two American psychologists who researched operant conditioning, another form of associative learning which is also called instrumental conditioning. Operant conditioning is a process which includes certain behaviors that a subject needs to perform in order to receive a reward or a punishment. The subject not only answers to the stimuli but also by its behavior causes changes to the environment (Mackintosh 1983).

In the 1890s, Edward L. Thorndike studied operant conditioning on different species of animals like dogs, cats, and chickens (Thorndike 1898). In particular, he placed the animal in a box called the operant box. In case the animal acted according to the right way, the box would open, and the animal would be able to get out and find food that was left outside the box. In the beginning, it was a difficult and long-lasting procedure for the animal to open the box and earn the reward. However, after placing the same animal in the box repeatedly, it started to learn and act correctly in a shorter period of time. After these observations, Thorndike formulated the first formal theory of learning, called law of effect. According to this principle, any behavior connected with pleasant results is likely to be repeated, and any response that produces an unpleasant effect is less likely to occur again (Thorndike 1927).

Later, during the 1930s, B. F. Skinner investigated and stated some significant principles of operant conditioning. He used rats and pigeons to create a way of learning based on reward and punishment. He experimented by training animals inside the known Skinner boxes. Inside the box, the animals were able to get food by using a small lever or by pecking at a food well. He observed the responses of the animal with a device designed to record the impact of food delivery on a subject's response. As a result, a positive reinforcement or a reward increases a behavior by adding a pleasant stimulus, while on the other hand, negative reinforcement or punishment decreases the probability of a certain behavior to happen again. There are a lot of rules that control the frequency and the timing of the reinforcers, like continuous or fixed-ratio schedule, called reinforcement schedules (Skinner 1990).

According to Skinner, punishments reduce the chance of the occurrence of a response and are divided to positive and negative punishments. A positive punishment is the decline of a behavior applying an unpleasant stimulus in case the behavior occurs, while negative punishment means the decline of a behavior by taking away a pleasant stimulus the time the behavior occurs. Shaping is a method of learning animal and human behaviors that they have never met before, by reinforcing the behavior. Extinction is a process of eliminating a trained response by diminishing the reinforcer. For example, if the reward of food is not delivered by pressing a lever in rats, then the behavior will be eliminated. It is noticeable that if individuals are taught to perform a behavior in one occasion, then they are able to behave in the same way and in other similar occasions. For example, the greeting "congratulations" is used to others' happy events. Discrimination refers to the ability to learn when a response is possible to be followed by a reward or not in different circumstances. In the previous example, humans learn not to say "congratulations" to someone in a bad situation since it may lead to negative results (Skinner 1953).

2.2.1.3 Observational Learning

In the early 1960s, Albert Bandura, a Canadian-American psychologist, introduced his social learning theory. It is an unquestionable fact that living organisms can also learn through observation. Bandura conducted several studies to investigate how observational/imitation learning impacts children's behavior (Bandura 1969). According to his theory, observational learning is composed of attention, retention, reproduction, and motivation. At the beginning an individual pays attention to the behavior of others; then the learner retains the information he observed. Afterward, he should mimic to perform the same behavior (reproduction), and finally he should have the motivation to mimic the behavior (Bandura and Walters 1977).

To sum up, learning by observation means that the subject should observe and then imitate the behavior of others. People are able to contact other people by using different languages. These languages have not only been officially taught to them, but they have also been learned through observation. In addition, they develop their personality and their social habits and abilities through experience they gain by observing other people. The mirror neurons that can be found in the ventral premotor cortex and inferior parietal lobe are considered to contribute to imitation. It has been suggested that mirror neurons explain many sides of social cognition, like the ability to realize the actions of others, to "read their mind," and to communicate by gestures and speech (Ramachandran 2000).

Although the precise substrate mechanism of action is still unspecified, observational learning plays an important role in social behaviors and communication through media and educational process.

2.2.2 Nonassociative Learning

The other simpler type of learning is the nonassociative learning, and it consists of several types like habituation and sensitization.

2.2.2.1 Habituation

Habituation is a process that decreases the behavioral response to a repeated and innocent stimulus. Several examples of habituation exist in everyday life. When someone hears a very loud sound for the first time, he may be annoyed and even frightened. But if the sound continues for a certain period of time, his annoyance and shock get reduced which is a typical case of habituation (Pinsker et al. 1970).

The Austrian-American neuropsychiatrist Eric Richard Kandel investigated the neural mechanisms of habituation examining the sea hare *Aplysia californica* because of its simplicity and its relatively large size of the underlying neural circuitry. *Aplysia californica* is a large shell-less sea snail or sea slug. The experiment was to apply a gentle touch to the siphon of *Aplysia* leading to a gill-withdrawal reflex. *Aplysia* hides inside the mantle shelf. Nevertheless, if the siphon is disturbed repeatedly, then the withdrawal reflex shows a gradual decrease. At the end, no response is observed. This steadily diminishment of the reflex after applying repeatedly a mechanical stimulus is called habituation. Kandel and his colleagues proved that habituation in *Aplysia* gill-withdrawal reflex (GWR) was due to a reduction on the synaptic transmission between sensory neurons of the siphon and motor neurons of the gill. The magnitude of the excitatory postsynaptic potential in motor neurons was reduced progressively after stimulating repeatedly the siphon (Kandel et al. 1976).

Habituation exists in short- and long-term form. In *Aplysia*, habituation can last for several weeks and is called long-term habituation (LTH) (Carew et al. 1972). It has been found that by this form of habituation, the sensorimotor pathway is suppressed and the presynaptic terminals and branches of the sensory neurons of the siphon are being retracted (Castellucci et al. 1970). However, the exact signaling pathways which after activation trigger long-term cellular changes are still unclear. Some recent studies suggested that LTH of the GWR relies on protein synthesis and activation of protein phosphatases 1 and 2A and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors. The role of RNA synthesis, calcineurin activity, and l-type Ca^{2+} channel activation in LTH in *Aplysia* has also been tested (Esdin et al. 2010; Ezzeddine and Glanzman 2003).

To conclude, despite the fact that habituation is one of the simplest types of learning, its neurobiological basis remains obscure.

2.2.2.2 Sensitization

Sensitization is the opposite of habituation. The term refers to a nonassociative learning type that increases the behavioral response to repeated and innocent stimuli. Sensitization contributes to the learning of noxious and threatening stimuli in animals. If the animal comes across a threatening and fearful event, then it is able to respond more robustly to other stimuli even if they are not harmful or frightening (Landsteiner and Jacobs 1935).

Except for habituation, other mechanisms of learning were also investigated using *Aplysia californica* (Castellucci and Kandel 1976; Pinsker et al. 1973). As observed in habituation, repeated disturbance of the siphon leads to no GWR in *Aplysia*. However, after a period of rest, the response showed quick recovery. The scientists applied an electric shock one time to the tail of the slug, and the gill-withdrawal reflex was restored. This process of the facilitation of a habituated response after the presentation of a strong tactile stimulus to another part of the animal is also called dishabituation (Pinsker et al. 1970).

Eric Kandel and his group studied the neural mechanisms underlying sensitization by experimenting upon *Aplysia californica*. According to their studies, the appliance of electric shock to the tail generates a strong gill withdrawal. The gill withdrawal exhibits a form of plasticity called sensitization (Kandel et al. 1976). Sensitization like habituation is a result of changes in synaptic transmission of only a few different types of neurons. These neurons are the sensory neurons that innervate the tail and the siphon, motor neurons that stimulate muscles in the gill and interneurons that receive information from various sensory neurons. The electric shock to the tail triggers the sensory neurons that innervate the tail. Afterward, these neurons stimulate modulatory interneurons that secrete serotonin on the presynaptic terminals of siphons' sensory neurons. The synaptic excitation of the motor neurons increases, and a receptor, called stimulatory G protein-coupled, is stimulated by the binding serotonin. This stimulatory receptor binds to a transmembrane protein which once activated is going to stimulate a G protein. Afterward, the enzyme adenylyl cyclase is activated and converts ATP into cyclic AMP (cAMP). Cyclic AMP (cAMP) plays the role of the second messenger and triggers cAMP-dependent protein kinase (PKA). Protein kinase phosphorylates K+ channels, and the action potentials increase as a consequence to the ceasing of K+ channels. Then, the influx of Ca^{2+} raises, and as a result the glutamate release from the presynaptic siphon's neuron to gill's motor neuron is increased. This augmentation of glutamate release is the mechanism that turns *Aplysia*'s gill-withdrawal reflex back to normal and ends habituation. Apart from *Aplysia* sensitization occurs also in other animals, and a similar procedure takes place (Bristol et al. 2004; Squire and Kandel 2000).

2.2.3 Features of Learning

Since learning is a composite process, learning ability differs due to reasons like experience, age, and mental state. Learning can happen in all ages of a living organism, but the process is not the same. For example, aged people find it more difficult than children to learn a new language. Some people are able to speak fluently two languages because they are exposed to them naturally from their infant age. In addition, experience helps people to learn easily new things relevant to already known information. Adults are also more capable to understand abstract thinking related to adolescents.

Learning ability is influenced by developmental disorders. People with attention deficit hyperactivity disorder (ADHD) or with the diagnosis of autism find it difficult to learn and develop social skills. On the other hand, degenerative diseases like Alzheimer's disease can affect the ability of learning as well as memory.

Different levels of intelligence result to different academic achievements, or there are talented people with flair to music or mathematics. Learning differs among individuals because of differences in motivation and emotion. Additionally, motivation can enhance the ability of people, in particular students, to learn (Mazur 2015).

2.3 Memory

Memory is the process according to which information is initially encoded, then retained, stored, and finally retrieved and recalled in the brain. All the living organisms need memory to exist. In particular, memory gives people the ability to remember the past, to acquire experience, and finally to learn (Arnold 2013). A lot of scientists, thinkers, and philosophers have talked and written about memory. “Our memory is a more perfect world than the universe: it gives back life to those who no longer exist” are some words of the French writer Guy de Maupassant (1903).

Memory consists of three distinct systems: the sensory memory, the short-term memory, and the long-term memory. Each one of these categories includes subcategories (Squire 2004).

2.3.1 Sensory Memory

Sensory memory refers to the representation of the stimulation of human sense organs for a brief period of time. Iconic memory means a brief recording of visual information, while echoic memory stands for the representation of auditory stimulation. Sensory memory is also represented in other sensory modalities and shows modality specificity (Anderson 2000).

2.3.1.1 Iconic Memory

The American cognitive psychologist George Sperling was the first to document the iconic memory, using the partial-report model. Specifically, his experiment was to present briefly a 3 × 3 or 3 × 4 array of letters to some observers. He saw that people were able to report all the letters in any indicated row (partial report) if this happened directly after the visual presentation. Moreover, if the individuals were asked to recall all the letters (whole report), they were found able to report only four to five. The probability of the presentation of each row was equal, which means that the observer had access to all the letters at the end of the display. The fact that partial-report shows an advantage compared to whole-report phenomenon led the scientists to conclude that there is a rapid-decaying iconic memory that holds at least 9–12 items (Sperling 1960). The exact duration of iconic memory has been calculated to be about 300–500 ms for young adults (Coltheart 1980; di Lollo 1977; Dick 1974; Mewhort et al. 1981; Neisser 1967).

2.3.1.2 Echoic Memory

Guttman and Julesz (1963) designed a creative experiment in order to measure echoic memory. A computer was used to create repeating patterns of white noise. White noise sounds like “shhh,” cannot be memorized or described, and consists of all frequencies mixed together at random. The computer was putting together a repeating segment of white noise with no gap between them. The subjects were instructed by the investigators to wear headphones, listen carefully to the noise, and write down what they heard. The subjects did not know that a sound was being repeated. In case the repeating part of white noise endured longer than a few seconds, the subjects were not able to recognize the repetition. They could only hear a whooshing sound with no pattern. On the other hand, if the segment lasted shorter than 2 s, the subjects could realize that they heard a repeated sound even if they were not able to describe it.

Echoic memory is the system used to preserve the exact copy of sound for a few seconds by giving individuals the capacity to detect a repeating pattern of frequencies.

2.3.2 Short-Term Memory

Short-term memory refers to the system that holds essential information in mind temporarily, in an available and active state for further cognitive activities (James 1950).

Short-term memory has the feature to decay rapidly. In case no practice of the information is conducted, it is preserved for a limited time, no longer than 30 s. The retaining of information for longer periods requires periodical rehearsal. During this process, the information is kept for greater time through reentrance to the short-term store.

Another feature of short-term memory is its limited amount of capacity which when talking about humans is around seven items plus or minus two. These seven items are called "magical number seven." The term "word length effect" refers to the fact that fewer words are recalled when their pronunciation is longer. According to the "phonological similarity effect," fewer words can be recalled when they have similar pronunciation, while a greater number of phonologically dissimilar words can be recalled. On the other side, if the words are familiar or belong to the same category, they can be retrieved more easily (Miller 1956).

Chunking is a property that increases short-term memory capacity and especially the amount of recalled items. The ability of a person to remember information can be improved if every unit is placed in a meaningful word or phrase. For example, it is easier for someone to keep in mind a telephone number if the digits are chunked into groups rather than try to recall ten digits in a row (Gobet et al. 2001).

The cerebral cortex seems to be responsible for the most types of memory and short-term memory as well. Different parts of the body, like the eyes or ears, send sensory information to the cerebral cortex where they are stored for a few seconds. The non-attended information are thrown away, while the attended ones will be stored in the sensory areas of the cortex or will be moved to the hippocampus and will be kept into the long-term memory (Jonides et al. 2008).

2.3.3 Working Memory

Working memory was introduced by Baddeley and Hitch in 1974 (Baddeley and Hitch 1974) and is related to short-term memory although it refers to a distinct procedure. This memory system is used to plan and carry out behavior and is based to the dorsolateral prefrontal cortex. Some individual uses working memory when trying to recall the partial results during the solution of a mathematic problem without paper or to prepare a cake without using the same ingredient twice. Thus, working memory is a mental workbench which not only keeps but also processes information. Opposite to the passive nature of short-term memory, working memory is an active procedure. Working memory is also linked by some scientists with intelligence (Baddeley 2003).

2.3.4 Long-Term Memory

Long-term memory is a brain system that deals with information from the past and stores it for a great period of time. Long-term memory appears capable to keep countless information, from something learned recently to long-lasting memories.

There are different aspects describing the engagement of information in long-term memory. According to one aspect, in the beginning information is stored in short-term memory, and afterward it is processed and transmitted to long-term memory. On the other side, there is the belief that information is processed separately and enters short-term and long-term memory at the same time (Goelet et al. 1986).

Long-term memory is divided in psychobiology into declarative and non-declarative memory.

2.3.4.1 Declarative Memory

Declarative memory is linked with the hippocampus and related structures and gives individuals the ability of conscious recall and declaration of the information. Endel Tulving divided the declarative memory into episodic and semantic memory, in 1972 (Tulving 1972).

Episodic memory refers to the process involved in recalling specific experiences throughout a person's life. In this type of autobiographical memory, an event is related to a context during a specific time in a specific place, answering the questions "where" and "when." For example, episodic memory is used to remember a holiday in a beautiful island (where) with family 2 years ago (when). People are not only able to remember these events, but they talk about them, declaring them. As a result, episodic memory belongs to the category of declarative memory (Tulving 2002).

Semantic memory refers to general knowledge, like information about things that we know or about the world in general. The fact that someone knows that the Big Ben is in London and the Parthenon is in Athens represents an example of semantic memory. This memory system, unlike episodic memory, is not linked with the specific time and place that a memory was created. An individual does not have to keep in mind when and where he learned about Big Ben and Parthenon (Squire and Zola 1998).

2.3.4.2 Non-declarative Memory

Non-declarative memory can be recalled unconsciously without effort, is not declared, and is expressed through performance. Non-declarative memory system includes procedural memory, priming, habits (conditioning), and nonassociative learning (Squire and Zola-Morgan 1988).

Procedural memory, which involves visuomotor learning, includes all the skills that some individuals hold, for instance, playing a guitar, driving a car, or writing. The difference between procedural and declarative memory systems relies on the difference between procedural and declarative learning. Procedural learning refers to how to learn something, whereas declarative learning refers to what someone learns. Procedural memory is expressed through behaviors and can be easily influenced by practice. For example, driving ameliorates over time, and a guitarist can improve his skills by practicing repeatedly.

Priming is a well-studied phenomenon of non-declarative memory that refers to perceptual detection of words and objects. During priming, exposure to one stimulus affects the response to another stimulus by the activation of certain representations or associations in memory, just before executing an action or task. Priming reveals the underlying mechanism of perceptual tasks that is formed without awareness and has been implicitly memorized. For example, if a subject sees the word "red," it will be easier to find the word "heart," since red and heart are closely connected in memory. Priming is assessed through perceptual and conceptual techniques like word-stem completion and word association, respectively. The first task is the ability of representation of words such as medication with the three letters med. The second task incorporates, for example, the free association of the word ship with the related words sea and port (Squire and Zola 1996).

Habits, which occur in conditioning, as well as nonassociative learning, have been already described in this chapter.

2.3.4.3 Explicit and Implicit Memory

The American psychologist William McDougal divided long-term memory into explicit and implicit memory.

Explicit memory is the process that facilitates the recall of past experiences and corresponds to declarative memory. Explicit memory is needed for someone to remember his holiday in a mountain.

In contrast to explicit memory, implicit memory retrieves stored information without any conscious awareness and is supposed to correspond to non-declarative memory. The fact that people are imitating the behaviors of people they have met or unconsciously sing a song that they heard before is attributed to implicit memory. This category of memory also includes priming effect (McDougall 1924).

2.3.4.4 Neural, Regional, Synaptic, and Molecular Mechanisms of Long-Term Memory

Neural

One of the basic aims of neuroscience is to find out how memories are encoded and stored in the brain. Richard Semon was the first to introduce the term "engram"—a memory trace, which consists of neurons that represent memory physically (Semon 1921). Later, the American psychologist Karl Lashley conducted his famous search by training rats. Specifically, he made them traverse a maze to gain a food reward, and after the experiment or before, he surgically removed various lesions of different cortical regions. His investigations were published to his famous "search of the engram" 30 years later (Lashley 1950).

Regional

Nowadays, a lot of brain regions are supposed to interact in order to encode, store, and retrieve distinct information for each separate memory process. Brenda Milner and her colleagues studied the role of the *hippocampus* in episodic memory through the observation of the case of their famous patient H.M. In 1953, an operation was performed to the 27-year-old young man H.M. with the aim of treating his intractable epileptic seizures. A bilateral mesial temporal lobectomy has been conducted including the hippocampus, amygdala, and surrounding cortices, leading to the decrease of the frequency and the severity of the seizures. However, a new amnesic syndrome occurred, and the patient was unable to remember anything that happened to him following his operation, whereas his perceptual and intellectual skills remained intact, as he carried out normally a wide range of tasks. He was able to achieve some retention of simple visual and tactual mazes, tasks that were not long enough for his short-term memory capacity though the rate of acquisition was extremely slow. After investigating the case of H.M. almost for 40 years, the scientists concluded that bilateral lesions of the hippocampus and parahippocampal gyrus cause a severe and enduring disorder in episodic memory, a memory system that relates events with specific places and specific time, and they shed light to the realization that the components of the limbic system are bottleneck structures through which information needs to pass in order to be kept long-term (Milner et al. 1968, 1998; Smith and Milner 1981). The left (dominant) hemisphere has been found to control verbal memory, while a specialization has been found for the right hemisphere for spatial processing, a phenomenon called hemispheric asymmetry of memory (De Renzi et al. 1977; Habib et al. 2003; Ojemann and Dodrill 1985).

Except for the hippocampus, other brain regions are also involved in the function of memory. In 1937, when Papez proposed his well-known emotional circuit, the Papez circuit (hippocampal formation (subiculum) → fornix → mammillary bodies → mammillothalamic tract → anterior thalamic nucleus → cingulum → entorhinal cortex → hippocampal formation) for controlling the emotional expression, he also showed that this circuit plays an important role in the transfer of information into long-term memory (Markowitsch 2005; Papez 1937). Modern brain imaging procedures provided information about the participation of brain regions like the cerebellum, striatum, amygdala, and other motor or sensory systems in non-declarative memory (Markowitsch 2005).

Synaptic Molecular

The distinctive property of the nervous system which is called plasticity was first proposed by Santiago Ramon y Cajal (1852–1934) as the potential of the brain to adapt to the environment, in a congress in Rome in 1894 (DeFelipe 2006). Donald

Hebb introduced a theory to explain the associative learning in his book in 1949. The Hebbian learning refers to the simultaneous activation of neurons which increases the synaptic strength between those neurons in a way that activity in one results to an activity in the other (Hebb 2005). Later in 1966, the Norwegian Terje Lomo was working with the hippocampus of anesthetized rabbits, studying the consequences of triggering the perforant path to dentate granule cells when he observed that high-frequency tetanic stimuli could lead to an enduring increase in efficiency of transmission at the perforant path-granule cell synapses (Lømo 2003).

In 1968, Terje Lomo and Tim Bliss followed up the preliminary results from 1966 and did the experiments that resulted in the discovery and fully description of long-term potentiation (LTP)—a cellular model of memory and learning in 1973 (Bliss and Lømo 1973). LTP represents an artificial form of plasticity and is measured both as an increase in the efficiency of synaptic transmission at the perforant path synapses and as the increase in the postsynaptic cell population spike (Bliss and Lømo 1973). LTP occurs in both excitatory and inhibitory neural synapses, and aside from the hippocampus, it has been investigated in the cerebral cortex, the amygdala, the cerebellum, and the spinal cord. However, since the hippocampus controls declarative memory, and LTP was induced in the hippocampus, it was concluded that LTP is a cellular model of the memory function (Lynch 2004).

Nowadays, it is widely known that several structural changes lie behind synaptic plasticity and memory formation. In a few milliseconds, glutamate is released from presynaptic neurons and activates the AMPA receptors and depolarizes the postsynaptic neuron. As a result, Mg^{2+} induces the removal of the NMDA receptor inhibition leading to the influx Ca^{2+} through the ion channel of the NMDA receptor. Moreover, voltage-gated calcium channels are also activated by the aforementioned depolarization, leading to further increase of Ca^{2+} supply. A few minutes since the beginning of the process, the influx of the calcium into the synapse leads to the activation of kinases able to modulate their substrates' activity. The substrates are responsible for local alterations at the synapse, like morphological change through cytoskeletal regulation. They also regulate transcription factors and lead to the induction of the transcription of RNA. Finally, in a few hours, the translation of the transcribed RNA into proteins will have taken place. Activated synapses capture these proteins contributing to the stabilization of synaptic changes (Lamprecht and LeDoux 2004).

2.3.5 Forgetting and Other Phenomena Related to Memory

2.3.5.1 Forgetting

Forgetting is a term described by Hermann Ebbinghaus, defined as the loss or modification of information already stored in long-term memory. During his experiments, he created lists of three-syllable meaningless words, consisting of a vowel between two consonants, like KET or SIP. He practiced a lot, and he was able to remember the list incorruptly by heart. He was aware of the duration and the times that he tried in order to learn the list. Afterward, he checked his remembering of the list intermittently. He observed that rapid forgetting took place initially and then a steady increase in forgetting followed. Forgetting is believed to occur because new information interferes as time passes. Although it could cause some trouble, it is considered to naturally clean and exclude outdated and useless data (Ebbinghaus 2013; Murdock 1985).

2.3.5.2 Other Memory Phenomena

Flashbulb memory is a category of memory linked with significant emotional incidents in an individual's lifetime. For example, someone is able to remember where and when he/she heard the bad news of the death of one's beloved person, since a flashbulb memory has been formed (Winograd and Neisser 2006).

Déjà vu describes the feeling of the physical presence in a place that the person has never been before or the feeling of the experience of an event that the person has not experienced before. Déjà vu creates an implicit familiarity of an unrecognized stimuli, as it unconsciously evokes a former situation and as a result provokes a familiar sense (Brown 2003).

Jamais vu is the opposite of déjà vu, as individuals have the feeling that they have never experienced a situation before, even though they know that they did (Cleary 2008).

Tip-of-the-tongue state is a state when a well-known or familiar word cannot be immediately recalled (Brown 2012).

The method of loci, also known as *the memory palace* or *mind palace technique*, is an ancient mnemonic device adopted in Roman and Greek rhetorical essays. Through spatial memory, it helps a person to enhance serial remembering. The trained individuals imagine themselves to walk through in a well-known environment, and they place what they need to remember in specific locations. In order to retrieve specific memories, the person reimagines navigating the environment "searching" for the placed items in order. A lot of mnemonists use this method to recall faces, digits, and lists of words (Legge et al. 2012).

2.3.5.3 Memory and Sleep

Sleep has been found to play a significant role in memory processes. The sleep-related mechanisms of neural plasticity contribute to the consolidation of memory and learning. Rapid eye movement and non-rapid eye movement sleep are important for learning and memory, and a sleep cycle controls memory consolidation through multiple ways, but the actual processes remain unknown (Born and Wilhelm 2012; Maquet et al. 2003).

The relationship between sleep and academic performance is of a great interest. It is widely known that sleep enhances learning and memory processes, while sleep deprivation worsens these functions influencing academic performance. Students with more regular sleep-wake patterns, such as fewer night awakenings, shorter sleep latency, and earlier rise times on weekends, have been found to gain higher grades compared to students that were sleepy during the day due to disturbed night sleep (Vatthauer 2009).

2.3.5.4 Memory Distortion

In 1932, Frederick Bartlett revealed the existence of a phenomenon called memory distortion. Memory distortion means that a memory report is different from the real experience. Bartlett investigated the course of memory, and he came up with the idea that memory transforms over time including omissions, deletions, and distortions. In particular, during his experiments, he asked the subjects to read a folktale the "War of Ghosts." According to the plot, there is a battle between two enemy tribes. He used the method of serial reproduction known to people by the game "telephone," when children sit in a queue and each one tries to reproduce the same initial story, having been heard by each previous player. Likewise, he asked the subjects to remember the tale they heard from their immediate predecessor with the most possible details and try to narrate it to the next one. He revealed that memory of the original story undergoes huge distortion after only a small number of repetitions (Bartlett 1932).

Since then, a lot of work has been done by scientist trying to identify the brain regions that are responsible for true and false memories. The medial temporal lobe has been suspected for false recognition. The prefrontal cortex plays a role in memory monitoring errors. Other studies suggest that true and false memories activate the same brain regions (Schacter and Slotnick 2004).

2.4 Disorders of Learning and Memory

2.4.1 Age-Associated Memory Impairment

It is well known among scientists that aging leads to a decline in the function of memory among healthy individuals. Kral, in 1958, was the first to use the term "benign senescent forgetfulness" (BSF) to separate adults with mild memory impairment from those with severe changes or normal memory systems (Kral 1958). Later, the term age-associated memory impairment was constructed, and criteria were presented with the aim of facilitating the communication among scientists about the memory loss that may occur in healthy elderly individuals in the later decades of life (Crook et al. 1986). In the mid-1990s, the term mild cognitive impairment was introduced by Peterson and his colleagues (Petersen et al. 1999). It refers to a transitional stage between age-associated impairment and dementia presenting with subjective memory complaints, lower scores on memory tasks, absence of dementia, and good levels of quality in activities.

During aging a lot of changes take place in the brain. Recent MRI studies have shown that atrophy of the medial temporal lobe and the hippocampus is a usual phenomenon in elderly persons and might lead to memory decline (episodic) (Golomb et al. 1993). Frontal lobes present with the greatest reduction in brain volume during aging (Hänninen and Soininen 1997); they have been found to underlie in several memory systems such as the working memory, the retrieval process which needs conscious mental effort, the temporal organization of memory, and source memory.

2.4.2 Amnesias

2.4.2.1 Introduction

The term amnesia refers to a situation characterized by the impaired ability of a person to learn new details and recall information from the past. Common reasons for amnesia not only include brain injuries, neurological deficits, and vascular incidents like a stroke but neurodegenerative and psychological disorders as well (Snodgrass and Corwin 1988). Amnesia can happen with or without the existence of other cognitive deficits.

Memory consists of multiple different systems, but not all of them are impaired in amnesia. While amnesic humans are not able to acquire information about facts and events (explicit memory), they keep the ability for several types of learning like conditioning and habit learning and skill learning. Explicit—declarative—memory relies on the structures of the medial temporal lobe and diencephalon unlikely implicit memory that depends on brain structures that remain intact in amnesia (Kopelman 2002).

2.4.2.2 Anterograde and Retrograde Amnesias and Memory Consolidation

Anterograde amnesia is called the failure to learn new information. The patient finds it difficult to remember new persons, situations, and words following the onset of amnesia. Anterograde amnesia is more severe when more locations of the medial temporal lobe are defected. On the other hand, retrograde amnesia refers to the damaged ability of an individual to recall events that took place soon before amnesia occurred. Thus, memories estimated in the time period before amnesia are lost, while old memories, like childhood events, remain. Retrograde amnesia is met alone or in combination with anterograde amnesia (Winocur 1990).

During the process of memory consolidation, after the initial encoding of the information, cortical and neural processes and reformation take place, leading to the permanent storage of memory. Retrograde amnesia supports the idea of memory consolidation proving that what has been learned is not immediately made stable. Memory consolidation starts after information which has been encoded in the neocortex are linked with a memory trace in the hippocampus and related structures in the medial temporal lobes as well as the diencephalon, i.e., the posterior part of the forebrain that includes the thalamus, hypothalamus, and ventral thalamus. This initial procedure engages a short-term consolidation process, which ends within seconds or minutes. Afterward, long-term consolidation begins. Even though the hippocampus and related structures store and retrieve the information in the beginning, as consolidation proceeds, the neocortex alone becomes capable of keeping the permanent memory trace and mediating its retrieval (Nadel and Moscovitch 1997).

2.4.2.3 Amnesias of Dementias

Dementias are disorders that have taken their name from their profound symptoms characterized of deficits in mentation. The pathophysiological reasons for dementias are considered to be cortical and subcortical. For example, Alzheimer's disease is a cortical disorder but includes decline of cholinergic neurons in subcortical regions, as well. On the other hand, vascular dementia is a subcortical disease presented also with atrophy of the frontal cortex. The predominating impairment in most dementias is amnesia which depends on the stage of the pathology as well as the participating brain locations (Economou et al. 2006).

Alzheimer's Disease

Alzheimer's disease refers to a chronic neurodegenerative illness that usually starts gradually and deteriorates over time and leads to the majority of cases of dementia. The cause of Alzheimer's disease is believed to be 70% genetic with many genes involved. The disease process is associated with plaques and tangles in the brain. In particular, the neurodegeneration in Alzheimer's disease (AD) may be attributed to the deposition of amyloid β (Aβ) peptide in plaques in brain tissue (Hardy and Selkoe 2002). It most often affects people over 65 years of age, although 4–5% of cases are early-onset Alzheimer's disease (Hardy and Higgins 1992).

Episodic memory impairment is the first and main deficit in Alzheimer's disease, while deficits in semantic memory follow (Perry et al. 2000). In fact, patients in the early stages of the disorder indicate a decline in retaining new information. They are not able to remember the names of other persons, appointments, conversations, and where they have left their bag or keys. This episodic memory decline does not regard only verbal context, but the known information about visuospatial context is restricted (Barbeau et al. 2004).

Patients with Alzheimer's disease also suffer from semantic memory impairment which is proven from their impairment on various tasks like basic word retrieval, naming objects, and recalling examples of a semantic category (Nebes 1989). They also find it difficult to define concepts and separate them from one another (Alathari et al. 2004). Alzheimer's disease is not related with perceptual implicit memory decline though there are some scientists that support the opposite. Habit learning is preserved in Alzheimer's disease, while fear conditioning is often impaired.

Medications for Alzheimer's disease improve cognitive deficits and the affective and behavioral presentations. Donepezil, rivastigmine, and galantamine have been proved to ameliorate cognition in patients with Alzheimer's disease. The mechanism of action of acetylcholinesterase inhibitors relies on the inhibition of acetylcholinesterase, leading to an increase in the available acetylcholine, stimulating postsynaptic cholinergic receptors, and reducing the deficit in cholinergic transmission attributed to the degeneration of basal forebrain nuclei (Birks 2006).

Vascular Dementias

There are several types of vascular dementias with different clinical symptoms depending on the etiology of damage and the region of the brain that is affected. Vascular dementias include stroke-related dementias (single-infract and multi-infract dementia), subcortical dementia, and mixed dementia (along with Alzheimer's disease). Single-infract dementia, caused by a single infract, is capable of leading to amnesia, affecting cortical or subcortical areas responsible for memory functions (Szirmai et al. 2002). The most prevalent subcategory of vascular dementias is the subcortical ischemic dementia, characterized by impairment in the procedural memory system due to deficits in subcortical nuclei such as the caudate, putamen, and substantia nigra (Cummings 1994).

The treatment of vascular dementias depends on the understanding and management of the cause. Manipulating risk factors such like hypertension, diabetes, and smoking could help to prevent the illness. The techniques of carotid endarterectomy and atrial fibrillation using anticoagulant therapy are secondary preventive methods. Cholinesterase inhibitors have been found to improve the cognitive symptoms of the disease (Román 2003).

Frontotemporal Dementia

Frontotemporal dementia describes subjects with dementia associated with focal atrophy of the orbitomedial frontal and anterior temporal lobes. As a result, it is divided into temporal and frontal variant. The temporal variant leads to semantic amnesia, whereas the frontal variant is connected with behavioral disorders as well as deficits in working memory and retrieval of information (Englund et al. 1994).

The frontal variant of frontotemporal dementia is also called behavioral variant. Patients with behavioral variant frontotemporal dementia are characterized by insidious changes in personality, interpersonal behavior, and emotional variety. These changes show progressive collapse of the neural circuits that take part in social cognition, emotion regulation, motivation, and decision-making. In addition, apathy characterized by reduced interest in previous activities and social isolation coexists with disinhibition that leads to impulsive actions along with socially embarrassing behavior (Piguet et al. 2011; Rascovsky et al. 2007).

The temporal variant of frontotemporal dementia is also represented by the term semantic amnesia. It was introduced in 1975 by Warrington and refers to the loss or the inaccessibility of events and ideas that have been pieces of an individual's personal knowledge. Recent memories are spared, and episodic memories along with the possession of new information are not noticeably affected (Warrington 1975). Taking into account that the most semantic memory are verbally coded, semantic amnesia occurs as difficulties in finding specific words, naming objects, recalling and linking facts, and understanding the meaning of already known words and concepts. The syndrome of semantic amnesia is caused by bilateral temporal lobe lesions located posteriorly, inferiorly, and laterally but not medially from the poles. As a result, the hippocampus and neighbor limbic structures stay intact (Squire and Zola 1998).

Lewy Body-Related Dementias

This category includes two dementia syndromes: the synonymous dementia in which Lewy bodies are cortical in location and Parkinson's disease, in which the pathology is primarily in the basal ganglia. The clinical presentation of both syndromes deteriorates over time, and the patients tend to present with identical cognitive impairments.

Parkinson's Disease

In patients with dementia due to Parkinson's disease, attentional problems are more severe than memory deficits. The cognitive decline must follow established Parkinson's disease, and there must be a gradual development. Working memory and visual-perceptual process are impaired. Decline in procedural learning also occurs, making these patients unable to perform mainly motor learning tasks. As a result, patients with Parkinson's disease become dependent on their caregivers, since not only their motor dysfunction but also working memory deficits prevent them from performing daily living activities.

Dementia with Lewy Bodies

Patients with dementia with Lewy bodies present with fluctuating cognition and pronounced variations in attention and alertness. In particular, this disorder includes early changes in complex attention and executive function.

Treatment of Lewy body-related dementias involves dopamine replacement by L-dopa and dopaminergic agonists in order to improve cognitive function rising psychomotor speed. Acetylcholinesterase inhibitors are also effective because they reduce visual hallucinations, apathy, anxiety, and sleep disturbances caused by cholinergic deficits of these patients (Papanicolaou 2005).

Huntington's Disease

Huntington's disease is an illness that presents with unequivocal, extrapyramidal motor abnormalities (choreoathetosis) along with progressive cognitive impairment. It is diagnosed either in family members with a history of the disease or in individuals that show an expansion in the HTT gene on chromosome 4 and atrophy in the caudate nucleus. Impairment in psychomotor skills, speed of processing information, and initial memory functions like procedural memory are the main deficits in the early stages of Huntington's disease, due to its frontostriatal etiology, characterized by a progressive nature. Deficits in visuospatial and semantic memory show no progressive decline.

Pharmacological treatments help to manage the symptoms as well as the social, physical, and occupational deficits of this progressive disease. First-generation antipsychotics are used to improve choreoathetosis and psychiatric symptomatology, but due to their implications, they have been replaced by the newer second-generation antipsychotic agents (Butters et al. 1985).

2.4.2.4 Traumatic Amnesia

A traumatic brain injury refers to any insult to the brain caused by a physical external force leading to alteration in consciousness and affecting cognitive function.

The cognitive impairments in people who survive after a serious traumatic brain injury are divided into four stages according to the time of occurrence related to the injury. The first two phases last some days and a post-traumatic delirium is included. The first stage is the period of an altered state of consciousness or coma. The second stage consists of different abnormalities in cognition and behavior, psychomotor activity as well as an inability to recall events and/or acquire new information, which is also called post-traumatic amnesia. Cognitive functions rehabilitate rapidly after 6–12 months (third stage). The fourth phase may include permanent damages in processes like attention and vigilance, memory and new learning, verbal skills, self-regulation of mood, executive functions, emotional reactions, and awareness of one's limitations (Kosmidis et al. 2006).

2.4.2.5 Transient Global Amnesia

Transient global amnesia was initially introduced by Fisher and Adam in the 1950s, and it describes an unknown pathophysiology well-recognized clinical syndrome. Patients present with a sudden onset of both anterograde and retrograde amnesia, without any other cognitive and neurological abnormalities. Transient global amnesia has a total duration of a few hours until 1 day and is observed mainly in middle-age to elderly persons (Fisher and Adams 1964).

Patients who develop transient global amnesia have memory deficits, but they retain their full consciousness and awareness. As a result their ability to carry on normal activities remains intact. Disorientation to time and place is the basic clinical feature of this entity. Memory for events during the acute phase is permanently damaged. The inner world of the patients remains to a specific point of time in the past, while the outer world occurs in the present time. The pathogenesis of transient global amnesia remains unclear. Some scientists support that focal ischemic lesions, migraine headaches, and brain tumors can be some causes. The medial temporal lobe is suspected (Szabo 2014). Other studies have suspected ischemic dysfunction in the medial temporal lobe, especially the hippocampus, to underlay in transient global amnesia (Webb and Rothwell 2013).

No semantic or procedural memory impairments occur during the episode of transient global amnesia (Papanicolaou 2005).

2.4.2.6 Amnesic Syndrome

The amnesic syndrome is defined as permanent and total disorder of memory attributed to organic brain dysfunction. The amnesic syndrome presents alone, without any other perceptual or cognitive disturbance. It is a mental disorder that affects short- and long-term memory with anterograde and sometimes retrograde amnesia. This decline occurs in a normal state of consciousness. The amnesic syndrome is associated with different causes that lead to damage to certain structures in the median temporal lobe and the diencephalon. It may result from close-head injury, penetrating head injury, subarachnoid hemorrhage, cerebral infraction, hypoglycemia, hypoxia, tumor, and thiamine deficiency as the result of heavy alcoholism (Wernicke's disease-Korsakoff's syndrome), carbon monoxide poisoning, and herpes simplex encephalitis (Parkin and Leng 1993).

The clinical manifestations of the amnesic syndrome involve disorientation, confabulation, and a lack of insight into the memory deficit. The term confabulation was introduced by Whitlock in 1981 and refers to "false statements that are not made to deceive, are typically more coherent than thoughts produced during delirium, and do not reflect underlying psychopathology" (Johnson et al. 1997). These manifestations are related to frontal lobe dysfunction produced by damage to neural links in a thalamo-frontal network (Johnson et al. 1997).

2.4.2.7 Psychogenic Amnesia

Psychogenic amnesias or functional amnesias are retrograde and present with reversible amnesia of autobiographical events. This type of memory loss is supposed to have psychological reasons since no obvious structural abnormalities are involved. Nevertheless, there are functional deficits in frontotemporal region that reverse after amnesia resolves (Savvidou et al. 2006).

Dissociative amnesia is subsequent to a traumatic experience, and according to DSM-5, it is defined as the inability of the individual to recall important autobiographical information of a traumatic or stressful nature, inconsistent with ordinary forgetting. The specifier for dissociative fugue refers to an apparently purposeful travel or bewildered wandering that is associated with amnesia for identity or for other important autobiographical information (APA 2013).

2.5 Conclusion

Learning and memory are closely connected brain processes. The application of the underlying biological mechanisms to the observation of the behavior is the aim of the field of psychobiology. Describing this aspect of memory and learning functions can be a useful tool for every scientist, leading to a deeper and more complete understanding of daily tasks and events. Memory is considered to be a big, rich, and awesome phenomenon, and it must be studied as such (Cahill et al. 2001).

A lot of light has been shed into understanding how the brain learns, forms, preserves, or loses memory. Conclusions should be derived from carefully investigating behaviors, taking under consideration the previous findings in the history of science. Actually, forgetting past lessons and experiences can be nothing more than a memory disorder.

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