Transcript

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LAURIE WILSON: Well ladies and gentlemen let's get underway. It's always a delight. This is the 18th year that the National Press Club has been involved with the Australian Society for Medical Research in the presentation of the ASMR Medal, the Medal this year for 2016. And just to begin things, we're going to present the medal formally to our recipient at the conclusion of tonight's event - well not the conclusion in the sense that we're going to socialise afterwards and have a few drinks and a bit of a chat, but certainly at the conclusion of the formal proceedings when the Chief Executive, Anne Kelso, of the National Health and Medical Research Council who's just joined us, in fact will be joining us in the room shortly, will make the formal presentation to that recipient.

But to begin, I'd just like you to formally welcome our recipient this year, Professor Theodore, or Ted as he prefers, Berger.

[Applause]

I suspect most people in this room know a fair bit about what Ted Berger does, but I'm sure he's going to tell us an awful lot more. But I must say, as a non-scientist and journalist who takes something of an interest in these areas, it is absolutely fascinating, clearly potentially- I mean more than ground-breaking if you like, if you can use that term. As I said at the outset, it's a great pleasure for us to be involved in this, 18 years. The first recipient of course was Nobel Prize winner Peter Doherty; Barry Marshall another Nobel Prize winner has received it; great Australian Sir Gus Nossal another recipient; outstanding young scientist, Professor David Sinclair a couple years ago, doing some brilliant work both here in Australia and in the US; and of course a number of quite imminent international figures, Baroness Susan Greenfield springs to mind who, as we know, has devoted her life not just to promoting the cause of scientists but as a scientist working in the area of particularly of dementia and Alzheimer's specifically.

Which brings us to our guest today, because while his work does not necessarily- well does not, if you like, relate to a cure for Alzheimer's, it nonetheless has potential, tremendous potential significance for those people suffering from Alzheimer's in terms of what it offers, particularly not just in that area but in a range of other areas but particularly in that area. So would you please welcome Professor Ted Berger.

THEODORE BERGER: Thank you, it's a real pleasure to be here. I want to thank the National Press Club for this opportunity, and I also want to thank the Australian Society for Medical

Research for this award. And I want to especially thank Sarah Meachem, the President of AMSR, for organising what's turned out to be a wonderful exciting tour of what's obviously first class research centres and institutions here in Australia, and I must say also an impressive number of members of the political system who support the research centres and the research entities that are here. So I want to thank those people in particular.

So I have an opportunity to present the work that I and my colleagues have been conducting to develop what is a new class of neural prostheses, what I could call a cognitive prosthesis. So it's a prosthesis to help the parts of the brain that are involved in higher thought processes, and in this case memory in particular. And I'm sure that most of you are familiar with other neural prostheses, such as those for sensory systems like artificial retinas, and of course cochlear implants that were developed in large part due to work that was done here in Australia. But major advances have also taken place recently in prostheses for motor systems, so that now we can have artificial arms, hands, and fingers that are controlled automatically by thought processes from the brain, which is just a remarkable thing to achieve.

But despite all of this, neural prostheses are also desperately needed for many other parts of the nervous system, and most importantly central parts of the brain that are many synapses removed from sensory system, sensory organs, and that are also many synapses removed from the motor neurons in

the spinal cord. So these are parts of the brain that are in the central regions and that have been damaged for a variety of reasons. And these types of prostheses are again what I would call cognitive prostheses, and what I'm about to describe is the first of its kind. There is no available cognitive prosthesis at the moment. What I'm going to tell you about, the work that I and my colleagues do, is the first time that there's been an attempt to develop a cochlear pros- cochlear prosthesis, strike that word, even though it's a wonderful thing - the first attempt to develop a cognitive prosthesis.

And the specific goal that we have is to develop a prosthesis for a brain structure called the hippocampus. The hippocampus means seahorse, because somebody thought when the looked at it that it looked like a seahorse, which probably meant they had too many wine drinks.

[Laughter[

I don't know, but it doesn't look like a seahorse to me but it looked like a seahorse to them. So it's called the hippocampus, and it's the part of the brain that's responsible for developing new long-term memories, that's its sole purpose and that's what it does. And the inputs to the hippocampus are of course the brain uses electrical activity everywhere, not solely electrical activity but electrical activity in large part for communication in the brain. But the inputs to the hippocampus are neural codes for short term memories. So a lot of the sensory systems in the brain

and some of the motor systems of the brain converge on the inputs to the hippocampus, and those inputs- what occurs at that point is activity that produces short term memories. And that means things that you can remember for 10 to 30 seconds, something in that range. It's not quite accurate, but it's somewhere- something like that. And the hippocampus then takes these neural codes, and it generates new neural codes for new long term memories. So long term memories means things that you can remember for hours, to days, to years, things beyond the 30 seconds.

And there are several stages or layers to the hippocampus, and these are points at which neurons form synapses or connections with other populations of neurons. So there are populations of neurons that drive the next population of neurons that drive the next population of neurons, et cetera. And at every point where there are these connections, the neural codes are changed. So they're not constant, they start as a particular form, they code short term memory, and as they propagate through the hippocampus they become different, they're re-encoded to be different codes. And what they come out as are codes for long term memory. So it's this process that we need to understand, it's this process of converting particular codes into different codes that we have to understand and that we have to mathematically model and eventually develop into a microchip format if we're going to solve the problem of how to replace the hippocampus.

When do we need to replace the hippocampus? When does it become dysfunctional? And without going into too much detail, the conditions that lead to loss of the ability to form new long term memories are things like stroke, epilepsy, Alzheimer's disease and other forms of aging, dementia, and even blunt head trauma for reasons that we actually partially understand, blunt head trauma leads to the loss of the ability to form new long term memories.

So what's the idea that we have to solve this problem? The idea is that when there's damage to the intrinsic circuitry of the hippocampus, in a lot of cases the inputs to the hippocampus are still intact. So there are areas that we can still record short term memories. So if we put our electrodes into the input regions to the hippocampus we can record short term memories, and if we can study the process that the hippocampus uses to convert neural codes into different neural codes, in other words to convert short term memory codes into long term memory codes, if we can mathematically model that and reduce it to a microchip format then the electrodes that are in the hippocampus that are recording short term memories, we can send those to the microchip which can be mounted on the skull underneath the skin so they're not even seen.

So the microchip can convert short term memories into long term memories and then that new answer can be transmitted down another set of electrodes where we bypass the damage parts of the hippocampus and we electrically stimulate the output of the hippocampus so that there's a new long term memory code and that

goes to wherever it has to go to be stored. So, we record short term memories- short term memory codes, we convert them in our device to long term memory codes, we electrically stimulate the output of the hippocampus with those new codes and we bypass the damage. That's the idea. But to be able to mathematically model this transformation of short term memory into long term memory, we need first to observe it, we can't do it without observing it before we understand it and we do that in the following way; we've developed training paradigms for animals and for humans in which we train subjects to recognise target objects. They're really very simple tasks that we present a single target to an animal, whether it's a rat or a monkey or a human, we present that for a short period of time and then we take it away. And after a delayed period we present several objects and the animal or the human knows that what it has to do is to recognise the object that it saw before, very simple.

But because it's- and if we have a short delay period, the animal can use short term memory to solve the problem but if we use a longer delay, the animal has to be able to produce a long term memory to be able to solve the problem. But in this way we can study how organisms develop both short term memories and long term memories and we can study the conversion in a way I'll talk about in a second but during the first part of this one, we present the target to the animal, the neurons in the hippocampus generate memory codes for that object. And what do these memory codes look like? They actually look a series of pulses. Neurons, just like electronic circuits use pulses wot communicate with other neurons. So, they're all or none events and

if you listen to them they sound like a da da dadada da da, they're- it's almost like a Morse code except it's more complicated than a Morse code. So, these pulses are generated whenever the cells are active.

So memory codes are, in part, temporal codes. As you just heard me- you know, I'm not a great singer but it was sort of like a song, but that da da dada da, it's a temporal code. What's coded is not the amplitude of the dot, but the time between dots. But the memory codes are more complicated than just temporal codes and how are they more complicated? They're more complicated because when hippo- when the hippocampus represents someone's face or the sound of someone's voice, or a picture or an event, it does that- not as single neurons but with populations of neurons and we don't know exactly how many but we're talking about hundreds, to thousands, to tens of thousands for any particular event. So, lots of neurons get into the act when they're representing a particular memory. So, the hippocampus actually uses spatio-temporal coding, different neurons of space and each of those neurons has a different temporal code and the neurons have a different temporal code because they're each paying attention to different features. So, the memory for my face includes my hair, the colour of my hair, my face, the shape of my overly sized nose, ears, everything else, there are many features and each of those features are coded by the different- either different single neurons or populations of neurons.

So, spatio-temporal codes are the name of the game and so what we do is to report these space time codes from two different regions of the hippocampus, we record from the short term memory part of the hippocampus and then we also record from the long term memory part of the hippocampus. So, we've got the short term code, the long term code so we can compare them and by using some relatively complicated mathematics, we can develop a model that allows us to predict, based on the short term memory code, what the long term memory code should be. And- excuse me, and so the- once we've produced that new long term memory code, if we're going to use this as a- this device and this system as a prosthesis, we have to take that long term memory code and put it back into the fray. So, once we've recorded the short term memory code, we've converted it to a long term memory code and then we put it back into the brain and we do that by using electrical stimulation. And again, what we do is to bypass the damage and in this way we complete the circuit with a device that does the same thing that part of the hippocampus does or used to do. And so we've successfully completed development and testing of such a prosthesis for both rats and for monkeys and how do we test this- how do we test the prosthesis to make sure that it works in a way that I claim it works, this'll be- I'm going to repeat a few things but we first show various visual objects to the animals and we record the memory codes from both the short term regions and the long term regions so we get the data.

And then by comparing those we developed a mathematical model that allows us to predict from

short term memory to long term memory. Then we inject a drug into the hippocampus that temporarily inactivates hippocampal function and we know that it does because in the presence of the drug, the animals demonstrate that they have a functioning short term memory but no functioning long term memory so if we make the delay between showing them an object and testing them for the object, ten seconds, they do just fine, but if we make it 20 seconds they fail, and I mean they fail. So, there is- it's very clear that when we inactivate hippocampal neurons, animals lose the ability to form new long term memories. So, we know we can do that.

So, our prosthesis- I'm sorry, three, four, five- our prosthesis has- I didn't actually finish that, sorry. I'm not used to reading, so. Usually I just talk so I don't- now I skipped a paragraph someplace, I'm sorry about that.

[Laughter]

I'm not used to this, anyway. So, when we- when this- when the hippocampus is inactivated and it's clear that the animals cannot produce a long term memory by themselves, they can't produce it but we can. We know what it is, we looked at it and we also have a mathematical model that allows us to produce one. So, the animal's making mistakes, it's making errors, it's responding at chance levels, but when- so what we do with what we know, is when we present an object to the animal, we introduce the long term memory code in the output part of the hippocampus. The animal

can't generate that code but we can. And so we electrically stimulate into the output of the hippocampus at the appropriate time to present the image, we electrically stimulate and that long term memory code goes to the part of the brain where long term memories are stored.

And so when the animal comes back and there's a match period, the animal knows that it has to retrieve a long term memory, so it goes to wherever it goes to retrieve a long term memory- that is its system does, and it actually finds one and it turns out it's the correct one, it's just the animal didn't produce it, we did. So, we can introduce the correct memory and in fact, we can also introduce the incorrect memory. So, if we want the animal to make a mistake, when we present the object, we can introduce a code for something else and then the animal will make errors. So, in this way, we satisfied ourselves that these procedures can be used to reintroduce the long term memory creation function, at least under the conditions that we've looked at. Now what- and again, we've done that both for rats and for monkeys.

Now we've recently begun developing a prosthesis for humans, and specifically for epilepsy patients, and that again with the help of many of my colleagues we had to develop new methods for how to insert the electrodes - I won't go through the details - but everything had to be redone because humans are not animals. So we had to develop new reporting methods and we did that, we've also developed successfully new input-output models for the conversion of short term

memory codes into long term memory codes. And these- the models for humans are much large than the models for animals. Humans are- they create memories that are much more detailed, et cetera, and so we had to develop very different- not very different but improved, we had to improve the modelling capabilities to be able to make the predictions that we needed, and we were able to do that.

The last step is that we need to be able to reintroduce the long term memory codes from our model back into the hippocampus to drive hippocampal neurons to the proper memory state. And we need to be able to show that we can improve human long term memory. And this is the part, this final step, that we have not yet done. So we're at a point where we have done everything else except the final test. And we have several patients that are already implanted, and they're waiting for testing. And during the course of the next year, two years, we'll be testing other patients and hopefully finding the result that we want to find. But we'll have to just see what we get. So in the next year, probably two years, we'll know the answer to whether or not this procedure and this whole set of procedures is going to work well.

Just to finish up, in terms of the microchip versions of these models, the microchip versions are underway. Our group has designed and fabricated and tested several generations of microchips. The designs are less than complete because we don't yet know all of the things we wanted to know about the microchip. But we soon will, and we're very close to knowing what we

need to include, and the designs that we have so far have been terrific. And importantly we've recently completed and tested a microchip designed with what's called sub-threshold principles. And this means that the chip has ultra low-power properties, which is extremely important in conserving power during functionality for a human - replacing batteries is not something that you do casually. And so anything that allows you to save energy is important. So that was actually a big step forward.

Lastly, in terms of commercialisation, we've recently been approached by two individuals for commercialisation of these cognitive enhancing technologies. The individuals in question, who I cannot name at present, are highly experienced entrepreneurs who have made multi-million dollar and multi-year commitments to developing this hippocampal prosthesis. So we have behind us now an incredible opportunity for very high levels of funding and very high levels of expertise in terms of knowing how to bring something like this to market. And it's not a trivial process to bring a device like this to market. There are a lot of ways in which trying to get this to market can fail, because there really are not- you're not talking about selling something to youngsters who like to play games, you know, and selling them millions of software packages to make billions of dollars. We're talking about something that needs to be approached with a lot more conservative tactics. But the company will be announced within the next one to two months, and has already created office space and begun hiring personnel. So the company has begun negotiating with all the universities involved to acquire intellectual

property that's essential for development of the device technology. So the foundation for really taking off with this technology, this cognitive enhancing technology has been laid down, and it's very promising.

So with that I thank you for listening, I hope that I've given you some view on this new territory which is developing, cognitive prostheses, cognitive-enhancing technologies, they will- this kind of technologies I expect will be developed for a lot more areas of brain function then just the ones I've talked about, and I expect that we'll be seeing cognitive-enhancing capabilities entering our lives in a very major way in just a few years. And that entrance of cognitive enhancement into the marketplace and into our lives is going to be something that will really change the course of human development. But thank you, I hope that it was useful and enjoyable for you.

[Applause]

LAURIE WILSON: Might be a bit more comfortable sitting down rather than standing. Thank you very much.

THEODORE BERGER: Thank you.

LAURIE WILSON: There you go. Thank Ted. Let me keep that medal from you for just a little while longer.

STEVE CIOBO: Sure.

LAURIE WILSON: Well present that, as I said, at the conclusion of proceedings today. I'm joined on the stage by Simon Grose, the Editor of Canberra IQ, one of the few specialising- journalists who specialises in science and technology in the national capital. And we're going to have a bit of a chat then I'm going to open it up to we have- also joined by former scientist I should say, he describes himself that way, Dr John Millard, who perhaps has some questions. But I'm happy to answer it to- open it up I should say for questions and answers to the wider audience. We have a microphone, we'll bring that to you. But let me kick it off.

One of the things you said was that a lot of your colleagues, if we look back a bit, said you were nuts, you weren't going to get anywhere here. And I'm reminded a little bit of Barry Marshall, who had to subject himself to- treat himself as a guinea pig to, if you like, prove the naysayers wrong when it came to the cause of ulcers and the impact of bacteria. I'm reminded of Graham Walker and cochlear, I think similar things were said about the ability to do that. In a sense cochlear to me as a layman is a sort of a if you like a lower level achievement - I mean it's a massive achievement, but yours is even in a higher plane again. How difficult was it to overcome that, and in many ways beyond- once you overcome actually continue to generate the level of support in the face of such scepticism, if you like?

THEODORE BERGER: Well I'll have to- to be truthful, it was very difficult. And …

LAURIE WILSON: [Interrupts] I guess what I'm getting here is, you know, this is a message for young scientists sitting out there listening to you.

THEODORE BERGER: Yes, yes. Yeah I know, I understand, and I'm trying to talk to them.

[Laughter]

LAURIE WILSON: My apologies.

THEODORE BERGER: It's alright. I knew where you were going. But part of what- I mean so it was very difficult. I mean the first reaction that most people had in talking about this when we started 20 years ago was that we were nuts. I mean people said are you crazy? You really think you can do that? And it wasn't a pleasant you are nuts, it was an ugly you are nuts. So when they said you're crazy, do you really think you can do that, they weren't sitting back and expecting a yes and helping me to explain the yes, it was- well anyway, it was what it was. But so the perseverance counts for a lot. I mean, people do look to see whether you keep at it. And if you keep at it and you keep at it, even the worst of your attackers will eventually think that maybe you've got something, maybe you're not really crazy, maybe you're following an instinct or an intuition that they should have but they don't and you have it. So there's a competitiveness that you can draw out of people just by staying at it, and staying active.

But that doesn't do you very much. It does you something, but it doesn't do you very much. I think

that what really helps is when you're selling the idea you look for reactions and explain what it is that you're going to do and most projects that are large projects like this have several parts. It's not one project. We had mathematics to begin with in the theory and development, we had neuroscience recordings and neuroscience things that we had to do, we had biomedical engineering, we had electrical engineering, you saw it all. You didn't see it all, but you saw a lot of it. But the problem breaks down into parts. And you watch who you're talking to and see when you mention part three they kind of raise their eyebrows a little bit and they lean forward and they want to listen a little bit more.

When you talk about part four they're looking like this at the floor and they're not really caring what you're talking about. So watch how they respond and then because you're going to have to break the problem down into pieces anyway, so take the pieces when you see what the response is and sell the whole project piece by piece and sell it to the right person by selling it to the person whose eyebrows went up when you talked about a particular part.

So we've in the very beginning, we very much, you wouldn't have guessed by looking at the titles of grants that we were working on a neural prosthesis. You wouldn't have known it. What we were looking at and working on to begin with was the use of a new modelling technique to understand synaptic transmission in the hippocampus and we were looking at the use of new design techniques to introduce non-

linear dynamics in microchips. So the whole problem broke down, we've got money for a while for developing the technologies to record from multiple locations in a partic… either a brain slice or an intact hippocampus and that's of course what we have to do if we're going to look at population activity to look at the codes from memories.

So you can sell different parts and we did that for many years until finally we found someone who had, we found an agency that had a vision that could- a scope of a vision that could match our scope of a vision and then we could start to sell the whole idea of a prosthesis and a memory prosthesis and then we were still crazy but at least we could sell the whole idea and once we got over that edge of you know being called crazy but yes at least we were supported for the whole problem then we could have many people working together on that problem.

LAURIE WILSON: Was this a case of you saying look I don't know whether we can achieve this but let's find out because ideally you ought to be… in other words at what point did you think you weren't nuts? At any point did you think this is achievable or let's just have a look and see?

THEODORE BERGER: No I actually never thought that I was nuts and…

[Laughter]

THEODORE BERGER: … and I always thought it was going to work and I still think it's going to work so I think that it's really important, I mean it's really important to believe in

your vision. If you don't believe in your vision, nobody else is going to believe in your vision; you have to be a stalwart. You just have to be. And that means you have to have thought through the idea enough in the beginning to think that it at least had had a damn good chance, you know, maybe it's not going to work but you know I sure think it's got a 90 per cent chance of success and then keep at it.

Of course there's a chance you may fail but there's always a chance you fail at life, I mean you have to take chances, you have to have ambition about an idea and work at it until the end. It just… don't give up.

LAURIE WILSON: Simon?

SIMON GROSE: Thanks for your talk…

THEODORE BERGER: Thank you.

SIMON GROSE: … you explain how you're translating short term to long term memory in animals and then you said that you've got a project to provide a treatment for epilepsy in humans. I don't get how the memory stuff in animals relates to the epilepsy stuff, what's the mechanism for the epilepsy proposed treatment and what do you- what is it aiming to achieve?

THEODORE BERGER: Sure, no that's fine. The issue in terms of epilepsy is that what happens during epilepsy and I'm sorry I don't mean to… I don't mean to talk down about this but epilepsy involves the repeated activity firing of many

cells at the same time and whenever that happens, there's a calcium load that occurs in cells that can kill them and that's what happens over time in epilepsy is that the cells fire repeatedly and they keep on firing and so eventually cells in a particular part of the hippocampus begin to die and so they have memory problems… of course they have epilepsy, but they have seizure problems and that's the main reason why they come into the hippocampus… into the hospital is because they've got seizure problems but… and it did, one of the consequences of the seizure problems is that they have memory problems and because of the cell death that accompanies the repeated seizures, they end up with the same kinds of memory problems that Alzheimer's patients have and so what we're trying to do with the… I mean the reason that epilepsy patients are so attractive is that they come into the hospital and to evaluate their seizures and the course of their seizures and the spread of their seizures they have electrodes implanted in the hippocampus and in other parts of the brain and the neurologists and neurosurgeons record from those electrodes usually for several weeks so they can see where the seizures start and how fast they spread et cetera, so they're already implanted with electrodes. They're already in the hospital. If we had to pay for that it would be an expense that we couldn't afford. So we go to these patients and ask them do you mind as long as you're here, letting us test you on these memory tests and we can record from your hippocampus and we tell them why we're going to do it. And sometimes they say no but most of the time they say yes and so it gives us a huge step forward to be able to work with them.

And the end point is that if we can develop… successfully develop a mathematical model for predicting the memory codes, they already have memory problems so we hope that by electrically stimulating the output of the hippocampus that we improve their memory so they have a baseline long term memory function which is less than yours and mine and so we hope that by stimulating them we'll increase that and that way we'll have proof that what we're doing actually improves that memory.

SIMON GROSE: And when… with the animal tests, are they recognising circles and squares and things like that, would they recognise them?

THEODORE BERGER: Well with monkeys they can be quite sophisticated. Rats can't be as sophisticated… with rats they're learning what's on the left and what's on the right. Then it's really very simple. But monkeys, we give them clip art images that are really quite complex so they have… these are clip art images of humans, sets of humans, boats, buildings, all kinds of things and these are the kinds of images that you can use for patients to be able to… I mean monkeys, they can even form concepts.

SIMON GROSE: So if… you say you worked out the codes, so is the code for a bunch of people or a bunch of both the same for all monkeys or is it different for each monkey?

THEODORE BERGER: Yes and that's a great question. That's a great question. So let me say one thing first is that we do not want, our goal is not to produce a table, a huge table of a code

for a tree, a code for a boat, a code for this, a code for… that's not what we're trying to do. What we're trying to do, that's why our approach is so important because this business of recording from short term memory areas and long term memory areas… the goal in doing that is so that we can learn the rule. We want to know the rule for how short term memory codes or… of any kind are produced into long term memory codes and it doesn't really matter what the content of the memory is, we want to know how those, how any individual code is changed into another code and so it's important for us to see, to give to the monkey or the human, many examples and from that we extract a generality of how a short term memory code of any kind if changed into a long term memory code. That's what's so interesting actually about the outcome of this testing is that we get to see this you know, general rule. It's really cool to think that you can analyse these codes that are quite complex for different classes of events and so that's really what our goal is but that's not what you asked me.

SIMON GROSE: No, no.

THEODORE BERGER: This is what happens in politics.

SIMON GROSE: That's fine.

THEODORE BERGER: You asked me a question and I answer with something else. Yes our policy for supporting child care is… so what'd you ask me?

SIMON GROSE: Well I asked you- I asked you about whether the, like, all monkeys have the same code for…

THEODORE BERGER: Yes, yes very good.

SIMON GROSE: But just… if you can keep that in your short term memory, or your long term memory. But it seems from what you're saying in that answer was that you want to get to a stage where- that there doesn't have to be a human being interpolating and writing codes, but you have developed the system to autonomous artificial intelligence.

THEODORE BERGER: Exactly.

SIMON GROSE: That's where you're going?

THEODORE BERGER: That's exactly right, it's exactly right. We do no want to have any of us involved in the process of doing this. We are right now when we're developing the prostheses, and testing the prostheses, but the whole point is so that- what we really want to do is to repair the circuitry. There used to be circuitry of a particular type that functioned, and we want to replace those wires, and the functionality behind those wires so that they do what they used to do. And we don't want to be there to say this particular pattern, yeah, you should remember this pattern, that pattern, no, no, no, you shouldn't bother with that pattern. We want the system to be able to convert short term memories into long term, just like it used to.

Now that means- I mean this is what's… another thing that's interesting is that you know we don't remember everything. We make- we make a lot of choices about what we want to remember and what we don't want to remember. Some things we don't make choices about, but other things we do make choices about. And most of the time we don't know what that choice- I mean I don't think I understand that choice process. And so part of what we're hoping is going to reawaken after we've repaired the circuitry is the patient's ability to decide when they want to make a memory and when they don't want to make a memory. And I'm not sure that I understand that process well enough yet, so we'll have to see how well it works.

Maybe what we need to repair is something that's more intricate than the wires and the functionality that we can see that I understand. That there may be other things that I don't understand, and that's important for how an individual says yeah I want to remember that there are two glasses here or whatever, or I want to remember- I'm curious about this book that you have here, so I'd like to remember what- you know you have it, so it must be interesting. So I've already made the choice to remember it's *Stand and Deliver*. So we make choices about these things, and I don't know how we put all that back together again.

SIMON GROSE: We've just- or Australia's just refreshed its ethical guidelines on the use of primates in research. Can you sketch your views of how you deal ethically with monkeys in the kind of work you're doing?

THEODORE BERGER: Well the… yes I mean there are strong ethical guidelines that we have to follow for how we treat primates, any kind of primate, and there are extensive rules that I couldn't repeat but - because they are remarkably extensive - but monkeys have to be treated very carefully, and we watch for their- you know for the ease, and the I don't know what to call it, but just the quality of their life in the home cages that they have. So they have a… there's a lot of attention to the quality of the monkeys' life and what their living is like. But beyond that as long as we're careful with the medical aspects of what we're doing for the monkeys, then a lot of the testing that we're doing is seen as being rational and important for understanding the medical needs of humans. So as long as we're pushing things in that direction then we're alright.

LAURIE WILSON: Let me go to the floor in a moment, I just want to ask one more question, and then we'll take questions from the floor, but let me ask one before I do. It looks like John Millard's going to get the first question after me, but I'm- as I said earlier I'm more than happy to invite questions from around the floor while we have time. This is clearly not a cure for Alzheimer's, we know that, we've had lots of addresses to the National Press Club in relation to dementia over the years, and that's always the question; is there a cure on the horizon. But clearly by, if you like, slowing the process of degeneration, and I presume- well sorry by returning long term memory, I'm wondering is that likely to slow the process of degeneration, and in effect still have a positive effect in terms of the life span of the patient? Certainly obviously a positive effect in terms of quality of life.

THEODORE BERGER: Yeah I don't… I don't know. But the… I mean what we're- what I think is definitely going to happen- I mean we are looking at this- the interaction between a neural degenerative process, which is continuing, despite the fact that we have this prosthesis implanted. And I guess the first issue that comes to my mind is that because the degeneration process is still going to continue, I think the question is whether or not the properties of the prosthesis that we've put together as a system, whether those properties are over time going to remain effective in being able to recreate long term memory for the patients. It may be that we have to change the properties of the prosthesis because over time there's sufficient degeneration that the algorithms and the models that we've included in the prosthesis, they won't be effective any more. And that's clearly likely to be the case, certainly in the limits of what we've included as an input-output function may turn out to be ineffective over time.

So I think that's… that's going to be a fight. It'll be something that we're going to have to watch, and I don't expect it to be easy. I think that there'll be new aspects to the solution that we'll have to look at, understand, and then include to keep the prosthesis from, you know- to be effective over the years.

LAURIE WILSON: I'm going to take a question from John Millard, then I'll go the rear there.

QUESTION: Thank you Laurie.

LAURIE WILSON: I'll get you to put your hand up a little later.

QUESTION: John Millard, I suppose you'd describe me as a freelance science journalist these days. Professor Berger if we go back to the history of science, say back to the 19th century, scientists were very much generalists who then took up a specialty, Pasteur, Faraday, Edison indeed, in fact if we go back even earlier Leonardo da Vinci, probably the ultimate in general scientists. This of course changed in the 20th century at the explosion of science and scientists became more and more generalists- more and more specialist rather, rather than generalised. You speak of the importance of interdisciplinary and conversion science, but to what extent do you think scientists these days should, perhaps like yourself, become more generalist in their- not just in their research fields, but in their approach to science?

THEODORE BERGER: Yes, yes. Well in my opinion the- well I think that there is always going to be two classes of science. One will be the highly specialised- highly specialised interest areas, highly specialised capabilities and talents, by one or two people working together in a lab with post docs and students. The specialty is going to be so sharp that it's the kind of thing that has to be held and refined by a small group of people. And while that's important for generating answers to the peak of growth in a particular science, when it comes to solving large problems, and I think large problems of keen interest to society, that has to be- those have to be problems that are solved at least in part by generalists.

You have to be able to- I mean the problem that we have here could never be solved by one person alone,

or by two people, or even by three people. We have to have people that are trained in neuroscience, people that are trained in biomedical engineering and electrical engineering, and in fact computer engineering, and computer science, and neurology and neurological surgery, those are… that's a minimum, right, the areas that I just rattled off. So we have to have people that are experts in those areas, and what we try to do is to put together a team of people that are absolutely at the top of their game for those individual specialties, but that also are generalists in the sense that they can see bridges between what it is that they do, and what it is that other specialists do. And that they're able to at least understand the language that somebody else is using when they're talking to them about what they can do, and they can turn around and talk back in a sufficiently general language that the other people in the group can understand what they do.

And it's never the case that you'll become so good at somebody else's speciality that you can replace them on the team. That's impossible, and in fact, you don't want anybody to do that. You want people who are so good at what they do that they're the best in their field. But you also want them to be able to crosstalk with you and to be able to explain what they do in your terms and understand what you say when you're talking about what you're doing.

And those turn out to be very special people. They are not a dime a dozen, and I've put together now something close to five or six teams like that for

different types of problems, and when I say that they're special kinds of people, I mean that. You cannot find these people easily, and part of the way you find them is by a talk like this, and somebody in the audience who is really good at what they do comes up and says that's really cool, I think I could solve this problem for you by doing that, or you should look into this aspect of my field, because I think there's an answer there for this problem that you have. So you find people like that.

Of course, it's most likely you're going to find them in your home area, but a lot of times, the people that are experts in certain areas- your university, no matter what it is, is never going to be the best in all areas, and so a lot of times we have to go to other universities. The people that are involved in this project come from Wake Forest University, the University of Kentucky; they come from a university in Hong Kong, two or three other places where they happen to have- they happen to be the best people in their area. And so it's critical now for these kinds of problems - and these- by these kinds of problems, I mean the large problems of societal interest, the big problems - it's really key that you have people that are the best at what they do but also capable of talking to you and talking to others.

LAURIE WILSON: [Inaudible]. Thank you.

QUESTION: I'm very interested…

LAURIE WILSON: [Interrupts] First you can identify yourself. That'd be good.

QUESTION: Oh. Sarah, from ANU. I just had a question. I'm very interested in the way you microstimulate the output of the hippocampal neurons. Do you have multiple electrodes and you stimulate them at different times? How local is that stimulation? Already(*) you've done optogenetics to selectively activate one area or different neurons. Thank you.

THEODORE BERGER: Yeah, no, it's a very, very… very good question you're asking about issues that are really key. Part of what I think she's referring to is that we can- we know when we record the electrical activity of neurons, we know that we can record from single cells, and that's important for finding out what these population codes are like. You want to be able to find out what individual cells do. But when we turn around and want to electrically stimulate parts of the brain with the long term memory code that we've worked so hard to get, you cannot electrically stimulate individual cells. You'd like to be able to record from individual cells and then go back and electrically stimulate individual cells, but you can't do that. With the techniques that we have today you can't do that.

So what we hope is that if we have 20, 40, 50 electrodes, we hope that the majority of those, when we stimulate, that the electrical stimulation will primarily activate the cells of interest. In other words, the ones at the output, when we record from those, we know what the output code is so that's the one we want to reproduce, so when we go to stimulate those cells, we hope that we're stimulating those individual cells to reproduce that code. And to a certain extent,

we're going to be wrong. The current is going to spread to more than a single cell. We're going to be stimulating more than a single cell. We're recording from individual cells, but we're stimulating more than individual cells. That's a problem.

So we have to hope that our electrical stimulation is restricted primarily to one cell or at least to a small population of cells, and to the extent that things work, then that must be what's happening. It may be that it's not happening as much as we'd like it to, but it works, so I'll take it. Even if I don't understand everything that we're doing, I'll still take it. But there's- you're identifying a key problem, is that our ability to record is very- our ability to look at how the brain works is extremely fine, and we can identify it with respective individual neurons. But our ability to manipulate the brain is not as fine. We lose the capability of very local control, and you mentioned optogenetics, and that's one of the ways that we can potentially solve that problem. So we're looking into that.

LAURIE WILSON: Question in the middle now.

QUESTION: Hello. David Grayden from the University of Melbourne School of Engineering. My question has got two components: one is electronic and one is wet. So I do research in bionic ear, bionic eye, and in those areas, especially the bionic ear, there's 16 to 22 electrodes which stimulate 3000- where 3000 nerve fibres used to be in [indistinct] cells. And that works fairly well for speech, which has a lot of redundancy in it, but for music, it's completely hopeless. And similarly for the

bionic eye, we can- 60 electrodes in a device, that can give people some rudimentary vision. But to recognise faces, we really need to break that barrier and get to the 1000 or so. So within what you're wanting to do, what technological advances do you think are needed to get that fine spatiotemporal code that you're looking for, to be able to move, say, beyond the nine positions of a grid that the monkeys do to recognising faces or storing faces and so on? So that's the dry part.

On the wet side, the reason the cochlear implant works so well is because of the brain's plasticity itself can adapt to that really crude signal. Do you believe that the higher levels of the brain may have the plasticity also to adapt to the cruder signal that you can produce?

THEODORE BERGER: Yeah, very good- very good questions. So let me answer the second one first. There's no question about the fact that the higher centres of the brains have the plasticity- have the capability for plasticity and it- and we know how to induce it. There's actually a lot of control that we know a lot about the biochemical mechanisms that are the basis for that plasticity. So we can play with it and we can manipulate it and we can work with it, but how exactly- what we need to do and how we need to play with it is another matter. It's going to take a long time to figure that out. I don't know exactly what's going- how that's going to work. In other words, to what extent can we- the general issue here is that if you stimulate some cells, if you stimulate with a particular pattern, you get a particular response.

If you stimulate them with the same pattern 200 times, you get 200 versions of the same response.

But in a lot of- when we're talking about plasticity, that means that in fact if you stimulate with a particular pattern, you don't get the same output. You get a different pattern, and the brain has the capability to respond differently to a history of activation, and in fact the hippocampus is one of the most plastic areas of the brain. It's really easy to stimulate hippocampal neurons and synapses with patterns that produce different responses from hippocampal cells. So one of the things that we need to understand is that the kind of stimulation that we're using may be causing plasticity, and that's either good or bad, I don't know, but we certainly want to know it. We want to know whether or not we're causing plasticity with the stimulation that we're using.

We do have some evidence that we are producing that kind of stimulation; that over the course of weeks, that the stimulation that we're inducing does cause changes. I'm not sure- we haven't done that enough, and we haven't worked with it enough to be able to quantify it in any reasonable way or for me to talk about it intelligently, but it is there, and the point you're raising is really important. Any time you're talking about stimulation, you better know how stable the response is or how different the response is.

So I think… and we may be able to use that to our advantage, I think that's one of the issues that I'm sure you're thinking about is how is it that we can use the

plasticity of some of these higher areas to actually use it to our advantage. And we'll just have to see. This is one of those areas where there's just a lot of work to do, and it's really interesting, and it's really important, and we haven't even yet opened the door to that.

LAURIE WILSON: Let me ask you just a final question, so in conclusion, an article that I read where you were quoted you're talking about… you talked about a lot of the work- well some of the work anyway that neuroscientists do, and you said they will find a result, but in effect what they're doing is only describing what they've found, not explaining it. So, you know, how do you- and I think it's fairly obvious what you mean, but the significance- it seemed to me what you're saying is you're saying, well not actually saying, you know, why is it significant? You found a result, but what does that mean? So… how important is that from a scientific perspective that you should always be looking that step further to say ultimately this result actually means something?

THEODORE BERGER: Yeah well I think it's critical. It's very easy to describe what you've done, and put out a paper. You know I did A, B, and C, and I got these answers and I filled out a table, and that's what it looks like. I mean that's… you almost wonder whether it's worth doing if that's all you're going to do with it. I mean there has to be an interpretational phase to what you do, and you want to recreate different contexts for considering your result. Not only do you want to interpret it, but you interpret it within different contexts so that the reader can be able to put your result into different frameworks, and so that your result may actually influence what other

people do. And it's important not to be afraid to do that. And I think that when we see cases where scientists are producing results and just describing it, like I said, you wonder why they even bothered. There's nothing to fear about suggesting what the result means.

It's very important to describe exactly what you've done, because that's the part that anybody can take away, but then it's important to interpret what it is that you've done, and make suggestions as to what it means, and how it influences how other people may think about how the nervous system works. If you don't do that you've wasted a lot of time, and a lot of times- I mean there are two reasons why people may not do it, one is they may not be able to think about those things, in which case they should find another career. But the… it also is the case sometimes that people are afraid to interpret their results in certain ways because of political concerns. You know you don't want to offend this person or that person, and that's ridiculous. I mean again if you don't have enough guts to do it you should find another career. But it's important to exercise the various possibilities of what your results mean and put those out there for other people to think about and consider.

LAURIE WILSON: Right, I might just ask everyone to welcome Professor Anne Kelso, Chief Executive of the National Health and Medical Research Council at this stage, we're going to thank you for your contribution in a moment, but please welcome Anne Kelso.

[Applause]

ANNE KELSO: Well thank you very much, and congratulations to ASMR for their selection of the ASMR medallist for 2016, Professor Ted Berger has given us the most extraordinary talk. And ASMR does a wonderful job every year, and I know most people in the room, perhaps everyone here knows that. ASMR is an immensely important part of our medical research sector, promoting medical research in the community and supporting medical researchers in all sorts of ways. And I think this medical research week is the highlight of the year for many people, and a time when everybody can celebrate what ASMR does, as well as have the opportunity to hear each year from an absolutely brilliant speaker. So each year we have the chance to be taken right outside our own field into something new, exciting, always at the leading edge, and often with a lot of other messages for scientists and researchers as well.

So thank you very much to Professor Ted Berger for a most inspiring and visionary talk. In this low key way you have given us the most extraordinary insight into an important frontier. And I'm really struck in thinking about first of all the most basic thing that this understanding of neurobiology, down to the level of electrical signals and populations of cells, can give us so much insight into something that is an important part of our experience of being human, and that is long term memory, identity, functionality in the world that depends so much on this rather magical function.

Now I'm an immunologist and we talk about long term memory in immunology, but that's a very different phenomenon from the long term memory that we've been hearing about tonight. And perhaps if I was starting my career again I'd be starting in neurobiology instead of immunology and tackling that next level of incredibly complex problems. But I think the other thing that has been most extraordinary tonight is to… get an insight into the vision of this man's research and that is absolutely inspiring. I mean to have this crazy idea, I know you don't think it's crazy, but I can appreciate that many people thought what an amazing leap of thinking to imagine that one can go from the neurobiology, from the electrical signals, the mapping of behaviours of populations of cells, to the idea of a neural prosthesis where you might actually be able to repair and replace those functions, not only in simple animal models, and of course mammalian animal models aren't simple, but even to imagine that one can do that for human beings.

So I think the progress that's being made here is truly inspiring, and I'm very struck that this is a whole new frontier for us in thinking about where neuroscience can now take us. But of course you've given us a lot more than that tonight, because you've told us something about the courage that it takes to have a big idea and to pursue it, the resilience, the self belief that scientists need to be able to pursue their ideas in the face of the people who say that's a crazy idea and of course it's not possible. And the… also your insights into specialisation versus generalisation, the importance of being able to pull together the right people around you who have these specialist skills that

enable you to do something that obviously the individual can't do on their own. So you've told us a lot about how to do brilliant, inspiring, and visionary science. So it's my very great pleasure to present you with this box, and this medal, and I believe I have the opportunity, if I know how to pull this out, to do something I've never done before…

LAURIE WILSON: There's always a first.

[Applause].

ANNE KELSO: [Indistinct]

THEODORE BERGER: Thank you very much, I'm really pleased.

ANNE KELSO: [Indistinct] Almost as bad as having a glass of wine in your hand.

[Laughter]

THEODORE BERGER: Only thing worse is having a beer in your hand. Anyway…

ANNE KELSO: Thank you, thank you again.

THEODORE BERGER: Thank you very much, thank you.

LAURIE WILSON: [Laughing] Thank you very much Anne. Well I… it's all very well to say it's almost as bad as having a glass of wine in your hand, but not if you're that well known

local wine maker Professor Brian Schmidt, who certainly like a glass of wine, who of course- who we pinched from the US. He's one of the people along with Ian Frazer, in terms of scientists, I mean there's lots of politicians in here but you can jump over those. Ian Frazer, Peter Doherty, even Professor Francois Barre-Sinousi is in here, who was involved in AIDS research. This is a copy of *Stand and Deliver* which I'd like to present to you, it's our 50th anniversary book…

THEODORE BERGER: Wow, okay.

LAURIE WILSON: So some of our more important speakers, and more to the point some of the stories behind the speeches as well, not just the speeches themselves.

THEODORE BERGER: Okay, thank you.

LAURIE WILSON: So I'd like to on behalf of the National Press Club, to go along with the medal, it's not nearly as important as the medal, but nonetheless a little bed time reading, that's appreciated. And also I'd like to give you membership, as a guest speaker, of the National Press Club of Australia. You mentioned earlier to me that you really like Australia, even though you broke your- actually you broke your foot in New Zealand, so you can't blame us for that.

[Laughter]

But you know if you're ever back in Canberra this will get you- this gets you into the car park, that's very important.

[Laughter]

But more importantly we do have a lot of affiliations with the press clubs and foreign correspondents clubs around the world.

THEODORE BERGER: That's great.

LAURIE WILSON: So I'd like to induct you, if you're prepared to accept the membership.

THEODORE BERGER: Absolutely.

LAURIE WILSON: Ted Berger, thank you very much, and congratulations.

THEODORE BERGER: This is wonderful.

LAURIE WILSON: Good. Time now for a… oh look I should say again I'd just like to thank the ASMR and Sarah, Dr Sarah Meachem particularly for… I think she… this is her… she moves on as President later in the year, so I thank you very much for your support, and obviously for the society. As I said at the outset we very much appreciate our involvement in this event over the years.

* * END * *

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