Speaker 1:

Welcome to Optimal Neuro|Spine Podcast, a podcast about optimizing our brain and spine in health and disease. Each episode leading neuroscientists, neurosurgeons, educators, patients, spine care, and quality improvement experts discuss their research, experience, emerging science, surgical advances, and insights about how to optimize neurological and spine care. Now here's your host, Dr. Max Boakye.

Dr. Max Boakye:

Welcome to the Optimal Neuro|Spine podcast. My distinguished guest today is Dr. Vania Apkarian, who is professor of physiology, anesthesiology, and physical medicine rehabilitation at Northwestern University in the Feinberg School of Medicine. He has been a pioneer in the use of magnetic resonance spectroscopy to study the neurochemistry of the brain and the development of novel analytical approaches to study consciousness. He has studied pain for over two decades, both in animal models and in functional magnetic resonance imaging studies in humans. His current interests include the cortical dynamics of pain as well as brain plasticity. His overall goal is uncovering brain mechanisms underlying the pain qualia in order to alleviate clinical pain conditions and achieve a more profound, theoretical and mechanistic understanding of the brain.

Dr. Max Boakye:

Dr. Apkarian, Professor. Welcome.

Dr. Vania Apkarian:

Thank you. Thank you, Max. Thanks for having me.

Dr. Max Boakye:

So you've studied pain for over two decades. You're considered an expert on chronic pain mechanisms. Let's start by you defining what is meant by chronic pain.

Dr. Vania Apkarian:

Yeah. I'd say it's a good question. And surprisingly, in fact, the answer, it tends to be a bit obscure. But by and large, the functional definition of chronic pain is pain that persists after the initial injury related healing process ends. So the more clinical definition is pain that is experienced for many, many months. And the definition from a clinical viewpoint has been changing a bit, depending on who you ask. Some people insist that increase pain that persists for at least three to six months should it be called chronic pain. Others can push that foot even further out to longer time durations. What is fundamentally the idea of chronic pain is that the injury events that may have initially induced a pain condition are long gone, and yet the perception is still there.

Dr. Max Boakye:

What is the epidemiology of chronic pain? How common is it?

Dr. Vania Apkarian:

Well, that's a very scary picture. This is something that in fact, both the US and the World Health Organization have realized how common it is. In fact, the most current estimates is that somewhere between 15 to 20% of the world population has chronic pain. That's a huge number. That's a number that trumps every other clinical condition in the world. And so in the US nowadays, the estimate of

chronic pain is that it costs society somewhere around $500 billion a year, both in care of patients, as well as loss of productivity by patients who simply end up being disabled with the condition. Since chronic pain does not kill people, traditionally its impact on society has always been underestimated. But most recent estimates are, these are the numbers. They're huge.

Dr. Max Boakye:

Okay. How well do we currently manage chronic back pain?

Dr. Vania Apkarian:

Well, how well do we manage chronic pain in general? We both the US, NIH, and the World Health Organization agreed that we do not have any treatments specific for any chronic pain. So we don't have any treatments that are been validated or scientifically tested that can actually properly manage chronic back pain. So as a result, chronic back pain or chronic pain, in general, is managed by a hit and miss sort of procedures.

Dr. Vania Apkarian:

Drug treatments tends to be drugs that have never been properly validated as to the efficacy for chronic pain. They are used because they work for acute pain and we substitute them by simply assuming that well, chronic pain is kind of acute pain but it's there for a longer time period, which is clearly not true. And which is what I have dedicated the last multiple decades of my life showing that that statement is not true.

Dr. Vania Apkarian:

So in fact, I think multidisciplinary management of chronic pain is probably the most successful treatment approach. It's very expensive. It's very hard to administer and it's used minimally because we don't have the resources for it. Otherwise, we really don't have any treatments that- Okay, let me not exaggerate. I should say that we have treatments that work in reducing pain by about 30% in 30% of the people who have the condition. And that's a very visible number.

Dr. Max Boakye:

What are some of the biggest misconceptions about the relationship between acute and chronic pain? Are the treatments the same for both conditions?

Dr. Vania Apkarian:

Traditionally, both scientifically and clinically, we have assumed that chronic pain is simply acute pain that's being continued. So in a sense, anything that works for acute pain should work for chronic pain. Yet, that has been also a lesson that we have learned very hard in that the best example are opiates. Opiates work fine for acute painful conditions. They're the best drugs we have for acute analgesia. And they have been used in millions of people for chronic pain. And the result has been the opiate epidemic that the US has been suffering and now, other countries, including European countries, are suffering from as well. Essentially that people do end up on opiates and a large number of them are addicted. And it becomes a direct healthcare pathway for opiate addiction and opiate related deaths.

Dr. Max Boakye:

So you've published some really seminal papers on the mechanisms of chronic pain. What are some of the most important findings that you've discovered in the brain and in chronic pain mechanisms in general?

Dr. Vania Apkarian:

I mean, all studies for the last more than 20 years have continuously demonstrated that chronic pain is different from acute pain, right? In a sense, if we do brain imaging in patients who have chronic pain, and we actually say what are the brain areas that reflect the pain that the patient is suffering from, but those brain areas tend to be very different from the brain areas we identified when we instead pinch the skin off of the patient or give them a heat stimulus that will give them an acute painful perception. So at least the wind activity related to the perception of ongoing pain seems to be different. And moreover both in human and animal studies, we have shown that there is in fact brain anatomical reorganization, connectivity of information, circuitry properties in the brain that are all changing as pain becomes chronic.

Dr. Vania Apkarian:

So, and in a very simple way, an acute painful stimulus is a perception that one associates with that stimulus from the outside, from the environment, while as the pain becomes more chronic, it seems like that perception of the pain becomes more introspective in its properties. And that in a sense, the brain circuitry that have to do with emotions, with motivation, with learning, are all being ramped up and reorganized and that they all become part of the brain network that's engaging the pain state.

Dr. Max Boakye:

So when I was in medical school, I was taught that pain was, you have a stimulus in your hand or leg, and it travels through something called a spinal thalamic track and ends up in the somatosensory cortex. So that's no longer the right way to think of it?

Dr. Vania Apkarian:

Well, that's the right way to think of it for an acute painful stimulus. That classic concept is absolutely correct as long as one is studying an acute pinprick injury, a skin lesion, those all activate that pathway. Now with that pathway, the properties of that pathway seem to shift in time as the pain become more chronic and it's shifting away from this sensory representational circuitry into more emotional circuitry.

Dr. Vania Apkarian:

So chronic pain is engaging all these brain limbic areas that have to do with emotional evaluation. And in a sense, it becomes more of a memory state, more of a learning and motivational state than purely a stimulus related state.

Dr. Max Boakye:

In one of your recent papers, and I'm quoting here, you wrote that, "chronic pain is associated with a global functional reorganization of brain activity. This concept of global reorganization starts with the hypothesis that chronic pain may be characterized as an abnormal network state." So basically, the brain networks are dramatically abnormal in essentially all patients with chronic pain?

Dr. Vania Apkarian:

In retrospect, it's not a very revolutionary idea, but until we demonstrate it remains unknown. But very simply, I mean, the fundamental problem with the chronic pain patient is that the patient is suffering, right? They're suffering, and they have to cope with this negative state of being, this unpleasant, negative reinforcement state, which is constantly there. That state of negative emotional state is going to impact basically information processing in the brain everywhere. And that's what we are showing that in fact, the amount of information shared across brain areas become abnormal. And they're abnormal in proportion to the amount of chronic pain that the subject is suffering from directly. It's in proportion to the amount of pain. But what is interesting is that that reorganization only happens if the pain is chronic or acute painful states, that doesn't happen. In a way that the level at which the brain is engaged with this negative state has dramatically shifted. And it affects all information processes in the brain. One clinicians notice probably quite readily in that chronic pain patients are suffering by many cognitive abnormalities that they complain about, right?

Dr. Max Boakye:

So these brain changes, is it different for back pain versus other forms of chronic pain or it doesn't matter, all pain is the same?

Dr. Vania Apkarian:

No. I mean, even the patients know the difference between different types of pain. And so the brain has to have unique states. And importantly, a person who has back pain does not confuse that back pain with headache pain, for example. They may have headaches or not. On the other hand, the question is very important. We think both exist at the same time, in a sense that all chronic pain patients have a whole brain reorganization. On top of that, they have reorganization of networks that are specific to the pain itself, to the kind of pain that they're having. So the brain is a very complicated network with billions of connections shifting in time. So that reorganization of the state of being in chronic pain seems generally shared across types of chronic pain. But on top of that, one could demonstrate that different brain regions and their connectivities and their information exchange across areas are unique. For example, for osteoarthritis versus chronic back pain, fibromyalgia, et cetera.

Dr. Max Boakye:

Can you talk about the role of the mesocorticolimbic system in chronic pain, the role of reward motivation? What have you discovered to be the changes in these emotional areas?

Dr. Vania Apkarian:

Right. So we think those are playing a critical role for both becoming a chronic pain patients and for living in chronic pain as well. We have demonstrated in a series of studies that the properties of these brain areas. So what is the meso limbic circuitry? The mesolimbic circuitry in a general sense is providing an emotional overlay of the cognitive calculations that the cortex is doing. In that sense, the properties of mesolimbic circuitry, the extent to which, in a sense one's emotional interpretation of their environment is a critical factor for a person developing a chronic pain.

Dr. Vania Apkarian:

Let me unpack that a little more. If we take two patients who end up having the same exact injury, one of them will develop chronic pain and the other one will not. What we have been emphasizing over the last 20 years is that it is not the injury properties that are determining who is developing chronic pain versus not. It is the brain emotional interpretational circuitry, learning, motivation circuitry, and how

that circuitry is designed to start with. When that injury happens is at least an important factor, if not the important factor where the patient now with the healing process, whether the pain goes away or if the pain persists. And if the pain persists, what happens is that this circuitry is in fact, pushing the cortical circuitry to reorganize this connectivity. As a result, we end up with this informational abnormalities that we think are fundamentally driven by learning signals that are coming from these limbic regions that are flooding the cortex and reorganizing the synaptic properties of the cortex and putting the cortex into a new state, which is the chronic pain state.

Dr. Max Boakye:

That is fascinating. You also wrote in one of your papers- and I'll have these on the websites, links to these papers. You wrote that, "it is quite striking that there's a clear overlap between the addiction brain secretary and brain secretary that causally link to the development of chronic pain." This is fascinating because it kind of begins to shed light on why opioids are front and center and there's the opioid epidemic. If there is such an overlap between the addiction areas and the pain, chronic pain changes. Can you discuss that?

Dr. Vania Apkarian:

Yes, of course. Yes. So that's my favorite topic nowadays is what we are studying in many, many different ways. And in fact, our center is now specifically funded to look to disentangle the brain in chronic pain versus the brain in chronic pain and with exposure to opiates. In a sense, what we see is that the brain dopaminergic circuitry, the circuitry that has to do directly with addictive behaviors where rewarding stimuli drugs can lead into addiction are causally also involved in chronic pain. And now we have shown that both in human studies, as well as an animal studies, when we change the properties of neurons in these regions, in this dopaminergic circuitry in animals, we can reverse chronic pain behavior. In humans, that circuitry is predictive of who will become chronic pain or not.

Dr. Vania Apkarian:

And as you implied already, that circuitry is definitely also involved in the opiate reward. In a sense the opiate addictive circuitry is the same circuitry that we think is also causally linked to chronic pain. So the confluence of the two in fact makes a really complicated system where the interaction between reward and the negative reinforcement and the existence of chronic pain and how they interact with the addition of opiates and opiate circuitry are very complicated system, which we're now studying both in human and in animal models, actually.

Dr. Max Boakye:

Wow. This is fascinating. I also want to ask you about the role of learning and memory for development and maintenance of pain. Once again, this review paper you wrote is fantastic. You wrote that you established the idea that chronic pain can be seen as a continuous state of learning where pain is repeatedly associated with negative mood and adversive emotions, leading to plastic changes, accommodating new memory traces and hippocampal neurogenesis. Can you expand on that? This is amazing. I never thought of pain that way.

Dr. Vania Apkarian:

Yeah, well, I mean, again, the old masters in the field knew these things better than us. But we have to rediscover them by new technology and actually put some real human elements into it. But if one psychologist, for example, Pavlov knew that the best way inducing a long-term memory was a painful

stimulus. And that's what learning neuroscientists have used for the last a hundred years or so, right? Yet the pain scientists had forgotten this idea. A very large portion of people who do learning and memory research, especially in animals begin with shocking the animal with an electric shock. That is obviously a very painful acute event. And that animal does not forget that event for the rest of their life.

Dr. Vania Apkarian:

Now, if we expand that to a patient who's in chronic pain, every time that pain goes up or down, that's a huge learning signal. That's a hypothesis we put out about 10 years ago, and we've been sort of pursuing it in different ways, both again in human and animal studies. And at least in modern neuroscience, learning and memory circuity all concentrate on the primary hub, which is the hippocampus, right? Hippocampus we know is the source of memory in coding, memory recovery, memory consolidation, reconsolidation, all of that.

Dr. Vania Apkarian:

So over the last 10 years, we've been sort of looking at hippocampal properties and how hippocampal properties are shifting and changing with chronic pain. And we now have evidence for that. Again, both in humans and animal models.

Dr. Vania Apkarian:

In humans, we see the hippocampal information sharing with the rest of the brain is another factor that determines risk for developing chronic pain. And that connectivity is continuously shifting as a person moves from an acute pain state to chronic pain. In animals we take that model now and start to [inaudible 00:21:34] the circuitry within it.

Dr. Vania Apkarian:

We recently published a paper showing that in fact, specific part of the hippocampus, if we increase the excitability of neurons in that region, we can completely block chronic pain behavior in animals. So the circuitry of the hippocampus is very complicated and it has different pathways with which it interacts with the cortex and different parts of it seem to be involved in different components of chronic pain. But fundamentally, all of that is saying that storage of information of the pain experience continuously impacts the subject's experience of pain itself. And then memory circuitry are a critical part of being in chronic pain.

Dr. Max Boakye:

You're using both animals and humans in your research and how do they inform each other the difference models?

Dr. Vania Apkarian:

Yeah, I know that's a very important question. We've been using both species in our research for more than 20 years and we continue to do that. But the important thing is that all animal studies start in reverse translation, in that the human brain imaging studies and hypotheses that we generate from human data is what we then use to explore the circuitry in a more mechanistic interventional way in animal models. And in that sense, once we identify these limbic circuitry components of limbic circuitry in human patients, then we go back into these circuits and look at how synopses are changing. The morphology of these neurons are changing. Their connectivities are changing and try to intervene. And

in that sense, try to identify circuits and targets for developing drug development specifically for chronic pain from this brain centric viewpoint, which is quite different from the classic approach, which has always targeted the periphery, the peripheral nerve, the spinal cord circuitry to find drug targets.

Dr. Max Boakye:

The changes that occur in the brain, I assume they're not good changes, right? They are maladaptive.

Dr. Vania Apkarian:

Well, that's a great question, Max. It's more complicated. It's both partly adaptive and partly maladaptive. In a sense that a patient who has chronic pain also has to create strategies with which to cope with this negative state of beingness, right? And those coping strategies, you can think of them as adaptive strategies, while the negative state of being as is always is the maladaptive. So there is a competition between these two efforts of the brain to cope with its existence. And we can, in fact, now begin to disentangle these one from the other, in a way. And there's a lot more to be done along those lines, but we now can, especially in animal models, we are able to show what components of reorganization are adaptive while what other components are maladaptive too.

Dr. Max Boakye:

Are these changes, permanent changes? Are they reversible?

Dr. Vania Apkarian:

Well, at least some of it is reversible, which is good news, right? How reversible they are remains unclear. But certainly there is good evidence that even brain anatomical changes can be reversed. In many ways that's good news. In fact, we can restore normality in such subjects.

Dr. Max Boakye:

First of all, are there any pharmacological tools that can reverse some of the changes and are there some non-pharmacological tools like meditation?

Dr. Vania Apkarian:

Certainly things like meditation and multimodality management tools should restore some of these functions back. The data is not very clear yet, but I suspect it will come. Pharmacological approaches when they are successful, they should also, in part, restore some of these things. But again, we need to have better pharmacology, better targets, more efficient treatment methods, which would then be useful and explore how they are impacting the circuitry in general. But we're not quite there yet.

Dr. Vania Apkarian:

To understand the circuit table. That's. I mean, in many ways we have made great progress in the field, but what we have learned is that how ignorant we are about the condition, how complicated the system is. You remember that I'm telling you that the whole cortical functional properties are reorganizing. The limbic brain connectivities are changing. So these are huge circuitry organizations. And we are just beginning to demonstrate these processes. The details of the control mechanisms, underlying them, and how to manipulate them all remain to be done in the future.

Dr. Max Boakye:

Wow. That's fascinating. What would you like surgeons like me and others who treats, for example, chronic pain from spine surgery, what would you like us to know that we currently do not know?

Dr. Vania Apkarian:

Well, I mean, there's this open question, how much of our interventions are causal, right? This is something we need to really keep in mind. If a huge amount of the chronic pain is determined and controlled by brain properties, how much of our peripheral interventions are actually really helping the patients and are there simpler alternatives. That's a very critical question. And in a way, those are testable questions, right? We can do proper control studies and identify how much peripheral interventions are actually helping people or not. In that sense. I think especially newer surgeons should be wary that are their alternatives to these patients before we start cutting specially neural tissue from these people. There is no question that cutting neural tissue has just as much probability of causing chronic pain as opposed to curing chronic pain.

Dr. Vania Apkarian:

The source of [inaudible 00:28:00] always creates or increases the probability of a patient turning into a chronic pain patient.

Dr. Max Boakye:

I see. So do only the minimum that's needed to address the problem.

Dr. Vania Apkarian:

Exactly.

Dr. Max Boakye:

How do you envision we'll be treating back pain in the next decade or two?

Dr. Vania Apkarian:

I am a firm believer in science. My primary assumption is that we have failed to treat these patients properly because we have been ignorant of the processes underlying it. So the better information we have about the circuitry, the causal links within the circuitry, the better we will treat these patients. I still do believe that there are magic bullet drugs out there that we need to develop. And that would give us much better responses to these conditions. At the same time, if these patients conditions are fundamentally linked to limbic brain properties, then even things like yoga and cognitive behavioral therapy, meditation, all of them have some validity for treating such patients. The question is, can we identify for a given patient what is the optimum route? And can we get to the point where we can actually cure these patients as opposed to managing them, which is what we do nowadays.

Dr. Max Boakye:

You've obviously have published some of the most seminal work in this field. What would you say is your most significant and gratifying contribution to this field?

Dr. Vania Apkarian:

I mean, it's a very simple concept and I was discussing this with my students today. What is our contribution? What we have said is that if you have pain perception, it's in your brain. Therefore, your

brain is a fundamental component of that perception and that the properties of your brain play a big role in that perceptual state. Classically, the field has always concentrated on the nociceptive affluent input, the spinalthalamic pathway. But pain is a subjective state and a subjective states interact with the whole brain history of your past. And that's how those subjective states come about. And that contribution to chronic pain is really what we have shown over the last 20, 25 years. And it remains kind of surprising in the field, but, we should move past that and start dissecting it into its components.

Dr. Max Boakye:

Fascinating. My final question is my magic wand question, which I ask most of my guests. If you had a magic wand and unlimited resources, what research would you do? What questions would you want answered?

Dr. Vania Apkarian:

I would do what I am doing, but at a much bigger scale. In a sense, our studies remain limited by costs and by resources. There is no question about it. We need much bigger teams of scientists doing these things at much, much more intense level. I think the path is clear and I'm very optimistic that we will get there. I am not sure if we will get there when I'm still around or not, but I'm trying very hard.

Dr. Max Boakye:

Excellent. Excellent. Where can the audience get more information on your work and more information in this area?

Dr. Vania Apkarian:

Well, my website has a lot of information. My publications are available. I think those are the general sources. Yeah.

Dr. Max Boakye:

Fantastic. I will put the link to your website on the show notes on the podcast websites. But Dr. Apkarian, I want to thank you very much for a fascinating introduction being mechanisms of chronic pain and its implications for treatment and management.

Dr. Vania Apkarian:

Let me finish by making two statements. First of all, we've been doing this research for more than 20 years and I should thank all the patients that have participated in all of our studies over many, many years who have committed time and effort and have contributed to the science. I should also thank all the students who have done all the work. And I did all the talking in a sense, and also I need to thank both NIH and the DOD for continuously providing us with the resources to do these studies. Without them we would not be able to do any of them.

Dr. Max Boakye:

Thank you. It has been a true privilege and pleasure to be able to speak to you on this most important topic. Thank you very much.

Dr. Vania Apkarian:

Thank you, Max. Yeah.

Speaker 1:

Thanks for listening to Optimal Neuro| Spine podcast with Dr. Max Boakye. If you enjoyed this episode, we hope you share it with others. Leave us positive reviews on social media or leave a rating and review on iTunes. Check out our website, MaxwellBoakye.com/podcasts for show transcripts and other information. Join us next time for another edition of Optimal Neuro Spine show.