

BRAIN SCIENCE PODCAST

With Ginger Campbell, MD

Episode #56

Interview with Neuroscientist and Former President of the Society for Neuroscience, Dr. Eve Marder

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INTRODUCTION

This is [Episode 56 of the ***Brain Science Podcast***](#), and I am your host, Dr. Ginger Campbell. Today's episode is an interview with Dr. Eve Marder from Brandeis University.

Before I get into the interview I need to make a few brief announcements. First, I am proud to announce that The Practical Psychiatrist website has awarded the ***Brain Science Podcast*** its semi-annual Community Service Award in Mental Health. You can learn more about this at the website psystone.com.

Also, if you are interested in learning how you can get continuing education credits for listening to the ***Brain Science Podcast***, be sure to listen for details after Dr. Marder's interview.

Finally I want to remind everyone that you can find Show Notes and links to all previous episodes of the *Brain Science Podcast* at brainsciencepodcast.com. And you can send me feedback at docartemis@gmail.com.

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I had the privilege of meeting today's guest, Dr. Eve Marder, at the Society for Neuroscience's annual meeting which I attended in Washington, D.C. last November. Dr. Marder is a full professor at Brandeis University, where she has been on the faculty since 1978. She just finished a very successful year as president of the Society for Neuroscience. Dr. Marder has won numerous awards and, as Wikipedia notes, She has done "seminal studies in rhythm generation, neuromodulation, and in computational neuroscience."

Today's interview has three main topics. In the first half of the interview we talk about Dr. Marder's career as one of the first women in neuroscience, and we talk about the *Society for Neuroscience*. In the second half of the interview we talk about her research into the structure and function of the stomatogastric ganglion of the lobster. Dr. Marder reveals why this circuit of only 30 neurons has fascinated researchers for over 30 years.

I know a lot of you listen to these episodes more than once, so if you want to skip ahead to the last half of the interview—the discussion of Dr. Marder's research—that part starts at 29 minutes and 10 seconds.

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INTERVIEW

GC: Eve Marder, it's a great privilege to have you on the *Brain Science Podcast* today, and I really want to thank you for taking the time to talk with me.

EM: It's a pleasure to be with you.

GC: Can we start out by letting you tell us a little bit about yourself?

EM: I am a working neuroscientist. And I realized the other day I've been in this field for about 35 years. So, you can see that I'm not quite on the tail end of my career, but I've been in the field quite a long time.

GC: Can you tell us how you got started?

EM: Oh, yes. As a young person—as an elementary school and high school student—I loved all kinds of fields. And I had no idea what I was going to end up being or doing eventually. When I was a very small child I used to always say that I was going to be a scientist; because as a child the first time someone asked me what I wanted to be when I grew up, and I said, 'A scientist,' they said, 'Oh, that's wonderful.' So, I found it was a very acceptable answer to give, so I used to always give it.

But as I went through high school I actually was one of the students who really loved school, and I loved all kinds of learning. I was extremely good in biology but I was also good in other things, and I really enjoyed many, many things. As a high school student I was quite involved in the local civil rights movement. I graduated from high school in 1965, so my high school years were during the free speech movement and the beginning of the civil rights movement.

GC: Where were you growing up?

EM: At this time I went to high school in Westchester County in New York. I lived in Irvington on Hudson, which is 10 or 12 miles north of the Bronx and north of Manhattan. I went to a very small high school, which was nonetheless a very fine school, paradoxically. Because this community had a very large number

of wealthy estates, and therefore there were a large number of people who paid very high property taxes and sent their children to the schools.

So, the schools were very well funded. And I had a number of excellent teachers. I really received, in retrospect, probably one of the best high school educations that any of my peers did—and certainly a far better education at that point than many people in the 20 or 30 years afterwards received in most public schools.

So, when I was thinking about what I wanted to do I actually entered college thinking I was going to be a civil rights lawyer. And that was because I was idealistic and I was engaged in the civil rights movement. So, I started, intending to study politics and to go to law school. Because I had placed out of many of my science requirements by the end of my freshman year, I realized that if I didn't take more science I wouldn't be doing it anymore, because I didn't have to.

And I thought, 'I'm going to miss it.' So, I decided in sophomore year to go back and take chemistry and biology, thinking at the back of my head, you can always go to graduate school in English if you have a biology degree, but it's not so easy to go to biology graduate school if you have a politics degree. So, I was being a little pragmatic.

And then I think the next really important step was that I'd had this wonderful course as a freshman in political theory. So, when I declared as a politics major, the next course I took was one in the politics of Western Europe. And I hated this course, because we had to learn the names of every single political party in every country in Europe after World War II. And it was just excruciating. At the end of that course I just decided, if this is what politics is all about this isn't for me. I'm going to go back and be a biology major.

Now, obviously I shouldn't have generalized from one bad course. Or maybe that's really what I wanted to do in any case. So, I went back to being a biology

major with not much thought behind it. And the real sort of turning point came my first semester of my junior year when I had a very good friend who was some kind of literature major, but had a sister who had been diagnosed as autistic. Later I realized she must have had a genetic neurodegenerative disorder. And she wanted to learn about autism, so she went to the first day of class in a course in abnormal psychology.

And she came back from this class and said, ‘Eve, you have to take this course, because the professor wears extraordinary clothes and he has a dueling scar.’ We were very romantic. So, I went to class. And yes, he was very distinguished, and he wore beautiful three-piece suits, and he spoke very well. And he definitely had a scar on his face that looked like what we imagined would be a dueling scar.

So, she and I took this class in abnormal psychology together. Now, this was 1967—probably the fall of 1967—and we were learning all about schizophrenia. And this was the time when schizophrenia was thought to occur as a consequence of the famous double bind hypothesis. It was a very different time in our understanding of mental illness.

But this professor said in passing one day, ‘Oh, there are some biological hypotheses that schizophrenia might actually have a real biological underpinning.’ And we had to do a paper. And at some point he said, ‘And there are some suggestions that deficient inhibition in the brain might account for schizophrenia.’ Well, I didn’t know anything about inhibition in the brain, and I was a biology major, so I decided to do my paper to answer the question, could deficient inhibition in the brain be causative for schizophrenia.

So, I went to the science library and I read everything I could find about inhibition in the brain. And it was in that process of writing the paper that I decided to be a neuroscientist. I must say there wasn’t all that much to read at the time. It would not be possible to do that today. But in 1967 there really

wasn't all that much known about inhibition, and there wasn't actually even all that much known about the brain.

So, that's what started me. And then the next semester I took the only neuroscience course available, and I learned the basics of cellular signaling. And I knew at that point that was what I wanted to do—that I was going to go to graduate school to study neuroscience. I think it's probably very likely I would have arrived at the same place by a different route. But it is amusing to think about the ways in which undergraduates, in particular, make decisions about courses that can change their life trajectories.

There's something else I should tell you about that time; which I think is quite important in the history of women and science, and I think we should talk about. When I was an undergraduate studying biology I was one of very few women studying biology. If there were 50 biology majors, maybe there were 4 or 5 women in most of my courses. And in my first neuro course I think I was 1 of 2 women in a class of 30. So, we were still relatively rare; although not anywhere as rare as the number of women in physics and math courses in junior or senior level.

The year I applied to graduate school was a year that changed the face of the life sciences research in this country—because I was applying in the fall of 1968 and I graduated from college in 1969. Right around my senior year was when the draft laws changed. Previously it was the case that graduate school was draft-deferrable, along with undergraduate education. And right around then they changed the law and went to the lottery. And so, graduate school in biology was no longer draft-deferrable, which meant that the pool of available men to go on into plain PhD programs dropped precipitously in that year.

As a consequence, when I arrived in graduate school in the fall of 1969 at UCSD, my class had 13 women out of 30. In the prior year there had been 2 women out

of 30. And what had happened at UCSD was they had accepted 60 people, of which 13 were women, and all 13 women said yes and matriculated, and 17 men matriculated. So, in that one- or two-year time frame, because the demographics of the applicant pool changed, the demographics of the graduate schools in biology changed across the country. What that meant was that by the time I was finishing my PhD, many more young women were receiving their PhDs and then moving on.

One of the things that I find so interesting is how rapidly the demographics of entering graduate school changed, and how slowly the demographics of women in major actual professorate levels—if you will—how slowly that has changed. And there are all sorts of really interesting conversations we could have about that. But I have no sense of humor about it, precisely because I lived that first year as we entered as a cohort in large numbers. And so, I find it very painful to realize that that cohort was not able to move as an intact cohort through the system.

GC: After you got your PhD did you go straight to Brandeis? Have you been there your whole career?

EM: No, I went to UCSD for graduate school. Partially I really wanted to go to California. I had romantic ideas.

GC: Well, especially at the time you were going to school.

EM: Exactly.

GC: My husband is the same age. In fact, as far as that whole draft deferment goes, that cost him a fellowship at Northwestern. He ended up in the Air Force instead.

EM: As did many men. Yes. So, I was finishing my PhD—I actually completed it in the fall of 1974—and it was time to look for a postdoc. And at the time I was

doing work in what might be called invertebrate neuropharmacology. For my thesis work I had tried to figure out what the neurotransmitters were in the stomatogastric ganglion of the lobster *Panulirus interruptus*—that's the spiny lobster that lives off the coast of La Jolla, where I was.

There were relatively few people working in that general area, and I ended up deciding to spend one year as a postdoc at the University of Oregon with David Barker, who was a very fine single cell neurochemist. And then I wanted to go to Paris to basically get further training in physiology and pharmacology. Specifically I wanted to work with JacSue Kehoe, who, as far as I was concerned, had published the most beautiful papers in invertebrate pharmacology of anybody in the world. And I was additionally fascinated to, obviously, go to Paris, but also to see how a woman who had two small children managed to combine family and science and do such elegant work.

On top of that, this being 1973-1974 when I was making these decisions, I was very disenchanted with the politics of the United States. And, not unlike the period in our recent past, the notion of leaving the U.S. for awhile seemed very attractive. So, I did that. I went to Oregon for one year, and then I moved to Paris.

I got there somewhere in December of probably 1975, and I stayed there until September of 1978, and spent those years as a postdoc; as a young American in Paris at a time when Americans in Paris were really not all that acceptable. I arrived having studied French for many, many years in high school and college, but never knowing how to speak the language. So, I arrived off the plane and I didn't understand a word of what anybody said to me. And then over the next few years I learned a lot of biophysics and a lot of French.

And I think this is a very important message that maybe you'll come back to. I constantly did things that people were advising me not to do. People always told

me, ‘Don’t leave the country for a postdoc or you’ll never get a job.’ And I would always say, ‘Well what’s this job stuff? I just want to do what I want to do now.’ When I first started graduate school people said, ‘Why are you starting graduate school? Don’t you know there’ll be no jobs?’ And I sort of said, ‘Well, all I know is I want to go to graduate school.’

I was never very concerned about long-term prospects. I only said, ‘Does this make sense for me now for the short-term future? Because this is what I want to do, and I’ll face the future when the future arrives.’ I always somehow had the confidence that things would work out in one way or another. So, when I went off to do a postdoc in Europe people said to me, ‘Don’t do that. You’ll never get a job.’

In retrospect, having gone to France I think helped me get a job, because it made me stand out from the crowd a little bit more; it made me a little more unusual. And it showed people that I had independence and the willingness to do what I wanted to do. I was never a cog in somebody else’s machine, so to speak. I came back to the United States in September of 1978 to start as an assistant professor at Brandeis, and I’ve been here at Brandeis ever since.

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GC: Before we talk about your research in some detail, I wanted to congratulate you on your successful year as president of the Society for Neuroscience. And I

suspect that the majority of my listeners are unfamiliar with the Society, so I was hoping you might talk about it for a few minutes.

EM: The [*Society for Neuroscience*](#) is an organization that represents approximately 38,000 working neuroscientists in this country and around the world. It was initially primarily based in the United States, Canada, and Mexico, but today something like 35% of its membership comes from Asia, Europe, South America, Australia, and all over the world. A large number of our members are young—graduate students and postdocs. And so the Society for Neuroscience sees as its mission, representing the career needs, the advocacy needs, and a variety of other needs that the broad membership has, as the membership as a whole tries to do its job and make important discoveries about neuroscience at every level of analysis.

The Society has what we can call maybe three main missions. One mission is every year it mounts a very large, very successful annual meeting. It's 4½ or 5 days long, and it's routinely attended by about 30,000 people. It consists of plenary talks and very high-level platform talks where very eminent scientists are often asked to talk about their own work. And then there are symposia and mini-symposia, which are suggested by the membership, about specific topics in the field.

And then there's a very large set of posters where individual groups of one, two, three, or four people will submit a poster that displays the outcome of their particular work. And so, the meeting allows people at every level of their career to present their work to audiences of their peers. So, that's one of the major activities of the *Society for Neuroscience*.

The second one of its major activities is it publishes the *Journal of Neuroscience*, which is one of the premier neuroscience journals. The *Journal* is published

every week, and is peer reviewed, and is a very, very successful part of the portfolio of journals in the field.

The third major set of activities that the *Society for Neuroscience* does, I can loosely call advocacy, career development, and public education. There are a number of activities that the Society organizes to benefit its membership, such as lobbying congress for additional funding for research in neuroscience, or creating a set of educational materials that can be helpful for K-12 teachers to try and work with their students.

The Society works very heavily on things like [Brain Awareness Week](#), which is intended to educate students and the public about advances in neuroscience. And the Society does a number of activities designed to promote public outreach and awareness of neuroscience through that part of its activities. Our members, I think, feel that as a whole the Society really helps represent them and makes sure that their work gets as broadly disseminated as it can.

GC: Yes, I have to say that as a person who came to the meeting as a science journalist, I was very impressed with the media department—how hard they worked to make everything accessible for us, organizing the press conferences and the press room. Everybody that was working in there was so friendly and helpful.

EM: Well, I'm glad, because Todd Bentsen, and Mona Miller, and that whole group worked very, very hard to try and facilitate anybody who can help get the message out about the importance of neuroscience work, and also can actually explain to the public what the findings are and how they might be interesting or important to them. We view it as part of our mission to figure out how to make everything that everybody's doing available and understandable to the greatest degree by the most number of people.

GC: I listened to the incoming president, Dr. Tom Carew, talk. One of his personal passions is public outreach and public education. Would you say that was also the focus of your presidency; or did you have a different focus?

EM: I think we all have a set of priorities. One of the things that I care a great deal about is trying to inform both congress and the public about the very tight interplay between basic science—fundamental work—and then the application towards clinical outcomes. One of the things that as a basic scientist always concerns me is that people can forget that sometimes there can be a very long time delay between the fundamental science that gets done and the way 15 or 20 years down the road that finding can end up in the clinic making real changes in the way a given disease is understood and treated.

And so, part of what I spent a lot of time doing was trying to help the Society in its advocacy and in its public education mission try and get the balance—the fine line between making it very clear that we all want to cure major brain disorders and we all want to do work that is important for human health, and that it is also extremely important to remember that much of that human health work will come from very strange and unexpected places and findings that come in all sorts of animals and all sorts of different contexts.

So, that was a major part of what I was trying to do, as well as open things up for additional advocacy and public outreach. And remember, I was president under the Bush administration, and Tom Carew is now starting out with the Obama administration. So, the politics and congress are quite different as well.

GC: Absolutely. You might feel like you've already answered this, but I was going to ask you what you think the most important thing you accomplished during your presidency was. Was it what you just said?

EM: Yes. And I think also reminding the *Society for Neuroscience* and congress of the other very important funding agency that deals with us. The NIH is the primary source of a lot of money for the funding of neuroscience, and its focus on human health is extremely important. The National Science Foundation—the NSF—also plays a very important role in funding basic work of all kinds, and also plays a very important role in education and outreach. And so, I also put some time and effort into reminding people that we as a Society had to pay a lot of attention to the NSF budget as well as the NIH budget.

GC: That's a good point. It's easy to forget that life sciences at the basic level are also funded by NSF.

EM: And a lot of very important work has been primarily funded by the NSF. Because so much neuroscience happens at medical schools, people forget that. But a lot of very, very important findings were either funded by the NSF throughout the whole time of the project, or sometimes were initially funded by the NSF and they moved to the NIH.

GC: So, that brings a question to my mind about the international membership. I know that a lot of those international members are graduate students that are studying in the United States, but you've also got a lot of scientists working outside the United States, and they have different funding sources and different funding issues. Did you find that there were particular issues that were of concern to the international members?

EM: I think one of the things that we had to start grappling with—partially in my presidency and partially in the year or two running up to my presidency, and that Tom is continuing to deal with—is how to be really helpful to all of our foreign members in the way in which they approach their own governments. We have been trying to work out liaisons with organizations like FENS, which is the [Federation of European Neuroscience Societies](#), and with IBRO, which is the

[International Brain Research Organization](#), and other international organizations.

We've tried to figure out how to be as helpful as our international partners wish us to be in creating materials—sometimes they're translated, sometimes we can brainstorm with them—but obviously the politics of science and science funding are different in every country. We were particularly helpful, I think, working in collaboration with our Canadian colleagues, because some of our effort went into building a set of materials with our Canadian colleagues that they then used to lobby their government successfully for increased funding for neuroscience.

It's a very complicated issue to try and figure out how we can be helpful to our international colleagues. But they obviously in their own local environments have to deal with funding realities, and bureaucratic conditions, and all sorts of differences in educational philosophies and educational programs all around the world. No two countries are the same. It's a balancing act for us. We want to be helpful, but we obviously don't operate in 150 countries.

GC: Right. What about the increasing barriers to foreign students and foreign scientists coming into the United States, even just for meetings?

EM: We worked very hard in helping foreign students and postdocs get visas. The *Society for Neuroscience* writes, I think some years it's hundreds and hundreds of letters in support of visa applications. We get hysterical emails, sometimes three days before the meeting, from someone saying, 'My visa application is sitting. Can you do something?'

And the office tries their absolute utmost to move things along with our government to make sure that they are given permission to enter. So, we have often taken a leadership role in trying to argue that the kind of scientific work

that we do should be more available to foreign workers. I don't have the sense it's as much of a problem in 2009 as it was several years ago.

GC: I hope that's true.

EM: I think that's true, but I'm not sure.

GC: I appreciate you taking so much time to talk about these issues, because I think they're important. But I definitely want to talk about your research.

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GC: Eve, do you want to start out by maybe just giving us an overview? You gave us a slight introduction earlier.

EM: I study a whole series of problems about how circuit dynamics arise from the interaction of groups of neurons hooked together, obviously by synaptic mechanisms. I use a preparation called the crustacean stomatogastric nervous system. The stomatogastric ganglion has only 30 neurons, and the stomatogastric nervous system is an example of an [central pattern generator](#). Central pattern generators are a group of neurons that can produce rhythmic motor patterns, even in the absence of timed signals from the muscles that they drive. So, for example, essential pattern generators found in your respiratory centers, that keeps you breathing.

And one of the challenges is to understand how you can produce a circuit that works as if it were an oscillator that endogenously produces rhythms, and then how those rhythms are modified so that the animal or the person can respond to changes in its environment. So, if we think about respiration, you have to be able to change the rate at which you breathe depending on whether you're sleeping or running a marathon, but the existence of the breathing rhythm is independent of the sensory input.

The reason why in the late 60's and the early 70's people were drawn to the stomatogastric ganglion was because it was a small number of neurons—only about 30—and they were very large. The cell bodies of these neurons can be about 100 or 120 microns, so they're quite large, and they're very easy to record from. And so, at the time it was possible to do experiments in this preparation that were just unthought of. You couldn't even imagine doing it in much larger vertebrate preparations like you would find in the spinal cord, or in a rat, or a mouse, or a human.

And over the years from, as I said, the late 60's and continuing on through today, a number of very important findings have been made using this preparation, precisely because it was at the time, early on, possible to do experiments you couldn't do anywhere else. And it still is possible to do experiments using this preparation that are still very difficult to conceive of in larger circuits.

GC: Could you give an example?

EM: Yes. Early on in the beginning of trying to understand circuits, before we knew very much, most people thought that to understand how a circuit worked all you would need to do would be to establish a wiring diagram. The idea was you would figure out what all the neurons were—who they were—and then how they were connected, and then that would tell you how the circuit worked. And people had in their minds electronic circuits where you would have a wire going

from place 1 to place 2, and you could imagine either an excitatory synapse or an inhibitory synapse, and then people just sort of assumed that would be sufficient.

Well, what happened is it became clear—partially through our work in the early 80's—that many properties of individual neurons and many properties of synapses were subject to neuromodulation. **Neuromodulators** are chemical substances that can do things like change the strength of a synapse, or change the intrinsic excitability of a cell, change the way it response to currents. And so, when we started studying neuromodulators on the stomatogastric ganglion we realized that the circuit could have many different kinds of outputs depending on its modulatory environment.

And that was something which the early workers on circuits just hadn't predicted. So, instead of there being a single output, there'd be multiple outputs where the circuit now would be reconfigured by its modulatory environment. And that insight is one which pervades the way we think about things like emotional tone and mental illness in the brain today. And so, that's the kind of understanding that can have very big general implications, but that you can study more effectively sometimes if you have a small, well-defined circuit.

GC: So, as long as we didn't have the ability to even define a circuit as small as the one you study, we could have the illusion that having the wiring diagram was all we needed.

EM: Exactly. Lots of people now have new tools with which they can study larger circuits—circuits in the mouse, or circuits in rats, or circuits other places—and people are working very, very hard to establish the wiring diagrams and conductivity diagrams of the larger circuits in the vertebrate brain. And I keep saying to them, the circuitry is necessary but not sufficient. You can't explain how the circuit works without the wiring diagrams. You can't get there without them.

But once you have the wiring diagram, that's when the real work starts. We've made incredible progress in the field because now it's possible to identify cells in these larger circuits. And you have to be able to identify cells before you can actually create a wiring diagram. So, they're only about 35 years behind us.

GC: As I was reading your papers I noticed one of the themes that kept recurring was that just even identifying the types of cells is more difficult than non-neuroscientists might imagine.

EM: Right. And that's because it's pretty easy to identify a motor neuron, because a motor neuron by definition is one that innervates or drives a muscle. It's pretty easy to identify a sensory neuron because by definition that's a neuron that responds to a specific sensory input, whether it's proprioceptive, or visual, or auditory, or taste, or whatever. But for the very large number of cells in the middle—all of those cells that make the circuits that do all the really interesting things in brains that we care about—identifying the cells can be very complicated.

Some of them have very characteristic shapes and very characteristic projection patterns, or have characteristic chemical signaling molecules in them, or have characteristic receptors, or have characteristic firing patterns. But all of those criteria are often needed to specifically categorize or subcategorize individual cell types in a complicated brain.

And so, there have been a lot of errors made and a lot of missteps made in trying to really identify cells in large brains, just because sometimes you don't have enough criteria that can allow you to individually identify cells or groups of cells as a class. You can make a lot of mistakes as you try and draw those wiring diagrams. But I think a lot of that's resolving now. There have been tremendous advances and the development of a lot of tools that really help.

GC: Do you want to talk a little bit about some of the tools that you're developing within the model you work with?

EM: We don't really develop tools so much because lobsters and crabs are not a genetic organism. So, a lot of the major advances that are being used in mice, and in flies, and in worms that allow people to express dyes in individual cells or groups of cells, those things are much more difficult for us to try and implement. What we do is in a sense a little bit easier. Because we can uniquely identify cells without expressing these new molecular markers, we haven't needed to do things like that. Does that make sense?

Why don't I sort of snap forward to the present and try and describe to you how, 35 years later—and sometimes when I give talks I make a joke about this—how is it that hundreds of people have been able to study 30 neurons from a crab or a lobster for 35 years and still find really remarkable things to learn from that same small circuit? What I can do for you now is try and explain to you what we're doing today that builds on all the wealth of knowledge that we've developed over the years, that I think is really quite new and important for the field.

Any two-year-old in the world will tell you that he or she knows that every individual human is different. And they can recognize them as individuals. And they also know that every cat and dog is different. And they can usually recognize them as individuals. But we as experimentalists have spent many, many years sort of defying that individuality, because we have always been terrified by the inadequacies of our experimental methods.

And because we're terrified by the kinds of measurement errors that it's very easy for us to make—no matter what kind of measurement you're making there's always the possibility of an experimenter-induced error—we have learned to rely very, very heavily on doing the same experiment many times and then calculating

means and standard errors as a way of validating that our effects are real and important, and reliable, etc.

So, for example, people will do the same experiment on 20 mice, and then average the results, and then they'll publish a mean and a standard error. And they'll compare those 20 mice in control with another 20 mice treated with something else, and they'll see a difference in the means and the standard errors. And they'll feel comfortable because the n has been large enough to make them believe that their data are reliable.

And that is, by the way, the way we and many other people always have to work. And there are very good reasons for it. And there continue to be good reasons for it. But, what that way of thinking walks away from is confronting the animal-to-animal variability in the population, or the human-to-human variability in the population.

And the stomatogastric nervous system has been so well studied for so long, and has such a simple circuit. There's one LP neuron in every ganglion. So, that neuron has been both extremely well studied and is an individual neuron that can be recognized over and over again. So, at this point in the history of our preparation we are now ready to ask a series of questions about individual variability because we have reached the point where, when you get animal-to-animal variation, we now feel we can trust our measurements well enough—after the years and years and years, and thousands of neurons that have been recorded from—to take at least part of that variability seriously.

So, what we have been trying to do is benefit from the simplicity of the preparation to really try and ask the question, how good is good enough. And what I mean by that is how tightly tuned do all the properties of an individual neuron, or the strength of all the synapses in the network have to be in order for the network to perform properly? In other words, the question is how different

can two LP cells be in two different ganglia and yet still have the ganglia work well enough for the crab or the lobster to be able to eat—which is what the ganglion helps it do.

Or, how many ion channels can there be of a certain type? In other words, does an LP cell have to have 492 sodium channels in every cell, or can it be 492 in one cell and 893 in another cell? How big can those ranges be? And so, this is a question that we can ask both using computational methods—building computer models—and doing experimental measurements. But we'd never be able to do this if we had a circuit that wasn't as well described or understood as ours is.

So, our circuit is just at the right level of complexity. It's big enough to have what we would call emergent properties—properties that depend on the interactions of cells and their synapses—and yet it's small enough so that we can record from every cell whenever we want to. So, that's what we're doing right now. We're trying to really frame a set of questions which we think are general to every problem in neuroscience, but that we can at least try and say, how tightly tuned does every part of the brain have to be for the brain to function correctly.

And if you think about this, this is crucial to understanding disease. Because if you think you've got to get every process in the brain tuned to within 1% then it would be really hard to imagine that everybody wouldn't be mentally ill. But on the other hand, you could imagine that some processes might have a pretty large range in which the brain can function well, and others might be more narrowly tuned. And so, we have to start creating a vocabulary to try and understand the range of properties across individuals consistent with healthy brain activity.

GC: And you've already made some sort of surprising discoveries in this area haven't you?

EM: Yes. The first thing that we discovered is that, much to our surprise, we found that the messenger RNA levels for a number of different ion channels can vary three-, or four-, or five-fold across preparations; or that some of the strengths of some of the synapses can vary quite considerably three-, four-, or five-fold across preparations. And those were much larger ranges than we would have expected a priori. One of the things that we're now looking for is the kinds of compensatory mechanisms by which cells might balance a small value in one property or parameter with a large or small value in another property or parameter to maintain constant function.

GC: So, when you make a discovery like this, that's really not what you expected, it leads to different questions, right?

EM: Yes.

GC: And that's exciting.

EM: Yes, absolutely. We came to this fairly gradually over the last 10 or 12 years, largely led by computational models we were building. We were building models that were designed to capture some of the properties of our cells. And it's very natural in building a model, and very easy in building a model to start playing with the parameters to see how sensitive the behavior of the model is to one or another of those properties. And it was some of those models that first suggested that there could be multiple solutions to similar outputs, and that those multiple solutions might have large ranges of parameter regimes.

And then that drove us back to the biology to ask how large can they really be, and how large are they really in the biology? Now it's driving us to go further and to do experiments that I would really call a paradigm shift. Now we're trying to measure in an individual animal as many parameters as possible so that we can look for correlations between four, or five, or six different parameters in the same

preparation. And that's an entirely different way of collecting data than people would usually do.

GC: So, your research findings really have implications for a lot of other areas.

EM: I think so. When I give talks people come up to me and say, 'Wow, you just changed the way I thought about the experiment I'm going to do.' And that might be someone working on rats, or working on monkeys, or something. I mean this is really an example of what basic science can do. Our work is not going to tell someone working on a mouse, that particular channel is doing X. Our work says maybe you should analyze your data differently to learn what you need to learn. Do you understand what I'm saying?

GC: Absolutely.

EM: There's sort of a difference in perspective that says, yes, you have to do the measurements you have to do in your system, but maybe if you design the experiments a little bit differently, or maybe if you analyze your data a little bit differently you'll see something that you might not have thought to see, by virtue of what we've learned. And we've learned a new way to see because we have this simple system to work with.

GC: Just to bring up a different topic that I think does relate. On the subject of plasticity—which a few years ago was a non-subject and now at least among those of us on the outside seems like a hot subject—your findings are totally consistent with plasticity, aren't they? I mean it shows that plasticity is really at a very basic level.

EM: Well, there are many different kinds of plasticity. But if you go back to neuromodulation you can see that the same circuit can do many different things, depending upon its modulatory environment. So, that's short-term behavioral plasticity. That tells you how hormones can influence behavior.

Then if you want to think about changes in circuits that underlie long-term storage of information, like stable memory formation, it becomes extremely important to know how outputs depend on the underlying parameters. Because if you teach an animal something and measure something and something changes, you need to know whether that's a change that's actually going to change the way the circuit works.

So, you have to have a way of framing that question. Sometimes you could have a 20% change be very important, and a five-fold change be very unimportant. And so, our way of thinking sort of changes the way in which people think about how to think about even memory formation in terms of the underlying neural mechanisms.

GC: In your papers that I read one of the ideas that stuck out in my mind was the fact that you pointed out that things like the channels have turnover compared to the life of the neuron, yet its basic function has to stay the same.

EM: Right. There's a whole conundrum in biology in general, but it's particularly acute in the nervous system. But it's a problem that biology faces—period. Which is how do you maintain constant structure and constant function despite the fact that you have these incredible turnovers of underlying molecules, and even cells in some tissues? So, for example, your gut epithelium is replacing itself constantly, but the epithelium has to maintain a constant function.

That's sort of at one level. In terms of the nervous system, or your heart, you have cells that will live in a healthy human for 70, 80, 90 years, and the channel proteins that give them their characteristic firing properties are turning over in minutes, or hours, or days, or weeks. And so, every single neuron in your body, as well as your heart cells, as well as other cells, are constantly rebuilding themselves. They're turning over their components at a very, very high rate.

And so, in terms of the nervous system one has to step back and say every single neuron is constantly replacing all of its molecular components, and yet that neuron and the circuit in which it's found have to maintain a good deal of stable structure and function. This is a problem that we've been studying for the last 15 or 18 years. And that problem moved from my laboratory via [Gina Turrigiano](#)—who developed what we now call synaptic scaling—to large numbers of people who are really trying to understand the interplay between what we now call homeostatic mechanisms in the brain with the plasticity mechanisms in the brain, to try and understand how the brain can be both stable and plastic at the same time.

GC: So, it's a pretty exciting time to be a neuroscientist.

EM: It is, it is. It's very exciting.

GC: Is there anything else about your particular work that you would like to share before we close?

EM: I don't think so. I think I've probably hit on the major things that we're worried about now.

GC: As we close, Eve, I'd like to just ask you if you have any advice for students who are interested in neuroscience?

EM: Yes, I have some very important advice; which is don't worry about the future, study what most fascinates you, and just really, really enjoy the work. Don't worry about all the dire prognostications about what will or won't happen. Don't worry about people saying, 'Oh, you'll never get a job, you'll never do this, you'll never do that.' If you really love what you're doing, I really believe it will work out.

GC: People have been saying there won't be any jobs for a long time, I guess.

EM: Since my first year in graduate school. And you know in my first year of graduate school there were not very many neuroscientists in the world. I'm not saying it's going to work out for every single individual, but I really do believe that there's so much fascinating work to be done, and that it's a time when the field is just exploding. There are so many important human health implications of so much of the basic and more applied work. It's a wonderful time to be starting. So, I would just say go for it.

GC: Thank you.

EM: Well, thank you.

[music]

I really enjoyed talking with Dr. Eve Marder today, and I want to thank her again for taking the time to be a guest on the ***Brain Science Podcast***. Before my closing announcements I would like to review a few key thoughts.

First, when I asked Dr. Marder about what tools she had developed I had in mind her work with the dynamic clamp technique. She didn't mention this during the interview, but she was instrumental in the development of this important technique that uses computer simulation to introduce artificial membrane or synaptic conductances into biological neurons, and to create hybrid circuits of real and model neurons. I think this was developed about 15 years ago, and it has become a widely used tool for the study of neural systems at the cellular and circuit levels.

However, I think Dr. Marder wanted to focus on what she sees as a key discovery, which is the role of neuromodulation. Her work with the 30-neuron stomatogastric ganglion provides information that has implications for scientists working with larger nervous systems. First, neuromodulation—which means that

the neurons are influenced by various neurotransmitters and other neuropeptides—means that having the wiring diagram is not enough.

Also, more recently her team has discovered that the variability of individual neurons is much more than had ever been expected. This finding has far-reaching implications. For example, I have talked in the past about why the digital computer is an inadequate model for the brain. Consider the implications from Dr. Marder's work. First, modeling any single neuron accurately would require modeling all the various neuromodulators and how they affect that neuron.

Even more significantly, Dr. Marder's work implies that individual neurons are highly dynamic, so that even if you could model a neuron accurately you would then face the problem of how to model the fact that its various characteristics may be constantly changing. Thus it appears to me that, at least for the foreseeable future, any attempt to model even a simple brain will require simplifying assumptions that will cause it to diverge from what real brains do. If you want to share your thoughts about this or any other episode of the ***Brain Science Podcast***, please join us in the Discussion Forum at brainscienceforum.com.

Now for a few closing announcements. For the last few episodes I have been encouraging you to visit the website brainsciencepodcast.com. While you're there I hope that you will complete the Audience Survey. Also, please explore the website and send me your comments and suggestions. My email is docartemis@gmail.com.

I want to thank Dr. Tim Stone at [The Practical Psychiatrist](http://ThePracticalPsychiatrist.com) website for choosing the ***Brain Science Podcast*** for its Community Service Award. Dr. Stone has worked for over 10 years as a psychiatrist at a community mental health center in Birmingham, Alabama. He started The Practical Psychiatrist website to provide

resources for mental health patients and their families. The first thing you will notice if you visit his website is that it has no advertising. So, if you go to the site psystone.com and you find it useful, please consider donating to his efforts.

I want to close by telling you about an exciting new project that is in its very early stages. I am researching how I can create accredited continuing educational materials that will allow physicians and nurses to earn CME—or continuing education credit—for listening to selected episodes of the *Brain Science Podcast*. I need your feedback to help me determine if there is sufficient interest to make this worthwhile. Write to me at docartemis@gmail.com. Right now I'm taking ideas and suggestions, and I will be compiling a list of people who are willing to be beta testers.

I would like to do something for psychologists also, but I don't know anything about how your continuing education requirements work. So, I could use some help, especially in that area. Any of you that have experience in the area of producing continuing education materials, your help would be greatly appreciated. I'm estimating that starting from scratch this will take at least six months to bring to reality.

Next month's *Brain Science Podcast* is an interview with Dr. Chris Frith, a neuropsychologist from University College in London. We will be talking about his book, [*Making up the Mind: How the Brain Creates Our Mental World*](#).

Meanwhile I hope you will check out my other podcast, *Books and Ideas*. The current episode is an interview with science historian Jennifer Michael Hecht. And there will be a new episode coming out at the end of April.

If you are looking for more science podcasts, don't forget to visit sciencepodcasters.org.

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

[music]

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Transcribed by [Lori Wolfson](#)

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