

Making Your Mind: Molecules, Motion, and Memory
Lecture One – Mapping Memory in the Brain
Eric R. Kandel, M.D.

1. Start of Lecture I (0:15)

[ANNOUNCER:] From the Howard Hughes Medical Institute. The 2008 Holiday Lectures on Science. This year's lectures, "Making Your Mind: Molecules, Motion, and Memory," will be given by Dr. Eric Kandel, Howard Hughes Medical Institute investigator at Columbia University, and Dr. Thomas Jessell, Howard Hughes Medical Institute investigator also at Columbia University. The first lecture is titled "Mapping Memory in the Brain." And now to introduce our program, the President of the Howard Hughes Medical Institute, Dr. Thomas Cech.

2. Welcome by HHMI President Dr. Thomas Cech (1:08)

[DR. CECHE] Welcome to the Howard Hughes Medical Institute and the 2008 Holiday Lectures on Science. The Institute initiated this series in 1993. In 1995 I had the pleasure of coming here and delivering the lectures on catalytic RNA, and since I've been President of the Institute it's been a great pleasure to be involved in choosing 18 terrific scientists to talk to students here in the auditorium. The Holiday Lectures are one of more than 30 research and education programs of the Institute and please visit our website www.hhmi.org to learn more about all of our activities. This lecture series focuses on the most complex organ in our body and arguably the one that most is responsible for making us human. Clearly without this organ you wouldn't be able to find this auditorium, and even if you got here you wouldn't understand a word that was being said. Clearly I'm talking about the brain and the nervous system. The nervous system is an extremely complex and sophisticated network of cells and we've recruited two of the best brains in the field to be our guides. Eric Kandel and Tom Jessell are both long-time Howard Hughes Medical Institute investigators at Columbia University in New York City. In these lectures Eric and Tom will open a window on cutting-edge research into how the brain develops and how it functions to mediate our movements, our perceptions, and our innermost thoughts and memories. It's an honor to introduce Eric Kandel to deliver our first lecture. Eric has been a long-time member of the HHMI community. He's a tenacious and insightful scientist and a tremendously engaging lecturer. He's been recognized and rewarded in numerous ways including the Nobel Prize in Medicine in 2000. In his first lecture Eric will set up the problem of understanding how the brain works, visiting some high points in the history of neuroscience that have led to our current understanding of the brain. We now have a brief video to introduce Eric Kandel.

3. Profile of Dr. Eric Kandel (3:56)

[DR. KANDEL:] New York is heaven. I mean I like Paris but there's nothing like New York and the academic scene in New York, Columbia, NYU, Rockefeller, Mount Sinai, Einstein, it's just absolutely terrific. The release of chemical transmitter glutamate... I frankly like belonging to a university. I feel there's something uplifting about it. It's a privileged existence, and Columbia is a very nice place to work, people are very interactive with one another, they're very generous to one another, and it's been very nice to see how neuroscience has grown at Columbia since we came here. It's really a terrific community. I really love teaching and I particularly love teaching medical students. I like the idea of being involved in the training of physicians, and when people ask me about this I strongly encourage them to teach. First of all I think it is essential for the scientific community to train other people, it's obvious. It's also important to learn how to organize one's thought about a topic and to be able to communicate with people who don't know the science very well, be all and up giving lectures like the Holiday Lectures which are designed for a general audience and to learn how to communicate your ideas in terms that other people can understand is very important. And teaching is very helpful for that. I hope

that we excite lots of kids to realize how wonderful science is and how exciting and promising neuroscience is, and we hope we do a good job.

4. The brain: Learning and memory (5:41)

Good morning, thank you very much for your gracious introduction, Tom. Tom Jessell and I are delighted to have the opportunity provided by these Holiday Lectures to interact with you over the next two days. In our four talks today and tomorrow Tom and I plan to give you a sampling of what the modern science of the mind is about and why this becomes such a central and exciting area within biology. We begin by asking "What is mind?" The major theme of the first lecture and without a doubt the most important discovery in brain science is that the various functions of mind thinking, feeling, acting, learning, remembering, creating works of art are a set of processes carried out by the brain. Mind is to brain as walking is to legs except infinitely more complex. The brain makes us who we are. It produces our every emotional and intellectual act. The brain determines our moods, it endows us with a capability for great joy and terrible misery. In his two lectures Tom Jessell will discuss with you how the brain develops the capability for mental functioning and once developed how the brain controls our behavior. I will begin our discussion of mind this morning by considering learning and memory, two of the most magical properties of mind because they're central to our existence, they make us who we are, they shape our knowledge. Learning as you know is the process whereby we acquire new information about the world and memory is the process whereby we hold onto that information over time. Most of the information we have about the world and most of our skills are not born into our brains but are acquired through learning. We learn the faces and names of our parents, our siblings, our friends. We learn the logic of algebra, the capability to dance, to engage in sports, to read music, to play the piano, to remember the words of the Star-Spangled Banner. As a result of this knowledge acquired by the brain during our lifetime we are in large part who we are because of what we learn and what we remember.

5. The devastation of learning and memory disorders (7:56)

Moreover, tragically, specific disorders of learning and disorders of memory haunt the developing infant as much as the mature adult: autism, attention deficit disorder, Down syndrome, affect the quality of life of young people that suffer from them. At the other end of the spectrum the normal weakening of memory age and the devastation of Alzheimer's disease haunt the elderly. Indeed we will learn this afternoon with our discussions with Jerry Fischbach and Kay Jamison that even illnesses that begin in mid-life or even earlier like schizophrenia and depression, have an impact on memory. It's hard to think of a mental disorder that doesn't have one or another effect on memory. We've learned a great deal about normal memory from studying these disorders of memory. We've learned that memory is the glue that binds our mental life together, that without memory life is made of a series of disconnected fragments that do not have any meaning in relationship to each other, in fact life becomes meaningless without the binding force of memory. Imagine life without any memory, imagine not being able to think where you were last week, last year, not being able to remember the first day you started high school. I'm going to show you an example of life without memory.

6. Video: Clive Wearing, a man without memory (9:18)

Clive Wearing, a brilliant musician, more than 20 years ago suffered a serious brain infection, herpes encephalitis that wiped out his memory. Here is a person whose life is a series of fragments.

[MR. WEARING:] How many years have I been ill?

[WOMAN:] About 20.

[MR. WEARING:] About 20. Can you imagine what it's like to have one night 20 years long with no dream? That's what it's been like, just like death. No difference in day or night, no thoughts at all. And in that sense it's been totally painless which is not something which is really desirable really is it? It is precisely like death. If we have no senses of pain you have no sense of any kind working either. I don't remember sitting down on this chair for example or the settee isn't it, that was unknown to me. I've never seen a human being since I've, that's the first photograph I've seen of anybody.

[WOMAN:] And who is that?

[MR. WEARING:] It's one of my sons. I can't remember his name.

[DR. KANDEL:] Tragic. Clive Wearing, this remarkable man, shows us how central memory is to our existence. Without it life is empty, it is meaningless.

7. The systems problem of memory: Where is memory stored? (10:32)

How then do we go about studying this magical process of memory? It is convenient to divide the study of memory into two parts; the systems problem of the memory and the molecular problem of memory. In the systems problem of memory we ask "Where in the brain is memory stored?" In the molecular problem of memory we go from mind to molecule, we ask "What is the molecular mechanism whereby this storage occurs?" In tomorrow's lecture we're going to go from mind to molecules and consider the molecular underpinnings of memory storage. Today we're going to discuss the systems problem of memory. Historically the systems problem of memory addressed an even larger issue and that is, can any mental process be localized to the brain?

8. Gall's insights into the brain (11:18)

The first person to address this question was a Viennese physician by the name of Franz Joseph Gall, an extremely interesting character who had a lot of insights into the brain, two of them were so profound that we continue to carry them and entertain them very seriously today, they're fundamental to brain science. The first idea was that all mental functions are biological, they come from the brain. He did away with the idea of dualism that Descartes was advocating, the idea that there is aspect, there are aspects of mind which are outside the body, the spiritual. He said every mental process from the simplest reflex to the most extraordinary symphony that Beethoven was composing, these are all products of the mind. He made the second point that the brain is specialized and particularly the outer part of the brain, the cerebral cortex, the covering of the brain, doesn't function as a single organ. It's a number of different organs, each of them mediating a different mental function. Now

9. An overview of brain structure (12:20)

in order to localize mental functions he had some knowledge of the brain. He knew that the brain was a bilateral symmetrical structure, it has a left hemisphere and it had a right hemisphere. He knew that it was a convoluted structure, it had infoldings called sulci and outpouching called gyri. These infoldings provide a means whereby you can take a large surface area like the cerebral cortex and pack it into a smaller space so you can put it safely within the skull. He also knew that the brain had four lobes, frontal, parietal, temporal, and occipital lobes, and he began to think how to localize mental functions.

10. Gall localizes brain functions based on skull shape (13:04)

And when he first began he realized that four functions are more than, not enough to explain what needs to be explained, an inadequate number of subdivisions. He needed more than four subdivisions because

when he read the literature in psychology and from his own clinical experience he realized that more than 40 different mental functions that he had to localize. So the question is how was he to do this? One way to do this is through clinical pathological correlations, to take people like Clive Wearing and see where is the lesion when one has a deficit in memory? But he decided he would do this a different way, he would do this by observing people very carefully. He didn't want to study the diseased brain. And he decided there would be 40 different functions and he identified them in different regions in the following way. He put the intellectual functions like comparison, thinking, cautiousness, at the front of the brain. He put the emotional functions like romantic love, parental love at the back of the brain, and he put sentiments like hope, happiness, in the middle of the brain. Now how did he decide to go about doing this? He thought himself a very careful observer and it struck him that one clue to how the brain works is to look at the shape of people's skulls because he was struck by the fact that people with different shaped skulls had different character structures, different kinds of personalities, and he thought that by looking at people's, the bumps on their skull he could get a very deep insight in how they functioned as intellectual and social human beings. The first thing that gave him a clue about this was the fact that when he looked at the brightest people he knew both among his classmates and among his teachers he found that they had a very prominent forehead, often had bulging eyes, and those that had a more shallow intellect had a more restricted forehead and sometimes a more prominent back of the head. I was extremely skeptical of this view. I thought this was just blatant nonsense. How could one make an assertion like that? But then I began to look around among my friends and I began to explore them and look at their heads and I found to my amazement that Tom Jessell, one of my brightest friends had a very prominent forehead, and some of the people in our group who had a shallow, you know, a shallow intellect had a less prominent forehead. So I really began to think that maybe there's something to this and I began to read more about Gall. How did he get to this view? And he really developed a very, very interesting theory. He thought that if you use your function like Tom uses his intellect, that part of the brain that represents that function, for example function of comparison, intellectual function, that would bulk up like a muscle when you're exercising, and that would cause the overlying skull to bulge out and this made an enormous impact. People when they first read about this got very excited and I could see there might be some merit to this.

11. Demonstration: Phrenology (16:13)

[DR. KANDEL:] May I have a volunteer? Would you consider coming up here for one second?

[CARRIE:] Sure.

[DR. KANDEL:] What is your name?

[CARRIE:] Carrie.

[DR. KANDEL:] Carrie. Would you turn around? May I examine your head?

[CARRIE:] Sure.

[DR. KANDEL:] No, face them. It's clear I don't even have to do much palpation to see extremely intelligent person. Thank you very much. May I suggest that all of you, with appropriate permission from your neighbor, turn to your right and palpate the skull of the person next to you to get an idea whom you're sitting next to. You don't want to spend the rest of your life with people that you don't know.

I want to tell you... Please, go ahead. I should also tell you, so you not only evaluate people for the intellectual capabilities, because after all we make friends on more than one quality of mind. The back

of the head is involved in romance so you can get a sense of how romantic the person is sitting next to you.

12. Broca challenges Gall's theory by studying brain function (17:16)

The French were more skeptical. The French tend to be very skeptical and the person to really challenge this in a very dramatic way was a giant in the field whom I like very much, Pierre-Paul Broca. He in about 1861, so this is about 40 years after Gall, said look I think that all mental functions come from the brain and I think it's very likely that mental functions can be localized to specific regions but this is not the way to go about it by feeling people's skulls. You have to get inside and see what's going on in the brain. And so he argued "I had thought if there were a phrenological science, that is a localization of function, it would be phrenology of convolutions of the cortex, not a phrenology of bumps in the head," and therefore he suggested that mental functions could be localized to specific regions but by correlating clinical pathological information. So he thought that if one examined people with specific disorders of brain function, see what symptoms that produces, one would really learn something. And

13. Broca studies aphasia to localize language in the brain (18:25)

he began to look around and he decided he would study a, he would study aphasia, a disorder of language, because he thought this was the highest mental function. If you get any insight into the biological base of language you would have a real insight into mental processes. And soon after he became interested in it he came across a fascinating patient, Leborgne. Leborgne had an extremely interesting disorder of language, an extremely interesting aphasia, in the sense that he could understand language perfectly well but could not express himself with language. Now you might think this is a paralysis of the vocal chords, but it was not, he could whistle a tune perfectly well, he could hum a tune very well. moreover he could not express himself in language and writing. He simply could not express himself in language even though his understanding of language is perfectly well. When he died and came to autopsy Broca found that there was a lesion in his brain at the front of the brain. He was now in a peculiar situation. He discovered this lesion in the front of the brain and he wanted to name it. He wanted to write a paper about it. He wanted to discuss it with people and he didn't know what to call it. So in all modesty he ended up naming it after himself. What choice did he have? He called it Broca's area. He then collected seven other patients that had a similar aphasia, difficulty in articulating language but not a difficulty in understanding it and he found that every one of those patients had a lesion in the front of the brain and in each case the lesion was on the left side, and this caused him to enunciate really one of the great principles of neuropsychology: "Nous parlons avec l'hémisphère gauche!" he said. "We speak with our left hemisphere." This is really one of the profound insights, and I should point out when I'm speaking about Broca this is the first person who really developed neuropsychology, the first person to take psychological data and neuroscience data and put it together.

14. Localizing brain areas that control motor functions (20:41)

This galvanized the scientific community. People got extremely excited. They began to believe that something is real about localization of function and they could study it specifically in experimental animals as well as in the human brain, and Fritz and Hitzig two German scientists influenced by Broca began to stimulate the surface of the cortex and they found that there is a strip we now call the motor strip right behind Broca's area also toward the front of the brain in which movements are represented in a very systematic way. So if you stimulate a certain area you activate the face, you stimulate a nearby area the arm, further medially the leg. We really are making progress in localization of function.

15. Wernicke: Complex brain functions are not in a single area (21:26)

And then another genius came along, Karl Wernicke, a person not dramatically older than you, was about 24 years old when he began to make this extraordinary contribution. He just graduated from medical school. In those days one graduated from medical school quite early. He was in Breslau, Germany at that time, an extraordinarily gifted guy. He encountered a patient who had aphasia that was the mirror image of the aphasia that Broca had described. Wernicke's patient could articulate language but could not understand it. When Wernicke's patient died and came to autopsy Wernicke found there was a lesion at the back of the brain. Again, you know, he was in the awkward position. What was he going to name this green region at the back of the brain? He had a precedent, Broca's modesty, so in all modesty Wernicke named it after himself, Wernicke's area. Now Wernicke was an extremely thoughtful human being. He looked at this, and he said look, Broca's area concerned with the expression of language, sort of like a motor function, is in front of the motor area. My area, Wernicke's area, concerned with the understanding of languages in the back of the brain where a lot of sensory information comes in. This really means that mental functions represented in the brain can't be represented by a single area. Complex mental functions he said, need to be localized not in a single region but in several regions interconnected with one another. So Gall was not only wrong about the fact that he had a crazy way of localizing function but he was wrong about thinking that highly complex mental functions could be restricted to a single area. They involve more than that.

16. Location of language areas suggest a model of language (23:21)

And he said to himself look isn't it interesting how these two areas, Broca's area and my area, are arranged in the brain. Broca's area the front of the brain near the motor strip, my area, Wernicke's area in the back of the brain where sensory information comes in. In fact you can see that the auditory cortex which carries information from spoken language is near Wernicke's area. The visual cortex, the back of the brain, occipital lobe, information about language that you read is in the back of the brain. Moreover he knew that the auditory cortex and the visual cortex hook on to Wernicke's area, and Wernicke's area has a direct pathway called the arcuate fasciculus to Broca's area. And look Broca's area is right near that part of the motor strip that is concerned with vocalization, with the actual motor apparatus for speech. And he put this information together in an extraordinarily prescient theory of language which although it was formulated, you know, in 1870 still explains 85 percent of the clinical phenomenon one sees now in an emergency room in cases of aphasia. He said it works like this: If you hear spoken language or you read a text that information is encoded neutrally and passed on to Wernicke's area where the understanding of language occurs. The information is then passed on through the arcuate fasciculus to Broca's area where the grammar for language is located and that hooks up to the area that is involved in the vocalization of language and it's connected to that.

17. Wernicke's language model predicts a conduction aphasia (25:17)

From this extraordinary model which holds to this day he was not only to give us an idea of how language is generated but he made a prediction about the fact that one would someday discover a new kind of aphasia which does not involve direct damage to either Wernicke's area or Broca's area. Can any of you guess what kind of a lesion, what kind of a disruption could give you a language deficit without interfering with Wernicke's or Broca's area? Yes?

[STUDENT:] A lesion in the arcuate fasciculus?

[DR. KANDEL:] In the fasciculus that connects the two areas, brilliant. You have a future as a neurologist without any question. A lesion that interrupts the pathway between Wernicke's area and Broca's area, what is now called in modern language a conduction aphasia. There you understand language and you express it but the connection between it can be quite vague. It's like a presidential

press conference: information comes in, information comes out but there's no connection between the two.

18. Video: A patient with conduction aphasia (26:27)

Here is a patient with conduction aphasia.

[DOCTOR:] And when we were getting ready to start this video tape the producer asked us to count to 10, remember that?

[PATIENT:] Yes.

[DOCTOR:] Can you do that again?

[PATIENT:] Why? 1, 2, 3, 4, 5, 7, boy, 2, gary, people, go, I can't...

[DOCTOR:] No that's really hard. Let me get you started.

[PATIENT:] I was stunned.

[DOCTOR:] Okay, 1...

[PATIENT:] 1, 2, 4, 5, 6, better, send, point, uh...

[DOCTOR:] Good enough. Let's...

[PATIENT:] Is that alright?

[DOCTOR:] That's fine.

[DR. KANDEL:] What is so interesting about this lady she clearly is very intelligent and she clearly understands the instructions and she clearly can express herself in a very good way but you could see how after a while she completely disconnects what she wants to do, what she's heard she should do, and what she actually does.

19. Left brain and right brain language functions (27:37)

What also came out of this is that we now understand from Wernicke and Broca's work how important the left hemisphere is for language because every natural language that you acquire, you learn a foreign language, that will be represented in Wernicke and Broca's area. Any, the grammar for any natural language, not for artificial language, any natural language will be represented in Broca's area, number one. Number two even if the language is not a spoken language, that is, a sign language is represented on the left side in Wernicke's area and Broca's area. So if you have a defect in Broca's area and you sign, let's assume you're a deaf person, you will not be able to sign, you will be able to understand other people signing because your Wernicke's area is intact but you will not be able to sign yourself because the Broca's area on the left side handles all languages including sign language. What about the right area? The right area is not involved in the logic of language. It's concerned with the intonation of language. Now when we speak to one another we communicate affect, emotion. I, in speaking to you, must convey to you that this is a great privilege for me, I immensely enjoy having the opportunity of interacting with you and I hope you are listening to the intonation of my speech that attempts to convey

that. So there is both the perceptive part and your part which involves Wernicke's area and the Broca's area on my part on the right side of the brain, not on the left side.

20. MRI identifies brain areas for recognizing faces (29:14)

So this raises the question we've localized language, we've localized the motor strip, we know something about the right hemisphere. Are all mental functions, can they be localized in the brain? Can we localize specific areas for faces, are there specific areas that are involved in our personality that make you who you are? Are there areas in the brain that are involved in social interactions that might be defective in autism? I think the answer is, we're beginning to identify areas involved in all of these. I'm going to give, going to give you one example but we can discuss the other examples later on. In the early stages until around 1950, almost everything we learned about the human brain and about mental functioning came from studies of patients with one or another disorder and from studies of experimental animals. But a major revolution occurred about 20 years ago that made it possible to study people like you and me, intact, behaving subjects, awake, responding to certain tasks, looking at objects, examining objects, and this was through imaging experiments. For example, with functional magnetic resonance imaging, a normal person, this is absolutely painless, can lie in a scanner and when they do a particular task that area becomes active, it fires action potentials, it becomes more active. That requires more energy, there's an increased blood flow, there's an increased oxygen, and that signal is taken by the scanner and is able to indicate what area the brain becomes active when there's an increased oxygen demand in that region that is being recruited. And Nancy Kanwisher, whose image I show here was one of the pioneers in this area and she was the first person to define a specific area that responded selectively to faces. We now know from her work and from Marge Livingstone's work that there are several areas that respond to faces and process different aspects of faces. In the monkey you can see similar areas. You can see it but with imaging you put electrode into any one of these areas, 95 to 97 percent of the cells respond to faces, like that if they look at Tom Cech's face. They respond to nothing else but faces. They will not respond to places, to any other objects, selectively to faces.

21. Q&A: Do basic brain functions reside deeper in the brain? (31:35)

So before I go on to take up the issue of, "Can memory be localized?" let me stop here for a few questions. Yes?

[STUDENT:] With the brain do you find that like more basic functions were like deeper in the brain or something, like the, like more human functions were towards the outside and basic ones are more central?

[DR. KANDEL:] That's a wonderful question. This is true. I mean the fact is that the cerebral cortex is a later development in evolution. I mean even in the mammalian brain of mice and rats have a cerebral cortex but it's not as elaborate, particularly the front part of the cortex is not as elaborate. What is conserved even among very simple animals, vertebrates for example that don't have a developed cerebral cortex, is that their instincts, their basic drives are there. The drive for food, for mates, for safety, those are all things that are quite deep in the brain and they're conserved throughout evolution. They then become modulated by higher cortical processes but the basic capability is there.

22. Q&A: Is there a correlation between brain size and intelligence (32:43)

These are wonderful questions. Yes? I'm sorry. The two of you, first the young lady behind you and then you in the red shirt.

[STUDENT:] Is there a significance in the size of the brain? For example a human who is considered to be very intelligent versus a dolphin for example?

[DR. KANDEL:] The dolphin brain actually I think is slightly larger than the human brain. There's not a simple correlation between a species as to whether or not a larger brain guarantees the fact that you will be more intelligent. As far as we know the human brain by the criteria we set which are anthropomorphic criteria... You know, we handle the functions that we are involved in better than any other experimental animals. Can we fly? Can we swim as well as a dolphin? Can we fly as well as *Drosophila*, no. So they have certain skills that we don't have.

23. Q&A: How is the brain organized in bilingual people? (33:33)

Yes?

[STUDENT:] You said earlier that Broca's area and Wernicke's area control all languages, correct, or are responsible for all languages. How does the brain organize like in a bilingual? For example is there any difference in like...

[DR. KANDEL:] This is a wonderful, wonderful question and I'm going to return to this in my last lecture. As you probably know the capability to acquire a foreign language is greatest in the early years of life, so after puberty it's possible to acquire foreign language but you never get a perfect accent. If you acquire the language early, let's say simultaneously, it is in both languages that you acquire, if you're bilingual, are represented in the same Broca's area just intermixed. If you acquire the foreign language somewhat later it becomes an attached area to Broca's area, an independent area. Judy Hirsch at Columbia was the one who showed that. Thank you very much. Those were very, very good questions.

24. Lashley's experiments cast doubt on memory localization (34:39)

Let me then go on and consider with you the issue of memory. So by the middle of the 20th century, even before imaging, one had a fair amount of confidence that many mental functions could be localized to the specific regions in the, in the brain and that raised the question, where in the brain is memory stored. Many people thought that memory is not like vision, hearing, even like language, it's such a diffuse mental process that it's usually connected to motor skills, it's usually connected to perceptual skills of various kinds. It is likely to be very diffuse, and in fact Karl Lashley, Professor at Harvard, supported this notion.

He ran a series of experiments that showed that memory is a diffuse property of the cerebral cortex. And the experiments were of this sort. He would run a rat through a maze that had a lot of blind alleys to get to a goal where the animal is given a food reward. And with a number of trials it ran this very rapidly and very successfully. He then began to remove small pieces of the cerebral cortex and he found that small lesions had no effect irrespective of where he took the lesion from. So there was no region that seemed to be specialized for maze learning tasks. Only when he began to take large parts of the brain, and again irrespective of where he took it from, did he interfere with this task. So small lesions had no effect whatsoever, large lesions had an effect. This caused him to argue that memory could not be localized to any part of the cerebral cortex. People were skeptical. They thought there was some weakness to his experiments and there were two aspects of it that were particularly focused in on. One is, he focused only in the cerebral cortex. We know there are a lot of structures, this came out in the questions, deep in the brain. Maybe some of those structures are involved in learning and memory, number one. Number two, rats are very smart and they can use a number of different strategies for learning a maze. So if you deprive them of their vision they'll use tactile cues, they'll use their sense of smell, they'll use other strategies in order to get there. So using a maze is not such a terrific task if you want to focus in on specific location of memory.

25. Penfield finds memories are localized in human brains (37:07)

The person who helped us the most in understanding memory research was Wilder Penfield, another giant in bringing psychology and brain sciences together. Penfield ultimately went to the Montreal Neurological Institute and developed an institute concerned with the cerebral cortex in people. He was a brilliant neurosurgeon and he focused in on a particular kind of epilepsy, a cortical epilepsy due to scar tissue in the cerebral cortex. When people are in severe accidents, when they have a severe brain concussion for example automobile accident, a football game, a bicycle accident they not infrequently are left with a concussion that causes, that leaves them with a scar on one or another part of the brain. That scar can give rise to seizure activity and that seizure activity sometimes can be controlled with medicine but sometimes not in which case you have to excise it. And Penfield was the first person to develop systematic ways of excising this. He realized that the brain has no pain receptors so if you infiltrate the scalp with a local anesthetic you could expose the scalp, you can open up the scalp, open up the skull, expose the brain and have an intact behaving patient who could talk back to you as you stimulated his brain. And you could stimulate Wernicke's area and Broca's area and make sure you don't damage any of those areas in the process of doing this operation. And he found that when he stimulated certain parts of the brain that he got certain predictable results. So for example when he stimulated a part of the somatosensory area he got a transient response of tactile sensation. The patient would describe tingling in the thumb, for example. If he moved the electrode to the motor cortex he could get protrusion of the tongue or other kinds of motor movements. But when he suddenly found, when he stimulated the temporal cortex, that he didn't simply get a transient response, he got a full-blown memory, people recalled earlier experiences in the most marvelous way. One patient recalled, this particular patient, hearing orchestral music. He heard a song that he loved from his high school days. It was so real and vivid to him that he was sure that Penfield had turned on a phonograph because otherwise he wouldn't hear it that clearly. The first patient that Penfield ever operated on was a woman who recalled the birth of her first child as if it was happening at the moment, all the pleasures involved in that. It was just extraordinary. She forgot the pain. She just remembered the pleasure. And when he mapped together the regions involved in these experiential responses they all mapped out to the temporal lobe, and to reach in deep to the temporal lobe which also gave very powerful experiential response, called the hippocampus. This is a region that lies just below the medial temporal lobe. I was a medical student at the time he was doing this and you cannot imagine the excitement he produced in the medical community. Larry Kubie, a teacher at Columbia, very gifted psychoanalyst, also a good neurologist, ran up to Montreal, tape recorder in hand because he was sure Penfield had discovered Freud's unconscious mental processes. People were recalling memories they hadn't thought about for years. A number of neuroscientists were skeptical. They thought that maybe he was eliciting some sort of an aura related with seizure activity in these patients.

26. The patient H.M. loses memory after brain surgery (40:53)

But the whole view of medial temporal lobe and hippocampus changed with the famous patient H.M. that some of you may have heard about. H.M. was 9 years old when he was knocked over by somebody riding a bicycle. That gave him a bilateral concussion in the temporal lobes which gave him scars in both temporal lobes. He developed epilepsy and that epilepsy was well controlled for many years, so he was able to finish elementary school, he was able to go to high school, he was able to start work in an assembly plant. But by the time he was about 22 or 23 the seizures could no longer be controlled with medicine. So he was living in New Haven, he went to a surgeon by the name of Scoville, William Scoville, who had, was very much influenced by Penfield. And Scoville operated on him and removed the scar tissue from the temporal lobe but he felt he had to go deeper than that to the hippocampus because some of the scar extended to that. This is the first time that both sides of the temporal lobes were significantly removed in an operation. Penfield only removed one side because he had only dealt

with scars on one side. As a result of that removal of the medial temporal lobe and the hippocampus H.M. has been without seizures. A friend of mine saw him a year and a half ago, he very rarely has a mild seizure, beautifully controlled with medication. But he was left with the most devastating memory loss, similar to Clive Wearing as a result of this procedure, and Scoville was beside himself. He was extremely upset. He called up Penfield and told him about this tragedy and Penfield understood and he said, you know, we knew the temporal lobe was important for memory. I had never had experience with bilateral removal. What we should do is to have Brenda Milner come and study this patient.

27. Brenda Milner finds H.M. retains some memory functions (42:59)

Brenda Milner is a very gifted psychologist. She had studied all the patients that I, Penfield, had worked on and she's extremely familiar with memory and medial temporal lobe. So Brenda Milner came down and she of course confirmed that H.M. had a tremendous memory deficit but she was able to also detect that there were aspects of memory storage that were perfectly intact. To begin with H.M. had perfectly good memory for things that occurred prior to the surgery. So he remembered as you and I do the childhood traumata of our lives, he remembered going to elementary school, he remembered going to high school. His intellectual function was the same, his IQ was unaltered, he remembered everything that happened prior to the operation which indicated to Brenda Milner that long-term memory, long, long periods of time are stored in other parts of the brain. We think these are stored in the cerebral cortical areas that process the information as it comes in, number one. Number two, she found that he had a perfectly good short-term memory so if you transiently introduced him to Tom Jessell he could focus on Tom Jessell and remember Tom Jessell's name as long as he repeated it. So that indicated that short-term memory is stored elsewhere and we have reason to believe that this kind of short-term memory is stored in the prefrontal cortex.

28. H.M. unable to convert short-term to long-term memory (44:22)

What H.M. lacked and lacked in the most profound sense is that he could not take new short-term memory and put it into new long-term memory. So for example he saw Brenda Milner repeatedly over this 30-year period. Every time she walked into the room it was as if he had seen her for the first time. He would sit down and read a newspaper. He would read the first paragraph of an article. He would forget it. He would start all over again. He would eat a meal. When he was finished he'd forgotten he ate it. He would start all over again. He looked at a picture of himself 10 years after the operation, he couldn't recognize himself. He had enormous difficulty in converting any short-term memory to long-term memory. This was extremely important because Brenda Milner had discovered a specific location. She showed that the hippocampus and the medial temporal lobe are absolutely essential for converting short-term to long-term memory. For many years, a period of over 10 years Brenda Milner thought that this applied to all areas of knowledge that everything that H.M. learned in short-term memory he could not convert into long-term memory.

29. Mirror tracing: H.M. can unconsciously learn new tasks (45:45)

And then she made another fantastic discovery. She gave a terrific lecture to the Society of Neuroscience meeting two weeks ago in which she said this was the most exciting moment of her scientific career. She found that in fact there were certain areas of knowledge in which H.M. could convert short-term to long-term memory, and that is he could learn certain motor tasks and some of you have performed these tasks. She had him do a mirror drawing task and that's a situation in which you have to draw the outlines of a star by looking neither at the star, or your hand, or the pencil but looking only at the mirror because you cannot see the star or your hand. This is the apparatus. Many of you have used that, others of you that have not had a chance to do so could do so later on outside. She found that

when H.M. did this he made a number of mistakes the first day but improved over 10 trials. The second day started off better and got better still, and the third day, perfect.

30. Student results of mirror tracing activity (47:02)

This is as good as you can do, in fact this is one of the students in this group, lots of mistakes at the beginning, perfect afterwards, and this is the average data for a whole bunch of students here. You people are as good as H.M. I am going to tell your parents that you've got a terrific memory. But there's one fantastic difference between you and H.M. You remember what you did the previous day and you remember how you progressed from day to day. So you understand you did better on Wednesday than you did on Monday because you did 10 trials a day, each of those three days. But when you asked H.M. how come you're doing better on Wednesday than you did on Monday, he would say "What are you talking about? I've never done this before in my life." He was completely unaware that he was doing this.

31. Different mechanisms for explicit vs. implicit memory (47:59)

So Brenda Milner discovered but we now know it to be a large area of mental life in which memory is stored in an unconscious way. So this made us realize that their... memory storage is not a unitary faculty of mind that there are at least two major kinds of memory processes that are stored at different sites and use different logic. They're called explicit and implicit respectively. Explicit memory is a memory for facts and events, for people, places, and objects. They involve the hippocampus and the medial temporal lobe. You take those out, you lose this, and it requires conscious recall. So if you ask yourself, you know, what was it like on the first date? You make a conscious effort to recall that. If you think about your last birthday, a conscious effort to recall that, you know, how to get back home. This requires a conscious effort to recall that. Everything that is stored in explicit memory that is hippocampal based requires conscious effort to recall. By contrast we all master a large number of motor and perceptual skills that once they're mastered become completely unconscious. These are stored in a number of structures, in the amygdala for emotional memory, in cerebellum for motor memory and in the simplest reflex pathways, which Tom and I are going to consider in later lectures, these allow you to store modifications of reflex strength, various motor skills or emotional things, and when you recall these it's an unconscious effort. Let me give you an example; when you first learn how to ride a bicycle you tell yourself put your left foot forward put your right foot forward. Once you learn how to ride the bicycle you don't talk to yourself. If you talk to yourself you fall off of the bicycle. When you rush to the net in order to hit a backhand you don't tell yourself get your shoulder around, you do this automatically or you're lost to begin with. What is amazing, what is absolutely amazing is, how much of explicit memory once it's mastered moves into implicit memory because it's more efficient. I am to this day amazed how much is carried out in memory implicitly. Some of the most remarkable creative skills after a while move into implicit memory.

32. Video: Clive Wearing plays piano despite memory deficit (50:31)

Let me show you what I think is an extraordinary example. This is Clive Wearing.

[NARRATOR:] Clive Wearing has one of the worst cases of amnesia in the world.

[MR. WEARING] I know what it is like to be dead now. Day and night, the same, blank. No difference between dreams or anything like that, no sense of it at all, the brain has been totally inactive, no dreams, no thoughts of any kind whatever.

[**NARRATOR:**] Clive was a renowned conductor, living in London when he was struck down by a virus in 1985. Parts of his brain were completely destroyed, including his memory. However, his ability to play music is unaffected.

[**WOMAN:**] Do you feel different when you play music?

[**MR. WEARING**] I've never heard a note since I've been ill. I don't know what it's like to play music. Maybe I'm unconscious.

[**WOMAN:**] You played us some music about two minutes ago.

[**MR. WEARING**] Not known to me, totally unknown. I never heard a note yet.

33. Summary (51:38)

[**DR. KANDEL:**] Let me step back and summarize what we've covered so far. We began by asking, can any mental process be localized to specific regions of the brain, and we saw that the answer was yes. But it's not a simple view, it's not that mental processes are localized to single regions in the brain. They involve the Wernicke scheme, they involve several areas that are precisely interconnected and we're going to hear more about that in the subsequent lectures. We then asked the question can memory specifically be localized to regions of the brain. And again the answer was yes and again the result is sophisticated. There are different kinds of memory storage, explicit and implicit, they're stored in different areas, one, hippocampus and medial temporal lobe, the other, amygdala, cerebellum and reflex pathways. Clearly we next want to know, and several of the questions already directed our attention to this, how do these regions involved in memory storage, how do they develop, how do they come to represent memory? And we're going to learn about that in the next couple of lectures so please stay tuned to what Tom Jessell will have to say to you.

34. Q&A: Did H.M. show any capability of emotional response? (52:48)

Before we end this lecture I'd be delighted to have some questions from you and see if I can answer them. Yes.

[**STUDENT:**] You said that the implicit mind is also responsible for emotional responses, and I was wondering if H.M. was able to show any capabilities with emotional responses.

[**DR. KANDEL:**] Yes he does show, for example if you showed him frightening images he shows an increase in heart rate. Patients like this will show this. William James was the first one to point out that there are both unconscious and conscious components to it, and it's very interesting with fear, for example when you see a tiger approaching you, unlikely to happen at the HHMI headquarters, but let's assume for a moment it does, your heart rate increases and you begin to make preparations to escape before you fully realize consciously that it's a specific kind of animal that is attacking you. So you see a... you identify danger qua danger before you identify consciously as the specific source of that.

35. Q&A: Are stem cells involved in implicit memory storage? (53:47)

Sir?

[**STUDENT:**] What sort of roles do stem cells play in acquiring memories, specifically implicit?

[DR. KANDEL:] This is a very interesting topic. There are stem cells in the hippocampus that continue to divide throughout much of life, they decrease as animals get older, and their role at the moment in memory storage is unclear. It's a bit controversial. So if you irradiate this region and selectively knock out those cells, lots of memory tasks, the hippocampal-dependent memory tasks are intact. Certain kinds of tasks, working memories, are in some cases even improved as if these new cells might serve as an inhibitory constraint. There are some memories, spatial memory, that are slightly affected. What is most clear from the studies that are now available and maybe we'll discuss this this afternoon is for reasons that one doesn't still understand, antidepressant medicine produces some of its therapeutic effects through these neurogenic cells in the hippocampus. If you knock that region out in a number of different ways the selective serotonin uptake inhibitors, for example, which are very effective antidepressants lose their effectiveness, and a colleague in my lab has carried out experiments in which she's done sort of a mouse equivalent of psychotherapy, it also loses its effectiveness. So it seems to have some role in overcoming the emotional states but not in, not a dramatically clear role in memory per se, but it's still an early phase in studying the relationship between memory and hippocampal stem cells.

36. Q&A: Can brains compensate for a lesion? (55:28)

[STUDENT:] I remember reading a study before about songbirds that learn songs. They would have the parts of the brain that remembered songs would become denser and they claimed that there was neural growth. Does that mean that people who have lesions there, who have damage in their brains, if they were to work on it for a long period of time could they regain some of their abilities?

[DR. KANDEL:] That's a terrific question. First of all the songbird has an unusual growth capability, and Fernando Nottebohm has described this in his, in certain birds it comes in with each, almost each year as the bird reacquires its singing capability. But the point that you make is that when there is a lesion of the brain can other brain areas begin to compensate is without a doubt true. And the most dramatic example of that is that, when a person has a stroke and becomes paralyzed for example in their left arm, a current strategy that's been proven very effective is to tie up the right arm and force the person to use the left arm so the residual brain that can in any way still control that movement, its power will be enhanced, and we will discuss mechanisms whereby this enhancement would occur in later lectures. So I've been asked to wrap up the discussion. Let me thank you all very much for being so attentive and for your questions. Thank you very much.

37. Closing remarks by HHMI President Dr. Thomas Cech (57:00)

[DR. CECH:] Thank you for a compelling lecture Eric and thank all of you in the audience for your really thoughtful questions. How much easier neuroscience would be if we could really understand how different parts of brain function were localized by feeling the skull. In our next lecture Tom Jessell will take us back to the womb to ask the question of how something as remarkable as the nervous system can develop in the first place.