BRAIN SCIENCE PODCAST

With Ginger Campbell, MD

Episode #12: Featuring *Memory: From Mind to Molecules*
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INTRODUCTION

This is the *Brain Science Podcast* - the podcast for everyone who has a brain - and I'm your host, Dr. Ginger Campbell. On the *Brain Science Podcast* I explore how recent discoveries in neuroscience are unraveling the mysteries of how our brains make us who we are.

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This is the *Brain Science Podcast*, Episode 12. First I would like to welcome any new listeners to the *Brain Science Podcast*. And also I want to remind everyone that I appreciate your feedback, both at the website brainsciencepodcast.com and through email at docartemis@gmail.com.

Today's episode is going to be about memory. Memory is one of the most fascinating and well-studied aspects of brain science, and today I'm going to get into some questions such as what is the difference between declarative and non-declarative memory, how do short-term memories become long-term memories, and do we know where our long-term memories are stored or how we recall memories.

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But first I want to get into a few announcements. I'm making progress toward getting the Discussion Forum up. My goal is to have it up by the end of June. Also I want to thank those of you have voted for me for the National Public Radio Talent Quest, and especially I want to thank those of you who left comments on the website. That's very much appreciated. You can still vote through the first week of June.

One thing that I'm thinking about doing is having a logo contest because I need a better logo for the *Brain Science Podcast*, and I especially need it for September when I'm going to be going to some big podcasting meetings and I would like to have a logo that I can put on materials to share with others. I haven't quite gotten the exact rules together on this. When I do I'll post them on the website. But if you're interested or have some ideas about this please go ahead and send me email at docartemis@gmail.com.

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Like I said, today we're going to talk about memory, which is a subject that we talked about a little bit in Episode 3 when we discussed Eric Kandel's autobiography. Today I hope to go into a little bit more depth on this subject. But before I start talking about today's book, which is *Memory: From Mind to Molecules*, by Larry Squire and Eric Kandel, I want to just talk about a few basic research principles.

First of all I want to mention the experimental animals that are often mentioned when you're reading about memory research. The first one is the *Aplysia*, which is a giant sea snail which has important qualities for neuroscience research. It has very large neurons and a fairly simple nervous system that's been well delineated—that is, every neuron does the exact same thing in every *Aplysia*. This is the one that Dr. Kandel has done much of his research on. He's uncovered much of the basic chemistry of memory at that level, and it's been then shown that the basic molecular processes extend from species to species.

Another important experimental animal is *Drosophila*, the fruit fly. And it's important because it reproduces so quickly and its entire genome is known. So, mutations can be created and their exact genetic location determined, and then the flies with these particular genetic mutations can be studied for their behavior.

Finally, real important animals in memory research are mice and rats. There are two key things about mice. One is as mammals they are representative of our family—which is that they have a cortex. And secondarily, their genome is also known and there are a lot of techniques that have been developed for making genetic modifications in mice so that you can study how changing a single gene affects behavior such as the ability to form memories. So, those are the three experimental animals that we'll be mentioning. And the experiments are described in much more detail in the book.

The other principle that I want to talk about before I get into the details of today's topic is the principle of how causation is proven in a scientific experiment. Let's say you want to prove that a neurotransmitter has a particular action. You have to do two things: you have to show that it's necessary, and you have to show that it's sufficient. To show that it's sufficient what you do is you apply the neurotransmitter—or whatever other thing it is you're testing, but neurotransmitters are a good example—and demonstrate that that thing specifically causes the effect that you're studying. Then to show that it's necessary, you block that specific thing and show that the effect disappears. So, it's really a two-fold thing.

And the point is that a lot of times there will be associations—that is, you will see that two things occur together—but it's important to realize that doesn't mean one caused the other. For example, say that a person always wears a certain shirt when they go to watch their favorite team play, and their team has a winning streak. That doesn't mean that their wearing that particular shirt caused their team to win. So, in science a lot of times there'll be apparent associations that then need to be tested.

And sometimes they will be proven to not work, such as about 10 years ago it was thought that estrogen replacement would have all kinds of different benefits in women. This was based on some observational associations. Yet, when they did a big study most of these failed to pan out, and it turned out that there was some harm. One of the things you'll oftentimes see in pseudoscience is the failure to appreciate the difference between associations and true causal relationships.

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As I mentioned, the book, *Memory: From Mind to Molecules*, contains very detailed descriptions of many different experiments, and it has really good illustrations of each experiment. I'm not going to have time to go into the details of the experiments, so if you really want to know these details you're going to want to get the book.

Not surprisingly, memory is something that has fascinated people probably from the beginning. And for a long time it was the realm of psychologists to study. It's probably only been in the last 50 years the biology of memory has been studied, and Dr. Kandel was one of the pioneers in this. So, we will be discussing things such as the difference between declarative and non-declarative memory, the difference between short-term and long-term memory, and questions such as how and where are memories stored.

One of the most important principles that has been discovered about memory is that retrieving a memory actually turns out to be a creative process. It's not like you have a fixed exact memory of anything that you just recall; you actually have to recreate the memory each time. And this point is important in understanding the fact that our memories are not only somewhat volatile, but also prone to error.

Now, you may recall that in the first episode about memory I mentioned a famous patient who's known as HM, who had bilateral destruction of his hippocampus, which is in the medial temporal lobe of the brain deep on the inside of the brain. This is the part of the brain that has been established to be important for forming long-term memories. Remember that HM was a guy who every day when the researchers worked with him, he would respond to them as if he had never seen them before, and the next day he wouldn't remember having ever met them—kind of like *50 First Dates*.

Four key principles emerged from about 40 years of studying HM. One was that the ability to acquire new memories is a distinct cerebral function that's located in the medial portion of the temporal lobes. HM remembered everything that happened before his brain injury, but he couldn't remember anything past that point. He couldn't make new memories.

But the second principle was that the medial temporal lobes were not required for immediate memory. He could retain some new information as long as he didn't get interrupted. Third, the medial lobes and the hippocampus can't be the ultimate storage sites for long-term memory, because he still had his long-term memory from before the injury.

And probably the most remarkable discovery was the fact that he did have the ability to learn some things and remember some things. He could learn how to trace an object in the mirror. He got better at this from day to day, even though he didn't have any conscious memory of doing this. This was the first evidence that there was another kind of memory besides the kind that we normally think of, which is like memories of events.

So, this brings us to the idea that there are two kinds of memory, which you might think of as the difference between knowing how and knowing that. Declarative memory is your memory of facts and events. Non-declarative memory includes motor skills, priming—which I will describe later—learning habits, classical conditioning, and learning non-motor skills like how to read reversed print.

We actually don't know how many different types of memory there are. But we do know that there are different forms of non-declarative memory and they seem to depend on different brain structures; like the amygdala seems to be involved in emotional memory such as fear memory, and the cerebellum seems to be involved in learning skills. The easiest way to remember this is just to remember that knowing how to do something seems to be different from the conscious recollection of it. Now, as far as we know, invertebrates have only non-declarative memory, since they don't have any hippocampus or cortex.

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I'm going to start out by talking more about non-declarative memory because some of the research that we have that explains memory was first done on this form of memory. One important principle is that non-declarative memory is not normally under our conscious control. And remember, this includes motor and perceptual skills, habits, emotional learning, as well as reflex forms of learning like habituation, sensitization, and classical and operant conditioning. You might recognize some of these because they've been studied for years by psychologists, especially back in the days of the behaviorists.

An example is the fact that when we learn how to play tennis, the skill of playing tennis is separate from our memory of taking a lesson. Why is it important that non-declarative memory has been discovered? Well, first of all this was the first biological evidence that unconscious mental processes actually exist. The behaviorists had been concentrating on these kinds of memories for years, but they had been under the mistaken assumption, in a way, that this was the only kind of memory.

People like Pavlov had to study two types of non-declarative memory. There was the associative, which would include classical and operant conditioning, and non-associative, which would be habituation and sensitization. I'm going to talk about these a little bit. Behaviorism obviously has fallen way, way out of favor. But one contribution that the behaviorists did make was that they showed that the rules that govern very simple forms of non-declarative memory are very general and apply not only to humans, but to very simple experimental animals.

The simplest form of non-declarative memory is habituation. This simply means that if a stimulus is encountered over and over again the animal basically stops paying attention to it. This means that we ignore familiar unimportant stimuli. It seems pretty basic. Eric Kandel demonstrated that habituation could be created in the *Aplysia*—the snail I was talking about before. He did this by showing that the gill withdrawal reflex was subject to habituation. And basically this just meant touching the animal and eliciting the reflex—touching it with a light touch—and then doing this repeatedly until after awhile it didn't withdraw to protect the gill because it learned that that wasn't anything harmful.

And along with demonstrating this he demonstrated that this caused short-term changes in the synapses. This was important because it showed that the synapse was somewhat plastic and that transmitter release could be changed at the level of the synapse. Also it showed that it didn't require any special memory neurons. And this is an important principle that becomes increasingly important as we go further into the study of memory. In fact, basically this memory of this reflex was imbedded in the neural circuit that produced the behavior.

Now, Kandel also studied the molecular basis of memory by studying sensitization; which was taking the same *Aplysia* and shocking it, and giving it a light touch. And so, the fact that it actually became more sensitive to the light touch was exactly the opposite of habituation. And he showed that this involved serotonin and also another molecule inside the cell called the second messenger. I'm not going to get back into the second messenger principle because I talked about this on the episode about neurotransmitters. As many of you may recall it gets pretty complicated, and we just don't have time to get back into it today.

But the key idea is that memory involves the cyclic AMP second messenger system, which is actually a ubiquitous second messenger system that's even seen in bacteria. So, it's not a special molecular thing for memory, it's using a signaling system that's already present in practically every cell. That's the key thing to realize. Now, this was actually a surprise to the early students of molecular biology, because they thought that they would find all kinds of unique proteins in the brain, and relatively few have been found.

After demonstrating sensitization in the *Aplysia,* Kandel went on to demonstrate that *Aplysia* could show classical conditioning that's like Pavlov's dog. And this was considered to be a big surprise because it had been assumed that classical conditioning would require a complex circuit; whereas there was a guy named Donald Hebb who had proposed it could be happening at the cellular level. And this is basically what was proven by Kandel.

If you're interested in the details of these experiments, they're in the book. But the key ideas are that a single synapse can participate in multiple types of learning. For a single synapse Kandel showed habituation, sensitization, and classical learning, and that even more complex forms of learning and memory still use these elementary mechanisms that involve synapse plasticity. This involves both the presynaptic neuron and the postsynaptic neuron.

One last note on classical conditioning. It turns out that even the fruit fly is capable of associative classical conditioning. And the way they do this is that they found that they can put the fruit flies in a container with a certain odor, and then give them a shock, and they can be taught to avoid these odors. The thing that's neat about *Drosophila* is that they mutate very quickly, and it's easy to isolate mutations and breed groups of flies with specific mutations.

And a guy named Ronald Davis isolated one of these; and it's called dunce, because it was the first mutant fly that was found to have a defect in short-term memory. It turned out this involved a defect in the gene for making the enzyme for breaking down cyclic AMP. In fact, they found several other mutant strains and they all involved problems with the cyclic AMP pathway. So, what this tells us is that cyclic AMP is probably involved in non-declarative memory in many different species, and probably across various different types of learning.

They also found that if they blocked the production of protein kinase—which is the messenger activated by cyclic AMP—the flies couldn't do the odor test. They couldn't learn to avoid the odor that was associated with a shock. They've discovered at least a dozen forms of learning in fruit flies that require the cyclic AMP pathway. The key idea here is that one type of cellular and molecular mechanism—that is, the cyclic AMP—has been identified that applies to several types of memory in species as dissimilar as *Aplysia* and fruit fly.

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So, you're probably wondering if I'm ever going to get around to talking about declarative memory, which is the memory that is conscious recollection—sometimes called explicit or conscious memory. Let's consider a few basics. One is that our long-term memory seems to be unlimited. A lot of what's been studied about this has been done with vision, and it seems like nearly half the cortex is devoted to processing visual information.

But, there doesn't seem to be a separate memory center where memories are permanently stored. Information storage seems to follow the same principle in both vertebrates and invertebrates. It seems to be stored in the same distributed assembly of brain structures that are engaged in the initial perceiving and processing. For a long times scientists were trying to find something called the engram, which is the sum total of all the changes in the brain that first encoded a particular experience. But basically the fact of the matter is that this is just a concept, because each memory really seems to be distributed.

Now, what does this tell us about expert knowledge? It tells us that expert knowledge doesn't really rely on some prowess of general memory, but is a highly specialized ability that comes through experience where we encode and organize particular types of information. The key for an expert is the ability to be able to recognize a large number of patterns.

There was a famous experiment that showed this in which they took chess players of different abilities and they showed them boards with 26 pieces on them arranged in real game situations. They were allowed to look at the pieces for five seconds and then later they were asked to reproduce the board with as many pieces as they could remember. The beginners could only remember about four pieces, while the Grand Masters could replace about 16. In contrast, if the layout was just random pieces, then the difference between the groups disappeared, because it turned out that the Grand Masters didn't have any special gift for remembering details that weren't meaningful to them. And general memory training didn't make people any better at this particular exercise.

So, basically it looks like if you practice a certain thing, those years of practice do change your brain, but the change and the effect is specific to that specific thing. I think we can all probably think of something from our own lives that demonstrates this. I know that when I see or talk to a patient, pattern recognition is very important in my job. I can recognize what's wrong with a person oftentimes very quickly—much more quickly than I could 25 years ago when I was just starting out. And I think the same thing can be said for anybody that's acquired experience and expertise in a particular area,

One if the things that interests people about memory is how we retrieve declarative memory. I think I've already alluded to the fact that this is actually a creative process. We often rely on cues, and sometimes weaker ambiguous cues generate something different from the original memory. It's important to realize that a very strong memory doesn't ensure its accuracy. This is surprising to most of us, but it's been well demonstrated.

And we've already talked about how mood affects our memory—how much we remember, and what we remember. And context is really important, and this you probably already know from personal experience. But a weird example of the importance of context is that they showed that if a person learns words underwater they can remember them better underwater. But, like I said, I'm sure you can think of an example of this from your own life.

So, retrieval seems to be most successful when the context and the cues originally present are reproduced. You know how like when you smell grass it might bring back memories. When I was younger every time I smelled cut grass it made me think of playing softball. A practical application of this is that if you're practicing for something, you want to practice in a context as similar to what you're going to have to do it in as possible. For example, if you're going to have to take an oral exam, it's good to practice orally.

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It turns out that forgetting is actually just as important as remembering. The rare person who has a so-called photographic memory may be plagued with an inability to see the big picture. Ordinarily we're better at generalizing, abstracting, and assembling general knowledge, rather than keeping a strict literal record of events. I was glad when I read this, because I observe this all the time; that I can remember the essence of something but not the details. And I used to feel that this was evidence of laziness on my part. Now I realize that's just the way the brain works.

There's long been a debate about what happens when we forget. There are two schools of thought. One is that everything that we have ever remembered is stored, and we could theoretically retrieve it by some process like, say, perhaps hypnosis. The other school of thought is that some details are truly lost and could never be retrieved. And right now the evidence is tending to support the second position.

For one thing, research so far seems to indicate that our memories are continually being resculpted. Now, most of this data comes from animal studies, but does indicate that there's an actual loss of information, such as a loss of synaptic connections. Of course, the more thoroughly something is learned initially, the slower it is to be lost. And a good example of this is when you cram for an exam and you can't remember anything the day after the exam; whereas if you'd studied something day-to-day over months and then took the exam you'd have some retention of the material.

I was never any good at cramming. In fact, when I was in medical school I made a rule for myself that I didn't even study the day before the exam. I had learned that I didn't remember anything that I learned the day before the exam. So, I tried to study, then I went in and I felt like when I took the exam I knew what I knew, and I was still going to know that after the exam. Of course, a lot of other people would take the opposite approach and probably make higher grades. But then when they got to the clinics they didn't necessarily have any functional knowledge.

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Now, it's usually in terms of declarative memory that we start to think about ideas such as short-term memory and long-term memory. Experiments for short-term memory have been done with monkeys, and they've done things like shown them a color patch and had a delay and seen how long they could remember the color patch. And the way they do this is that they reward the monkey for being able to recognize the same patch after a delay. And they actually, back in the 70's I think—maybe the 80's—did single neuron recordings on the monkeys so that they could see what parts of the brain were being used during this. And this is where they came up with the basic ideas that the frontal cortex was involved and also working along with the sensory cortex.

Long-term memory: For years the search was for the place where long-term memories were stored. And at this point the evidence seems to be pretty overwhelming that there's not a specific place for long-term memory, but that it's distributed among all the various structures that were originally involved with perception and analysis. The key thing of long-term memory seems to be creating connections between these various parts.

We know that the hippocampus and areas of the cortex near the hippocampus are required for making long-term memories, and it appears that basically what these structures are doing is something like acting as pointers. So, they're making a temporary connection between all these various parts that needs to last long enough for the permanent connections to be made between the different parts. There's still a lot of work to be done.

A lot of work has also been done to show the time-dependency. For example, retrograde amnesia is when you have like a head injury and you don't remember, not necessarily what happens after, but there's a period of time from before the event you can't remember. And this indicates that there's a critical time period where the memory has to be laid down—that is the connections between the various parts of the brain need to be laid down—and if it's not, that memory won't be made.

I've seen this many times. The most common situation is a car accident where a person gets knocked out. And the typical thing is at first they'll be saying, 'What happened? What happened?' At first they have short-term memory loss, too. They don't even remember when you tell them. I mean you say to them, 'You were in a car accident,' and 30 seconds later they're going to say to you, 'What happened?' They don't even remember that you just told them that they were in a car accident. If they don't have a real serious injury usually after a little while—an hour or so—they get to where they quit doing that. They remember that you told them that they were in a car accident. But they don't remember the accident.

Usually at first if you ask them what they were doing, they might not even remember eating breakfast in the morning. As they gradually recover they get up to where they remember everything except a little bit of time right before the accident. And that appears to be the piece that they never get back, because that's the part that hadn't been laid down—or the circuits hadn't been formed. And, of course, this has been studied on a more detailed level with animal experiments.

So, the key difference between long-term and short-term memory is that short-term memory seems to involve changes at the synapse; it's transient, it doesn't require any kind of anatomical changes or protein synthesis. In order to get long-term memory you need to have anatomical changes and protein synthesis. And this means that there has to be time for the second messenger systems to be activated, and send messages to the nucleus, and turn on messenger RNA and transcribe new proteins. So, there's a time dependency in there.

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Now, one of the things that I think is important to realize about memory is the fact that people that have, say, photographic memories, aren't necessarily all that smart. They might not have very good comprehension. In fact, not being able to forget things can even make people a little bit crazy, because it's really normal for us not to remember a lot of stuff.

And then there's this feature called flashbulb memory, when you remember something extremely vividly; such as for me, I remember where I was when I heard that President Kennedy had been shot. I was about eight years old. A lot of people feel this way about 9/11 now. I think we've talked before about that these memories usually have an emotional component and the amygdala is thought to be very much involved in this.

But an important thing to realize about these memories is that their vividness does not necessarily guarantee that they're more accurate. This is a very important thing to understand. One of the things that has been discovered about long-term memory is—and I'm not going to get into all the molecular mechanisms of this, because I want to emphasize the key feature—that the mechanism seems to be pretty much the same across species, both for short-term memory and for switching to long-term memory. These mechanisms seem to have been conserved.

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The last part of this book, *Memory: From Mind to Molecules*, discusses several different types of non-declarative memory such as priming, perceptual learning, emotional learning, skills, habits, and conditioning. I've decided that I'm not going to try to get into those today. If those particular areas interest you, you might want to get the book.

Here are a few of the conclusions summed up at the end of this book. One is that the discovery that each monkey's cortex is slightly different disrupted the long-standing notion that the cortex was totally hard-wired. And as we talked about in Episode 10, we also know the cortex changes with experience.

Another sort of surprising finding is the fact that we don't normally lose very many neurons during aging. That's not what causes us to have weaker memories as we age. It appears that the problem is more of a loss of the modulatory input from the hippocampus. And in rats and mice they've even demonstrated loss of synapses.

It's important to realize that there are a lot of unanswered questions in this field, even though it's one of the most well-studied fields of neuroscience. We still don't know how and where memory storage occurs. We don't really know how memories are retrieved or lost. We don't know why it's so easy to confuse a memory with a dream or something imagined. We've just barely begun to uncover the genetic aspects of memory.

The authors conclude that the key to the future is going to be a multidisciplinary approach. We're going to need to use genetic techniques and other techniques from molecular biology, anatomy and physiology, and imaging techniques. There's a lot of excitement about what can be learned with the new imaging techniques, but right now they really can't get down to the neuronal level. And then the psychological behavior testing that the psychologists have developed over the years is really useful; especially when it's combined with these other studies.

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I hope this episode has taught you some new ideas about memory, and perhaps made you curious enough to want to learn more. Before I close I want to just summarize what I think are the main ideas that you should try to remember. First, there are two types of memory—declarative and non-declarative. The discovery that there are many types of memory that are unconscious—that is, the non-declarative memory—is kind of surprising, but it's pretty exciting. Emotional memory involving the amygdala has attracted a lot of recent attention, and I'm sure we're going to learn more about that in the future.

Now, the idea that there is short-term and long-term memory is probably not a new one to you. Many of you probably also knew that the hippocampus and the surrounding structures are essential for laying down long-term memory. On the other hand, it's probably a new idea to many of us that there are many subtypes of memory, and that we've just begun to unravel these. And most of these subtypes of memory I didn't really get into in this episode.

One of the most important things that has been learned in recent years about memory is that memory retrieval is a creative process, and it's subject to error. One thing I didn't mention is that experiments have been done that show that it's very easy to instill false memories in people.

But moving on, at the molecular level the mechanisms of memory seem to be similar across species from the simple non-vertebrates up through humans. Remember that the cyclic AMP second messenger system, which is seen even in bacteria, also seems to be the same one that's being used in memory.

We still don't know exactly how memories are stored, but they seem to be stored in the parts of the brain that perceived and interpreted the original event. This is kind of surprising, and I think this is probably the thing that is the least known fact about memory in terms of the general population. When they talk about things like the functional MRI they'll say this place lights up when you see a certain face, and I think that people jump from that piece of information to the conclusion that that's the place where that face has been stored. Which is an inaccurate conclusion.

One last point; and I think this will be relevant to our future discussions. And that is that the existence of non-declarative memory reminds us that much of what our brains are doing is not accessible to our conscious awareness or control.

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I want to thank you again for listening to the *Brain Science Podcast*. I hope that you will send me feedback at docartemis@gmail.com, or post comments on the website at brainsciencepodcast.com. Don't forget that I am relying on your word of mouth to help the podcast grow, so please remember to share this podcast with a friend.

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Thanks again for listening. I look forward to talking to you all soon.

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