Chapter 1

Introductory Chapter: Eat, Learn, Remember

Aise Seda Artis

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http://dx.doi.org/10.5772/intechopen.82365

"Cogito ergo sum"

"I think, therefore I am"

René Descartes

1. Introduction

Is act of thinking simply enough to prove existence? At the age of artificial intelligence (AI) and virtual (VR) while talking about machine learning (ML), deep learning (DL), and Internet of Things (IoT), it is not easy to answer that.

What should be the proof that it is not a robot but a human being? Can it be the consciousness, being conscious of self-thoughts? According to Amit Goswami, consciousness is the ground of being. It is the continuing stream of awareness of surroundings or sequential thoughts, the highest state of awareness anyone can attain. It helps us learn and adapt to changing circumstances far more rapidly and effectively. On the other hand, the key to consciousness is the memory. Newly discovered neuronal rosehip cells might be the exact answer to the question by time [1]. Rosehip cells might be helping us to form memories, the building blocks of our existence.

2. Memory hypothesis

Maybe the best definition of memory is done by Oscar Wilde: "Memory is the diary that we all carry with us." It is simple, yet comprehensive. Memory is mainly the outcome of learning. Here, learning refers to the process by which experiences change our nervous system and hence our behavior.

Today, what we know at present is just a small piece of the phenomenal mechanism of memory. Every person's brain holds billions of bits of information. In order to remember, the information needs to be encoded, stored, and retrieved. Long-term memory has a vast, difficult-to-estimate capacity. We routinely access this data store shorter than the blink of an eye. Actually, memory is both a result of and an influence on perception, attention, and learning. We can hold onto some memories for hours or days, even without constant rehearsal—such as the scheduled time of a luncheon or the place we parked our car before leaving for a vacation. Furthermore, the time needed for consolidation varies enormously depending on our interest and/or previous familiarity with the topic.

The other edge of the sword is forgetting. Forgetfulness is sometimes a blessing physiological event, and sometimes part of a serious pathology, e.g., Alzheimer's disease (AD). The most common causes of memory loss are dementia, depression, stress, sleep deprivation, nutritional deficiency, medications, alcohol, tobacco, drug use, head injury, and stroke. Amnesia, a partial or total loss of memory, can be either of two types: One is retrograde amnesia, meaning amnesia for events that preceded some disturbance to the brain, such as a head injury or electroconvulsive shock. Damage in the thalamic areas may cause retrograde amnesia. The other type is anterograde amnesia, referring to amnesia for events that occur after some disturbance to the brain, such as head injury or certain degenerative brain diseases. Hippocampal lesions may also be the reason. Hippocampi are important in learning, but not for reflexive (skill) learning. Hippocampus and medial thalamic nuclei play a role in limbic thoughts (reward and punishment). People with anterograde amnesia are unable to consolidate information about location of rooms, corridors, buildings, roads, and other important items in their environment. The ability to remember the position or location of objects and places is called the spatial memory. Spatial memory has representations within working, short-term and long-term memory. It is sometimes considered in the context of episodic memory, one type of declarative memory. Bilateral medial temporal lobe lesions produce most profound impairment in spatial memory, but significant deficits can be produced by damage that is limited to the right hemisphere [2].

Long-term memory is often divided into two further main types: explicit (or declarative) memory and implicit (or procedural, nondeclarative) memory. By definition declarative memory is the memory that can be verbally expressed, such as memory for events in a person's past ("knowing what"). On the other hand, nondeclarative memory is a collective term for perceptual, stimulus-response, and motor memory ("knowing how"). In that case, the memory formation does not depend on hippocampal formation, located in the temporal lobe of each cerebral cortex. The term hippocampal formation typically refers to the dentate gyrus, the hippocampus proper (i.e., cornu ammonis), and the subicular cortex.

Information transfer within the nervous system is basically provided by the nerve cells. Neurons are the basic units of the nervous system. The synapse, the connection of two neurons, is the functional unit of the brain. Physiologically, memories are stored in the brain by changing the basic sensitivity of synaptic transmission between neurons as a result of the previous neural activity. New or facilitated synaptic pathways are called memory traces that can occur at all levels of the brain. A memory trace, also known as an engram, is a theoretical

http://dx.doi.org/10.5772/intechopen.82365

means by which memories are physically stored in the brain. All memories are not processed through the same steps. There are different neural mechanisms mediating several types of memory, all of which is caused by electrochemical and structural changes within the synapses. Common to all forms of memory is the cellular and circuitry changes in the nervous system. To understand the mechanisms underlying learning and memory that involve changes at the molecular, cellular, and network levels is still a major goal for neuroscientists.

Learning does not occur through a single way; it can take at least four basic forms:

1. Perceptual learning: Learning to recognize a particular stimulus. Perceptual learning involves learning to recognize things, not what to do when they are present. It can involve learning to recognize entirely new stimuli, or it can involve learning to recognize changes or variations in familiar stimuli.
2. Stimulus-response learning: Learning to automatically make a particular response in the presence of particular stimulus includes classical and instrumental conditioning.
3. Motor learning: Learning to make a new response
4. Relational learning: Learning relationships among individual stimuli. It is commonly classified into:

    a. Spatial learning
    b. Episodic learning
    c. Observational learning

Learning and memory are strongly associated with electrical activity in neurons, particularly in the hippocampus. We can study learning and memory in hippocampal neurons by examining how they respond to different patterns of input. To investigate brain mechanisms involved in identifying the origin of memories, event-related potentials (ERPs), long-term potentiation (LTP), and long-term depression (LTD) are recorded. While ERPs are used for humans, LTP and LTD are appropriate and commonly used to describe changes in cellular mechanisms underlying synaptic plasticity mainly used for synaptic plasticity at in vitro and in vivo rodent studies [3].

The synaptic plasticity and memory hypothesis have been a subject of interest for many scientists. The idea that learning results from changes in the strength of the synapse was first suggested by Cajal at the end of the nineteenth century based on insights from his anatomical studies. Hebb developed more refined models in the 1940s and defined the modulation of synaptic connectivity as a critical mechanism of learning. For the experimental purposes, in order to examine changes in the neuronal components of a specific behavior during or after the modification of that behavior with learning, different behavioral systems were developed [4]. The first models helped to define the neuronal changes that underlie learning and memory through simple forms of procedural memory such as habituation, sensitization, and classical conditioning. *Aplysia* gill-withdrawal reflex is maybe the best known among these models emerged at 1963 by Kandel and Tauc. By allowing electrophysiological recording

from individual neurons, these systems provided the first experimental insight into the cellular mechanisms of memory [4, 5].

Modulation of neurotransmitter release changes synaptic strength, and this is a mechanism learning and short-term memory. It is well demonstrated in both the gill-withdrawal reflex of *Aplysia* and in the tail-flick response of crayfish. The plasticity occurred at the sensory neuron inputs onto the motor neurons that control the reflex response and thus directly modulate its magnitude. The results showed that clear structural changes in both the pre- and postsynaptic cells can accompany even elementary forms of learning and memory. Memory storage does not depend on specialized, superimposed memory neurons whose only function is to store rather than process information. The sensory-to-motor neuron synapses playing a role in the gill-withdrawal reflex are also the cellular substrates of learning and memory. The capability of memory storage is built into the neural architecture of the reflex pathway [4].

Stimulation with a high-frequency train of action potentials was shown to produce a prolonged strengthening of synaptic transmission that is called long-term potentiation (LTP), in all three of the major hippocampal pathways [4]. N-Methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type glutamate receptors (NMDARs, AMPARs) are ionotropic receptors and important for synaptic plasticity [6]. NMDA receptors control Ca^{2+} channel that is normally blocked by Mg^{2+} ions. They are blocked by a drug called AP5 (2-amino-5-phosphonopentanoate). AMPA receptors control Na^{+} channel. The early phases of expression are mediated by a redistribution of AMPARs. When open, they produce excitatory postsynaptic potentials (EPSPs). Evoked potential that represents EPSPs of population of neurons is called population EPSP [3].

LTP and long-term depression (LTD) are two forms of activity-dependent changes, and both are believed to represent cellular correlates of learning and memory [6]. LTP and LTD are induced by specific patterns of activity. Because NMDAR-dependent calcium influx induces both LTP and LTD, the cell must have a way to decide whether to potentiate or depress a synaptic connection. For LTP induction both pre- and postsynaptic neurons need to be active at the same time because the postsynaptic neuron must be depolarized when glutamate is released from the presynaptic bouton to fully relieve the Mg^{2+} block of NMDARs. Conversely, LTD can be induced by repeated activation of the presynaptic neuron at low frequencies without postsynaptic activity. LTP initiates as a predominant amplification of AMPARs [7]. But the behavior of NMDA can largely explain the critical features of LTP: synapse specificity, cooperativity, and associativity. Unlike most neurotransmitter receptors that respond simply to the presence or absence of their cognate transmitter in the synaptic cleft, the NMDA receptor is also sensitive to the state of the postsynaptic membrane in which it resides.

Besides electrophysiology, electrochemical methods like voltammetry are versatile tools for detecting, monitoring, and measuring various neurochemical species. The "gold standard" for assessing ion-channel function is the patch-clamp electrophysiological technique on millisecond timescales with up to single channel resolution. Histopathological tests including immunohistochemistry and immunofluorescence give important clues to neuroscientists [8–10]. Cognitive behavioral and neuroimaging (among them most useful being functional magnetic resonance imaging (fMRI)) techniques are also commonly used [11]. Common

behavioral testing paradigms for animal memory are fear conditioning, passive avoidance, object recognition, place learning and cue discrimination, water maze, and other mazes like T-maze and radial arm mazes [12]. Cognitive neuroscience aims to reduce cognition to its neural basis using newer technologies such as fMRI, repetitive transcranial magnetic stimulation (rTMS), and magnetoencephalography (MEG) as well as older methods such as positron emission tomography (PET) and electroencephalography (EEG) studies [13].

Although it is now clear that long-term synaptic plasticity is a key step in memory storage, it is important to note that to store a complex memory, changes in synaptic function must occur within the context of an ensemble of neurons to produce a specific alteration in information flow through a neural circuit. A second important challenge is to understand how the basic processes of memory storage are altered with age or disease, including AD. It becomes of critical importance to understand in sufficient detail both the basic mechanisms of memory storage and the changes that take place in disease to design specific compounds that can be used to restore cognitive function [4].

3. Eat

In the early 1800s, continental Europeans like Savarin verbalized the idea of "you are what you eat" that has been preached at the East for centuries. The mucosa of the gastrointestinal tract is the largest surface that interacts with the external environment. The gastrointestinal tract contains approximately 500 million neurons which collectively constitute the enteric nervous system and represent in total numbers as much as that contained in the spinal cord. Intrinsic primary afferent neurons (IPANs) that form 20% of the enteric neurons comprise in the detection of certain inflammatory mediators and inflammation with the gastrointestinal tract [14].

Inhibiting nitric oxide (NO) synthesis during learning that food is inedible in *Aplysia* blocks subsequent memory formation. Memory that food is inedible arises in three steps: (1) chemoreceptors responding to food on the lips, (2) receptors signaling active efforts to swallow food within the mouth, and (3) receptors signaling differential gut responses to success or failure to swallow [15].

On the other hand, a growing body of preclinical literature has demonstrated bidirectional signaling between the brain and the gut microbiome, involving multiple neurocrine and endocrine signaling mechanisms [16]. Li et al. observed a correlation between dietary-induced shifts in bacteria diversity and animal behavior that may indicate a role for gut bacterial diversity in memory and learning [14]. Studies have shown that protein-induced proliferation of gut bacteria in mice augments spatial memory, and the ingestion of probiotic mixtures by healthy volunteers improves problem-solving abilities and has anxiolytic actions [17, 18]. Recent findings have resulted in speculation that alterations in the gut microbiome may play a pathophysiological role in human brain diseases, including autism spectrum disorder, anxiety, depression, chronic pain, obsessive-compulsive disorder, and memory abilities (including spatial and nonspatial memory) [16, 19].

4. Learn

It is well established that the hippocampus is one of the most important brain structures involved in learning; and lesions in this area cause impairment in learning, with location and severity of lesion influencing the severity of the effect on learning. But it has been proven that even in the absence of the hippocampus, learning can still occur. This suggests that other brain areas like the amygdala and olfactory bulb also play a role in the formation of new memories [12].

It is an important challenge to understand how the basic processes of memory storage are altered with age or disease, such as AD. It becomes of critical importance to understand in sufficient detail both the basic mechanisms of memory storage and the changes that take place in disease to design specific compounds that can be used to restore cognitive function [4]. The presence of amyloid plaques and neurofibrillary tangles in histological sections of the brain is required for the definitive diagnosis of AD. The cognitive decline is observed earlier than the visualization of the plaques. Amyloid-β peptide (Aβ) is the major component of the amyloid plaques. A large body of evidence accumulated in the past 15 years supports a pivotal role of soluble Aβ oligomers (AβOs) in synapse failure and neuronal dysfunction, disrupting LTP and LTD mechanisms in AD [6, 20].

Through varied mechanisms, gut microbes shape the architecture of sleep and stress reactivity of the hypothalamic-pituitary-adrenal axis. They influence memory, mood, and cognition and are clinically and therapeutically relevant to a range of disorders, including celiac disease, alcoholism, chronic fatigue syndrome, fibromyalgia, restless legs syndrome, and multiple sclerosis (MS) [21]. MS involves an immune-mediated process in which an abnormal response of the body's immune system is directed against the central nervous system, causing chronic inflammatory demyelinating disease. Since gut microorganisms play an important role in the development of the autoimmune system and are associated with a variety of autoimmune and metabolic diseases, it is speculated that gut symbiotic microorganisms play an important role in the susceptibility to MS [22].

Parkinson's disease (PD) follows a defined clinical pattern, and a range of nonmotor symptoms precede the motor phase. Evidence suggests that environmental factors have an important role in triggering and/or propagating the pathology of PD; the olfactory and gastrointestinal systems are gateways to the environment. The neurodegeneration process that leads to PD seems to start in the ENS or the olfactory bulb. The intricate relationship of governing host and microorganism interactions suggests that when this relationship is abnormal, the microorganisms may cause the pathogenesis of disease or promote the progression of disease. The microbiota may alter adult hippocampal neurogenesis. Hippocampus and lateral ventricle have the function of generating new neurons in adulthood. Adult hippocampal neurogenesis has a role in learning and memory and can affect the pathogenesis of many neurological disorder-related diseases and symptoms, such as epilepsy, depression, AD, and Parkinson's disease (PD) [23].

5. Remember

"Remembering the past is a form of mental time travel: it frees us from the constraints of time and space and allows us to move freely along completely different dimensions" said Eric Kandel. Learning is a behavioral change due to an experience. Memory is storage and recall of information. It is widely accepted that learning process consists of at least two stages: short-term memory and long-term memory. Models of memory include distinctions among very short-lived memories like sensory memory, which has a lifetime measured in milliseconds to seconds; short- to medium-lived memories like short-term memory and working memory, which persist for seconds to minutes; and memories that may persist for decades, which we call long-term memory. Working memory is often referred to as a mental juggler, because it is what allows the brain to do many different things at once. And, memory itself can be broken down into two types: explicit and implicit. Explicit (or declarative) memory is recall of personal events/personal facts (episodic memory) or recall of facts (semantic memory). Implicit (or nondeclarative) memory is recall of reflexive motor skills or perceptual skills.

The rule of thumb for memory is "use it or lose it." Forgetting might be a problem; but sometimes the thing we remember might cause the trouble. One of the major problems in memory research in humans is its fallible nature. Having the ability to recall memories does not necessarily mean they are accurate. Our ability to store and process what is going on and using the classified information basically relies on memory being a constructive, fallible process. Children's memory is more susceptible to suggesting and implanting of false memories than adults. Since the underlying neurophysiological mechanisms for such an association are similar to the one that occurs when a genuine memory is formed, it is not surprising that the subject behaves as if the (false) memory was formed by a perceived real experience [24]. The formation of false memories in humans often occurs as a result of recombining mnemonic elements of discrete experiences into a new, reconstructed memory that is not a veridical representation of the past. These memories are not formed de novo and require pre-existing memories as a platform onto which distinct experiences can be incorporated to update the memory itself [24].

6. Conclusion

Recently, memory research has accelerated and we have seen an explosion of new knowledge in neuroscience. A set of persuasive evidence for the long-sought memory engram and engram cells has now come of age. The evidence has been obtained by combining multiple technologies, each addressing a specific level of complexity. Here, you will read a tiny part of the accumulated knowledge to elucidate the usefulness and limitations of these into clinical practice and daily life.

Eat to live, live to learn, and remember to value everything just as much as they deserve.

Acknowledgements

I would like to thank Author Service Manager Ms. Romina Rovan and Commissioning Editor Ms. Lucija Tomicic-Dromgool for their constant help and patience.

Author details

Aise Seda Artis

Address all correspondence to: aseda@yahoo.com

Istanbul Medeniyet University, Istanbul, Turkey

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