

BRAIN SCIENCE PODCAST

With Ginger Campbell, MD

[Episode #69](#)

Interview with Neuroscientist, R. Douglas Fields, PhD, Author of *The Other Brain: From Dementia to Schizophrenia, How New Discoveries about the Brain Are Revolutionizing Medicine and Science*

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“I want to kind of get across the idea that the book is not a textbook. What I hope that it gets across is the excitement of doing science, and having a revolution in science unfold in real time. You know we hear about all these scientific revolutions in an historical context, but to have one happening right now in real time is very exciting. Our whole idea of the brain is changing.”

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INTRODUCTION

This is [Episode 69](#) of the *Brain Science Podcast*, and I’m your host, Dr. Ginger Campbell. Today we are going to be talking about glial cells with Dr. R. Douglas Fields. I’ll tell you more about that in just a minute.

First I want to remind you that you can get detailed show notes and transcripts for all episodes of the *Brain Science Podcast* at brainsciencepodcast.com. If you need to reach me, you can send me email at docartemis@gmail.com.

For those of you who are using the Brain Science Podcast app on your iPhone or iPod Touch, I am happy to report that all the transcripts are back in the application. I'm glad this problem has been resolved, because being able to get transcripts right on your device is one of the best features of the Brain Science Podcast application.

Today my guest is [Dr. R. Douglas Fields](#). Dr. Fields is the chief of the section on nervous system development and plasticity at the [National Institute of Child Health and Human Development](#), which is part of [NIH](#).

Dr. Fields' new book is called, [*The Other Brain: From Dementia to Schizophrenia, How New Discoveries about the Brain Are Revolutionizing Medicine and Science*](#). We'll be talking about the highlights from this book. I'll be back after the interview to review the key ideas.

And also please stay tuned for the announcements at the end, because I have an important announcement to make about the future of the *Brain Science Podcast*.

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INTERVIEW

Dr. Campbell: My guest today is Dr. R. Douglas Fields, the author of, *The Other Brain: From Dementia to Schizophrenia, How New Discoveries about the Brain Are Revolutionizing Medicine and Science*. Dr. Fields, it's great to have you on the show today.

Dr. Fields: Well, thank you.

Dr. Campbell: Doug, would you mind starting out by just telling us a little bit about yourself?

Dr. Fields: I'm a neuroscientist, and I'm interested in the mechanisms of memory, how the brain develops, and how functional activity regulates development of the brain—that's early childhood experience, or activity in fetal development.

Dr. Campbell: I noticed from your blog that you started out your career as a marine biologist. How did you end up becoming a neuroscientist?

Dr. Fields: I have a PhD and a Master's degree in marine biology, and I still enjoy marine biology. I've always studied nervous systems. I was interested in sharks—shark brains and their sense of [electroreception](#). So, although I was always interested in the ocean, it was related to neuroscience. So much of the biological world is in the ocean, if you're a biologist you're going to find yourself studying marine organisms, one way or another. And they make great model organisms for studies of the nervous system. So, that's how it developed.

Dr. Campbell: Last year I interviewed [Dr. Eve Marder](#).¹ I think she spent her entire career studying one ganglion inside of the lobster. So, I certainly understand, and I think my listeners appreciate the importance of the various marine species.

Dr. Fields: We've actually co-authored a paper² together, and shared a mentor—[Ted Bullock](#). So, I know her work very well.

Dr. Campbell: Yes, she was a wonderful guest.

¹ Eve Marder was interviewed in [Episode 56](#) of the *Brain Science Podcast*.

² Bullock, T. H., Bennett, M. V., Johnston, D., Josephson, R., Marder, E., Fields, R. D. "Neuroscience. The neuron doctrine, redux." *Science* 310. 5749 (2005): 791-3. Perspectives

So, how did you end up studying [glial cells](#)?

Dr. Fields: Well, like most neuroscientists, I wasn't interested in glial cells, in particular. Most neuroscientists don't go into neuroscience to study non-neuronal cells—and that's what glia are. We haven't really defined them yet, but glia are not neurons. Glia (the word means 'glue') don't fire electrical impulses, and they were just thought to be support material for the brain.

What I was interested in studying is how activity regulates formation of the brain in terms of forming connections between neurons. And in stimulating neurons in my lab, using new techniques, I was able to see that the information was leaving the neurons and going into a part of the brain, or types of cells, that were not neurons. So, I was forced to begin looking at this other part of the brain that really is not involved in any of our understandings of how the brain works.

So, it was the data that led me into studying glia, because this really violates our basic understanding of how the brain works. That's something called 'the neuron doctrine,' which is that all information processing in the brain takes place by neurons through electrical communication across synapses. And here in my studies, and other studies (others were making similar observations) I was startled to find that information was leaving neurons and going into a part of the brain that involved cells that were not neurons, and couldn't communicate with electricity. So, we were wondering what this meant.

Dr. Campbell: And that's the reason why you call your book, *The Other Brain*.

Dr. Fields: That's right. I call it *The Other Brain*, because we've studied the neuronal brain for a hundred years. All of our ideas about how the brain works are based on this idea that I just briefly described, of neurons communicating electrically through synapses. And that has been studied in detail. But, in fact, 85% of the cells in the brain are not neurons. Neurons are only 15% of the cells in

the brain. So, it's the other brain in the sense that this is a new frontier—an unexplored part of the brain.

Dr. Campbell: One of the things I like to do on my show is just talk about what it's like to actually do research science. When you first started getting the evidence that the glial cells were doing surprising things—obviously you were surprised—did you at first think it was some kind of experimental error, or had someone else gotten past that point, and you were replicating their work?

Dr. Fields: That's a good question. And it's always one of the great excitements in scientific research to make an observation that completely undermines your prior thinking. But perhaps I should tell you a little bit about the experiments. In the past, neuroscientists like myself studied neurons communicating with electricity, and we used electrodes to do that. We would make these very sharp electrodes, and stick them into neurons, and then record the electrical signals with powerful amplifiers. And that's how the brain was probed and studied.

But glial cells don't communicate with electricity, so this method was never going to uncover the other brain, because the technique is deaf to the communication that was going on between glial cells. So, the discovery of the other brain involved new technology, and this was imaging technology. It was microscopy that allowed us to see and study living cells with a fluorescent dye. Much like a glow stick, this dye will fluoresce when it mixes with another compound. That other component is calcium. Now, calcium ions in neurons are very important for communicating.

So, the experiment that I was doing—and others at the time—was to put this dye into cells in a dark room under a microscope, and the computers watch this cell fluoresce. We could actually stimulate the neuron and see that neuron light up. And that meant that it was firing electrical impulses because calcium ions were coming into the neuron. But, as I did that, we saw that after the neuron lit up, all

of these other cells in the culture, that were not neurons, began to light up. So, somehow the information was going from the neuronal brain into these glial cells. That was a very startling finding.

At about the same time, or even earlier, there were scientists like [Steve Smith](#) and his colleagues—now at Stanford—who had grown these non-neuronal cells in a culture dish, and did this kind of live cell calcium imaging, and put on a drop of neurotransmitter, which neurons use to communicate across synapses. And when he did that, he saw that these glial cells began to light up. And not only did they light up, they began to send waves of light from one cell to the other. So, those waves of light meant that calcium waves were going between cells, and these glial cells were communicating with chemicals.

Dr. Campbell: OK. And so then the question is why?

Dr. Fields: Exactly.

Dr. Campbell: Maybe we should take a few minutes to talk about what glial cells are, in the sense of what we already knew about them, and maybe the main types—some of the basics for people that might not be familiar with them?

Dr. Fields: Yes, I think that would be useful. Everyone knows what neurons are; but they only comprise 15% of the cells in the brain. They communicate across synapses with electricity. The other 85% of the cells are not electrically excitable; and they're called 'glia,' which means 'glue.' And they were understood to be support cells for the neurons, providing structural support; and also understood to be important in regulating the chemical environment around neurons, cleaning up after neurons. So, they were considered housekeeping cells, in a way, and more or less dismissed from the mainstream interests of neuroscientists.

Glia take up the neurotransmitters after neurons release them to communicate at a synapse. I'm sure all the listeners know how synaptic communication works. We've seen this now on TV—where a neurotransmitter is released from a neuron to communicate with the next neuron—in commercials for various drugs. So, this is very well known. But those neurotransmitters, once they're released, have to be removed. And they're removed by glial cells. So, that's one of the things they did. While it was easy to dismiss that function as being uninteresting, we now realize that that put the glial cell in a position of control. And we'll talk more about that later.

Now, that's one kind of glial cell. There are actually four main kinds. Another kind is a [microglial](#) cell. These are the immune cells of the brain, and they're very important in every aspect of nervous system health and disease. The brain does not have access to the immune cells in the blood, so it has its own exclusive guard cells, and these are the microglia. So, these are very important in removing infectious agents and cleaning up after injuries.

Then the last category of glia is myelinating glial cells. [Myelin](#) is the electrical insulation around axons—which are the wire-like fibers that neurons send impulses from one neuron to the other over—and those impulses can't be sent unless the fibers are insulated. And glial cells form this insulation, called myelin. The cell that forms that in the brain is an [oligodendrocyte](#); and a [Schwann](#) cell forms that in peripheral nervous systems. So, there are four main kinds of glia.

Dr. Campbell: Could we talk a little bit more about myelin? Because I know we're going to come back around to it when we talk about your work. But the importance of myelin is more than just insulation, isn't it?

Dr. Fields: Yes. Well, that's something that's changing rapidly—the view of myelin—because in the past it was viewed as interesting mainly in disease. Myelin is the insulating layer around an axon. It looks a lot like electrical tape

wrapped around a wire. In fact, the glial cell will wrap membrane—up to 150 layers of membrane—around this axon-like wire; and it looks just like electrical tape.

Without that insulation nerve impulses will fail to propagate; and that insulation can speed up the speed of impulse transmission 100 times. So, it has a very important role in communication in the brain. You can see this in a young baby. Myelination takes place after birth, and the young baby can't lift its head, or walk until these circuits become myelinated. And you can see this also in people who have multiple sclerosis and lose vision, and motor control, and that sort of thing.

So, glia form that insulating layer. But maybe we'll talk a little more about the new realization that myelin is involved in learning and in controlling information processing in the brain, beyond synaptic control of information processing. That takes place by virtue of the fact that myelin controls the impulse conduction speed.

Dr. Campbell: Yes. Do you want to talk a little bit more about that?

Dr. Fields: OK. Well, traditionally all of the understanding of learning is based on changes in synaptic connections. What is a memory? A memory is forming a new connection, or strengthening a connection. And that means making a synapse stronger, or making new synapses. And that's certainly a very important part of learning; and I study that in my lab.

But once you have done this synaptic signaling, then an impulse needs to be sent to another part of the brain in order to carry out a complex kind of function—perhaps playing the piano, or catching a fly ball in left field. That requires information going from one part of the brain's cerebral cortex to another to carry out all these complex cognitive processes. And, much like a train system, where the timing between different stations in a train circuit is critical to the overall

performance of that train system, we now realize that the timing of the information from one part of the brain to the other is very critical.

And one of the things that controls how fast information is flowing between points in the brain is myelination. So, we've been surprised to find, using new imaging techniques (by 'we,' I mean the field) that we can actually see physical changes in the brain taking place after people learn to read, after they learn to juggle, or play the piano.

And these changes are seen in parts of the brain that involve these connections—which are called [white matter regions](#). These are beneath the cortex of the brain, where all the neurons and synapses are. These are the wire-like connections, like buried telephone lines, deep in the brain. And this is what's changing. So, it's startling to see these changes in a part of the brain where there aren't any neurons—just glia and these axons.

Dr. Campbell: So, this implies that the myelinating glia are a big part of that old saying that the neurons that fire together wire together?

Dr. Fields: Yes. We think so; because that's certainly the most important rule—neurons that fire together wire together. For example, [Pavlov's dog](#). You have to present the food and the bell at the same time, or those two ideas don't get associated. And at a cellular level that means the neurons that are activated by the bell and the food have to send signals to neurons controlling saliva, at the same time, so they get associated.

Well, how will that ever happen if those neurons are not the same distance apart? The information is not going to arrive at the same time. Information flows very quickly through the brain, but it would be like someone coming from New York to Washington, DC, and someone coming from Pittsburgh to Washington, DC: they're not going to arrive together unless the speed of the shorter pathway is

slowed down and the speed of the longer pathway is sped up. And that's where changes in the velocity of transmission can affect learning. Myelin is an important part of that control of the conduction velocity.

Dr. Campbell: Can you talk a little bit about how scientists proved that the myelinating glial cells actually do both detect and influence this neuronal signaling?

Dr. Fields: In my lab we've studied that in great detail, and we've found and described three different ways—molecular mechanisms that allow glia to sense neural activity. And that was a big surprise, because how would a glial cell on an axon sense electrical impulses flowing through it? But in my lab we grew fetal neurons in cell culture—special cultures that allowed us to stimulate them electrically. We have little platinum electrodes in there that let us stimulate the [action potential](#) firing in these axons. And then we plated glial cells that form myelin on those axons. And in doing these studies we can see that when we stimulated the axon, the glial cells received the signal, because we could see them glow with the calcium dye.

And then we began to block possible signaling molecules that the axon might release and that the glial cells could sense. And in doing that we found three different ways that activity can communicate to myelinating glia. And then we followed these cultures and found that when we stimulated the axons, we got more myelin. We get more myelin based on accelerating the development of glia. So, you get more mature glia that make more myelin; and also, a mature glial cell can form more myelin when the axon is stimulated.

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The *Brain Science Podcast* has been sponsored by [Audible.com](#) for almost three years. I know that many of you enjoy listening to the titles we talk about on the

podcast in audiobook format. *The Other Brain* is not yet available, but I'd like to recommend another book that I listened to recently that I really enjoyed. It was [*The Secret Life of the Grown-Up Brain: The Surprising Talents of the Middle-Aged Mind*](#), by Barbara Strauch.³ If you're new to Audible, you can get this as a free audiobook download by going to audiblepodcast.com/brainscience.

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Dr. Campbell: You've shown that if a lot of signals are going through that axon, the signal conduction is going to stimulate the glial cell to add myelin, and therefore speed things up in the future?

Dr. Fields: What we have shown so far is that an unmyelinated axon can become myelinated. And we wonder about whether a myelinated axon can form more myelin. We think that's very possible, but that's a more difficult thing to study. And we are studying that. But clearly we can find strong evidence that an unmyelinated axon that becomes electrically active is stimulated to have more myelin formed on it.

And that's important, because myelination takes place through the first 20 years of life in the human brain. And that, in and of itself, is kind of remarkable. If it was just insulation, why wasn't it done when we were born? What we're realizing is that unmyelinated axons in postnatal life are being myelinated according to the environment that we are experiencing, so that your brain is different from my brain, everyone's brain is different, because we're reared in a different environment. And that's what gives each of us our unique abilities.

One of the unique aspects of human beings is that we cheat evolution by evolving our brain in the environment that we're born in. And other animals, that are born with full myelination completed at birth, don't have that opportunity. So,

³ Note: I misspelled Strauch's name during the podcast. The transcriber has omitted my mistake.

the brain is developing all the way through adolescence according to our experiences. And much of this rewiring of the brain involves changes in synaptic connections; but myelination is also going on.

Dr. Campbell: Is this the reason why we have more brain plasticity when we're young—or one of the reasons?

Dr. Fields: It's definitely one of the reasons. And that's called the 'critical period of learning.' For example, if you learn to speak a foreign language after puberty, you will speak it with an accent; but if you learn before puberty, you won't. And that's because there are different critical periods for learning different kinds of skills and functions in the brain.

And it makes sense. We're all born with the ability as a baby to understand any sound in any language. But if you never hear that sound—for example, the Japanese culture never hears the sounds 'r' and 'l'—why have a brain circuit that can distinguish a sound you'll never hear? Well, the answer is, you don't. You get rid of that circuit because it's not useful.

But what that means is that after puberty a Japanese person has lost the circuitry to distinguish those two sounds, and can't hear the difference between an 'r' and an 'l.' And the same thing applies to us. There are Chinese sounds—'ching' and 'chang'—it sounds the same to us; and a native Chinese speaker would hear completely different sounds.

So, it turns out that myelin has another function, and that is to close this critical period of learning. And that was kind of a surprise. But what we know is that after the circuits become functional, and form these connections according to the experience and learning, myelination then proceeds, and myelin inhibits further sprouting of these axons and further forming of connections.

I'll give you another specific example. If you put a patch over the eye of a newborn kitten for a couple of weeks, and then take it off two weeks later, the kitten is blind forever in the eye that had a patch on it. There's nothing wrong with the eye, but the connections from the eye to the brain required electrical activity, interaction, vision—required visual input to wire properly to the right part of the brain for vision.

The same is true in people. That's why doctors want to correct cross-eyed conditions early, or cataracts in infants: they want to correct it, because if you correct it too late, the brain has been miswired, and you cannot correct the visual problem. It doesn't matter. Studies by [Strittmatter](#) in experimental mice found that when they blocked a specific protein that is in myelin, this critical period opened up—that you could rewire visual inputs to the brain of a mouse after this critical period had normally closed.

That was a big discovery in the field, and kind of a surprise. And it relates back to an earlier discovery that myelin is the reason that spinal cord paralysis is permanent—one of the reasons that if you injure a nerve in your arm it will regrow, but if you injure a nerve fiber in your spinal cord you're permanently paralyzed. And why should that be? Work by [Martin Schwab](#), and others, found that myelin was inhibiting axon sprouting. So, the axon that had been severed would start to grow and try to reconnect, just as would happen in the arm, but the minute it touched myelin it collapsed.

And that was a big surprise. But he went on to identify that there are proteins in myelin, and he found these proteins and isolated them. When these are blocked in experimental animals, then the axons can sprout again, and this can lead to improvement in mobility in these animals after spinal cord injury. And this is now being studied in clinical trials in people.

But the big mystery was why did nature booby-trap myelin to block axon outgrowth, with the consequence that people would be permanently paralyzed? It didn't make any sense. But now we see that it does make sense if you realize that the first two decades of your life are spent, in humans, making the brain to be ideally suited to the environment that you're in, and then once it's tuned to that environment through synaptic connections and myelin, then it is really no longer plastic: that's pretty much the brain you have for the rest of your life.

Of course, you can learn; but if you or I take up the violin now, we're not going to be concert musicians. A high school kid can take it up and three years later be giving an amazing performance with the violin. And we know that. But now we're getting to know that part of the reason for that is the other brain—glia—are closing the critical period by forming myelin.

Dr. Campbell: Before we move on, I want to talk about one other thing related to myelin. One of the subjects that I enjoy talking about on this show is brain evolution. And you talked in your book about the significance of myelination in evolutionary terms, and said that was the key thing that distinguishes vertebrates and invertebrates. Would you talk a little bit about that?

Dr. Fields: Sure. I'm glad you are interested in those things. As a former marine biologist I definitely have a zoological viewpoint on these things. And it is interesting that the reason for the success of vertebrates (vertebrates are the animals with backbones, like dogs, cats, and dinosaurs; invertebrates are like snails and worms), the main difference in the huge cognitive ability between vertebrates and invertebrates is due to the other brain—due to glia that form myelin.

So, myelin was invented by the vertebrates. Invertebrates don't have it. And what this did was it allowed the nervous system to become miniaturized and become concentrated. In an invertebrate, like a shrimp, for example, they don't

have myelin, and so neurons are placed throughout the body where they need them. So, there will be some around the mouth and some down by the tail. That's necessary because they don't have a way to send impulses over long distances at a high speed. The only way to increase the speed would be to increase the diameter of the axon; the same as you can get more water through a fire hose than a garden hose, if you make it bigger.

But there's a limit to that, so that the squid, for example, had giant axons. You can actually see the axon—it's a millimeter in diameter. But if we applied that solution in our optic nerves, our optic nerves would be three feet in diameter—just the optic nerve. If you have myelin insulation, you no longer need this fat axon; it can be a micron in diameter and conduct at high rates. Now you can concentrate the brain, get more neurons into the same amount of space, and specialize and concentrate these neurons into a brain.

The difference between our brain and the brain of a fly is not the neurons. The neurons work pretty much the same in invertebrates and vertebrates, right down to the same neurotransmitters. The big difference is glia.

Dr. Campbell: So, I guess this is just another reason why we don't really need to worry about giant insects.

Someone asked me this question, and I honestly didn't know the answer. I guess I would assume from what you've said that there aren't any Schwann cells or oligodendrocytes in invertebrates. Do they have any types of glial cells?

Dr. Fields: That's a very interesting question; and it's an area of intense research right now, trying to find the evolution of myelin. Because the first time we see myelin in vertebrates—and I've done electron microscopy studies—it's every bit as elaborate and as fully developed as it is in us. So, it comes out of nowhere. It's amazing, because it's such an intricate structure. If you can

imagine what's involved in a cell recognizing an axon, and wrapping 150 layers of membrane around it, it's a very complicated cellular process. Yet, it's fully formed in the body and in the brain the first time we find it.

So, people are interested in looking in earlier animals, and trying to find the forerunners of myelin. Definitely there are glial cells in invertebrates, and whether these are the same cells that gave rise to myelin-forming cells in vertebrates, or if they're a kind of an analogous cell trying to do a similar function is an issue.

So, you do find in shrimp, for example, some cells (they're actually called 'Schwann cells,' but they shouldn't be, in my view) which are non-neuronal cells that will adhere to axons, and begin to kind of insulate them by forming shingle-like layers around them. So, invertebrates definitely have glia, and they perform many of the same functions, and we're now just trying to understand what those glia are.

It's particularly important in doing this in flies, because of the power of genetics in flies. If we can find out what a glial cell equivalent microglial cell is in a fly brain, for example—we can then begin to do genetic studies, and knock out different genes in these animals, and begin to understand how these glial cells do what they do. Very often those same genes are found in vertebrates.

Dr. Campbell: When we were talking about the types of the glial cells, you mentioned the ones that take up the neurotransmitters in the synapse. Are those [astrocytes](#)?

Dr. Fields: Yes.

Dr. Campbell: I don't think we named them before. Do they do anything else that's interesting, that we might talk about?

Dr. Fields: Well, they're called 'astrocytes' because they looked like stars in the early studies where we were using the classic stains we used to stain them. They were also called 'spider cells.' But I think that 'astrocytes' describes them quite well. But we now know that they don't actually look like stars at all—that those stains were just staining the skeleton—and only in the last five years have we found, using new methods to stain the whole cell, that they're extremely bushy, large cells—very complicated.

One astrocyte will wrap around 100,000 synapses, and can control those synapses. But these astrocytes are arranged in the brain in a tile-like manner. They don't overlap. That was a surprise. So, somehow these astrocytes, we think, are controlling groups of neurons, putting a different higher-level structure on the brain.

So, the things the astrocytes do are they take up neurotransmitters, they release neurotransmitters, but they also release growth factors—which are substances that stimulate neurons to live and grow, and protect them after stress and injury. Astrocytes release antioxidants—very power antioxidants. Astrocytes respond to disease. So, after a stroke or a brain injury, the first responders are astrocytes and microglia. And we can see them change their structure in their genes, and they begin to spew out different kinds of chemicals that initiate the healing process.

Astrocytes also take up ions. When the neuron fires, it fires because it is a battery. But those batteries involve the flow of ions—in particular, sodium and potassium ions. And as those ions are dumped out of a neuron, they build up, and the battery in a neuron, in effect, weakens. Well, an important function of an astrocyte is to take up that potassium that neurons release when they fire, and dump that back into the blood stream.

Astrocytes provide the nutrients to neurons. So, they are associated with capillaries, and deliver glucose and lactic acid to the neurons, providing the fuel. In fact, that's how brain imaging works. We now know—and this is a recent discovery, as well—that astrocytes can control the blood flow on a micro scale in the brain.

So, when you see these beautiful images of functional MRI, where you see a little red blob in this part of the brain that says these neurons are active when you're doing this kind of a process, you're not actually seeing neurons. You're actually seeing glia responding to neurons needing more oxygen and nutrients, and controlling the diameter of capillaries. So, that's another thing that astrocytes do.

And the last thing I'd like to mention is that astrocytes can give rise to other kinds of cells. They have stem cell like properties. And that's an important function. So, astrocytes do a lot of things.

Dr. Campbell: Are the astrocytes the ones that make up the [blood-brain barrier](#)?

Dr. Fields: Yes. Astrocytes are involved in regulating the blood-brain barrier, and they are a component of the blood-brain barrier. That's important in stroke, and in migraine, and conditions that involve controlling local blood flow. So, what happens there is a neuron is active, the astrocyte will sense that activity, and then the astrocyte releases substances that control the diameter of the blood vessel. Astrocytes also release substances that control the permeability, or diffusion of substances through the capillaries in the brain—the blood brain barrier, so-called.

Dr. Campbell: We're going to take a short break, and when we come back we'll talk a little bit about the role of glial cells in health and disease.

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Dr. Campbell: Doug, in *The Other Brain* you give a very high-level overview of the role of glial cells in a wide variety of diseases, ranging from spinal cord injury to mental illnesses, like addiction. I thought perhaps you might like to pick one area to talk about today, just to give listeners a feel for the impact that these new discoveries are likely to have beyond basic science.

Dr. Fields: Let me put it another way to tell you what is most exciting to me about these new discoveries on the other brain; because, in a way, we understood that glia were important in disease, but somehow the other shoe never dropped, and we didn't realize, well, if they're so important to disease, they might be important in normal cognitive function. So, as kind of a transition to this subject let me review again the most startling things that we've learned.

First of all is that glial cells can communicate. And they can communicate among themselves without using electricity: they communicate chemically. That was the first surprising discovery. Secondly, that glial cells can sense neural activity, so they can pick up activity in a neuronal part of the brain and communicate that through the glial part of the brain. And the third thing was that they can control information flow through neurons, through synapses in another part of the brain.

Those are the three things that made it very exciting to me, and most people, because this meant information processing in the brain was involving a lot more than neurons. It was information being picked up in the neuronal brain, communicated non-electrically through a non-neuronal brain, with a different mechanism of communication—like cell phones broadcasting these signals, instead of like land lines—that neurons use to communicate across synapses, and then control a synapse somewhere else in the brain. That was interesting.

An example of disease that I guess kind of reinforces that is chronic pain. Chronic pain is different from the normal kind of pain that we experience, that saves you from burning your hand on a stove. That's obviously very important.

But chronic pain has always been very mysterious. It develops after an injury has healed. So, you injure your back, and it will get better, but the pain doesn't go away, and sometimes can become excruciating, and get to a point where these people are suffering from chronic pain to the extent that they can't work. Normal sensations are extremely painful—they can't put on a pair of socks, vibrations in the floor from walking are intolerable, that sort of thing. It's very mysterious.

The reason it was mysterious for so long is that we were not understanding the other brain. We assumed that the pain had to do with nerve endings, entirely—nerves. Our only treatment was to give powerful pain-killers, or narcotics—morphine. And that would work, but as you know, morphine loses its potency. That's called 'tolerance;' meaning that the same dose is no longer effective in reducing the pain.

That was mysterious, too. But the fact is you have to continually increase the dosage to get the same pain-relieving effect. And then what happens is you now have a pain patient who may be addicted to narcotics, because if you withdraw the narcotics, suddenly a person will experience excruciating pain. And it's the same pain that a junkie quitting cold-turkey from heroin experiences: light and sounds become excruciating—normal sensations.

So, considering the other brain has eliminated a lot of these mysteries, because it turns out that the glia in the spinal cord (microglia, mainly; but also astrocytes) are monitoring the pain information—the neural activity in pain fibers. And they respond to that pain—that initial injury—and they release substances that are important in the healing process, but they intensify the pain by exciting neurons.

Now, that's fine right after an injury—supersensitivity is fine. It makes you leave this injury alone, so it will heal. But that needs to subside with time. And if these glia don't stop releasing these substances that excite pain neurons, then you will continue to feel excruciating pain after the injury has healed. This new

understanding is leading to new treatments that are based on blocking the signals from neurons to glia that allow a glia to sense neural activity; and also blocking the substances that glia release that excite neurons.

And at the same time, beginning to understand the other brain in a function we thought was strictly neuronal, has led to insights into addiction, because it turns out that glial cells have the same receptors for morphine and oxycontin, or the same kind of chemicals. And what happens is glia try to maintain a homeostasis—a balance of activity. And when morphine would lower the activity, the glial cells would try to compensate for that by releasing substances that are excitable.

That brings back that higher-level of activity of the brain, and in the pain fibers, and now you'd need more morphine. Glia would release more of these excitatory materials, and so this ratcheted up to a point where, if you then removed the opiate, then you would have the brakes released on this process, and there would be extreme excitation and pain.

I think that's one good example. It's hard to pick just one, because there are so many: spinal cord injury, Alzheimer's, and neurological disease.

Dr. Campbell: Before we close, I want to make sure that we talk a little bit more about the implications of the discovery that the glial cells have what looks to be two-way communication with the neurons. Can you talk a little bit about the work of [Mark Ellisman](#)? Wasn't his work important in this area?

Dr. Fields: His work was important in determining that glial cells—astrocytes—really were much more complicated and bigger cells than we thought; and that they had this non-overlapping domain on the brain. So, the work I talked about earlier, I was actually thinking of Mark Ellisman and [Eric Bushong's](#) work.

Dr. Campbell: The discovery that they made of that tile-like way that they're arranged, with their own unique territories, wasn't that in the hippocampus of a rat?

Dr. Fields: In the hippocampus, yes, originally—which is the part of the brain involved in memory. But that has been now generalized to many other regions of the cortex; so it's not unique to the hippocampus.

Dr. Campbell: But the fact that it is in the hippocampus brings up a lot of questions for me. You mentioned earlier that the astrocytes also might act as stem cells. We know that the hippocampus is also one of the places where we actually can get a few new neurons. I'm wondering if they might actually be coming from glial stem cells. Has anyone been able to prove that one way or the other yet?

Dr. Fields: Well, yes. Mature neurons can't divide, so you're not going to get new neurons born from other neurons. And we now know that there are new neurons born in the adult brain. You're correct; the hippocampus is one area that shows neurogenesis in the adult, in response to things like exercise. The field has now studied and found the molecules that are involved—like growth factors, [BDNF](#), and what not—that are liberated with exercise, stimulating these neurons.

All the antidepressant drugs that are used were recently, in the last few years, discovered to stimulate the birth of new neurons in the brain. And we didn't ever suspect that, or know why. Neurons can't make new neurons, so it has to be a cell that can divide. And it turns out to be a primitive glial cell that gives rise to these new neurons. So, these treatments for depression are working, in part through glia, to stimulate the birth of new neurons. And this advice we hear to do exercise, and what not, to promote neurogenesis, is also working through glia.

There is a new mysterious kind of glial cell that I didn't mention, that may be a fourth kind of glial cell in the CNS; and this cell is a stem cell. It's a glial stem cell. (I use the vernacular: stem cell has a narrow meaning in biology.) But the point is these cells are scattered throughout the human adult brain. 5% of the cells in the brain are these glial cells that can go on to form new neurons—new oligodendrocytes and new astrocytes—in the adult. And there's a lot of interest in that.

But back to your question about the tiling and the communication between the other brain and the neuronal brain, I think it's important to emphasize that glia are doing something different than neurons. So, it's a new dimension of brain function, and it's expanding our complexity of the brain. Glia don't communicate rapidly, like neurons do; so they're not going to be involved in reflexes and things. They communicate slowly. These waves of calcium that I described take place over the order of seconds or minutes.

And then your question about the non-overlapping domains shows that there is a huge large-scale control on the brain. One astrocyte is controlling 100,000 synapses. This, again, is different from neurons. So, the other brain is doing something different from the neuronal brain. But a lot of the things that our brains do involve coordinating information among various parts of the brain, and also changes with experience that take a long time—learning to play the guitar, or something like that.

[music]

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[music]

Dr. Campbell: Well, obviously, we've only scratched the surface of this exciting area. There was one other thing I wanted to ask you about. You mention many different scientists in your book, but I was particularly interested in the story of Dr. [Ichiji Tasaki](#).

Dr. Fields: Oh, yes. He was a wonderful neuroscientist here at the National Institutes of Health, and he discovered how impulses are transmitted through myelinated fibers. And I was pleased to know him. He worked here seven days a week, and walked to work every day, until he was 98. He made a number of fundamental discoveries of information transmission in the brain, and recorded and used mathematical modeling to understand the brain. And he was an early pioneer in understanding the importance of glia in the brain.

Dr. Campbell: You mentioned in the book that he had some instrumentation that showed that axons were basically twitching when they fired impulses. Was this an important clue to figuring out how the glial cells were able to detect their signals—or an indirect clue?

Dr. Fields: It really is. The only reason I'm hesitating is that paper right now is not yet published.

You've covered so many areas, but I think one other thing I'd like to comment on is psychiatry. In a way, it's easy to understand, in retrospect, how glia are involved in neuronal disease—cancer, Alzheimer's, Parkinson's, and these sorts of things. And they definitely are. But the idea that they'd be involved in mental illness, like schizophrenia or depression, seemed very remote.

But the new research is showing that glia are involved in many of these disorders. And part of this has come about by using gene arrays that allow us to study what genes are abnormal, say, in a brain of a person with schizophrenia. And many of these genes turn out to be genes that are only in glial cells—myelinating glia. That's made people realize the flow of information through the brain probably is what's being disrupted in many psychiatric illnesses, where myelinating glia could be involved.

Secondly, all of our treatments for mental illness are based on controlling synaptic transmission—that is, the flow of a neurotransmitter from the presynaptic neuron to the postsynaptic neuron. They're treated with drugs like [SSRIs](#), that inhibit the re-uptake of a neurotransmitter and sustain that signal. Well, glia cells—the astrocytes that we were talking about—are the cells that normally perform that function.

So, although we never would have thought of non-neuronal cells being involved in mental illness, schizophrenia, depression, now it makes perfect sense that the cells controlling these neurotransmitter levels would have a role in mental illness. This opens new opportunities for new drugs, and also the realization that some of the drugs we're using now are probably acting through glia.

Dr. Campbell: And also, it sheds some light on some of the long-term side effects that you see, like with the drugs for schizophrenia, that then later cause Parkinsonian symptoms. That probably is involving glial cells, too, isn't it?

Dr. Fields: There's no doubt that glia are involved in mental illnesses. So, there are fewer astrocytes in the cortex of people with schizophrenia and depression. So, the glial cells are changing. Part of that is the normal course of the disorder, and part of that probably does have to do with reactions to the drugs that are being used to treat these conditions.

Dr. Campbell: Well, Doug, what do you think is—from your standpoint—the most exciting question that you would like to see answered before the end of your career? Is there one, or is it a many kind of question thing?

Dr. Fields: It is many. Right now, in the near term, I'm interested in this form of learning that doesn't involve synapses—that involves glia—controlling impulse propagation through the network: the role of myelin and learning. I'm very interested in that right now. And that's what my lab is mainly focusing on; because we focused our interests and had such a narrow-minded view of learning—just this 25 nanometer space at the synapse—and now we're beginning to realize that, like an Internet, you have to look at the flow through this whole circuitry if you want to understand learning and improving performance. So, that's one thing.

I'd like to understand in general more about the other brain, because this is a new discovery. You know I want to kind of get across the idea that the book is not a textbook. I hope it's an enjoyable read. It's meant to be that. What I hope that it gets across is the excitement of doing science, and having a revolution in science unfold in real time. You know we hear about all these scientific revolutions in an historical context, but to have one happening right now in real time is very exciting. Our whole idea of the brain is changing.

This information is only now getting out into the textbooks. It really isn't even in the textbooks yet. And there's nothing out for the popular audience. So, it's that

delight and discovery of doing science, and having your old ideas overturned, that is something I really hope people take from the book.

Dr. Campbell: I thought it was an excellent example of storytelling in its finest sense, from that point of view.

Do you have any advice for students who might be interested in exploring this area further?

Dr. Fields: It is a growing area. That's another thing that's interesting: how do you overlook half the brain for a hundred years? It's because there weren't people studying glia, and it wasn't considered important, and so it didn't get published. And so, it wouldn't have been the best career path before, because you're not going to get funded and you're not going to get published unless you're working on things that are trendy. And that's always a problem. I mean there's nothing sinister about that; it's just the way societies work. And science is very collaborative.

And to get around that we and other scientists started a new journal, and then we were able to publish our work in this journal. And then people began to hear about it. And now it's very well received. And all the journals are publishing now in this field of neuron-glia interactions, and see that it's very important.

So, I think that students who want to study glia won't have any problem now. Just bear in mind as an object lesson that when you look through the history of science, it's not always the trendy stuff that is the future—that it's often very obscure aspects of science or the interface of two disciplines that don't really seem to fit together. That's where these new understandings and new fields develop. So, young people should always be looking for that in the course of science.

Dr. Campbell: That sounds like good advice. Is there anything else that you'd like to share before we close?

Dr. Fields: Well, I think you've probably covered it pretty well.

Dr. Campbell: Your book has a website?

Dr. Fields: Yes. It's theotherbrainbook.com.

Dr. Campbell: And you have a blog in various things associated with that.

Dr. Fields: Yes, I've been blogging for [Scientific American Mind](#), and [Psychology Today](#), and [The Huffington Post](#). And there is a blog associated with my book website, but I'm not keeping it up to date right now, because I've been so busy with the book.

Dr. Campbell: I know how hard it is.

Dr. Fields: But the thing about the book's website is people can go read the first few chapters and see if they find it interesting.

Dr. Campbell: OK. Well, I really appreciate you taking the time to talk with us today. This will probably go out in a couple weeks, and I'll send you links to everything.

Dr. Fields: Please do; and I'll put it up on my website.

Dr. Campbell: We left some stuff out, but I think we gave them a good introduction.

Dr. Fields: Yes, I do, too.

[music]

I want to thank Dr. Fields for taking the time to be my guest on the *Brain Science Podcast*. You will be able to get links to his website and detailed show notes and episode transcripts at brainsciencepodcast.com.

In our interview we kind of skipped around, so I want to go back and review a few of the key ideas about glial cells. First of all, remember that glial cells are the non-neuronal cells in the nervous system—including the brain and spinal cord—and they actually make up 85% of the cells in the nervous system.

Glial cells do not generate action potentials, which is why for a long time scientists didn't realize that they were able to communicate. However we now know that they are able to communicate. The main way that the glial cells communicate is by a transmission of a calcium wave; which Dr. Fields talked about quite a bit today. They also communicate by something called 'gap junctions,' which we didn't have time to talk about, but which I did introduce back in [Episode 8](#) of the *Brain Science Podcast*.

Another thing we didn't really talk about much is the fact that, not only do glial cells have receptors for neurotransmitters; they are also able to communicate by releasing neurotransmitters. Two key ideas about the way that they communicate are that they communicate much more slowly than neurons do, and over larger areas of the brain. So, as Dr. Fields emphasized, their role in communication in the brain and nervous system is definitely different from that of neurons.

Glial cells were once thought to be only support cells. It is true that they provide essential supportive functions. Some glial cells—specifically Schwann cells and oligodendrocytes—make myelin. Some—especially the microglia—are involved in immune function. And others are involved in forming the blood-brain barrier,

and cleaning up the neurotransmitter that's left in the synapse after a signal. But the thing that is revolutionizing how we look at glial cells is our new appreciation of the fact that they both monitor and influence neuronal signaling.

They also appear to be essential for brain plasticity; which is a subject that we have talked about several times in the past. They are very important during the critical period of brain development. Glia are also important for synapse formation and synapse health. Glial cells are involved in some way in every brain disease, and learning more about how they work offers new hope for treating many conditions.

Now, there were a couple of things Dr. Fields said that I think could lead to some possible misunderstanding. One is that he said that we don't make any myelin after the age of 20. I think that recently there has been some evidence that new myelin is able to form even in adulthood. And this is, of course, part of our new appreciation of the fact that our brains are more plastic as adults than we once thought.

Another thing that Dr. Fields alluded to was the problem of chronic pain patients becoming addicted to narcotics. While it's true that some patients do develop addiction, I think it is important to note that addiction and tolerance are not the same thing. So, if you're on a narcotic for a long period, you will definitely develop tolerance. And if you suddenly try to stop using the narcotic, you will have signs of withdrawal. But that does not necessarily mean that you're an addict.

An addict is a person who uses escalating doses of a narcotic or other substance. An addict basically is a person who will ingest however much of their chosen drug they can get their hands on. I can tell you from my personal experience as a physician, there's a big difference between addicts and chronic pain patients who have tolerance. The fact that so many physicians even misunderstand this

distinction is a source of much suffering, because doctors are often reluctant to give their patients adequate dosing because of the mistaken belief that they are all going to become addicted.

Tolerance does not equal addiction. So, if a person stays on a relatively stable amount of a narcotic, the fact that they would go into withdrawal if you suddenly took that away from them does not make them an addict. However, it's probably more important to appreciate the significance of the discovery of the role of glial cells in chronic pain and addiction, and that this, again, offers new hope for treating these difficult conditions.

As always, there's a lot more information in the book that we did not have time to talk about today; especially on the topic of why myelinated fibers are able to conduct so much more rapidly than non-myelinated fibers. So, I definitely recommend Dr. Fields' book, [*The Other Brain*](#). It is a good combination of neuroscience and scientific history, and I think that you will all enjoy it.

Before I close, I need to talk candidly about the future of the *Brain Science Podcast*. First a little background: From December 2006 through December 2008 I produced two episodes of the *Brain Science Podcast* every month, and I also put out an average of one *Books and Ideas* podcast a month. Then last January I moved to my current monthly schedule, which made things a little bit more manageable.

But in recent months I have come to the conclusion that podcasting is unlikely to ever produce an income proportional to the time and energy that I have invested. In fact, in 2009 I lost money. Considering the quality of the content I have created in the last three-and-a-half years, I have to admit I am discouraged. And I think I'm a little burned out.

So, I've decided to take the summer off. I need a break from the constant pressure to create new content, and I also need some time to reevaluate my goals, and see how I really feel about podcasting. Do I want to continue it as a hobby? I have an interview scheduled for September, but I'm not sure what I'm going to do after that.

If you are new to the *Brain Science Podcast*, this break in new episodes will give you plenty of time to get caught up on the older episodes, since most people like to start at Episode 1 and work their way forward. If you're a long-time listener, I hope you will use this as an opportunity to catch up on any episodes you might have missed.

Be sure to stay subscribed. I plan to put an announcement in the feed next month for the sake of the people who aren't listening to this announcement. There are a lot of people who don't listen to the closing announcements.

If you haven't already done so, I hope you will check out my other podcast, *Books and Ideas*, at booksandideas.com. And if you're looking for more science, don't forget my website, sciencepodcasters.org, which is a great place to find podcasts from a wide variety of scientific fields.

As always, I would appreciate your feedback. You can send me email at docartemis@gmail.com, or join the *Brain Science Podcast* [Fan page](#) on Facebook and post your comments there. I also hope that you will go to brainsciencepodcast.com and sign up for the [newsletter](#), so that I can keep you informed on what's going on.

I want to thank everyone for listening and sharing the *Brain Science Podcast* with their friends, family, and colleagues. I will, during the summer, be maintaining the websites. I've got lots of loose ends to try to get caught up with. I will be answering emails, and you can also follow me on Twitter as [Doc Artemis](#).

I hope to talk with you again soon.

[music]

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