In Search of Memory

(The emergence of a new science of mind)

Eric R. Kandel

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This book is a passionate praise of scientific inquiry. The initial biography of the author, from a childhood in nazi-occupied Vienna to a youth of liberal education in the USA, set the character of Eric Kandel as a determined person. His family escaped, when he was 9 years old, the nazi prosecution of Jews in 1939. The book accounts for his personal biography at large put in the context of the research of his time and his contribution to neurosciences. He accounts also for the results of many other European researchers that unfortunately had to leave their countries during WWII.

The book is hard to put down, Kandel masters scientific writing and gives a clear and chronological history of the fascinating discoveries of the neurosciences in the twentieth century, The book also accounts for the personal quest of the author to find the ultimate biological explanation of human behaviour, that is, how learning processes and memory are sustained by neurological mechanisms, electrical, chemical and genetic. Memory is the essence of all of us. When we lose our memory we fade away. As Kandel puts it: ‘we are who we are because of what we learn and what we remember.’

The book is organised along three different types of content. On the one hand the personal biography of the author that allows the reader to enjoy the motives, illusions and emotions of a researcher, a detailed explanation of research findings that introduce the reader to the big names in neuroscience during the nineteenth and twentieth centuries, and a chronological description of the research focus of Eric Kandel. This last part is specially well organised as the book progresses from the initial results to ever deeper questions to explain human behaviour, from the electrical observations of neurons to the DNA explanation of learning. A fantastic intellectual progression of the author that made him win a Noble Prize in 2003.

Kandel started his personal scientific journey studying psychoanalysis. The fact that Freud was Viennese and Jew made his attraction for psychoanalysis much stronger The fascination for Freud’s explanation of human behaviour made him start the studies of medicine in 1952, at the precise moment when the DNA structure was about to be unraveled. By the end of his college years, Kandel study of biology made him depart from the non-biological explanations of psychoanalysis and concentrate on a strong experimental approach to science.

The book devotes a long section to explain the findings of Ramon y Cajal, a neuroanatomist contemporary to Freud, whom Kendal considers ‘the most important brain scientist that ever lived’. The fact that Santiago Ramon y Cajal was Spaniard and actually the founder of the Spanish National Research Council to which the IIIA, the Artificial Intelligence Research Institute, belongs, made me especially proud when reading the book. Ramon y Cajal set in the 1890s the fundamental principles that govern our understanding of the brain: (i) the neuron is the basic building block that gives structure and function to the brain, (ii) axon terminals and dendrites are connected at special sites, later called synapses, with a small gap between the two cells, (iii) neurons have connection specificity, neurons don't connect among them indiscriminately, they form specific pathways called neural circuits through which the signals travel, and (iv) dynamic polarization, that is, signals in a neural circuit travel in only one direction. The last principle proved to be crucial in the understanding of the function of the brain and an avalanche of research was made to find specific pathways, specially when Cajal showed that there were three types of neurons, the sensory neurons (to respond to pressure, light, sound or chemicals), motor neurons to activate muscles and glands, and interneurons as relays between sensory and motor neurons.

Kendal first results were obtained from the analysis of electrical impulses on neurons. He gives in the book a clear chronology of the electrical analysis of neurons. The results obtained by Edgar Douglas Adrian in the 1920s allowed to register and amplify the electrical impulses along the axons. Adrain's results included the fact that the action potentials that traverses a neuron (for around a millisecond) are all the same. The open question of how the propagation of the electrical impulse along the axon was produced was answered by Julius Bernstein who proposed that the neurons had a difference in potential (-70mV) from inside (positively charged) to outside (negatively charged) and that there must be specific channels that would allow for potassium ions (positively charged) to leak out of the cell and create a locally negative charge inside the neuron that will attract the positive potassium ions that just left the neuron to keep them near the membrane of the cell and thus maintaining the difference in potential. The hypothesis he made is that the propagation of an electrical signal was based on local changes in the permeability of the membrane. Physics and chemistry became, thanks to Adrian's and other precursors' work, the theories that could explain the behaviour of the brain. Later, Hodgkin and Huxley discovered that the permeability of the membrane was selective to sodium or potassium in a way that a permeability inwards of sodium ions followed by a permeability outwards of potassium ions explained the upstroke and downstroke of the action potential that was of 110mV; larger that the prediction by Bernstein. The flux of ions was regulated by special channels (later found to be proteins) sensitive to the type of the ions. The influx of the sodium channels increasing the resting potential from -70mV to +40mV activates the opening of the channels to relieve potassium ions that will get the potential back to -70mV. Another crucial finding in the explanation of the electrical propagation was that the imbalance of ions after an action potential has traversed the axon is eliminated thanks to a special protein that transports excess of sodium ions outside the neuron and excess of potassium inside it. Both won the Nobel Prize in 1963. Actual images of the channels were taken as late as 2003.

The fascinating account of research made by Kendal continues on the findings that led to understand how the electrical signal traversed the synaptic gap. This point was a matter of controversy between 'electrical' and 'chemical' explanations. Otto Loewi found evidence of chemical transmitters between neurons in the 1920s. The chemical theory was the winner in the competition as Bernhard Katz showed the existence of two types of channels, voltage channels as described earlier and chemical channels that account for the communication between neurons and that activate the action potential in the next neuron in a neural pathway. Katz also showed that when the electrical signal reaches the presynaptic terminal it opens voltage channels that admit calcium ions that start the process of release of the chemicals that will then activate an electrical signal in the next neuron via special channels in the receiving cell. Moreover, he showed that the neurotransmitters are released in packets of several thousand molecules. These findings happened around the second World War and the description of the results and the protagonists of the findings allow Kendal to also explain the influence that the Popperian thinking had in the research of the time. All the results mentioned here made that not only chemistry and physics were fundamental in the understanding of the brain but also biochemistry became essential.

In the context that Kendal sets along the initial chapters of the book and are somehow summarised above he begins the explanation of how he started his research on the study of the neuron. He initiated after graduation a laboratory practice that allowed him to learn how to do precise electrical measurements on neurons that allowed him to confirm already known results about the action potential electrical values. This training proved to be essential in obtaining accurate results later in his career. His first research position was at the National Institute of Mental Health led by Wide Marshall. There he slowly forgot his interest on psychoanalysis and started a scientific study of memory based on biological grounds.

A discussion on the history of science that studied the localization in the brain of different mental capabilities deepens into several nineteenth century researchers and set the scene to explain the state-of-the-art in neuroscience when Kendal put the question to himself of where is the memory localised in the brain. The facts that the memory is distinguished into short and long term memory and that the importance of the hippocampus to transform short into long term memory were known to Kendal when he started his work. A succinct chronology of how these facts were established is given in the book. Kendal explains his first experiments in the study of the hippocampus, the key organ of memory. However, Kendal made an important move by selecting a simple animal to allow him to study the basic learning processes: a giant sea snail called Aplysia, an animal with a few large nerve cells. He extended Cajal's ideas by assuming that different types of learning implied different types of neural activity, and each pattern would change the strength of the synaptic connections in different ways. He explains the experimental setting devised by him to test the Pavlovian types of learning: habituation, sensitization, and classical conditioning. He showed that even several simple reflex mechanisms of the Aplysia could be modified by learning (e.g. gill-withdrawal). The explanation of these processes is in my opinion the most interesting part of the book where the reader feels the passion of the author describing in detail the experiments, the findings, the excitement of scientific discovery. Kendall's expertise in the management of electrical apparatus proved essential in this part of his career. Several studies, in a plethora of animals, inspired by Kenda's initial results, supported the idea that learning is preserved through evolution as it is essential for survival. He found that the connectivity of neurons was specific, in the same way as Ramon y Cajal proved the connection between populations of neurons was specific. Kendal, in fact, completely mapped all the neurons involved in the reflex of gill-withdrawal and published an influential paper in Science on 1969 describing the interactions among them.

Ramon y Cajal suggested that the strength of synapses would be modified by learning. Kendal proved that conjecture to be right in experiments with Aplysia, and showed that when conditioning is applied the synapses get strengthened and with other learning mechanisms they get weakened. He moves then to explain the next step in his research, that was in fact what motivated him at the beginning of his career: how short-term memory becomes long term. He and his collaborators discovered that short and long term memories were stored, in simple cases, in the same places. The transformation from short to long is due to anatomical changes in the number of synaptic terminals, some terminals are removed and others are created. The number of synapses in the brain is not fixed and varies with learning. The anatomical changes may also lead to the creation of new pathways, new neural circuits. The book gets extremely exciting as these results were proving in biological terms different theories conjectured by several psychologists during the late nineteenth and twentieth centuries.

The molecular biology of memory was the natural next step. The research continued by finding interactions between mediation circuits, between sensory and motor neurons, and modulating circuits that tune, thanks the release of serotonin, the behaviour of the mediation circuits, by producing inside the cell cyclic ATP that in turn enhances the release of glutamate. Certain receptors of serotonin at the cell membrane would not act as channels but as producers of enzymes inside the neural cell that increase the release of glutamate. Chemicals will increase the electric response on subsequent cells in the pathway. These lasting changes accounted as the chemical explanation of short-term memory. The repeated propagation of certain signals into a neuron makes the release of protein kinase A that moves into the cell nucleus to activate certain genes that generate the needed proteins that will produce the structural changes by creating new synaptic connections that account for long-term memory. The proteins move to all terminals but generate new terminals close to those where a high amount of serotonine is found. A fascinating explanation that was the result of three decades of intense work. Inspired by these findings, several studies in different animals showed that Kendal and his collaborators had found basic learning and memory mechanisms that were common to many species.

The last part of the book goes backs to the initial questions about memory in humans, discusses the challenging pharmaceutical findings to increase learning abilities, the prospects to chemically treat mental illnesses, and conciousness. Many exciting questions without a clear answer yet but that will make this century an exciting time for research in the neurosciences. The results already obtained and those in the roadmap for the next decade will certainly have a strong impact in artificial intelligence as new biologically-inspired mechanisms will probably change the way we model machine learning.

A detailed glossary and set of references completes this book that is indeed a great reading to get introduced and excited about the past and the future of neuroscience. An unputdownable book!