BRAIN SCIENCE PODCAST

With Ginger Campbell, MD

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Interview with Miguel Nicolelis, MD, PhD, Author of *Beyond Boundaries: The New Neuroscience of Connecting Brains with Machines—and How It Will Change Our Lives*

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INTRODUCTION

Welcome to the *Brain Science Podcast*. I'm your host, Dr. Ginger Campbell, and this is Episode 79. Today's podcast is an interview with Dr. Miguel Nicolelis, author of *Beyond Boundaries: The New Neuroscience of Connecting Brains with Machines—and How It Will Change Our Lives*. Last month I presented an overview of the key ideas in *Beyond Boundaries*, but I'm very happy to be able to discuss these ideas in more detail with Dr. Nicolelis.

I want to get right into the interview, but I do want to mention two things. First, this interview stands alone, so don't worry if you haven't listened to Episode 78. Also, I want to remind you that detailed show notes and free episode transcripts are available for all episodes of the *Brain Science Podcast* at brainsciencepodcast.com. You can send me feedback at docartemis@gmail.com.

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INTERVIEW

Dr. Campbell: Miguel, I want to thank you for taking the time to talk with me, and welcome you to the *Brain Science Podcast*.

Dr. Nicolelis: Thank you very much for the invitation. It is a great pleasure.

Dr. Campbell: You're welcome. Could you start out, Miguel, by telling us a little bit about your background? I'm curious about where you're from, and how it is that you came to go from medical school to a career in research.

Dr. Nicolelis: I'm originally from Brazil. I was born in São Paulo, the largest city in Brazil, and went to school there; first to medical school at the University of São Paulo, and then I got my PhD in general physiology at the same university. And in 1988 I came to the United States to do my postdoctoral work in the laboratory of John Chapin, at Hahnemann University then, in Philadelphia. And that's where I started developing the original ideas that led to the work we do today.

Dr. Campbell: Because of the coverage of the mainstream media, I know that many of my listeners are going to be familiar with your lab's work—especially the work that shows the monkey controlling the robot arm with its brain, because that's gotten a lot of press. But I'm most interested in learning what your experiments reveal about how our brains work. What do your experiments tell us about how our brains make us who we are?

Dr. Nicolelis: Yes. Actually that's, in my opinion, too, the most relevant contribution. Because when I started, back in the mid '80s, as a graduate student, we were still living this love affair with the single neuron in neuroscience. We thought, at that point, that by knowing everything we could about a single cell—what we call a 'neuron'—we would basically understand the basis of behavior, and the whole business of the brain: that is, to generate these models of reality in our interaction with what we call 'reality'—the statistics of the external world—as well as define what we call our 'sense of self.'

But at that point—the late '80s—I started getting interested in understanding how populations of neurons interact. And I was influenced heavily by my mentor, Dr. Cesar Timo-Iaria, who got me into neuroscience. I was actually working in applications of computer science in medicine when I was a medical student, studying—believe it or not—patterns of hospital infection, and how bacteria exchange DNA and get multi-resistant profiles against antibiotics.

But then I met Dr. Cesar, and I started actually thinking—given the subjects that he introduced to me—that the whole issue of neuroscience had been framed on the wrong premise; and that, in fact, a single neuron would not be more than a single vote in an election. Although, in Florida, a single vote may count, in general elections it doesn't count by itself; it's the whole that matters. And I started wondering why neuroscientists had not—at that time, in the mid '80s—tried to look at how populations of single neurons interacting with one another produce the business of the brain.

And that's when I learned that this was a major technical hurdle. And lo and behold, I found the only other person in the world at that time that was really thinking alike—John Chapin, here in the US—and I moved here 22 years ago to try to, first, develop the technology that could allow us to measure how large populations of neurons interact, and from that point on, try to ask exactly the question that you posed: how are the populations of neurons working in circuits capable of generating the entire range of behaviors, and the entire illusion of our self?

Dr. Campbell: Can you talk a little bit about why the earlier work seemed to support the idea that you are really basically challenging—especially the idea of the single neurons—where it's at? You sort of alluded to the fact that it was related to technical difficulties. So, how did that affect the data that was generated?

Dr. Nicolelis: Well, from the late '20s until the mid '80s, we only had developed technologies that allowed us to listen to the electrical firing of a single neuron, one at a time. Most of the theories that were framed during that period—and until this day, actually—were centered on what we could measure. Since we could only measure one neuron firing at a time, most of the theories took that as the frame of reference; and they started building assumptions that individual neurons could carry or sustain behaviors. And it was pretty difficult. The technology needed to move from 1, let's say to 10 neurons recorded simultaneously. It took us awhile; it took almost 50 years.

But the moment we started looking at that—the moment we gained the ability to record the electrical signals of 10s of neurons that belonged to a particular circuit, we started realizing the system was much more dynamic, and information was coded in a much more distributed way than we had thought before. And now, as we are approaching the capability of recording 1,000 neurons simultaneously, I think neuroscience is up for a total revamp of its classical theories.

We can show now that functions are not localized in a single area of the brain—particularly in the cortex—that there is a whole different gestalt to how these things get processed, and how information is processed in the brain. So, behaviors are the result of the collaboration of widely distributed activity through many cortical and supercortical structures and loops.

And we actually can see the limits of plasticity (that you have mentioned in several shows before as one of the key foundations of this new neuroscience that is emerging): the fact that the brain is never stable, but is continuously learning and adapting itself to new events, changes in our body, internal and external changes, and also changes in the environment; that plasticity doesn't limit itself to the physical limits of the body; that actually our brains are capable of assimilating any tools—artificial instruments—that we build, as an extension of our sense of self.

We actually are becoming an expression of the type of technology that we create. So, our brains not only create this technology, but they make it sure that whatever works—whatever tool that is capable of augmenting our reach—becomes assimilated as an extension of the internal brain model of our self.

Dr. Campbell: Like when we watch kids texting on their phones at a mile a minute, those of us who are older, we are able to incorporate texting, but not quite with the fluidity that they do.

Dr. Nicolelis: Yes. But any tool you use—your car, your computer, your laptop, the mouse to handle your computer, a racquet to play tennis, a violin, a piano, silverware to eat with—anything we use, the theory goes now, we become proficient users of tools and proficient tool-makers at the same time, because our brain is intrinsically involved, not only with creating these tools, but also making sure that they can be readily assimilated by our brains.

Dr. Campbell: I think in the interview I heard on *Triangulation*, you made a comment—and it's in your book—about how we can be no longer limited by our physical body and brain in our head. And I didn't totally get that until I started thinking of it—like you just said—in terms of how we change our maps. Is that really the basis of that idea?

Dr. Nicolelis: Yes. The moment you are able to now get the electrical signals from the brain and use them to control the movements of an artifact—an artificial tool; let's say, a robotic arm that is located on the other side of the planet; or for that matter, on another planet, on the surface of Mars—the moment you are able to send your brain activity to make that object move according to your voluntary will, and more recently, as we demonstrated a couple months ago, you are now capable of receiving feedback—sensory information—from that device back to your brain, and feel what that device is doing, that's what I mean by going beyond the physical limits imposed by our biological body.

Our brain is liberating itself, now. And it already had done that in indirect ways—language was one way; printing was another way—so we can leave a legacy of our mental exercises to other generations, by leaving records of our ideas. That's one way to go beyond the limits of the physical body. But what I'm talking about now is even more far-reaching, because you now can do that in real time.

With this technology, in the next few decades we will be able to operate our voluntary motor will and to receive, to interpret signals that come from devices that are far removed from our bodies—and, quite frankly, could work in any kind of environment—from a nano environment to, as I said, the surface of a different planet.

Dr. Campbell: It sounds kind of like a William Gibson novel.

Dr. Nicolelis: Yes. As I said in a conversation I had in a meeting a couple of weeks ago, science fiction writers need to work harder now, because we are getting close to them now.

Dr. Campbell: I want to talk some more about the implications of your work, but I want to go back to the technical parts for just a minute. When I was in medical school, and when you were in medical school, we were at that stage of the single cell recordings; and, as I recall, really when they first did those single cell recordings, if you weren't working with something with huge neurons, like the *Aplysia*, which neuron you recorded from was somewhat random, wasn't it?

Dr. Nicolelis: Yes. It still is, with extracellular recordings. When you put these electrodes in the brain, you really do not choose, for the most part, which cells you are going to sample. But the beauty is, as I describe in the book, that to our shock, when we started implanting these multielectrode arrays and sampling, almost randomly, the cells that we were recording in a piece of cortex, yet we could get the information we needed to make, let's say a robot arm move according to the desire of the subject.

And then, we moved the electrode in another animal in a slightly different position (and, of course, we are never going to sample the same cells in different animals, because it is impossible), yet, if you had the same mass of neurons—let's say 300 neurons recorded simultaneously—you would get the same amount of information. The information was proportional to the mass of neurons that you could sample. And that was a big shock again, for us.

As you mentioned in a previous broadcast, the difficulties involved many steps. First of all, the original electrodes were rigid—metal electrodes are very rigid—and with a single recording spot at the tip. There was a thin tip, so you could actually penetrate in the tissue and record from the extracellular space. Or if you wanted it intracellularly, to actually be able to sample the activity of hundreds of cells, we had to change this configuration and create more flexible microfilaments that could be implanted and left in the brain, so you could record this for months or years, depending on the species that you worked with.

So, from that simple technology advance—that actually took almost three decades—the whole approach of looking at the brain changed. And, now, our theories are changing accordingly. We actually can see a brain in action now, with much better spatial and temporal resolution, and actually looking at the process of generating a behavior in a more natural way.

Dr. Campbell: Because before, the only recordings they made were when the animals were asleep; since, if they moved, the electrodes would have moved, and quit working—or broke off.

Dr. Nicolelis: Yes. For the most part, most of the literature was done in anesthetized animals. And even when you had awake animals, the animals were heavily restrained. We published an article 10 years ago, where we showed the differences between the same stimulus—the same physical stimulus, mechanical stimulus— being delivered under anesthesia, in an animal that was awake but restrained, and in a freely behaving animal.

And the changes in how the brain responded to the same physical stimulus were stunning—suggesting that most of what defined the mainstream theories of neuroscience that we know, that have resulted in many Nobel laureates, are actually valid for a particular state; and that's the anesthetized state. But when you let the animal wake up and engage itself with the environment, the brain changes dramatically, in a way that it responds to what comes from the environment and what the animal wants to do.

Dr. Campbell: I found that really fascinating, because in past podcasts I've spent a lot of time talking about the importance of the interaction of the embodied animal with its environment. And that certainly goes along with that.

When you first did those early experiments, you were working with rats. Is that correct?

Dr. Nicolelis: Yes.

Dr. Campbell: That's how you developed the electrodes, and the basic principles?

Dr. Nicolelis: Yes.

Dr. Campbell: What was the most surprising thing you discovered doing that? I know there were lots of surprises!

Dr. Nicolelis: Yes, in 25 years, we have seen a lot of stuff here in the lab. But the first thing was this: how dynamic this system is. Again, another thing that you mentioned: the classical concept of the receptive field. I'm a somatosensory physiologist by training; I'm specialized in touch. And for us, until the mid '80s, the 'receptive field'—this concept—was defined as the spatial area from which a stimulus, when applied, will drive a particular neuron to fire.

There was no time in this concept; it was just a spatial location in the skin that, if you apply a mechanical stimulus, a neuron somewhere in the system (it applies to neurons at all levels of the somatosensory system, the concept of receptive fields) that neuron will fire if a mechanical stimulus is delivered to a particular patch of skin. Well, when we started this work, we started doing that, but we allowed time to become part of the experiments.

So, we'd look at how the receptive fields vary as a function of post-stimulus time—in a millisecond scale. And we used, in a very conservative way, steps of 10 milliseconds after the stimulus was delivered to the skin, to see how the response of the neuron varied around that spatial domain. And we saw that the spatial domain varied dramatically as a function of time; it was never the same spot, if you fractioned the response of this neuron using both space and time. So, we realized that receptive fields could not be defined only on spatial coordinates. The receptive field is a spatial-temporal construct; is a probabilistic construct.

So, that starts changing everything, because then, you go one step up, and you talk about the maps that we all talk about—the homunculus that exists in many areas of the brain. And lo and behold, we did the same experiments, and the map was not static at all. We never saw the homunculus—the way you see in these pictures in textbooks—if you have a behaving animal that is engaged in doing something meaningful.

This was the beginning. John Chapin and I realized that lots of stuff would change. And 20 years later, I think we are about to have a major change in these concepts in mainstream neuroscience.

Dr. Campbell: When you decided to move from working with rats to working with monkeys, was that move motivated by a need to get people to pay attention to the results that you already had, or because you wanted to find out things you couldn't find out while working with a rat?

Dr. Nicolelis: We thought that we had to move to monkeys to make sure that these principles that we were observing in rodents were valid; and that our new theory of how the brain works actually could be validated in a modern experimental model that was closer to humans, and was accepted to be the closest we could get to the human brain. We thought, really, that without that validation, the ideas we had—and we published many studies in rats; and we continue to publish—that something would be missing there. Someone could always raise the objection that, *Oh, OK, that may be true in rats—in lower mammals—but in primates it's different.*

We were almost sure that that was not the case, but we had to validate it. And it turns out that, not only we validated everything we saw in rats, but we were able to go a step beyond when we designed this paradigm that we call 'brain-machine interface.' Because then, using the motor system, not the somatosensory system, we could actually measure very precisely the type of behavior that the animal was producing, or was intending to produce. And in that sense, when we established this possibility of linking brains and machines, and showed that robotic devices, or even virtual devices could be controlled by the brain activity of these animals without any movement of the animal's own body, that allowed us to test all sorts of conceptions.

The original motivation of all this work was to demonstrate an alternative view of the brain. So, it was a basic science question. It was only recently that we realized that all these ideas, once we had demonstrated them, had a tremendous clinical application potential in many disorders. Because once you change the way you see the brain, and your theories on how the brain works, you actually can start proposing a completely new array of therapies to treat neurological disorders; that have never been thought before, because all these therapies were based on the classical dogma of single neuron physiology and localization neuroscience.

Dr. Campbell: Yes. I think it's fair to say that the new ideas you're proposing have as much of a potential for revolutionizing medicine as the discovery of plasticity. Don't you?

Dr. Nicolelis: Yes. You know, Jon Kaas and Mike Merzenich—good friends of mine— in '83 published the classical cortical plasticity paper that started the revolution. There were a few reports before, but this series of papers in '83[1], that Jon Kaas and Mike Merzenich got, is a mega watershed event for neuroscience, in my opinion. And I think what we have been doing lately goes really in that direction—as I have talked to Jon Kaas many times about it—by showing the

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[1] Merzenich, Michael, Jon Kaas, et al. "Progression of change following a median nerve section in the cortical representation of the hand areas 3b and 1 in adult owl and squirrel monkeys." *Neuroscience* 10, No. 3 (1983): 639-65.

Merzenich, Michael, Jon Kaas, et al. "Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation." *Neuroscience* 8, No. 1 (1983): 33-35.

limits of plasticity are not really curbed by our physical body. Our brain has evolved capabilities to incorporate new models of self and new models of interacting with machines that we didn't expect in '83, but actually, in my opinion, form a continuation of the revolution that the discovery of cortical plasticity, and brain plasticity, in general, made.

Dr. Campbell: For the sake of somebody who might be listening who is not familiar with any of these experiments, perhaps you could pick one of your favorites and just take us through it, and show how that demonstrates what we've been talking about. Would you mind doing that?

Dr. Nicolelis: Sure. You mean one of the brain-machine interface experiments?

Dr. Campbell: Yes.

Dr. Nicolelis: Oh, OK. One of my favorites (although, of course, the experiments with Aurora started everything, in the sense of showing the complete concept) is the experiment we did three years ago with monkeys that were trained, here at Duke, to walk on treadmills upright—a bipedal locomotion pattern—and, as they're walking, we are recording the brain activity from multiple cortical areas, and actually from the electrical signals alone, predicting the steps—the locomotion pattern that the animal was instructed to produce.

So, that was the first step. At that point, in collaboration with my good friend, Gordon Cheng—who was in Japan at that time, at ATR Laboratories in Kyoto—we tested the notion whether we could send these signals, that we knew we could use to predict the locomotion patterns of the monkey, all the way to Japan, in real time, and make his latest humanoid robot, CB-1, actually walk under the control of the brain of the primate here at Duke. And that's exactly what we did. Gordon designed a phenomenal Internet connection that could circumnavigate all the firewalls around the world that we have to go through, got the signals to Kyoto, and made CB-1 walk under the command of the primate brain that was walking here at Duke.

At the same time, he was also able to get visual images to be sent back to Duke from Kyoto, so we could project these images in front of our monkeys. And so, the monkey would be in the room, walking and looking straight ahead, and actually facing the back of the robot and seeing the legs moving. The monkeys were rewarded every time the robot made a step that was correct. By doing that, we were able to actually turn off the treadmill here in the United States, so the monkey didn't need to walk anymore, but he could still send the brain activity to make the robot walk. And they actually continued to do that as long as they were rewarded for that task.

In that sense, we actually established this brain-machine interface, and made a robot walk. And the step of the robot was about 20 milliseconds faster than the step that the monkey's body was making, following the same electrical command coming from the brain. In other words, the electrical signal generated by the monkey's brain was able to make the robot move a little faster than the time it took for the brain activity to leave the monkey's brain and reach the animal's leg muscles. So, that was when we realized that, not only we could scale space—meaning we could get these signals out of the brain, and make an artificial body across the planet move; a body that was much bigger, and capable of producing much bigger forces than this little monkey's body—but we could also scale time. We could enact this behavior faster than the biological machinery could do.

I think this experiment is emblematic—in my opinion. It shows the potential of all these ideas. Because, at the same time as we recorded the brain activity of these monkeys as they were doing these tasks—as we did with other monkeys controlling upper limbs, and more recently, controlling whole bodies or virtual bodies— we noticed that brain cells in different areas of these animals' cortexes were changing their firing patterns to actually assimilate the robotic components that the brain was starting to control. So, the allegiance of these neurons could very quickly be shifted from only firing in relation to the monkey's own body's movement, to the movements of a robotic arm or a robotic leg.

And that's when we realized that we were dealing with a completely different view of the brain. I think at that time, in 2007, I made the conscious decision that we had stumbled into a completely new framework. And that had to be disclosed, and the old dogma had to be challenged frontally; because, as you know, it is not easy to defeat a classical dogma in science. It's one of the most difficult things. It may take a generation for you to just be able to do that. But at that point I think we all made the decision that it was clear that we could not keep all this under the rug. The old theory had to go.

Dr. Campbell: And this result, as amazing as it is, has really been reproduced. In your book you described an experiment with a rat, and another experiment with a monkey, which had a similar result, in the sense that you had neurons that would fire only when the robot arm, or whatever, was moving, some that fired when both the monkey's arm and the robot arm was moving, or just when the arm moves—and in the case of the rat, the paw pushing on the lever. So, this is a reproducible result.

Dr. Nicolelis: Oh, absolutely. Other groups have reproduced it, too.

Dr. Campbell: It's really amazing to me that the animals don't even have to use the joystick; they somehow figure out how to use just their brain. Have you been able to get people to do this?

Dr. Nicolelis: Yes. We did. We already published a study in 2004, with 11 patients that were neurosurgical patients. These patients had to undergo a neurosurgical procedure for treating Parkinson's disease at that time—they were receiving an implant to perform a procedure called 'deep brain stimulation'. Since we had invented an electrode that helped these surgeries—to decrease the time of the surgeries—we got permission from the patients, and from the institutional oversight groups here at Duke, to basically record brain activity with the same probe. I actually asked the patients to play a videogame that was very similar to the one that we used originally with our first primate studies. And the patients did that.

And now we have a total of 42 patients studied during surgical procedures. And we actually can do the same thing. Some reports from clinical studies have shown that the patients can do the same thing. In fact, in our latest intraoperative recordings we have seen that patients can learn the task without even doing movements. They can just learn visualizing what is the objective of the task; and they can imagine trajectories of this artificial device—be that a cursor in a computer, or a robotic device—without even moving their own bodies to train: which gives us hope that someone that is paralyzed, in the future may actually be able to get trained on tasks like that, and to control robotic devices, even though they cannot move their own bodies. So, you're literally training the brain directly.

Dr. Campbell: The electrodes that you developed to do your work, are they the same electrodes that are used for those deep brain stimulation electrodes that Parkinson's patients have?

Dr. Nicolelis: No, they're different.

Dr. Campbell: But the technology that was developed to make your work possible is similar?

Dr. Nicolelis: Well, no; the technology is also different. Our technology is based on flexible metal filaments that are covered with a particular isolating material. And now, we actually can use these same electrodes for both recording and stimulating. This latest paper that we published in *Nature* about a month ago, we actually designed a way to use the same electrodes to both record and stimulate. The result has been very, very good; to the point where we are expanding the density of elements in our, what we call now 'cubes'—because they're now three-dimensional.

Because our goal is in the next three to five years to be able to record up to 10,000 neurons simultaneously. We are getting close to 1,000 now; but going from a 2D design to a 3D design, I think we will be able to get one order of magnitude more neurons recorded. You know, we're in the third generation of this technology, and now it's becoming really ready for the Holy Grail, that is to be able to apply this in clinical studies.

Dr. Campbell: And we need a lot of electrodes in order to get enough resolution?

Dr. Nicolelis: Yes. As we discussed in the beginning, what counts here is the mass of neurons. The mass of neurons is proportional to the amount of information that you get out of the system. We estimate that to barely control a whole body exoskeleton—that's our objective—you will need a mass of neurons in the order of 10,000 cells.

Dr. Campbell: We're going to take a quick break, and we'll be right back.

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Dr. Campbell: Miguel, we've been talking about some of your experiments; and there was one question that I can't figure out where to fit it in, so I'm just going to throw it out now. Your work means that there's no such thing as 'grandmother cells?'

Dr. Nicolelis: No, they don't exist. They also are a construct of our own minds trying to explain what we see. And, as you can relate now, they emerge because of, as I said, this love affair with the single neuron. Since we could only record single neurons, they now suddenly discovered that there were neurons responding to faces. They said, *Ah ha! I know what it is; a single neuron codes for a face*. And that's where the 'grandmother neuron' comes from. But that theory doesn't resist a simple theoretical experiment of killing (I'm sorry) grandma in the brain. So, if that cell dies, would you not recognize your grandmother's face anymore? And that's not true. We know that we lose neurons all the time, as adults. You may lose that little cell that responds to a face, and you're still going to recognize the face of your grandmother. Thank heavens! Right?

And that's because it does not depend on a single cell; it depends on a circuit. And it doesn't even depend on a circuit only in the inferior temporal lobe, as lots of people like to say. You have cells responding to complex images like that all over—in supercortical structures, too. So, not even that is real. And besides, people cannot tell what these cells respond to, because they simply don't know the parameter space. They have tested grandmother faces, or Bill Clinton's face, or Hollywood actresses' faces; but they haven't tested other stimuli, because they simply don't know. So, these cells may respond to all sorts of other stuff that we simply don't test for.

Dr. Campbell: Right. And that's what your work seems to indicate that we should expect to happen.

Dr. Nicolelis: Right. And actually I can tell you that (this morning we were just discussing this) this is not only true for a primate brain; not even for a mammal brain. People that work in worms, in invertebrates, have seen the same principles. They have seen that networks of neurons can perform multiple tasks, and no single neuron is attached or assigned to only a single task. And it could not be. Imagine if you were a little animal with 600 neurons available; if you only attach one neuron to a given function, you're gone.

Dr. Campbell: Yes. So, we didn't emphasize that principle before, but you just brought it up: the fact that any neuron can be part of more than one ensemble of neurons—and more than one at a time. Right?

Dr. Nicolelis: Yes. And there was a principle that was proposed—I think in its original version—way back, by Donald Hebb in the '40s. But, of course, it was a theory; it was merely speculation, because nobody could measure that. Gerry Edelman talked about that, too, when he compared ensembles of neurons to the kind of genetic code that we have to encode amino acids with different sequences —triads of nucleotides. He called it the 'degeneracy principle.' But that, again—it had never been measured. So, in the last 10, 15 years, studies in invertebrates and vertebrates, mammals, primates have pretty much found the same thing. But it was never enunciated as a principle. And I think that that's what, in the last 10 years, the results that we got here in the lab have allowed us—because we look at mice, rats, owl monkeys, rhesus monkeys, and more recently, intraoperative recordings. And so, there is no doubt for me that that is a universal principle of brain networks.

Dr. Campbell: The next thing I'd like to talk about is the role of feedback. You mentioned just briefly, before the break, that you're starting to actually provide the feedback signals directly to the brain. So, that would be brain-machine-brain interface. Right?

Dr. Nicolelis: Yes.

Dr. Campbell: Would you talk a little bit about the feedback signals, and the challenges?

Dr. Nicolelis: Yes. That was a major challenge, as you can imagine; because to reproduce any motor behavior truly, from locomotion to grasping objects, you need to provide to the subject, feedback. You need to provide sensory feedback—tactile, proprioceptive feedback. And all the major experiments that have been done in the last 12 years until now, on brain-machine interfaces, contemplated mainly using visual feedback to instruct the subject on what was going on. And visual feedback is very important, but it cannot, by itself, allow people to judge how much force they're applying to an object when they're grasping that object, or what are the details of the terrain when they're walking autonomously.

So, that was a challenge that eluded the community for several years—for the last five or six years people have been trying pretty hard to do that. So, what we decided to do was to actually use the brain, directly, as our delivery target. So, we got these artificial devices—in this particular case, a virtual arm, that the animal learned to control by using its brain activity—to send back to the brain directly, using a technique called electrical microstimulation, an electrical message that was created artificially to encode, or to describe the tactile features of the objects that this animal was exploring with a virtual arm.

And what we learned, to our surprise, was that if the pattern is delivered under certain conditions, the brain can really readily learn, in just a few sessions, how to handle this new artificial message—that we call an 'artificial touch,' now. It's almost like creating a sixth sense. So, we open a direct communication between that visual arm and the brain, without using the skin, without using vision, or anything, but just an electrical message delivered directly to the brain. And the brain basically learned the statistics of that code, and in a couple weeks, was able to give meaning to what that message was, and basically interpret the texture of the objects that we presented to the animal through that new sixth sense.

So, that opens a total new avenue for research, because it suggests that we could actually augment the perceptual capabilities of the brain by encoding all sorts of physical energies that we normally do not perceive, because of the band limitation of our sensory systems; that we could actually enhance our ability to perceive all sorts of things—magnetic fields, infrared light, you name it—just by creating a new type of dialogue with the brain.

Dr. Campbell: I think you mentioned in the book, doing an experiment where you have, was it rats, living in a magnetic world—or where the information was… That's the same idea.

Dr. Nicolelis: Yes, it's the same idea.

Dr. Campbell: I couldn't help but think about Michael Merzenich's work with the cochlear implants here; because I interviewed him a couple of years ago, and he was talking about how, when those were first developed, the problem was the low resolution, but that people did learn to make sense of the information that they had. No one thought that the cochlear implants—well, probably not no one; obviously, the people developing them thought they would work—but many people thought they wouldn't work because of that. It was a surprise to everyone that the brain was able to make sense out of that low resolution signal. And I guess this is another example of that—although you've got more resolution, right?

Dr. Nicolelis: Yes. I mean it's the same issue. The difference here is that we can now create a mechanism for encoding signals that are very strenuous; very,

very different from anything we have ever perceived. You can argue that, both in the cochlear example and what we did in tactile coding, you are somehow trying to get something close to a percept that we already used to have—at least, for most of us. And I think the analogy with the cochlear implant is pretty good. It is very similar to what we were able to do here; with the difference that we are encoding messages from objects that really do not exist in reality.

But in the case of what I am proposing for the future, it is to use principles like what we learned from the experiment we just did, to basically allow brains to really broaden dramatically the perceptual experiences they can have directly with the external world; because now you're talking about creating new sensory senses—new pathways directly to the brain—to interpret things that we normally do not perceive. And that has, in my opinion, a far-reaching future; because we are not talking only about rehabilitation (of course, that's where things are going to come first), but in the future, you could be talking about augmenting normal human perceptual capabilities.

Dr. Campbell: So, not only are the maps that our brain has, plastic, but our brain can make new maps.

Dr. Nicolelis: Oh, yes. And actually, I don't even use the word 'maps' anymore. 'Maps' gives us an impression of a static 2D or 3D; and that's the reason they were used, actually. When Penfield first described them in humans, and Sherrington, in animals, I think this was actually the intent: to show that there was a static, carved-in-stone representation of the world. But I think that, once this revolution comes—in neuroscience, I mean—the word 'maps' is going to disappear; because they carry too much baggage with them.

I like to talk about dynamic representations, or dynamic models. That's what I think the brain is doing: the brain is creating; continuously creating and updating. Perhaps that's the reason our childhood is so long—and as a parent, I seem to be getting evidence that it is becoming longer and longer—because the brain has to simulate the statistics of the world into models of reality, and a model of self. And these models are very dynamic; so they're changing continuously with new experiences.

And since today the bombardment of information is so tremendous, it may take longer for these models to stabilize. And that's perhaps one explanation for why some psychologists are suggesting that our process of maturing, or the brain maturation process, is taking longer than it used to. So, young adults, they're in their mid-20's when they actually reach a state of maturation that our species used to have when we were 12 or 13; because the demands are different, and the burden on the brain to create these models has become much higher.

Dr. Campbell: That's interesting; I hadn't thought of that.

What is required in order for us to incorporate something that's outside of our body into part of our self image? Is there a key requirement?

Dr. Nicolelis: I think there are. We are not completely sure about all of them. We know that, certainly in terms of tools, what we see in the experiments, the incorporation is easier depending on how close to the normal behavior the utilization of the tool becomes. So if you, for instance, get these animals to control a robotic device in a time that is close to the normal reaction time of the animals to control their own hands, or arms, or legs, then it's much easier for things to happen, and for the simulation to occur. If you impose a delay that is several seconds, things don't work as well.

Dr. Campbell: So, it looks like the correlation between the brain and the movement, or the object, has to be close enough that the brain sees a correlation?

Dr. Nicolelis: Yes, exactly. The brain has to detect some sort of correlation. And the correlation between the behavior—the movement itself—and the feedback is also very important; be that visual or tactile, it doesn't matter. And, in fact, the more feedback you provide, the better. So, that's the reason everything that we do follows these principles, in terms of having these brain-machine-brain interfaces operate in the more natural context we can. And that's when we get the best results.

It's pretty much like when you learn to play the violin, or to swim: in the beginning it's pretty awkward; things are kind of strange—or when you're learning to ride a bike—but, as time goes by… For instance, I like to bike, a lot. At a certain moment in my life, the bike becomes part of me. I could feel that very clearly. And the moment I discovered, a few years ago, that you could actually attach your feet to the pedals (using clips that lock your feet on the pedal), after a few days of doing that, you really literally could experience the sensation that the bike was part of you.

And I think the same is described by car racing pilots—pilots that race very fast cars, like Formula One or Indy cars—because now the cockpits are very tight, and they are custom-designed. That's something that came in the last two decades. It used to be that you just put a seat, and whoever was going to pilot the car went there and sat, and that was it. Now they select the pilot ahead of time, and they actually mold the cockpit to have a perfect fit for the pilot's body. And pilots report they can sense the asphalt as if they are touching it with their fingertips.

We all have that feeling when we're driving; but these guys have even a more exquisite capability—to the point at which some of the best Formula One drivers report that they can actually define the adjustments of their car suspensions, or the tires, better than the computers that the car companies use to do that in a race. So, the expertise of the pilot, most of the time, is actually adjusting the car to the surface that the car is going to race on. They can do that better than machines, apparently. I believe that's because the cars have become part of their bodies for the sake of their brains.

[music]

Dr. Campbell: Before we close, I guess we should address a question that I'm sure is going to come up for some listeners. Miguel, how do you explain all the data that appears to support the old way of looking at the brain?

Dr. Nicolelis: Well, there are many ways to do that. We just discussed some—in the case of the anesthesia, context dependence. So, if you anesthetize an animal, you really dramatically reduce the dynamics of the brain circuits. And they converge. As you're collapsing these dynamics, the system converts to a state that is pretty well explained by the old dogmas—by the localization—because you collapse time, primarily. So, things become less dynamic, less changing; so you start seeing maps and receptive fields reduced to just a spatial dimension. That's one thing.

You mentioned in your podcast before, in the case of the classical idea, the Broca's area. You know, that was the big blow for the distributionists in the 19th century, when Paul Broca reported a patient that he had seen suffer a stroke, and go aphasic (couldn't speak anymore). After a few days the patient died, and they found this huge lesion in the frontal lobe. Well, it turned out that that lesion also destroyed a lot of the underneath white matter—the nerves that go and cross from many regions, including Broca's area. And now, of course, we know, a hundred years later, there are many areas in the brain involved in the generation of language and speech; it's not only that particular spot.

That actually (I mentioned that in the book) was very similar to the spot that the phrenologist, Franz Gall, almost 80 years before, had defined as the speech area in the phrenologist's map of the brain. Paul Broca didn't like that. He didn't want to get himself associated with the phrenologists, because they were already discredited by the time he published his study. But you cannot escape that it is in the same spot.

But that's one of the reasons. A lot of this data is based on lesions that destroy not only the gray matter, but also the white matter underneath. And if you remove the connectivity of a circuit, then you start having deficits that are very serious. So, for a long time, this was an impediment to moving forward with visions that are more, as I said, based on distributed representations of information in the brain. But I think, case by case, they are going down; including another one that I'm hoping to discuss in the next book—the famous cortical column.

Dr. Campbell: You barely alluded to that in the book.

Dr. Nicolelis: Yes. I had a whole chapter about it, but we decided there was too much, and so I left that for one of these days when I write the second book. But basically, we know now, from most of the recordings and experiments that have been done (and the cortical column in the '60s was holy; was the sacrosanct finding of neuroscience), well, nobody has been able to find the function for it. And it's certainly not the functional unit of the cortex, at all. It is an anatomical unit, in the sense that you can see bias for vertical alignment of axons and cells in the cortex; but there is no function assigned to any column in the cortex—it is not like the liver.

And that is a major, major blow. People say, *Oh, we all know about that.* But, in reality, this is not already some established truth; so much so, that if you get a textbook in neuroscience, you still see the cortical column described as the functional unit of the cortex. But it's not. There's plenty of evidence out there that discredits that idea. It's just waiting for the fatal blow. It's one of those things that is ready to be tumbled; but someone has to make the final push.

Dr. Campbell: The thing that's confusing for someone like me—that's just kind of following neuroscience as an interest, rather than as a profession—is sometimes sorting out which things are still useful. I mean lots of what we know about single neurons is still valid; it's just that that approach is incomplete, and doesn't allow us to understand how complex the system really is.

Dr. Nicolelis: Absolutely. But that's true in several natural sciences these days. We used to think that reductionism would solve all our problems. And it did pretty well in physics and in chemistry; but in biology, to the despair of a lot of people, we are seeing that you cannot explain complex biological systems using the reductionism approach.

You really cannot explain how networks of genes, or networks of cells, or even networks of brain areas interact and produce complex emergent behaviors, by cutting down these systems to the elementary particles that make them. Because nobody has found a way to go down there and reconstruct the system back, and make it work, and explain these emergent properties.

So, we got fascinated by the success of physics, I think—particle physics, I mean; high energy physics—and we thought that we could apply the same ways of thinking. When I go to these meetings, I drive a few physicists crazy, because I tell them that not even physics could have existed without a complex brain behind it.

The most stunning intellectual success of our scientific endeavors, that we can honestly say is the description of our cosmology—the elementary particles that make matter—well, all those theories and all the interpretations that we give to that experimental data depend on the way we think; depend on the way our brains work. And that is something that I would like to explore more in the next few years; because reductionism is not going to solve the riddle of the brain, at all. There's no chance. We will have to invent a completely different approach to do that.

Dr. Campbell: It's a good thing that there are people like you, and Olaf Sporns —who I interviewed recently; who's working on the Connectome Project—who are looking at this from the complex systems point of view.

Before we close, I would like to ask you one of the things I ask all my guests, for the sake of my student listeners. Do you have any advice for students?

Dr. Nicolelis: I usually tell my own students, and the students in Brazil, that I visit often—since I'm from there—that this is a spectacular moment to be in science; but it's also a pretty difficult moment to be in science. On one side, we have opportunities to inquire into nature with tools, and ideas, and the ability to collaborate with so many people at the same time, that are unique. No generation had before what we have available today.

On the other side, somehow we are losing our connection with society. And it's difficult to communicate to society how important science is—and how beautiful it is, actually—and how fundamental it is to maintain the kind of support and the kind of involvement that we had before, in terms of promoting the scientific inquiry as one of our most important activities as a species.

We're in this conundrum where we have a unique moment and unique opportunities to do science, and at the same time, a difficult environment. And what I keep telling students is that, in these moments, it is your passion that carries you. If you're really passionate about this, this is the best of all worlds. You really need to believe in what your passion is; you need to pursue what your dreams are, no matter how impossible they are.

I have seen around me, over the years, people that have ideas, that when they were graduate students or in high school, they sounded completely crazy. And these people have succeeded in making those ideas become real fundamental research programs that are influencing a lot of our thinking today.

So, that's what I tell my students and the students I meet all over the world: that it's really fundamental to believe in your own instincts, and to go for it; because it's worth it. After thirty years in this business, I can tell you that I could not ever have done anything different, or taken any other route. It is worth it.

Dr. Campbell: Is there anything else you want to share before we close?

Dr. Nicolelis: No. I'd just like to thank you for such a nice conversation. It's wonderful to be able to discuss these things in a very open and highly intellectual environment. So, thank you very much for the invitation.

Dr. Campbell: Well, thank you for writing *Beyond Boundaries*; because it introduced me to this new way of thinking about how the brain works. I mean I knew that the single neuron wasn't going to get it done; but you proved it.

Dr. Nicolelis: Thank you! I appreciate it.

[music]

I want to take a moment to thank everyone who has helped support my work during 2011. Your generosity helps keep me going. If you're interested in helping support the *Brain Science Podcast*, go to brainsciencepodcast.com and click on the tab at the top of the page, labeled Donations.

I really enjoyed talking to Miguel Nicolelis, and I highly recommend his book, *Beyond Boundaries: The New Neuroscience of Connecting Brains with Machines—and How It Will Change Our Lives*, to all listeners, whatever your background. I'd also like to encourage you to listen to Episode 78, which provides a summary of the key ideas we discussed today.

And I especially want to remind you that you can get a free transcript of this episode at brainsciencepodcast.com. I know a lot of you listen to episodes multiple times, but I suspect that you may forget that these transcripts are available. Don't forget, you can also get these transcripts right on your iPhone, iPad, or Android device via the *Brain Science Podcast* app.

Since I recorded this interview a few weeks ago I have been thinking a lot about the implications of this work, and it's really hard to know where to begin. The localization approach to understanding the brain is deeply entrenched; especially for those of us coming to neuroscience from clinical medicine. For us, the association of neuroanatomy to function has been largely unquestioned. In making the transition to an understanding based on ensembles of neurons that are widely distributed in the brain, I think perhaps we should remember a few key principles.

One is that brain function relies on a large number of connections between neurons. Thus, when we are thinking about parts of the brain that have been traditionally associated with specific functions, it's very likely that these locations are critical in terms of connecting networks of widely distributed neurons.

Secondly, we need to remember that there is a difference between the so-called 'necessary and sufficient conditions'. Thus, in moving to a more distributed view of the brain, we may begin to acknowledge that certain locations in the brain, that are associated with specific functions, are necessary, since the function is lost if they are damaged; but they may not be sufficient, because the function may actually rely on connections to many other parts of the brain. Like I said during the interview, it appears that focusing only on the localized functions of the brain is insufficient for capturing its true complexity.

Of course, today's discussion has barely scratched the surface of this fascinating topic; which is why I encourage everyone to read *Beyond Boundaries*, by Miguel Nicolelis. It is a highly-readable book that is appropriate to readers of all backgrounds.

If you would like to comment about today's episode, you can send me feedback at docartemis@gmail.com. You can also post comments on the *Brain Science Podcast* Fan Page on Facebook, or in our Discussion Group at goodreads.com. If you want to look for me on Twitter, I am @docartemis.

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

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