Transcript of RELIEF podcast with David Seminowicz:

RELIEF: Hello, and thanks for tuning in to RELIEF's podcast series. I'm Neil Andrews, editor of RELIEF. I'm thrilled to have the opportunity to speak today with David Seminowicz. David is an associate professor in the Department of Neural and Pain Sciences at the University of Maryland School of Dentistry in Baltimore, US, where he runs a lab that studies chronic pain. In particular, his lab is interested in discovering the brain mechanisms of pain. His group performs brain imaging research in humans and in animals with the overall goal of identifying brain regions and circuits that change with chronic pain. He's also interested in determining how interventions restore normal brain function. Today David will talk about his work on brain imaging and pain. David, welcome to the podcast. Thanks for being here.

David Seminowicz: Thanks very much for having me.

RELIEF: Why did you become interested in studying brain mechanisms of chronic pain in the first place?

David Seminowicz: I wasn't always interested in pain research, but I have been interested in brain imaging for a long time, since my undergraduate days, and I was generally interested in cognitive and emotional functions. My first research project was in PET imaging of major depressive disorder, and from there I discovered pain research, sort of by accident. But I soon found it to be an even greater challenge. And I realized there was a lot of overlap between pain and depression in terms of the brain mechanisms involved, and that both of these conditions were really poorly understood in terms of what we know about how the brain is involved in creating these either depressive or pain experiences.

So both diseases are very complex. I soon discovered thereafter that chronic pain has a really great societal impact and shortly after that decided that this field—neural imaging of chronic pain—was something that I could study for a very long time. And so it's kept me in business, until at least now.

During my PhD studies, I focused specifically on how pain and cognitive function interact, and from there I've expanded into other areas, still looking at cognitive systems, but now how they're disrupted in various chronic pain

disorders and how different treatments can reverse some of those abnormalities.

RELIEF: Before we talk about some of your specific research, in general, what happens in the brain during chronic pain?

David Seminowicz: That's a very big question that I could really spend the next 20 minutes discussing. What we're looking at is neuroimaging of the brain, so we're looking at a certain level that involves brain regions and the interaction between brain regions. I should point out that every time we do something like learn something new or experience something new, the brain changes in some way. With chronic pain, there are a lot of these new adaptations going on, and so it might not be surprising that the brain changes in many ways. Depending on how you're looking at this—at the level of epigenetics, genetics, the cellular level, brain regions, or brain networks—you can find changes at all those different levels.

We focus on large-scale changes, anatomy, connections between regions, and functional networks. I'll try to avoid in this podcast going into too much detail about the specific anatomical structures, because they really don't matter that much for the clinical implications. But we really see abnormalities in structure and function at a lot of different levels and a lot of different networks involved in cognitive, sensory and emotional functions. Chronic pain can lead to changes in the way that an individual attaches meaning or value to pain, and it's associated with disability, decreased quality of life, disrupted mood, and so on. All of those things can contribute to brain changes. A great challenge for us is to figure out how the brain changes that we see in a person with chronic pain relate to the different symptoms associated with the given disease.

RELIEF: Are all of these changes that you see reversible? Or is it that if someone has chronic pain, once you see these changes that are going on in the brain, there's nothing you can do?

David Seminowicz: Yes, at least some of them are. We've shown this in a couple studies and continue to look into this in our ongoing work. For example, in chronic low back pain patients, we observed abnormal structure and function of an area called the left DLPFC [dorsolateral prefrontal cortex]. That was abnormal in terms of how it compared to matched healthy subjects who had never had any type of chronic pain in the past. Then we

followed the patients after treatment. Six months after treatment, the anatomy and function of that area, the left DLPFC, had returned to normal. But that's a really promising message for patients. If the brain changes are telling us something about why pain persists, you're essentially not doomed to a life of chronic pain. We can reverse some of these brain changes, and those changes might correspond to improvement of symptoms. There are now a number of ongoing trials in my lab, and in several other labs around the country and around the world, looking at how different interventions affect brain abnormalities and reverse some of these changes that we see.

RELIEF: In the chronic low back pain patients that you mentioned, what was the treatment—were these drugs that were used?

David Seminowicz: In that study we were looking at spine surgery or a technique called facet joint block. It turned out it didn't matter so much which treatment the patients were getting. As long as the treatment was effective for that patient, we saw relative reversal of some of those early-on changes.

RELIEF: Let's delve into your research a little bit more. What are the most interesting things you've learned so far from your studies about the role of the brain in chronic pain? Let's talk first about animal studies, and later we'll talk about studies with patients. Can you study these brain changes in animals—that's the first question. And then, what have been some of the most interesting things that you've found in that regard?

David Seminowicz: I'll back up a little bit and tell you about the structure of the lab and how we approach our experiments. We're looking at changes over time [all the way] from a normal healthy brain compared to somebody who's experiencing acute pain, to somebody who's living with chronic pain, and then through studies that look at intervention to recovery, which hopefully leads to the normalization of that brain again. So we're looking at the full spectrum of the normal brain to chronic pain and back to normal again.

We do this in a number of ways, mostly using structural and functional MRI techniques, and also some other techniques. We're also using rodent imaging, and we typically use rodent imaging in situations where it's not easy to test a problem in human subjects. The best example of that is we've seen a number of these brain changes, like the ones I mentioned, in people

with chronic pain, but it was never certain whether chronic pain actually leads to some of those changes in the brain or whether people with different brains are more likely to develop chronic pain, which is an equally plausible hypothesis.

Using animal studies and longitudinal designs, we can examine the animals before they experience an injury that leads to chronic pain, and then scan them at multiple time points (this is using MRI again), and look at how the brain changes over time. One of our first studies, and this was work done at McGill University, looked at gray matter changes in rat brains over time, and found that there were some changes in prefrontal areas that really happened very late after the injury and that those changes corresponded to the development of anxiety-like behavior. That told us two things: that the brain changes and that is associated with the development of chronic pain, but we can also figure out how those changes relate to specific symptoms. In chronic pain, patients aren't just dealing with sensory problems; they very typically have disruptions of emotional processing and mood. And so there we were able to use animal studies to make that causal link.

The second part of the question was some of the findings from patients?

RELIEF: Yes.

David Seminowicz: One of the really exciting findings was the reversal of the brain changes in chronic low back pain after treatment. We were also able to support that finding in another study that looked at cognitive behavioral therapy as an intervention for chronic pain. That was really nice because we saw a similar change in, again, the left DLPFC, with cognitive behavioral therapy. That correlated with recovery as well—so the better a person got, the more recovered that brain area was.

We're seeing similar changes in migraine. The lab is now focused on studies in orofacial and head and neck pain, and migraine is one area that we're focusing on. We're starting to get data from studies looking at reversal of changes there. In general, we're starting to see a lot of overlap between different pain populations in terms of, particularly, cognitive network disruption. We've now seen that there's cognitive disruption in chronic low back pain. And we've also seen this in fibromyalgia, temporomandibular disorder and migraine. We're hoping that in all of those cases effective

interventions are able to normalize some of those cognitive-related brain changes as well.

RELIEF: When you talk about networks and circuits, this just means how different areas of the brain relate to each other or how they're connected to each other?

David Seminowicz: Correct. These are networks, and it depends what type of imaging modality you're using when you're talking about a network, but for studies using functional MRI, which is mostly what I'm talking about, we're talking about the interaction of brain regions that participate in different cognitive and emotional functions. Studies have been able to identify a bunch of different networks, maybe eight to 10 to 15 of these networks, that are really reliable. We can see them on an individual level, and we can see them on a group level. And they correspond to the performance of specific tasks, or the lack of performance of a specific task, for example.

RELIEF: Great. You mentioned migraine earlier, and I'm aware that you're involved with a clinical trial of migraine now. Can you describe that trial and what you are testing?

David Seminowicz: This is a fully randomized controlled clinical trial of stress reduction, which includes mindfulness meditation for episodic migraine. This is a study in collaboration with Jennifer Haythornthwaite and her group at Johns Hopkins University, and it's still ongoing. We're still recruiting and enrolling, hopefully, our final patients soon. Like in our other intervention studies, we scan the patients at multiple time points. So we scan them before they've undergone any intervention, and then we scan them at multiple time points, during and after the intervention, to see how the brain's changing over time and how that relates to the treatment. Generally, the questions we're asking in the study are, is the intervention effective? What are the brain changes that are associated with that effective treatment? Then, third—and this is a big question—can we predict which patients are going to respond to the intervention? We want to be able to make that prediction based on their baseline neuroimaging data, so before they've undergone any intervention. That's going to be really big if we're able to do that.

This is a double-blind study, which means even though we've seen a lot of the patients go through the whole trial—we do followups for one year—

unfortunately we won't be able to look at the results until the entire study is complete. We have a couple of years before we're going to know all of the results coming out of that study, unfortunately. But it is coming.

RELIEF: In addition to migraine and chronic low back pain, you're also interested in a condition called burning mouth syndrome, which I think most people don't hear a lot about. What is this condition? And what have you found so far?

David Seminowicz: Yes, a lot of people have not heard of burning mouth syndrome (BMS). Usually when I give a talk, at whatever venue, I take a poll of the audience and ask, 'how many people here have heard of this?' It's always really surprising to me how few people out there, even in a group of people that studies chronic pain, are aware of this disorder. Burning mouth syndrome is, as the name implies, a chronic pain disorder, and the major symptom is spontaneous burning pain of the tongue, the lips and the hard palate, and often other areas of the mouth. Its diagnosis requires ruling out any other disease, such as fungal infection, but there are many other things that might be causing the burning pain. In other words, the cause of the burning in burning mouth syndrome is entirely unknown. Our approach has been to study this disease as a brain disorder, like we do with all of the other disorders we study in the lab, first by identifying the underlying pathology, and then trying to find effective treatments that might target those brain abnormalities.

This area has been, if you don't mind me continuing on this, one of the biggest challenges in my career. The patients are generally hard to find. It's not that it's a particularly rare disease, but it's somewhat unusual in its presentation. It often affects mostly postmenopausal women, and those postmenopausal women might also suffer from other orofacial or other pain conditions or other general problems that arise as we age. For this reason and others, I think that BMS is commonly misdiagnosed, and it's often attributed to other medical problems. Sometimes the patients go through treatments for the wrong thing. This ultimately leads to underdiagnosis of BMS.

I'm fortunate to work with a fantastic clinician, Dr. Tim Meiller, who runs an oral medicine clinic here at the dental school, and his team does a complete workup of patients to ensure the patients have an accurate diagnosis of BMS. Then we test them for two full days, including just about all the techniques

that we use in the lab, including functional and structural MRI, EEG, quantitative sensory testing, saliva samples, and a number of questionnaires. We're really just throwing everything at this to figure out what is really disrupted in burning mouth syndrome.

We have published one study on this so far, and we hope studies are ongoing; we're still looking for patients. We hope to have more coming out in the next few years. In the first study that we published, we showed a combination of abnormal brain gray matter in patients compared to controls. So the brain changes, and that's something that we've seen in other chronic pain populations as well. We also saw changes in connectivity, so in some of those networks that I was referring to, we saw some changes, but only when the spontaneous burning pain was present in the patients. So a lot of these patients don't always have that ongoing pain, and we see changes in some of these networks only when the pain is present. So that's a brain change that's really specific to the presence of ongoing pain. By studying those different states, we're able to parse out brain changes that are specific to the disease that likely developed over a long period of time from those that are really dependent on the presence of ongoing pain.

RELIEF: When you look at people with burning mouth syndrome, migraine or chronic low back pain, and you see the changes that are going on in the brain, will this help with the development of brand new pain drugs—so someone could look at the pattern of brain activity that you see during chronic pain and how it's different from someone who doesn't have chronic pain, and then you could develop brand new drugs based on that? Is that realistic?

David Seminowicz: Some of the research that we're doing now, in collaboration with other people who use other techniques, like electrophysiology, cell biology and pharmacology, is taking an approach where I think we will develop new drugs, by finding brain areas that are abnormal, figuring out what receptors or other proteins expressed there are different, and what we can actually target pharmacologically. But neuroimaging provides a way to develop new treatments through a few different ways. We can first identify, where are the targets? What are the brain regions that seem to be consistently abnormal in chronic pain? We can figure out where certain drugs act in the brain, and then if that overlaps with the regions that we want to target, we could use those drugs. We could also look at how drugs—and this also applies to nonpharmacological

interventions—affect general brain function, looking not just at brain regions, but also at brain systems. How that relates to symptoms is something that we really want to know. When we're treating chronic pain, very often we're not going to be able to relieve all of the symptoms associated with that disease, but we might be able to target specific symptoms.

I want to give one example of a way that I think neuroimaging really is going to lead to some, potentially, new drug development or treatment development. The technology, not surprisingly, is advancing rapidly, and we at the University of Maryland have a fairly extensive group focused on using high-frequency MRI-guided focused ultrasound, which is a fairly new technology. This technology can be used to do three things. It can create a lesion, and so focused ultrasound is used clinically here to treat disorders such as essential tremor. It can also be used to simulate very specific brain areas. In rat work, it has been used to stimulate very small structures, and we can observe the behavioral changes in those rats when we do that stimulation. That's something that will be coming for human use. The third thing it can do is that it can be used to open the blood-brain barrier. The blood-brain barrier is essentially, as the name says, a barrier; it's a wall between the body's systemic vascular system and the brain. A lot of drugs that we can deliver don't necessarily make it into the brain, but using focused ultrasound, we can open the blood-brain barrier at a specific brain target, and we can allow the drug to get in and target that specific brain area. Technologies like these, I think, in combination with all the work that we're doing, are going to lead to new interventions, whether they're drug or non-drug.

RELIEF: Great. In the last part of the podcast, let's talk about some controversies that are going on in the pain field. As you well know, there have been some very controversial papers in the pain field that have asserted, or people have interpreted as asserting or claiming, that there is a specific area or areas of the brain that are selective for pain, meaning that there's an area of the brain whose specific role is to process pain signals. Can you explain this idea, whether or not it's true, and why it's causing so much controversy?

David Seminowicz: I think when anyone makes a claim that, say, brain region X is specific for a given behavior, perception or experience, we should be very skeptical of that claim. For pain, I'll give an example: the

posterior insula. This is one of those regions that has sparked a lot of discussion in the field. The posterior insula is an area where there's abundant data about its role in pain. For one thing, it's consistently activated in our neuroimaging studies. When we, say, give a subject a painful stimulus, they say they're in pain, and the posterior insula is activated. You can also stimulate the posterior insula electrically. So when people are undergoing awake open brain surgery, you can actually stimulate that area, and a lot of people will report experiencing pain.

Very often lesions restricted to a very small part of the posterior insula will lead to a condition known as central chronic pain, so that's evidence that supports the role of the posterior insula in pain, but there's also a lot of evidence that suggests it's not specific to pain. For example, there are a lot of other cognitive and perceptual processes in the brain that will activate the posterior insula. I can't name them all here, but there are a lot. And there is some other evidence that people with very large lesions, sometimes involving the entire insula, not just the posterior insula, are still able to experience acute pain.

So the posterior insula is important in pain, and nobody's going to deny that. But there doesn't seem to be enough evidence to say that it's necessary or specific to experience pain. Pain is really complex—it may be the most complex experience a person can have, and chronic pain further complicates that experience. I don't necessarily find the idea of a brain area having specificity for pain to be a very controversial topic in the field. Most of us are contributing important data on the role of specific brain areas to pain. But most reasonable people in the field understand that brain regions act as part of larger networks, and any given region can have a multitude of functions. So when we talk about a brain region role, we have to consider that brain region as acting as part of a larger network. Yes, we as a field should generally avoid big claims about specificity, and when we see those claims in the media or elsewhere, we should take them with a bit of skepticism.

RELIEF: Another controversial issue, and something that's gotten a lot of attention, particularly in the media, is whether researchers could use brain imaging as a way to determine if someone is in pain—that it could be used almost like a lie detector test, in the courtroom, for instance. Can you talk a little bit about this issue and what you think about it?

David Seminowicz: The term ‘lie detector’ immediately makes me cringe a little bit. But this idea of a brain biomarker of pain is certainly something that is a big topic. Again, I'm going to say that I don't generally find this idea to be too controversial. It's all about how you interpret the finding of a brain biomarker of pain or the need for such a brain biomarker. There are obviously some important legal and medical ethical issues to consider, but there have been some major advances in this area. Tor Wager's lab at the University of Colorado in Boulder came out with the first major paper on this topic where they were able to decode pain in healthy subjects. They could, using what they called the neural pain signature or neurological pain signature, use that code to detect whether an individual was experiencing a painful or a nonpainful stimulus and how painful that really was. They could predict with really high accuracy how much pain an individual was in at a given time. It was really impressive work. And as the technology improves, it's sort of guaranteed that we're going to have these brain biomarkers of pain, not only from functional MRI studies like that study was, but using other brain imaging technologies as well.

But again, we have to really be aware of the ethical implications, and we have to think about what this biomarker will be really useful for. Pain is an individual experience, and everyone talks about pain in a slightly different way. If I give two people the same stimulus that is generally painful, one person might find it excruciatingly painful, and the other person might find it only mildly painful. And so we typically use pain rating scales. For example, rate, on a scale of zero, meaning no pain, to 10, the worst pain imaginable, how intense the pain was. People give us the ratings, and those ratings tend to be pretty reliable. For people who are able to communicate their pain, this would be the same situation for a person with chronic pain; there's no reason to really expect that we would need a brain biomarker to show that the person was in pain. We know that they're in pain, and we can treat the pain, and we want to know that the treatment's effective. And we will say it's effective when the person tells us that they're no longer in pain.

On the other hand, there are some cases where a brain biomarker could be really useful. For patients in a persistent vegetative state or a coma-like state where they're unable to communicate, it might be really useful to be able to use a brain biomarker to tell us if those patients are able to experience pain; that's one potential use for the biomarker. But again, that technology is coming, so we should be anticipating that it's going to be here and what we are going to do with that technology when it's ready.

RELIEF: That's actually a great transition to the last question, which is looking towards the future. In your view, what are the most important questions that are still out there about understanding the role of the brain during chronic pain? And what does the future look like in terms of addressing those questions? Are we going to make progress?

David Seminowicz: Yes. I'd say we've really just started scratching the surface with neuroimaging studies of pain. Earlier studies were really interested in what regions are activated when we do certain cognitive, sensory or emotional tasks—what brain regions are activated or deactivated when we do that. Now, the field is really looking at how different brain networks are interacting, how these change over time, and how experiences, such as chronic pain, can change the interaction between those networks. And this is how our brain works; we have different networks coming online and offline that are involved in the different experiences and things that we're doing throughout the day. We're really just getting there, and now the field is ripe. It's ready for us, too, to take advantage of these new analytical and data acquisition technologies.

I'm going to highlight a couple areas that I think are coming in the near future. I think I've already touched on these a little bit previously, but I think we're going to be able to understand how the brain changes in that transition stage from acute to chronic pain. Say a person has an injury, say to the back. Vania Apkarian's lab at Northwestern University has been doing a lot of really innovative work on this topic. He's looked at the transition from subacute pain, which is just shortly after an injury, to chronic pain, and how does the brain change over time that predicts whether an individual is going to end up in the chronic group or if they're going to recover and be pain-free after a while.

Using the brain marker technique that we just talked about, I think that's going to let us predict pain states. Right now the brain decoding that I talked about was useful at just telling whether a person was experiencing acute pain at the moment, but taking that a little further, we're going to be able to understand whether a person is experiencing a different pain state. That's eventually going to give us a better understanding of how the brain is reorganized in the short- and long-term with persistent pain.

Then we have the treatment studies. Like the study that I mentioned we're doing with migraine and the ones that we did with chronic low back pain, there're a whole bunch of these intervention studies going on now in my lab and in many other labs. The results from all those studies are going to be coming out in the next five or so years. From those studies, we're really going to get a better feeling of how different types of treatments change the brain in certain ways.

We can put together all of those areas of research to really come up with an individualized medicine approach. So we can identify what's changed in an individual. We can know how this relates to certain symptoms. And then we can figure out which interventions are most appropriate for targeting those brain changes. For example, if I know a given intervention, let's say cognitive behavioral therapy, is really effective at reversing abnormal connectivity of, let's say, the pregenual anterior cingulate cortex (I just picked a region off the top of my head), and that's the same region that's disrupted in a given individual, then maybe CBT is the best treatment for that individual. Then we can monitor over time how the brain is changing and how that corresponds with their changing symptoms.

I think we can take from that a really positive message that all the research that we're doing is really leading to ways that we can provide real relief for people suffering from chronic pain.

RELIEF: I think that's a great note to end on; it’s a very optimistic and exciting future. So David, thank you so much for taking the time to talk to RELIEF about your work on brain imaging and pain. It's been a fascinating discussion, and we really look forward to following your research and seeing how this field evolves. So thank you very much.

David Seminowicz: My pleasure. Thank you.