

# What changes in the brain when we learn?

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*We have, in the next place, to treat of Memory and Remembering, considering its nature, its cause, and the part of the soul to which this experience, as well as that of Recollecting, belongs. (Aristotle in his treatise On Memory and Reminiscence)*

### **Abstract**

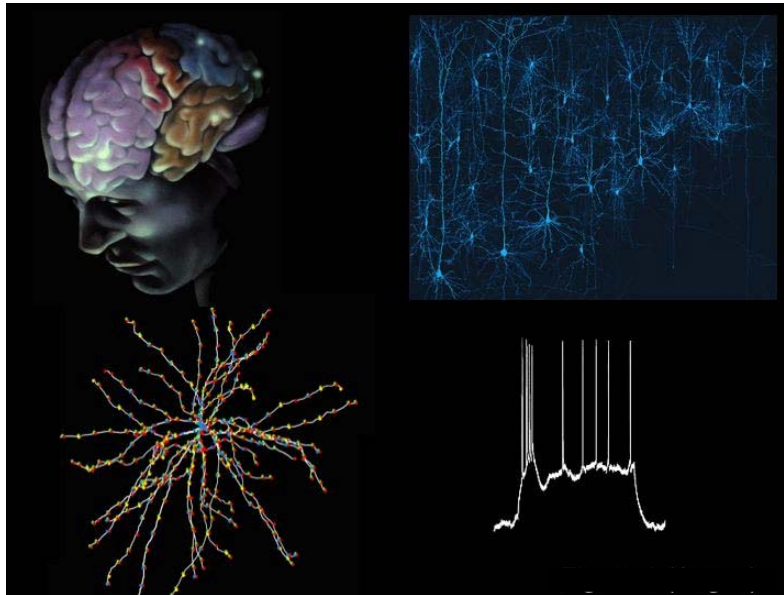
*In many ways we are the albums of memories we have collected in our brain. The creation of this ever-changing brain-album is made possible because of the amazing tendency of the neuronal substrate to constantly change following new experiences. These physical changes undergo progressive stabilization in the brain, sometimes forming long-term memories. What are the physical changes underlying memory in our “brain machine”? The developments of new optical, electrical and molecular technologies enable one, for the first time ever, to view the living brain while it changes and learns. The major recent advances in this fascinating field of research are briefly summarized herein. A brief introduction to the brain “life-ware” is provided, followed by a highlighting of the main modifiable (plastic) neuronal mechanisms that may support learning and memory in the brain. It is worth emphasizing that when the unique learning mechanisms that brains utilize are eventually unraveled, we could then help to cure memory deficits, expand our memory capacity and begin building learning machines that will successfully behave in, and adapt to, the ever-changing environment that surrounds us.*

### **The substrate for learning in the brain – nerve cells and synapses**

Each of the 10 billion nerve cells (neurons) that compose our brain is an independent electrical entity (“microchip,” Fig. 1, lower left). When stimulated (e.g., by sensory input, by direct electrical stimulation or by other neurons connected to it, see below) it generates a series of prototypical electrical signals called “spikes” (Fig. 1, lower right). Each of these spikes has a rather constant shape and amplitude. It is therefore of a digital type – it either exists (in full amplitude and a fixed duration) or it does not exist at all. When a sensory stimulus arrives (e.g., a word appears on the paper you now read), millions of neurons in your visual system fire a series of such spikes. These spikes represent (encode) the sensory (e.g., visual) stimulus. Similarly, when you hear a piece of Bach music, million of neurons in the auditory system fire spike trains and, collectively, this firing in the activated network of neurons (Fig. 1, top right), represents this piece of music in your brain. When you move your hand, millions of neurons in the motor system of your brain fire trains of spikes, thus representing (and planning) the movement. In other words, the internal language of the brain is composed of specific groups of neurons that fire, at a particular time, a series of spikes, thus representing an item (a face, an emotion, a memory, an idea) that is being processed by the brain at that time.

Most neurons are not connected electrically to one another. Rather, they interact with each other via a unique apparatus called a “synapse” (originating from the word “synapsis” – meaning clasp [or grip] in Greek, Fig. 1, schematic dots in lower left and Fig. 2). The synapse forms a tiny physical gap between the synaptically-connected neurons and is unidirectional (i.e., a given synapse connects cell 1 to cell 2 but not *vice versa*). When a spike occurs in neuron 1, a chemical (a neurotransmitter) is released at the synapse, and this neurotransmitter binds to specific receptors in cell 2. The latter then responds to the neurotransmitter with a small electrical signal, called a “synaptic potential.” Unlike the “all-or-none” nature of the spike, the synaptic

potential is analog (rather than digital) in nature - it may be very small (tenth of a millivolt) or larger (several millivolts) and, for a given synapse, it may attain either a positive sign (“excitatory” synapse) or a negative sign (“inhibitory” synapse). The synapse is therefore a chemical device that transforms digital signals (spikes) in one cell (the pre-synaptic neuron) to an analog signal – the synaptic potential - in the other cell (the post-synaptic cell). The strength of the synapse (the efficacy of the synaptic connection) may vary; yet each synapse typically retains its signs, it is either excitatory or inhibitory.



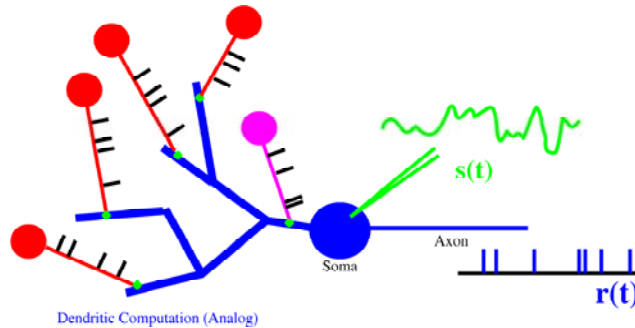
**Figure 1.** *Brain ingredients.* Our brain is a home for billions of interconnected nerve cells (top right). Each individual nerve cell (lower left) is a tiny input-output electro-chemical microprocessor with a tree-like structure (the dendritic tree). It receives over its surface many thousands of synaptic contacts (schematic color circles) originating from the axons of other nerve cells. When these synaptic contacts are activated (e.g., in response to a sensory input), the cell fires an output in the form of a train of prototypical electrical signals, called spikes (lower right). Our thoughts and feelings, sensory perception and motor actions are all represented in the brain by a code that is carried by these spikes and is distributed among neuronal networks consisting of large numbers of nerve cells.

How does the synaptic potential (the input to a neuron) generate an output in the form of a spike train in this neuron? When many (hundreds) of excitatory synapses bombard a given neuron (and not too many inhibitory synapses act at the same time) then individual potential of each synapse sums up with that of other synapses and, if a certain positive voltage threshold is reached, then the receiving (post-synaptic) neuron responds with a spike (or a series of them, Fig. 2). The neuron is therefore an input-output electrical device that transforms (via its synaptic connections) the analog synaptic signals that it receives (over its receptive, or input, region - the *dendritic* tree, Fig. 2) from many other neurons to a series of digital signals – a series of spikes (generated on the neuron’s output process - the *axonal* tree, Fig. 2).

## What changes in the brain during learning?

What, then, could change in the brain “life-ware” described above – the neurons and their synapses – when we learn? Some possible neuronal mechanisms that are not mutually exclusive come to mind:

- (i). New nerve cells may grow (and new neural networks are then formed) when we learn something new.
- (ii). The strength of *existing* (synaptic) connections changes, thus functionally changing the connectivity (and the activity) within the *existing* neural networks in response to a sensory stimuli.
- (iii). New synapses are formed between neurons that were not connected before, thus effectively creating new networks of neurons that, when active, represent a new memory.



**Figure 2.** The neuron as an input-output electrical device. Many thousands of pre-synaptic neurons (red) contact the post-synaptic neuron (blue) via corresponding synapses (green dots) that are distributed over its dendritic tree. Each of these red neurons fires a series of spikes (black lines) -- e.g., in response to a sensory input. The spikes arriving at each of these synapses are transformed to a local graded (analog) potential along the blue dendritic tree. These barrages of synaptic potentials from all the red cells are summed up at the cell body of the receiving cell ( $s(t)$ , green line) and (if  $s(t)$  is sufficiently positive) a spike train,  $r(t)$ , is elicited in its axon. Note that each of the red cells receives thousands of synaptic inputs. Clearly, changing the strength of the synapses will elicit a different output in the blue neuron (and in the network as a whole). This change in synaptic strength is considered to be a major mechanism underlying memory and learning in the brain.

(i). *New neurons for new memories?* Although in recent years it was found that in some regions of the adult mammalian brain new nerve cells do grow, this growth is rather sparse, and it is unlikely that our new memories are stored by these new nerve cells. An interesting counter example of this is the brain of songbirds, where the males during the courtship period generate a typical song and, only during this period, a large number of new nerve cells grow and were shown to play a key role in the generation of the song. These cells then die, and the singing of the song subsides until the next courtship period. This fascinating example, in which physically new networks serve a new function, is the oddity rather than the rule.

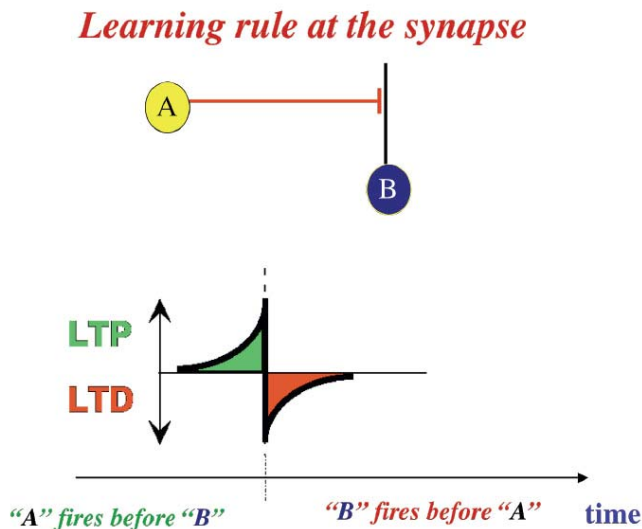
(ii). *Adjusting synaptic strength for new memories?* The strength of the synaptic connection can indeed change very rapidly. It was shown that when synapses are repeatedly activated, their resultant post-synaptic potential might become larger or smaller, thus effectively changing the strength of this synaptic connection. Indeed, synapses are probably the most modifiable (plastic) elements in the nervous system. Furthermore, after a short period of activation, the change in synaptic strength may last for hours and days (long-term potentiation, LTP, or long-term depression, LTD, in the synaptic strength), and probably even longer (the question of whether one needs to “replay” memories by reactivating the neural networks involved—e.g., while

dreaming--in order to stabilize the changes that correspond to the new memory is an issue under investigation). But what are the rules that “decide” when a synapse will become stronger or weaker following its activity?

The Canadian psychologist Donald Hebb (1949) was the first to formalize a tentative rule for changes that may occur in the connection between nerve cells: *“When an axon of cell A is near enough to excite cell B or repeatedly or consistently takes part in firing it, some growth or metabolic change takes place in one or both cells such that A’s efficiency, as one of the cells firing B, is increased.”*

One may succinctly summarize the “Hebb learning rule” as stating that *“when cell A persistently participate in firing cell B, then these cells are more strongly connected to each other.”*

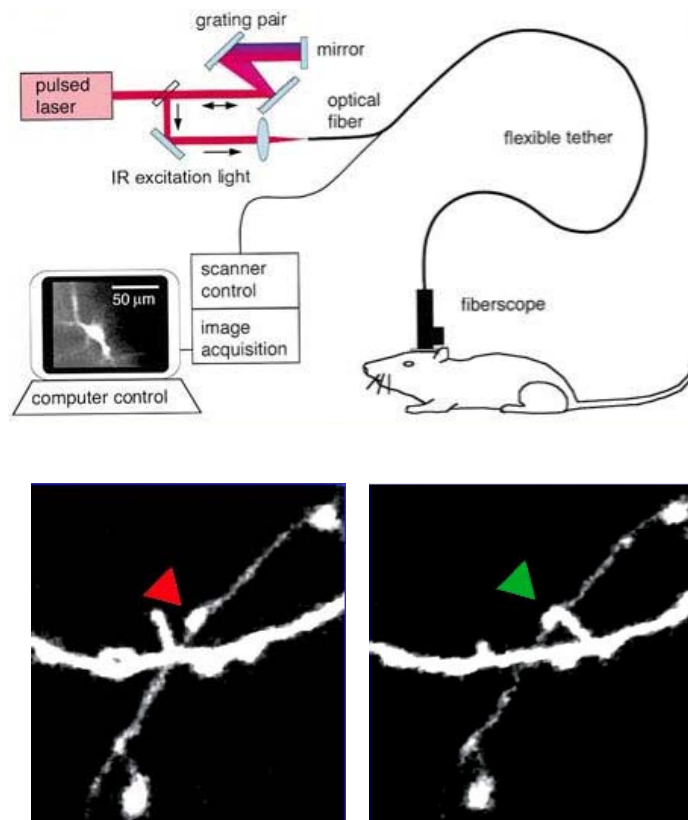
Indeed, recent experiments in pairs of synaptically-connected nerve cells demonstrate that, in many systems, the Hebb rule does hold true. Furthermore, in many cases the “anti-Hebbian” rule also holds. Namely, if cell A is consistently not involved in firing cell B, then the synapse between them is weakened (Fig. 3).



**Figure 3.** The “Hebbian” rule for synaptic plasticity. Cell A (the pre-synaptic neuron) is connected via a synapse to cell B (post-synaptic neuron). When cell A fires first, and cell B at a later time fires a spike, quite consistently, then the synapse is strengthened (LTP – green), whereas when cell B fires first and cell A fires later (so that there is no causal relationship between their firing) then the synapse is weakened (LTD, red). It was experimentally found that the time window for this type of synaptic plasticity is on the order of 10ths of a millisecond. Therefore, this mechanism per se cannot explain learning of the type of classical Pavlovian conditioning, in which the time between the ringing of the bell and showing of the food could be at the seconds time scale.

(iii). *Forming new synapses for new memories?* The development of the two-photon microscope in recent years enabled one to follow a given synaptic connection day after day in the living brain and explore how stable this connection is and whether new synapses are formed. It was recently found that new synapses are constantly formed (by creating a very small new protrusion – called a dendritic spine – that forms a synapse with a nearby axon, see Fig. 4), and old synapses may disappear. In other words, in our densely packed nervous system, a slight shuffling in its fine anatomy (without changing its gross anatomy--e.g., adding neurons or growing new long branches) enables the formation of new contacts between preexisting neurons.

This relatively new discovery has shifted our thinking about memory storage in the brain. Whereas it was previously thought that most of the changes associated with memory rely on changing the strength of *existing* synapses, it is presently believed that the formation of *new* synapses may play a key role in learning and, in particular, in stabilizing long-term memories.



**Figure 4.** An optical view of anatomical changes in the living brain. Schematic drawing of the two-photon microscope system, containing a small microscope stage, mounted on the head of a mouse, with a laser beam entering the brain via a small hole in the skull. This system enables one to repeatedly view the same location at a mm resolution (the size of a single synapse). The lower left picture shows an axon (thin white line) of one nerve cell crossing nearby (but not contacting) a dendrite (thick white line) of another cell. Several days later, a synaptic contact is formed at that same location between the axon and the dendrite (green arrowhead). This anatomical rearrangement of synaptic contacts during behavior is thought to be one of several physical bases for the learning and memory processes in the brain (see Trachtenberg et al., 2002).

Whatever the biological mechanism, whether it is the growth of new synapses or the strengthening or weakening of old synapses, both mechanisms establish functional new networks that *when active*, could, in principle, represent (store) new memories (e.g., new learned capabilities). Repeated imaging of the brain while one rehearses a given practice in order to learn a new skill (e.g., playing a piano) shows that the brain region that represents the acquired skill (e.g., the region representing the movement of the fingers) “grows.” This growth implies that a larger neural network (more neurons are now more tightly connected to each other) is involved in the refined (and more coordinated) learned movement of the pianist fingers. To the best of our knowledge, no new nerve cells are added to the brain of an expert pianist. But more nerve cells are recruited (via the strengthening of the synaptic connections in the network or by adding new synaptic connections to it) following acquisition of a skill. The capacity of the brain to constantly rewire itself is so vast (the number of its synapses is on the order of  $10^{14}$ ), that establishing new functional networks while we learn does not necessarily destroy old memories. Indeed, with such a huge number of synapses in a

single human brain (10,000 times larger than the number of people in the world), we can learn much more than we do.

It should be emphasized that the physiological changes in the synaptic strength as well as the morphological changes (the formation of new synapses) are all supported by sophisticated genetic machinery that is responsible for generating and maintaining these changes. The molecular basis for memory is a very active field of research today, and its details are beyond of the scope of the present article (Dudai 2004). The interested reader is advised to dive into the fascinating Nobel lecture by Eric Kandel (winner of the 2000 Nobel Prize), entitled "*The Molecular Biology of Memory Storage: A Dialog between Genes and Synapses*" which can be found at <http://nobelprize.org/medicine/laureates/2000/kandel-lecture.html>.

### **Epilogue: Emotional learning, sleep and memory, and brain-inspired learning theory**

The problem of the biological basis of memory in the brain has many facets, and only a few were summarized above. One intriguing question is the neural basis for emotional learning and memory. A specific brain region called the amygdala is known to be involved in emotional responses and, in particular, in fear conditioning and the formation of long-term memories of fear associations. Synaptic mechanisms such as LTP were implicated as being the basis for such associations (Ledoux 2003). But why is it that emotions are so powerful and so hard to control and relearn (especially those that cause behavioral disorders)? What is it, at the synaptic level, that makes it so hard to forget (get rid of) strong emotions, whereas we tend to rather easily forget names or faces or other skills that we have acquired but stopped practicing them? This puzzle remains yet to be unraveled.

Another intriguing question is, what the role is of different brain areas--from the hippocampus to the cortex to the limbic systems--in the process of acquiring and storing memories. The hippocampus is considered to be the brain region where new facts and events are initially processed and stored, whereas certain neocortical regions are believed to store this information for a longer time. Retrieval of old memories activates other brain regions. So it seems that different aspects of memory are distributed over different brain regions and, indeed, a local damage may yield specific loss of one aspect of memory (e.g., damage to the hippocampus may destroy the capability to acquire new memories, but old memories are retained). Importantly, new molecular techniques pave the road for a deeper understanding of the cellular mechanisms that underlie memory consolidation and retrieval. In this context it is worth mentioning the growing behavioral, electrophysiological and molecular studies demonstrating that sleep contributes to memory consolidation. A good review on the aspects mentioned above can be found in a special issue of the journal *Neuron* (2004) that is fully dedicated to the question of memory in its many facets.

But what is still missing for providing a real breakthrough in understanding how memory is represented and stored among distributed networks of neurons and their synapses, and how these memories are retrieved (e.g., via associations), is a *learning theory* (a mathematical model) that will incorporate the experimental data into a comprehensive picture. Without such a theory we will remain with a collection of (most important) experimental facts that will not provide the deep understanding that



is required for describing as complex a system as the learning brain. Indeed, without such a theory we cannot say, “we understand how the brain works.”

Happily, in the last two decades, many powerful theoreticians, physicists, mathematicians and computer scientists have joined this endeavor. New mathematical theories are being developed to describe: How is memory distributed in neuronal networks? What is the memory capacity of such networks? How do such networks retain memory while facing the constant death of cells and synapses? and How does the brain make predictions based on old memories, and consequent changes when these predictions are proven to be successful? (see Dayan and Abbott 2001; Hopfield and Brody 2004; Gutig and Sompolinsky 2006).

We are at an age of “brain-renaissance,” in which a variety of disciplines--biology, physics, psychology, computer science--and many brains join forces to try and develop such a theory. There are good reasons to believe that the big “brain-eureka” is just around the corner.

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