Making Your Mind: Molecules, Motion, and Memory
Lecture 3 – Making Your Mind: Molecules, Movement, and Memory
Thomas M. Jessell, Ph.D.

1. Start of Lecture 3 (0:16)

[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 third lecture is titled "Plan of Action: How the Spinal Cord Controls Movement." 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 (1:07)

[DR. CECH:] Good morning and welcome back to the Howard Hughes Medical Institute's Holiday Lectures on Science. Our speaker this morning is Tom Jessell. In his previous lecture Tom discussed how the nervous system develops from a few cells in the embryo to the complex network of neurons in the mature organism that mediates our every movement and our every thought. Tom's research path has been fascinating. What he really wanted to do was to understand how the motor system worked but he realized that in order to understand function he really needed to understand how it develops in the first place. He has spent many years studying neuronal development, identifying important genes and molecules involved in the process. In this lecture we will see how understanding neural development at the molecular level has led to breakthroughs in understanding neural function. Here is a brief video to introduce Tom.

3. Profile of Dr. Thomas Jessell (2:19)

[DR. JESSELL:] I think it, an interesting question to ask these days is, what is going to be the most effective way of really understanding brain function, the way that the circuit controls behavior and with molecular biology and the tremendous power that that has provided, many of the most exciting advances I think over the next few years will come from taking advantage of genetics, but not to understand the individual genes but simply to take advantage of the fact that nerve cells that contribute to a circuit are different from each other, and so then with advances in imaging technology at the single-cell level, combined with the ability to visualize an entire population of neurons that contributes to behavior, maybe then that will allow us to gain access at the level of resolution that is really going to provide some interesting answers. Would one advise anyone to go into science these days as a career? I think the answer is a resounding yes, that if you're curious about the world around you then choosing to explore that through science in any particular field, I think, can be one of the most rewarding ways of spending one's time. The ability to explore a particular problem as deeply as you can is a very, I think, a very precious, a very rare opportunity that is not afforded by most career paths which are constrained by realities in one way or another. Not that science doesn't have its own demands but when stripped of all of those you're really focusing on a problem that allows your ability to think imaginatively and creatively and in some small way make advances towards an understanding of that problem.

4. Neural circuits: Controlling behavior, particularly movement (4:18)

Good morning again. Eric Kandel and I are really delighted to join you here for this second set of Holiday Lectures in brain science. And in Eric Kandel's lecture, the grand finale of this series, you're going to return to the brain's memory systems and discuss how dynamic events at synapses enable you to store and recall memory and so shape your everyday lives. What I will be doing is really picking up

where we left off yesterday asking, once a neural circuit is assembled, how that circuit controls behavior. Now that seems a deceptively simple question, but answering it in any system has turned out to be one of the major challenges in modern neuroscience. And we're going to be addressing this general issue in the context of one particular set of circuits and systems, and those are the circuits that control your ability to move. And I just want to demonstrate and emphasize the importance of movement with this simple device here. So this is the human body stripped away of all its extraneous parts just to show that the brain is designed to control behavior and that behavior is movement. Thank you. Because when we think about it what distinguishes you from these poinsettias or other plants is your ability to move yourself from one place to another in response to internal commands, in response to changing conditions in the outside world. So what we're going to be trying to do is to understand how movement and circuits are linked together, how the operation of circuits control movements, control behavior. Now as we saw yesterday the circuits in the spinal cord are linked directly to the activation of muscles, the effectors of movement. So by studying circuits and movement we have a way perhaps of quantifying, objectively, movement and its relationship to behavior. I gave you one example yesterday with the EMG demonstration of the way that we can monitor simple aspects of movement

5. Video: Computer analysis of human movement (6:39)

but I wanted to try and explore how movement is really monitored and quantified in greater detail, and so to do that I went along to the Motion Analysis Laboratory in the Hospital for Special Surgery in New York City and subjected myself to their analysis of movement. And so what you're going to be seeing here is something like a scientific Project Runway. So if we could have the first video. So this is what you've seen. So this is me strapped up with EMG electrodes and with reflectors so that I'm filmed and you can monitor, transform this motion into individual stick figures, and you can see the pattern of muscle activity on the left and right side during locomotion. So this is the alternating pattern that controls every aspect of movement.

6. Damage to motor systems by disease and injury (7:35)

And when one sees, begins to see with this glimpse just what is so complicated about taking a single step it makes you perhaps appreciate all the more what is involved in more sophisticated forms of motor behavior. So we're looking here at Michael Jordan on the left and Margot Fonteyn on the right in full flight. So these are motor behaviors that take years of learning and practice, and so we're going to be exploring how some of these more sophisticated motor tasks are also encoded by brain circuits. And another more stark reminder of the importance of motor systems comes when we appreciate what happens when that system fails us, and that can fail in neurodegenerative disorders and in spinal cord injury. So as we look here on the left-hand side we're looking at Lou Gehrig, the famous baseball player who suffered from a motor neuron degenerative disease called amyotrophic lateral sclerosis that I will talk about in more detail, and on the right we're looking at Christopher Reeve who, as you know, suffered a spinal cord injury that left him paralyzed. So one of the additional aims of trying to understand the way in which circuits control behavior is to understand them at a level that we can intervene in a positive way in helping neurodegenerative disease and traumatic spinal cord and other brain injuries.

7. Motor neurons get input from multiple sources (8:58)

So to begin to approach these questions, let's go back to the circuit that we analyzed in developmental terms yesterday, the core elements of a spinal motor circuit. And we saw yesterday that motor neurons innervate muscles, flexor and extensor muscles, and I'm going to be talking about, initially, three ways in which circuits impinge on that motor output. We'll deal with the role of sensory neurons in providing feedback information that monitors the state of muscle contraction. We'll be talking about local circuit

interneurons, the neurons shown in orange, that serve to coordinate motor output, and we'll also deal with the way in which descending pathways from higher centers in the brain, from cortical input, control the spinal motor system.

8. The proprioceptive sensory feedback system (9:46)

So to begin we're going to focus on this proprioceptive sensory feedback, the sensory feedback system that monitors the periphery and conveys this back into the central nervous system. Now this is a complicated circuit, but in its simplest form it consists of proprioceptive sensory neurons that monitor the state of muscle contraction, and in the muscle there's a specialized strain gauge called a muscle spindle which senses the contraction of the muscle, activates the sensory neuron, feeds that back into the central nervous system, and as shown in this diagram, the most direct feedback is through a monosynaptic, a single synaptic connection with the spinal motor neuron.

9. Demonstration: Testing a student's proprioceptive reflex (10:30)

So this is a reflex pathway that perhaps you'll be familiar with but I just want to demonstrate it for you in a little more detail. So in order to do this what I'm going to ask is a volunteer from the audience and I have a brave soul here who has agreed to subject himself. So if you sit on this chair, what we're going to do is try and demonstrate this monosynaptic reflex circuit. So this is part of a standard neurological exam and because neurology in different countries has acquired different disciplines and different traditions, we could examine you with this American neurological hammer, metallic and spiky, or this more reassuring and larger British hammer. So I think given my background I'm going to use the British hammer. So what I need you to do here is to cross your legs, and then, I should assure you that if we fail to find a reflex it's my neurological technique and not the fact that these reflexes don't exist. So let's just see what happens if we... ah, ah-ha. So within about a twentieth of a second from the muscle being activated that impulse is transmitted back into the central nervous system, activates the motor neuron and causes muscle contraction. Thank you. You're alive, yeah.

10. Diagram showing the knee-jerk reflex circuit in action (11:51)

So what we've been looking at here in that demonstration is shown here. So we have the hammer activating the knee activating the sensory neuron. That information is traveling centrally, activates the motor neuron, which then contracts the muscle, all in the space of about a 20th of a second here. So this is one example of the proprioceptive system in action.

11. Proprioception is a subtle "sixth sense" (12:18)

But proprioception does much more than that for you. And it does that in a much more subtle and, perhaps, way that is more difficult to appreciate. Nevertheless for the last 200 to 300 years people have argued that in addition to the five major senses — hearing, vision, touch, taste, and smell — there's a more mysterious sixth sense which is proprioception. The French philosopher Diderot asked you "What really sets a limit to the space that you feel you occupy?" You would answer "My sight and my touch." And then he would reply "Yes, that's true by day, but at night in the dark, or even by day when your mind is preoccupied?" And it's that automatic role of proprioception that one takes for granted and controls many aspects of movement. And I want

12. Demonstration: Proprioception makes raising a mug easy (13:12)

to give you another demonstration if you like of how one takes proprioception for granted. So you all had Howard Hughes mugs, I think, so if you can locate those mugs, then what we're going to do is a

very simple set of motor tasks. I think now is a good time to stand up, a little seventh inning stretch, and raise your mug for the Howard Hughes Institute in appreciation of their sponsorship of these lectures. Thank you. So you see how easy that was to do. And the reason... now you can all sit down. The reason that that was easy is because you were using your proprioceptive system, and one way of demonstrating that is to do the same tasks in the absence of activation of the proprioceptive system.

13. Video: Without proprioception, standing or raising a mug is hard (14:04)

So in some rare individuals, viral infection eliminates the proprioceptive system, kills proprioceptive neurons. So this is a different virus than you heard about from Eric with Clive Wearing. This selectively destroys proprioceptive sensory neurons. So what happens if you try and stand up from a chair or lift a mug if you're missing your proprioceptive system? If we could have the first video to demonstrate that. This is a patient with this viral infection, Charles Freed.

Charles Freed has lost control of his body. A rare virus has ravaged his nervous system leaving him with no sense of touch below the neck and unable to sense how his limbs are moving. Charles is not paralyzed but he has lost his proprioception, the hidden sixth sense that tells the brain where the body is in space. Proprioception is so basic to our experience of being in the world that most of us are unaware that we have it.

So that's the first task that you did naturally, getting up from the chair. Now let's look at raising a mug. So you can see here that he's trying to grasp the handle of the mug with extreme difficulty, something you did naturally and then needs both hands to raise that in the simple task of raising that mug from the table to his mouth here. So all aspects of motor control and movement that you take for granted depend as we'll see on the proprioceptive system.

14. Genetically killing proprioceptive neurons in mice (15:42)

So this is a human condition. Can one study what has happened to spinal cord circuits in the absence of proprioceptive system in the laboratory? And this is a question that Silvia Arber began to ask some years ago and she reasoned that if we could take advantage of the genetic distinctions between different classes of sensory neurons then perhaps one might be able to generate, using genetics, mice that lack proprioceptive sensory neurons. So what we're looking at on the left-hand side are molecular markers in mouse of proprioceptive sensory neurons. Some of them are transcription factors shown in red, some of them are other proteins in the cell body shown in blue — parvalbumin. And both of these have the property of selectively labeling the proprioceptive neurons leaving the touch, pain, and temperature neurons intact. So it's possible then using one of these genes, parvalbumin, to generate mice in which proprioceptive sensory neurons are killed by expression of a cell-specific toxin, in this case diphtheria toxin. So the design of these experiments is to express diphtheria toxin selectively in proprioceptive neurons. This toxin is probably the most potent toxin known to man. A single molecule of this protein expressed in a cell is sufficient to kill a neuron. And so what Silvia Arber showed is that mice in which this toxin is expressed in proprioceptive sensory neurons lack those neurons and you can see this by monitoring the projection of the sensory axons into the spinal cord. So on the left-hand panel what you're looking at is the termination shown in blue of proprioceptive sensory axons, in the ventral region of the spinal cord close to motor neurons. On the right-hand side are mice in which these neurons have been killed, and you can see that the entire lower half of the spinal cord is devoid of proprioceptive axons, whereas all of the other sensory neurons and their termination are intact.

15. Video: Behavior of mice that lack proprioception (17:45)

So how do these mice behave in the absence of a proprioceptive sensory system. So we're looking on the left here at a wild-type mouse running along a walkway and on the right a mouse in which its proprioceptive sensory neurons have been eliminated. So you can see that the mouse again is not paralyzed, but has this extreme difficulty in taking one step to the next.

16. Mice lacking proprioception have irregular muscle activity (18:09)

So this is an indication then that in this experimental system we can mimic the human condition of loss of proprioception, and one can go further in this system and ask what has happened in the spinal cord under conditions in which proprioceptive input is lost, and how does the motor pattern change under those conditions? And to do that, one can again use this methodology of EMG recording to monitor patterns of muscle activity reflecting motor neuron output. And so, if we look here, on the left-hand side we're looking at a wild-type mouse, monitoring the EMG pattern from two different muscles in the same leg, the hip and ankle flexor and you can see that there's a nice phasic relationship. These are experiments that Turgay Akay performed. So there's a perfect rhythm between these two muscles, but if you look in the absence of proprioception, you now find that that rhythm has degraded and now both sets of motor neurons, both muscles are active at the same time and so there's a wholesale disorganization of the pattern of motor output as a consequence of the loss of proprioceptive input. So these simple experiments and observations demonstrate how crucial proprioception is to one... one's everyday aspects of movement, and I'll come back to proprioception later in this talk.

17. The role of interneurons in controlling motor patterns (19:32)

But I will switch now from the contribution of proprioceptive sensory neurons to the way in which local circuit interneurons control pattern. So interneurons, if you like, are the sort of middle management of spinal motor circuits. They have some intrinsic capacity to control movement but they also respond to commands from higher centers, from cortical regions and even from sensory input. But one of the interesting things about interneurons is that they control many aspects of fine motor pattern that contribute to different strategies for locomotion.

18. Video: Walking versus hopping (20:08)

So within the animal kingdom all animals move from place to place but they use different ways of achieving that location, and we can get some idea of this by looking at these two examples of locomotion. So we're looking here in the wild at a giraffe and the important point... notice here is the alternating movements of the legs, whereas here with a kangaroo, what you can see here is that there's a co-activation of the hind limbs there, so that the... these two different strategies of locomotion presumably reflect different aspects of spinal motor control and the circuitry. And in your handouts you received a small flipchart which you can look at later which illustrates yet further examples of the way in which different animals have solved locomotor strategies. So this one just shows a horse here and you can see, these are photographs taken about a century ago from the great high-speed photographer Eadweard Muybridge, and what you can see is a different locomotor pattern here in the horse. I'll show that once more.

19. Video: Dr. Jessell's muscle activity when he hops or walks (21:20)

And the horse like many mammals, many animals, has the ability to alter their locomotor gait, from walk to trot to canter to gallop. And this property is not confined to animals like horses, it's also seen in humans. They have the ability to alter gait pattern. I'll show you one demonstration of this. So here on the left, your experimental subject is walking, and on the right is using a different locomotor strategy to get to the same place, and again you can monitor this, see the individual limb movements, see

the alternating pattern of muscle activity on the left, the co-activation on the right. So interneurons are the final mediators of this and presumably they're responding.

20. The role of inhibition from the opposite side for walking (22:05)

So how can we begin to understand the interneuron circuitry that contributes to these different aspects of locomotion? So let's look into the spinal cord at interneuron circuits. This is a simplified view but it just points out two classes of interneurons that are influencing motor output. So we have one excitatory interneuron shown in this light orange color which both provides direct input to motor neurons but also activates an inhibitory interneuron, the dark orange neuron, that crosses the spinal cord and serves to inhibit the motor neurons on the other side. This is part of a circuitry that was defined by Ole Kiehn in Stockholm in Sweden. And if one thinks about, it the important aspect of achieving this alternation, left is active while right is inactive, is that these interneurons, the light interneurons, the excitatory interneurons, stay on their own side of the spinal cord, so that they can excite motor neurons on the same side, avoid exciting motor neurons on the opposite side.

21. Video: Mutant mice lacking crossed inhibition hop (23:10)

And it turns out that part of the reason that they stay on their side is that there's a midline repellant barrier, very much of the same way that one saw in the guidance of axons yesterday, that keeps those light excitatory interneurons on their same side. So genetically, if you eliminate that barrier, what you might expect to happen is that those interneurons would now cross onto the other side and provide excitation of the contralateral motor neurons as well as the ipsilateral. So let's have a look and see what those genetically mutant mice behave like. So now what you can see is that these mice are hopping like a rabbit or a kangaroo. So under these conditions, manipulation of one set of interneurons has completely changed the locomotor gait of this experimental system, and again we can monitor the consequences of that change in interneuron pattern by looking at the EMG activities on the left-hand side, you can see wild-type alternating pattern, on the right-hand side you can see the synchronous EMG bursts from motor neurons, or synchronous motor bursts here. So this gives you an indication of how the intricate interneuron circuitry of the spinal cord is really controlling our everyday movements.

22. Reactivating damaged interneurons using sensory stimulation (24:29)

But there's another reason for focusing on interneurons and that is because interneurons also mediate these top-down commands from higher centers in the brain. So motor commands come down, activate local interneuron circuits, and in a sense permit motor output. And in cases of spinal cord injury, when the spinal cord is damaged, you lose those descending motor commands, so those interneurons are ineffective at controlling motor output, and the reason that one sees paralysis in spinal cord injury is in a large part of the loss of these descending commands. So how could one possibly restore interneuron function under conditions of spinal cord injury? Over the last few years several groups have postulated that perhaps we could reactivate interneuron circuits by using the sensory feedback system. So in paralysis you're not activating your sensory system. So if you could find a way of reactivating the sensory system, perhaps that would train interneuron circuits to reactivate the motor system, and so in spinal cord injury there are new strategies where patients are supported and then are asked to walk on a treadmill or aided to provide locomotor activity which activates their sensory system and retrains those interneurons to produce coordinated motor output, and we can see some startling examples of that again by monitoring EMG activity in spinal cord injury patients before and after these training protocols, and so this is work from Susan Harkema just showing EMGs from many different muscles before the sensory training and after the sensory training. So in this way there's perhaps new hope for spinal cord injury through the knowledge of circuitry that is driving motor output. So up to this point we've seen how proprioceptive system is important and crucial for motor output, how the interneuron system in part

works together with the proprioceptive system to control output, and after the break we're going to discuss how descending systems impinge on the motor system.

23. Q&A: Do organisms that change gait have multiple interneurons (26:42)

But let's take a break now and I'll be happy to take questions on what we've talked about so far.

[STUDENT:] I was wondering if organisms like people and horses who have the ability to change their gait, do we have multiple interneurons between the...

[DR. JESSELL:] Yes, so this is a good question of really how, what is the circuitry underlying the ability to change locomotor gait patterns. It almost certainly involves a combination of spinal cord interneurons, but also these top-down commands, because if one thinks about it you can control your gait pattern at will. So that's not a rewiring of circuitry in the way that I showed you, that just implies that the circuit is controlling it, but presumably what these descending commands are doing are selecting different interneuron modules for activation as a function of the particular type of walking behavior you want to execute. So it's a complicated circuit and I've just given you two simple examples of the role of cortex and spinal cord.

24. Q&A: How do muscle spindles sense contraction (27:52)

I'll take your question up there. Yeah, yeah?

[STUDENT:] You mentioned earlier that the muscle spindle senses a contraction and transmits that information to the proprioceptive system. I was wondering how does the muscle spindle sense the contraction?

[DR. JESSELL:] Yes, so that's a very good question. So the end... and I didn't show this in high detail, the question is, how actually is that transduction process in the periphery relayed centrally? And so the muscle spindle is a specialized type of muscle fiber that sits in between all of the major muscle fibers that are controlling the force of contraction. So it acts like a strain gauge, so it is moved passively as a consequence of the movement of the major so-called extrafusal fibers and the sensory ending wraps around those intrafusal special strain gauge muscle fibers. So as the fiber itself changes presumably, and this is not well understood, there is a change in the sensory ending, maybe a mechanical change that activates ion channels that then trigger an electrical impulse, an action potential that is then transmitted centrally back into the spinal cord. So it's a very specialized mechanism, a very refined and sensitive mechanism for monitoring small differences in the state of muscle contraction.

25. Q&A: How does polio cause paralysis? (29:18)

[STUDENT:] In patients with polio does the virus attack the spinal cord, like, temporarily? Because I know some of them do regain their movement, so how does that...

[DR. JESSELL:] Yes, so the question is, how does polio cause paralysis? So polio is another example of the virus that will attack motor neurons and it does so by binding to a specialized receptor that is expressed on motor neurons as well as on other cell types. So it does affect those cells and like many viruses the specificity of its action reflects the ability of a viral protein to interact with a host cellular protein and then direct that viral toxicity to a particular cell type. So a lot is known about the nature of the receptor and it certainly is expressed by motor neurons.

26. Q&A: Are proprioceptive signals also sent to the brain? (30:08)

[STUDENT:] You know how you said the sensory neuron sends a signal to the motor neuron for the, for the muscle to contract? Is there a signal that's sent back to the brain so that the brain understands that the, that the muscle has contracted?

[DR. JESSELL:] Yes. These are great questions. So I gave you the simplest form of proprioception which is the reflex form. But what you saw with Charles Freed I think is probably reflecting the other pathway of proprioception, which is not simply fed back onto the muscle, but is fed back into the brain via a pathway that projects from the spinal cord to the cerebellum and then from the cerebellum to other higher senses in the brain. So this is a much more complicated role for proprioception than I described. I'm sorry but we're going to have to move on and we can talk about additional questions later.

27. Hearing and vision also control motor behavior (31:05)

So we've seen how proprioceptive and interneuron systems control motor output. Now let's begin to address the way in which higher centers in the brain control motor behavior. So intuitively, you know that many of your senses interact with the motor system. When you hear someone talking to your left, you instinctively turn your head in that direction. So the auditory system control can influence motor behavior. I'm going to try and give you some examples of the way in which the visual system converges with other sensory systems, the proprioceptive system to control motor behavior. Now this is an important aspect of everyday aspects of movement, and I'll just try and illustrate. So any of you athletes here? Any of you hurdlers? That's good. So what you're doing is you see the hurdle in front of you, you have to use visual information together with proprioceptive information to assess the height of the obstacle, to be able to coordinate your movement as you jump over that. So this implies that there must be some convergence between visual information and the proprioceptive system to control accurate motor output. As you walk over rough terrain you are doing this routinely.

28. Video: Ian Waterman—vision compensates for proprioceptive loss (32:31)

I want to try and demonstrate the convergence between these two systems by resorting or returning to the condition of proprioceptive loss. So what we've seen is that these two systems converge. What you saw with Charles Freed is that when the virus destroys proprioceptive sensory neurons even though the visual system is converging, it was doing a poor job of substituting for the proprioceptive system. But are there conditions in individuals where the loss of one sensory system can be compensated by the overactivity or the re-wiring of a different system? Could, for example, the loss of proprioceptive sensory feedback be compensated for by the presence of visual input, and I'm going to show you one example of an individual with a similar viral lesion of proprioceptive sensory neurons who remarkably has been able to co-opt his visual system to control movement in an impressive way. This is a patient called Ian Waterman. I have to scan the path ahead, not immediately in front of my feet, probably about six or eight feet ahead, so I'm planning all the time exactly what's coming up, so that I'm going to be aware of where I'm going to place my feet, so I don't compromise myself. So this is a very different set of motor capacities than we saw with Charles Freed, and as you saw, Ian Waterman, took him three years to learn how to use his visual system, now monitors his movement by constantly looking at his feet, constantly looking at the consequences of his actions.

29. Demonstration: Touching thumb to fingers using proprioception (34:12)

So under these conditions it appears that the loss of proprioceptive system has been compensated by the presence of visual input. But how can we really demonstrate that? That in this case we're using vision to compensate for the loss of proprioception? So I want to try and examine what happens in Ian Waterman when we remove the visual input and then examine motor tasks, and in order to do this, what I'd like to

ask you to do is to perform a very simple motor task, which is to take your hand and to touch your thumb on each of your fingers in turn, backwards and forwards, and you'll notice that you do a pretty good job of doing this placement. And if you shut your eyes you can do it. Again, this is your proprioceptive system at work. And if you were to try and touch the fingers of the person sitting to the right of you with your eyes shut, I think you'd find it difficult, maybe you can practice that later. So

30. Video: Waterman touching thumb/finger without visual feedback (35:08)

your proprioceptive system permits you to perform these motor tasks even in the absence of vision. But what would happen with Ian Waterman, who has lost his proprioceptive system, if you now deprived him of vision? So let's look at Ian Waterman performing the same task with visual feedback. He's looking at his hands basically. And he does about as good a job as you do in achieving this finger placement. But now if one gets him to shut his eyes, you can see that the ability to perform this precise placement is dramatically degraded there. Occasionally he touches, so there are other sensory systems that are presumably converging, but this begins to imply that his visual system is crucial and this is how he describes it, and I would just encourage you if you want to read more about this remarkable individual his neurologist Jonathan Cole wrote a book called "Pride and a Daily Marathon" which accounts, recounts the period from when he first was exposed to this virus at the age of 19 and his gradual recovery and his ability. It's really, it's a dramatic account.

31. Functional MRI localizes brain activity during touching task (36:24)

And you can also assess what has changed in Ian Waterman's brain under conditions in which he's learned to use the visual system. So if you perform functional magnetic resonance imaging of the sort that Eric introduced, then what you find in Ian Waterman is that when he's using visual feedback to control movement, an area at the front of the brain, the orbito-prefrontal cortex, the area shown in red there, is highly active. This is an area involved in high-level visual processing and is not normally active in you or me when we perform simple motor tasks. And even in Ian Waterman, if you deprive visual feedback, then you lose the activity there in a different region of the brain. So Waterman has somehow managed to reorganize his brain circuits to compensate for the loss of proprioception. So this is one example of the way in which the visual system under some circumstances can have a dramatic impact on the precision of motor behavior.

32. Demonstration: Using spatial memory to clear an obstacle (37:24)

Now as you walk around in the world, you are looking at objects in front of you and that raises the possibility which is shown for example here, coming back to our hurdling analogy, that you see the hurdle well before you have to scale it. And so are you using information, are you using visual information, and in fact storing that information, perhaps in a form of short-term memory, to encode that information and use it at an appropriate time to guide the motor system? And again, just to try and demonstrate that you and I have this capacity to store visual information, retain it for a period of time, and then let it loose at the right time, I want to do another small demonstration, for which I'll need another volunteer. So what is your name?

[EMILY:] Emily.

[DR. JESSELL:] So Emily, come over here. Thanks. So what we're going to do is to show that you have a visual memory. So if you stand somewhere around here, and I would like all of you to be prepared in case something goes awry here, but all we're going to ask you to do is to look at that obstacle, to look at it and then shut your eyes and then walk towards it and try and scale it, try and walk over it, with your eyes shut.

[EMILY:] Okay.

[DR. JESSELL:] We're on your honor here, yeah.

[EMILY:] I'll try.

[DR. JESSELL:] You can do it. Do you want to have another go?

[EMILY:] Sure.

[DR. JESSELL:] Okay. Don't... so I've tried this and it took me about ten goes before I could do it so, so come a bit, come a bit closer, yeah. Okay. Yes! Thank you. These will be around afterwards if anybody wants to try this.

33. Analyzing a cat's ability to remember obstacle location (39:33)

So humans have the ability to store visual information and transmit that into accurate mode of behavior for five or six steps. So how can we begin to analyze experimentally the nature of that stored visual information? So Keir Pearson in Canada decided to see whether other animals — cats — could behave in the same way and begin to analyze the circuitry underlying this behavior. And so this is a very similar task here. You have a hungry cat which is searching or moving towards a source of food but there's an obstacle in the way and you can see that the gaze of the cat falls on the obstacle but very soon the cat straddles the obstacle and is intent on the food, and unbeknownst to the cat, Keir Pearson has slyly removed the obstacle while at the time that the cat is still interested in the food.

34. Video: Cat remembers obstacle location for many minutes (40:24)

And so the question now is, the cat saw the obstacle, got distracted by the food, it didn't see the removal of the obstacle. How would the cat behave as it moves forward as the food is moved away? And just to illustrate that I'll show you two videos of this sort of example. So here is Keir in the background. There are now two obstacles, now the cat just straddled the first, there it's quietly removed while it's eating the food. The food is moved. So even though the obstacle wasn't there, the cat retained a memory of that obstacle and then performed a motor task suitable to scale it. Let's look at another video which really addresses, how long does this stored memory last. So now the obstacle is there, it's going to be removed. The cat was particularly hungry. Four minutes later now... So this memory is stored for some considerable time. And if we try and plot that then what you find is that cats have the ability to retain that perception of an obstacle for up to 10 minutes or so, so this is a considerable memory feat, if you like, and it raises the question of where in the central nervous system is the trace of this memory, and you'll see this begins to address some of the issues that Eric will continue in his next lecture.

35. Animations: Neurons in parietal cortex are active during straddling (42:02)

And a region in the central nervous system in the posterior parietal cortex known as Area 5 seems to be involved in this process, and one can demonstrate that by eavesdropping on the activity of neurons in that region as a cat is performing this task. And so what we're going to look at now is a sort of cartoon, but at the same time we're going to be listening to the activity of a single neuron in Layer 5 of cortex as the cat is performing this simple obstacle avoidance task. So this clicking you hear is the activity of that neuron. You can see that while it straddles, the neuron is firing, it stays firing... ...because it still had one leg over, and now when it's past, the neuron is essentially silent.

36. Quantifying neuronal activity in Area 5 parietal cortex (43:05)

And we can quantify that, and you can see that these little yellow bars represent the period when the cat is actually straddling the obstacle, and every time it passes over the obstacle — this is work from Trevor Drew and Keir Pearson — you can see that this neuron fires a burst of action potentials, and when you maintain the object for a long period of time, the neuron continues to fire. So in this way, this region of the parietal cortex is somehow correlated with the storage of that obstacle memory and presumably that information is then transferred down to the spinal cord at an appropriate time to influence movement.

37. Inputs to motor neurons can compensate for one another (43:50)

And so this is one way in which one can begin to examine the nature of circuits by which top-down commands influence motor output. So in these three small segments, we've analyzed circuits for motor control, the way that motor neurons are influenced. We have dealt with the influence of proprioceptive sensory neurons, of local circuit interneurons, as well as descending commands, and found that all three systems contribute to precise movement, and that the absence of one system can be compensated for by the presence of another.

38. Compensating for loss of motor neurons due to ALS (44:26)

But what about motor neurons themselves? They're the fourth element of this circuit. It's harder to imagine how you could reorganize circuitry if motor neurons themselves are missing, and tragically this is the case in many neurodegenerative diseases, I mentioned amyotrophic lateral sclerosis. That is a disease of motor neurons where normal motor neurons gradually undergo atrophy. They begin to die, the muscle itself withers away, and finally motor neurons are lost from the spinal cord. And this is a dramatic and rapidly progressing disease, and as I mentioned, one of the people who actually lent his name to this disease is Lou Gehrig the baseball player, shown here in his Columbia student days here, but what you can see is, in a sense, through analyzing Gehrig's batting statistics, some advanced sign of the disease pre-diagnosis. So for many seasons he performed remarkably well, batting at about .350 or so, but then in 1938 and 1939 you began to see a dramatic decline in his hitting statistics. This was before diagnosis, and eventually he was diagnosed with this disease and died a few years later. So how in ALS patients can you think about restoring motor function? Changing upper circuits is not going to do any good if the motor output itself through the neurons is gone. So perhaps one way is to combine what we learned in yesterday's lecture about the way circuits develop and neurons become different, with modern advances in stem cell technology, to think about... can we make new motor neurons from ALS patients? And if so, could we use those motor neurons, either in cell replacement, perhaps, or in drug discovery to find better ways of treating motor neuron disease?

39. Using stem cells to create new motor neurons in mice (46:21)

So I want to give you an example now of the way in which the understanding of... eventually the understanding of circuits and the understanding of development might come together to treat motor neuron disease. So as you learned in yesterday's lecture motor neurons can be distinguished by the transcription factors that they express. So we can use genetics in mice as a test case, for example, to label living motor neurons by expressing the marker protein. So we can use the transcription factor promoter to express a green fluorescent protein which will label living cells, and then in that animal, all motor neurons would glow green. This is one such animal, a mouse embryo in which all motor neurons and their axons have been labeled with green fluorescent protein. So from this animal, it's possible to make, to derive stem cells, and then because we know how to make motor neurons through the developmental pathways that I discussed yesterday, we can add small molecule chemicals, including hedgehog ligands, to those stem cells and get them to become motor neurons in essentially unlimited

numbers. So each of these round clusters you see on the top right contains about 10,000 cells, about half of which are motor neurons, and just one is shown in larger magnification. Then you can take those motor neurons and test their ability to form functional connections. So you can transplant them back into the spinal cord and then monitor their ability to send axons out of the spinal cord and innervate target muscle. And so we're looking at a section on the left of the green labeled motor neurons in the ventral spinal cord, just where they should be, sending axons out along all of the major axon pathways, and eventually forming synaptic connections, these blue-white dots at the end of the green axons.

40. Using skin cells to make patient-specific stem cells (48:19)

So this shows that in an experimental system in mouse you can actually make motor neurons from stem cells and get them to form functional connections. Could you do this in a human? Could you even do it in an ALS patient, make patient-specific motor neurons? It turns out that now one can do that. Work by Kevin Eggan and by Chris Henderson has established the feasibility of doing this, and the way that you do that is to take an ALS patient and collect a small number of skin cells from that patient, and then you use specialized transcription factors to convert those skin cells back to stem cells, and then you have a population of patient-specific stem cells which can be induced to develop into motor neurons by the normal developmental signals, as well as the local circuit interneurons. And so now one is in a position, in a patient-by-patient manner, to obtain motor neurons and interneurons and any other cell type you think is relevant to the disease, and think about whether you can reintroduce those cells, or perhaps more promisingly, use those neurons for drug design to find agents that block the progression of the disease and the death of motor neurons. So in this way it might even be possible to address loss of motor neurons as well as the loss of circuits.

41. Summary (49:38)

So in this lecture then we've considered the spinal motor circuit from three different perspectives. Yesterday we talked about the development of these circuits, and today I've tried to give you some glimpse of the way in which the organization of these circuits, and the ability to manipulate individual neurons in the circuits, helps us understand the way that these circuits control developmental function, and perhaps with the understanding of these circuits, we will eventually get better ways of thinking about preventing spinal cord injury, preventing neurodegenerative diseases that affect the motor system.

42. Q&A: Does proprioception compensate for vision in blind people? (50:17)

So I'll stop there and be happy to take questions. Thank you. Okay in the front.

[STUDENT:] In blind people does that mean that the proprioceptive circuits make up for the lack of visual?

[DR. JESSELL:] Yes, so each, so the question is how easily do different sensory systems substitute for each other? And I think we talked about this a little bit in yesterday's discussion, but in many cases the loss of one sensory system can be compensated at least in part by the overreliance or the overelaboration of a different sensory system. So I think it's thought that people who have lost the sense of vision use tactile cues, use auditory cues in a much more effective way. Now the underlying circuitry by which those changes of... these compensatory changes have occurred is unclear but one can begin to probe those circuits now.

43. Q&A: Is all neuroscience research targeted to disease? (51:18)

In the back.

[STUDENT:] I feel like all of the research is just, in neuroscience it's just addressing diseases and is there any investigation that's not disease-based, and, I mean, could you elaborate on that?

[DR. JESSELL:] Yes. Eventually what one would like to do in one's research is to discover things that have some practical value. There's an enormous reward in just working out how things work but in most cases, knowing how things work leads to something of practical value to humanity, to society, and so one can think about two types of research and, one is applied research and the other is perhaps not yet applied research, and so I think all basic research eventually is going to increase the basic understanding of the way biological systems interact, with relevance. So the initial motivation for trying to tackle a problem can be one just of pure curiosity, but the more that you focus on this, the more that you would like that understanding not to be for its own sake but to have some value.

44. Q&A: Is ALS inherited? (52:46)

[STUDENT:] How is ALS inherited?

[DR. JESSELL:] Yes, so the question is, is this motor neuron degenerative disease an inherited disease or a sporadic disease? And the vast majority of people who suffer from ALS don't have a hereditary component. About 15 percent of the disease is hereditary and in a few cases we know the gene that is responsible for the disease, but 85 percent of cases appear sporadically with no family history, and so that raises the question of, what is the cause of the disease in those cases? And one of the promising, exciting things about the ability to make stem cells from individual ALS patients is that you can study a wide range of non-genetic, non-hereditary forms of the disease, as well as manipulating the genes that you think do cause the disorder in a few cases.

45. Q&A: What is the mechanism behind phantom limb pain? (53:45)

[STUDENT:] It's been reported in many cases of amputee patients, that they've reported proprioceptive sensations, tactile sensations and pain, and clearly they don't have any neural systems left in limbs that they don't have, and I was just wondering how this occurs or happens.

[DR. JESSELL:] Yes, so this is the phenomenon of phantom limb pain as popularly described which is a remarkable and, again, tragic when a patient loses, when an individual loses a limb quite often they will have strange sensations, the continued presence of that limb, as well as extreme pain, in some cases, localized to the missing limb. And even though you've lost the sensory neurons and it comes back to the question we talked about earlier, those sensory neurons feed onto other neurons that relay that information up to higher centers in the brain. So the loss of the initial sensory neuron somehow reverberates down that circuit of neurons, that cascade of neurons and there are thought to be changes within the central nervous system that are consequent to the loss of the sensory cell. So even though the initial peripheral sensory neuron is gone, the brain is tricking itself into thinking that that sensory information is still being processed, is still being received, and that is thought to underline many of these sensory phenomena following amputation.

46. Q&A: Are motor neurons responsible for muscle atrophy in space? (55:08)

Let's have that one right in the back in white. Yeah.

[STUDENT:] I was wondering if like muscle atrophy due to loss, like, lack of gravity in space has to do with the motor neuron atrophy.

[DR. JESSELL:] Yes, so the question is, what are the different ways that muscle can atrophy. So one way that I described is when the motor neuro itself is lost but there are several different diseases that affect the muscle cell itself without targeting the motor neuron first. So under conditions of weight loss, you might imagine that many aspects of the sensory system are fooled because now the normal weight load that is activating sensory neurons is removed, so what are the consequences of that? So there are many complicated reasons why muscle properties would change when they lose their weight-bearing load. It's probably not related to an effect directly on the motor neuron, but because it's a loop in a sense, any manipulation in one point in the loop could reverberate around that circuit. So I want to thank you. We should unfortunately move on now. I want to thank you for all of the questions and for listening to these two lectures. Thanks very much.

47. Closing remarks by HHMI President Dr. Thomas Cech (56:38)

[DR. CECH:] Thanks Tom for a great talk. The work on motor memory in cats and humans is truly remarkable. I also enjoyed seeing you in your role, not as a researcher but as an experimental subject. In our next lecture Eric Kandel will return to talk about the role of specific molecules in memory.