BRAIN SCIENCE PODCAST

With Ginger Campbell, MD

Episode #3

Discussion of the Book, *In Search of Memory: The Emergence of a New Science of Mind*, by Dr. Eric Kandel

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INTRODUCTION

This is the *Brain Science Podcast* Episode 3, and I'm your host, Dr. Ginger Campbell. In this episode we are going to explore memory by discussing Dr. Eric Kandel's autobiography, *In Search of Memory: The Emergence of a New Science of Mind*, which was published by Norton in 2006.

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DISCUSSION

Before I start talking about Dr. Kandel's book I want to tell you a little bit about his background. Dr. Kandel won the 2000 Nobel Prize for Medicine for his work with *Aplysia* and rats in a study of long- and short-term memory.

He was born in Vienna and came to the United States as a child in 1939 to escape the Nazis. He ended up going to high school in Brooklyn, and then to Harvard. He went to medical school and then did his residency in psychiatry. He was planning to be a psychoanalyst, but he discovered research in 1955 and never looked back.

In his book, *In Search of Memory: The Emergence of a New Science of Mind*, Dr. Kandel describes his life as a pioneer in neuroscience. This is an unusual autobiography because the emphasis is on the history of science rather than his personal life. He gives a very excellent introduction to the field of neuroscience because he describes all the key discoveries.

His own particular interest was in memory, and that will be the material that I'm going to focus on today. Probably the reason why he was interested in memory was because he was very fascinated with why his own childhood memories of Vienna were so vivid. This book is also an excellent book for anyone interested in the history of science. It gives a comprehensive perspective on how far our knowledge has come, especially in the last 50 years.

I find it kind of interesting to compare Dr. Kandel's life story with that of Sigmund Freud. Dr. Freud was going to be a neurologist—this was in the late 1800's—but at that time neurology was such a primitive science that he ended up going into psychiatry. In contrast, at the time that Dr. Kandel came along—which was around 1955—neurobiology was just beginning to take off. And so, instead of becoming a psychoanalyst he went into basic research.

Early on one of his important choices was what experimental animal to study. He chose the giant marine sea snail, *Aplysia*. So much research has been done on *Aplysia* that this choice now seems obvious. But back when he made the choice in 1959, there were only two researchers in the entire world working with *Aplysia*.

One reason for this was at that time it was assumed that the human brain was totally different from the brains and nervous systems of other animals. But 50 years of research has revealed that there are surprisingly few proteins unique to the human brain, and there are no unique signalling systems. This might not seem as surprising now as it did before we understood how much DNA we share with lower animals.

In 1959 when Dr. Kandel started his research, DNA transcription had not yet been unraveled, and we didn't yet know how DNA leads to protein synthesis. So, the bottom line is that one of the effects of Dr. Kandel's research was the uncovering of how much of our nervous system we have in common with other animals.

One of the things I really appreciated about Dr. Kandel's writing is that he is very gracious in crediting others for their discoveries. He often notes how developments in other fields like molecular biology allowed his research to go forward. This book would make an excellent gift for any young person interested in science. Dr. Kandel shows how science is constantly building on the work of others.

He also demonstrates through numerous examples how good science is really done. He emphasizes the importance of asking the big questions and of being willing to forge into the unknown. He shows how hypotheses are formed and, more importantly, tested.

I think this is important, because the way science is taught in school now, there isn't much instruction in the scientific method. The findings are presented as if they are fact and there is no discussion of how scientific ideas become established. This is reflected in the fact that there are a large number of Americans who actually think that intelligent design is as scientific as evolution. And obviously, if they really understood how the scientific method works, they would know that there is no comparison.

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So, let's talk about what Dr. Kandel learned from the *Aplysia*. Now, when you go to my website, I was not able to post a picture of the *Aplysia* because I couldn't find an image that didn't seem to be copyrighted. But all you have to do is do a Google image search and you can get a lot of images on *Aplysia*, which will also lead you to lots of research information if you want to learn more.

But at any rate, he chose *Aplysia* because it has very large neurons and a relatively simple nervous system consisting of only 20,000 neurons. By 1985, after 15 years of work, he had shown that simple behaviors in *Aplysia* could be modified by various forms of learning such as sensitization and habituation. Sensitization is when a stimulus is presented and it makes the neuron more sensitive in the future. Habituation is when the same stimulus is tending to be ignored in the future.

So, what were some of the key discoveries? One is that short-term memory (and this means on the order of minutes) involves strengthening or weakening of the synapse—that's the connection between neurons—by the presence or absence of the neurotransmitter glutamate: because glutamate turns out to be the main excitatory neurotransmitter.

In contrast, long-term memory requires an actual structural change of the synapse. This means protein synthesis, which means a chemical messenger has to go from the synapse to the nucleus and actually deactivate a gene that is normally blocking the protein synthesis. Dr. Kandel was able to prove how this is done in the *Aplysia*.

There are three new principles that come out of this work. One is that activating long-term memory requires switching on genes. And I don't know about you, but I didn't really think of memory as being something with a genetic component. There is a biological constraint on what experiences get stored.

The baseline situation is suppression of forming new memories. So, that actually has to be inactivated. The chemical messenger comes from the synapse, goes up to the nucleus and basically turns off the gene, and then the proteins needed for making new synaptic terminals are synthesized. The growth and maintenance of new synaptic terminals is what makes memories persist.

Dr. Kandel did his original work with *Aplysia*, but the same mechanisms were shown to exist also in fruit flies. Fruit flies are wonderful experimental animals because genetic changes can be produced in very sort periods of time. Of course, the memory that we're talking about in the *Aplysia* is an implicit memory rather than explicit or conscious-type memory.

But before we talk more about that, lets' go back and talk a little bit more about the difference between short- and long-term memory. In mammals, including people, the hippocampus is required to form long-term memories. The hippocampus is an area of the brain that is located on the inside surface of the temporal lobe. The temporal lobe is the one that you would point at if you pointed right above your ear.

A lot of what we know about the hippocampus is the result of the research of Brenda Milner and her work with a patient who is known as HM. HM was a man who had his hippocampus (destroyed) and was not able to form any long-term memories. She worked with him for many years.

In 1962 she was able to demonstrate that there is more than one kind of memory, because she showed that there is an unconscious memory that exists outside of the hippocampus. And I'm going to talk about this more when I talk about the difference between implicit and explicit memory in a little while.

If you want to think about how the hippocampus works, you might think of if you ever saw the movie *50 First Dates*: In that movie Drew Barrymore's character wakes up every day forgetting what she has done the day before, and lives the same day over and over again. Now, in real life a person who has this kind of brain damage would actually only be able to remember something for a few minutes. They wouldn't be able to keep a whole day. But still, the basic principle is the same.

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When they got ready to study explicit memory they needed to move to a higher animal, and they used rats. In rats the hippocampus is essential to forming spatial memories. The researchers were able to show, first of all by using sections of the rat hippocampus grown in culture, that the biochemistry was very similar to that which was seen in the *Aplysia*.

They also showed that if they knocked out a single gene in the rat they could knock out a spatial memory. In contrast they found that if they blocked the suppressor gene they made brilliant rats—that is, ones that could learn the mazes much faster than a normal rat.

Finally, before I move on to my discussion of the difference between explicit and implicit memory, I want to point out that all this work with various species—including *Aplysia*, fruit flies, and rats—has helped to prove an important principle. This is that the molecular mechanism of memory is the same in all animals.

Spatial memory in rats is an example of explicit memory. The key difference is the role of attention. With implicit memory the starting signal is involuntary. It starts at the level of the synapse and the process is a bottom-up process. With explicit memory it is top down, since the signal to form the memory begins voluntarily.

Why is attention required for explicit memory? Well, the most obvious reason is that there is much too much sensory input for us to process all the input at a conscious level. And that's true even if you're a rat. At the same time we all know that it's really hard to remember something if you're not focused.

So, here we begin to enter the field of cognitive neuroscience, which results from the interdisciplinary work of neuropsychologists and brain science. This is the kind of stuff that you often find described in *Scientific American Mind* magazine. I hope to talk more about cognitive neuroscience in the future.

But first I want to come back to considering how the discovery of scientists working with other animals sheds light on human experience. First, as I mentioned, we share molecular mechanisms and signalling pathways with other animals. Sometimes the neurotransmitters—which are the chemicals that communicate signals between neurons—vary between species; but the general mechanisms have been conserved and elaborated as one moves forward in evolution.

Knowing this makes it less surprising to discover that our memories are a very complex phenomenon. A perceptual or even an emotional memory has both a conscious and an unconscious component. An example would be Dr. Milner's patient, HM. The way that she showed that there was an unconscious memory was that she was able to show that he could learn new tasks even though he couldn't remember that he had learned them.

She did this by having him draw a figure in a mirror. And if you've ever tried to do this, it's very difficult. By the end of several days he was much better at it, even though he had no memory of ever having performed the task before.

Another example of this that's even weirder is the phenomenon of blind sight. This is when people have damage to their occipital lobes and so they can't see anything consciously, but if their retinas are still working and some visual signals are going to the lower parts of their brain they may be able to see on an unconscious level. And there are ways of testing and showing that they can do this; and it's really pretty strange.

Near the end of his book Dr. Kandel talks briefly about consciousness, which he defines as a state of perceptual awareness. He also describes it as, "…selective attention writ large." And in people he says, "It is an awareness of self, and an awareness of being aware." Consciousness is a big subject that I am also going to talk about more in future podcasts.

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In closing this discussion I want to say again that I really recommend this book to readers of all backgrounds. It can serve as either a great introduction or a review of the principles of neuroscience, and it is a valuable history of neuroscience. And it should be read by anyone—especially young people—who is curious about how science is really done.

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I would very much like to have your feedback and comments. One of the things I am thinking about doing is starting a daily blog post in which I just cover one simple principle at a time about neuroscience. So, I would appreciate your email or comments on this. You can send me email at docartemis@gmail.com, or you can post comments at the website, which is brainsciencepodcast.com.

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I hope to post the next *Brain Science Podcast* in about two weeks. The topic is going to be *The Great Brain Debate: Nature or Nurture*, by John E. Dowling of Harvard.

In the meantime, I hope that in addition to leaving me some comments or sending me some email, you will listen to my other podcast, *Books and Ideas*. Next week on *Books and Ideas* I'm going to be talking about the relationship between science and philosophy.

So, please take care, and I'll see you then.

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Transcribed by Lori Wolfson
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