The Anatomy of a Memory:
Insights Into How Information is Stored in the Brain

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"We are what we are not only because we think ("cogito ergo sum") but also because we can remember what we have thought about. Every thought we have, every word we speak, every action we engage in –indeed, our very sense of self and our sense of connectedness to others- we owe to our memory, to the ability of our brains to record and to store our experiences. Memory is the glue that binds our mental life, the scaffolding that holds our personal history and that makes it possible to grow and change throughout life.

Larry R. Squire and Eric R. Kandel

(*Memory: from Mind to Molecules*, 1999)

INTRODUCTION

How we learn and remember are questions that have been central to three intellectual disciplines: philosophy, psychology and biology. Until the nineteenth century, the study of learning and memory was restricted largely to the domain of philosophy. Later, this theoretical approach was gradually replaced by more experimental studies, initially in psychology and then in biology. The questions posed by these two disciplines concerning learning and memory storage began to converge, and today psychologists and biologists have joined forces to open up the "black box" to study how the brain and behavior allows us to learn and have memories.

The neurobiology of memory can now be studied at two different but complementary levels, one aimed at brain structure, circuitry and behavior, and the other aimed at individual nerve cells and the molecules within nerve cells. The first is concerned with neural systems of the brain

important for memory - *where are memories stored*?. The second is concerned with the cellular and molecular mechanisms of memory storage - *how are memories stored*?

Concerning the question of where memories are stored, the modern view is that there is no single locus in the brain where all memories reside. Many parts of the brain appear to participate in the internal representation of memory by encoding different aspects of the whole. Specific brain regions have specialized functions (language, vision, and motor control, for example) and each contributes in a different way to the storage of whole memory.

The aim of my study is an attempt to answer the question of how memories are stored. But first, I will describe some of the more fascinating and intriguing discoveries that have emerged from the efforts of all the scientists who, with this questions in mind and after two decades of intense experimental work, have provided a series of remarkable insights into the the biological basis of learning and memory.

BRAIN PLASTICITY AND MEMORY

One of the more striking and perhaps most surprising findings in the biology of memory is that learning alters the physical structure of the brain. This remarkable plasticity exhibited by the brain is fundamental to our individuality. The different environments to which each of us is exposed and the different amount of information each of us has acquired modify our brain in unique and sometimes permanent ways. Of course, each of us shares the same basic brain anatomy which results from commom blueprint of our species. However, this blueprint is plastic, or changeable, and therefore its specific details will vary from person to person according to our individual experiences. But not all of the experiences we encounter in our daily life leave a lasting trace in our brain. Our interests, preferences, motivations and personality play an important role in determining the quality, quantity and persistence of the information we store in our brain.

We experience the world through our five senses: touch, sight, hearing, taste and smell. Each sensation is analyzed by specific receptors on the surface of the body and then transmitted to the area of the brain known as the cortex, where most sensations are elaborated and become consciousness. Each sensation is represented in specific sensory cortical areas. A common feature of these cortical areas, primarily those devoted to touch, vision and hearing, is that they all represent our body surface in a topographic manner which resembles a map; neighboring cortical regions respond to neighboring sites of the body. It has been shown that even in adults, these maps are not static but undergo plastic changes according to how the sensory pathways are used over time.

In a series of important studies, Merzenich and his colleagues (1992) examined one area of the somatosensory cortex, where the hand is represented, before and after stimulation of the digit skin surface. In experiments with monkeys, they discovered that the cortical area which represented the trained finger, had become significantly larger than the corresponding area in untrained animals. Likewise, Pascual-Leone & Torre (1993) analyzed differences in the hand representations of adults who had become proficient as Braille readers. Using magnetoencephalography, they found that the scalp area was larger for the right index (reading) finger as compared with the left or with the right finger of non-Braille readers.

Elbert et al (1995) found a similar reorganization of the somatosensory cortex in a group of string players. Violinists and other string players provide an elegant model for the study of brain plasticity since differential sensory inputs reach the two sides of the brain where the left hand and the right hand are represented, respectively. During practice or performance, the second to the fifth digit of the left hand are continously engaged in fingering the strings and so in frequent shift of position and pressure. The other hand, which manipulates the bow, performs a task which requires much less individual finger movement and fluctuation in tactile and pressure inputs. The results of their study showed that the representation of the digits of the left hand of string players is larger in comparison with fingers of the right hand or with fingers of the left hand of control subjects. The same authors observed that these changes were more pronounced in string players who begin

studying their instruments by the age of 12 years. This result is not surprising considering that our brain is most modifiable when it is young.

A similar effect of musical training on brain plasticity has also been observed in the auditory cortex where acoustic stimuli are processed. The younger the subjects starts playing their instrument, the stronger is the cortical activation in response to piano tones (Pantev et al, 1998). Indeed, a significant enlargment in the cortical representation is observed particularly in musicians who begin to practice before the age of 9 years.

Increased hippocampal volume has been reported in small mammals and birds who often engage in behavior requiring spatial memory, such as food storing. The role of the hippocampus in spatial navigation had been well documented also in humans. For example, Maguire et al. (2000) carried out a structural MRI study in licensed London taxi drivers who must undergo at least 2 years of training to learn how to navigate between the thousands of places in the city. The analysis of MRI scans of 16 taxi drivers revealed an increased volume in only two regions of the brain, the right and left hippocampus compared with those of controls. What was particurarly intriguing in this study was the dramatic correlation between hippocampal volume and the amount of time spent as a taxi driver suggesting a strong relationship between local plasticity in the structure of the adult human brain and increased exposure to an environmental stimulus.

MAKING MORE SYNAPSES: A WAY TO STORE INFORMATION?

What causes increases in the volume of active brain regions? It has been assumed that the brain stores information by changing the strength of the connections between neurons. These connections are called *synapses* and represent a specialized junction through which information passes from one neuron to another. Synaptic transmission can be broadly divided into two steps: a transmitting step, in which the first neuron (pre-synaptic) releases a chemical signal, called neurotransmitter, and a receptive step in which the transmitter binds to specific receptors located on the surface of the second neuron (post-synaptic). Within each neuron, the information is then propagated

unidirectionally, from its receptive site (i.e. cell body, dendrites or tiny dendritic projections called spines) to the axon. The axon terminates with small swellings called varicosities, which are filled with packages of neurotransmitter.

The search for structural changes that may accompany learning is difficult since, if there are any, they may be small and widely distributed implying a serious "needle-in-the-haystack" problem. One way to study this issue is to expose the animals to enriched environments so as to maximize the amount of sensory stimulation each animal receives. Such studies were among the first to suggest that the structure of the brain can be altered throughout a significant portion of an animal's life span. For example, when rats were placed in large, toy-filled cages (the yuppies of the rodent world) and compared with rats housed individually or in standard cages there was

an increase in the brain size and cortical thickness. These changes were later shown to be due to an increase in the number and size of synapses (for review, Greenough, 1984). In addition, the same "yuppie" animals also showed faster acquisition of other tasks when compared with isolated animals, suggesting perhaps that the increase in synapse number may improve the animal ability for new learning.

How closely the synaptic changes induced by these global and non-specific manipulations of the environment resemble those induced by learning and memory is still unclear.One way to begin to address this issue is to train animals in a specific task and then demonstrate specific changes in dendritic fields of neurons in regions suspected of being involved in the performance of such a task. Perhaps the most convincing study of this sort was conducted by Chang and Greenough (1982). They observed that when young adult animals were trained in a maze, structural changes occured in the visual area of the cerebral cortex. However, when they learned the maze with one eye blocked by an opaque contact lens, only the brain regions connected to the open eye showed larger dendritic fields. In another study, it was shown that training in a set of complex motor skills was associated with structural changes particularly in the motor region of the cerebral cortex and the cerebellum, a structure that coordinates motor activity. It is important to note that exercise by itself is not

sufficient to induce neuronal changes. Indeed, when animals were placed in running wheels no changes occurred within the cerebellum, whereas when they were trained to challenge a complex obstacle course (acrobat rats) a 30% increase in synapse number was observed (Black et al., 1990).

A major contribution to our current understanding of the mechanisms that underlie memory storage has come from studies of the hippocampus, a brain region involved in memory formation. The role of the hippocampus in human memory was first suggested in 1957 by Scoville and Brenda Miller who reported the story of the amnesic patient H.M., now considered the most famous patient in the field of memory research. This patient suffered of a severe and intractable form of epilepsy. Scoville decided, as a last resort, to remove the inner surface of the temporal lobe, including the hippocampus, in an attempt to treat his epilepsy. This treatment solved the problem of the epilepsy but it left the patient with another big problem, a very specific deficit in memory processing. Brenda Miller has carried out a remarkable study by examining this patient continously for 40 years and reporting how some of his memory abilities were dramatically affected with respect to others. All these observations led to some important conclusions. First of all, the hippocampus plays an important role in the acquisition of new memory. H.M. lacked the ability to transfer new short-term memory into long-term memory. He was unable to retain, for more than a minute, information about places and objects and to recognize people he met again and again, after his surgery, including the same Brenda Milner. Second, the hippocampus is not the final storage site in the brain for long-term memory. The patient H.M. retained good long-term memory for events that occurred years before the operation. He remembered his name, the job he had and his childhood events. This suggests that the hippocampus mediates the initial steps of memory storage and that it transfers information into other cortical areas where long-term storage of the memory resides. Third, not all forms of memory depend on the hippocampus. For example, patient H.M. could learn new motor skills, like tracing the outlines of a star while viewing his hand in a mirror or operating a computer. Yet at the beginning of each new day's test he could not remember having done any of these tasks before.

During the last three decades, much effort has been directed to understanding how the hippocampus consolidates memory, i.e. how short-term memory is converted into long-term memory (Squire, 1992). This is not an easy issue to address if we consider the large number of neurons and synapses in the brain of both mammals and humans. In 1973, Bliss and Lomo found that repetitive stimulation of a specific area in the hippocampus of rabbits produced a long-lasting form of synaptic plasticity called Long-Term Potentiation (LTP) which persisted for hours and in some cases even days. Since its initial discovery, several laboratories have used LTP as a cellular model to study how information is stored in the mammalian brain. These studies have recently benefited from the introduction of novel techniques for imaging living neurons and synapses. We now know that LTP is associated with the structural remodeling of synaptic connections. This structural plasticity consists of 1) an increase in the receiving apparatus of the neuron i.e. an increase in the number and size of postsynaptic dendritic spines and 2) an increase in the transmitting apparatus i.e. the growth of new presynaptic varicosites (for review, Yuste and Bonhoeffer, 2001).

However, the interpretation of changes in the number and structure of synapses in the mammalian brain remains controversial and leaves open the question: what is the contribution of indivual synapses to the learning and memory process? This problem can be overcome by using a simple nervous system such as that found in many higher invertebrates. For example, the nervous system of the marine mollusk *Aplysia californica* contains only 20,000 nerve cells grouped into 10 major ganglia, each of which functions as a small brain. Many of these cells are so large they can be identified with the naked eye. This, in turn, has facilitated identification of the nerve cells which are involved in specific behaviors and has allowed one to study what happens to these neurons when the animals learns. Exploiting this reductionist approach, Eric Kandel and his collegues have analyzed the nerve cells mediating simple behaviors such as the gill-withdrawal reflex of *Aplysia.* This reflex is represented, on an elementary level, by the direct synaptic connections between identified sensory neurons and their follower motor neurons and can be modified by two simple

forms of learning: sensitization and habituation. Following sensitization, the animals reacts stronger to a noxious stimulus, whereas following habituation the snails learns to ignore a neutral stimulus. Both forms of learning gives rise to a short-term memory lasting minutes to hours and a long-term form lasting days to weeks (for review, Kandel 2001). In each case, the memory for sensizitation is reflected by an increase in the strength of the sensory to motor neuron connection whereas the memory for habituation is reflected by a decrease. Using this model, Bailey and Chen (1983) first demonstrated that long-term sensitization induced a dramatic increase in the number of synapses per sensory neuron and that these changes persisted for as long as the change in the gill withdrawl reflex lasts. As the memory decays, synaptic terminals are lost and they gradually regress back to their initial number.On the other hand, following long-term habituation the number of synapses between sensory and motor neurons decrease. The next step was to reconstituite this simple model in vitro by placing the sensory-motor neuron synapse in the presence of serotonin (5-HT), a modulatory neurotransmitter normally released by sensitizing stimuli in the intact animal. Thus, a single application of 5-HT produces short-term changes in synaptic effectiveness, whereas four of five applications of 5-HT over a period of 1.5 hr (or continuous application of 5-HT for 1.5 to 2 hr) produces long-term changes lasting one or more days.

Using this experimentally accessible preparation I have recently examined the time course of the facilitation induced by repetitive pulses of 5-HT in culture and found that there is a significant increase in the strength of the sensory to motor neuron synaptic connection that persists for at least 1 week. The ability to follow this long-lasting synaptic plasticity over such an extended time period now allows me to address a number of questions central to an understanding of the mechanisms that underlie the persistence of long-term memory: Is the stability of long-term memory achieved, at least in part, because of the relative stability of synaptic structure? If so, what are the cellular and molecular processes that serve to stabilize synaptic structure? Do alterations in the stability of synaptic structure lead to alterations in the persistence of memory storage?

Answers to these questions may eventually provide important insights into the mechanisms that underlie the family of memory-related dysfunctions associated with normal aging and disease.

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