Transcript of RELIEF podcast with Roger Fillingim

RELIEF: Hello, everyone, and thanks for tuning in to RELIEF's podcast series. I'm Neil Andrews, editor of RELIEF. I'm really happy today to have the opportunity to chat with Professor Roger Fillingim, who is a professor at the University of Florida College of Dentistry. His research focuses on biological, social, and psychological factors that may influence the experience of pain, and he's here today to talk about his research in these areas. Professor Fillingim, welcome to the podcast, thanks so much for being here today.

Roger Fillingim: Thank you, Neil, and thanks for having me.

RELIEF: So I just had mentioned biological, social, and psychological, and that's known as the biopsychosocial model of pain. So can you tell me a little bit about that; what is the biopsychosocial model of pain?

Roger Fillingim: Sure. The biopsychosocial model of pain is a conceptual way of looking at pain, and it tells us that pain is created by a combination of biological, psychological, and social, and cultural factors even, and that these factors – biological, psychological, and social factors – interact with each other to ultimately create the experience of pain that we have. And this model of pain broadens the view of pain and the number of topics and variables we need to consider in order to better understand a patient's pain, so it goes far beyond traditional biomedical approaches.

RELIEF: And why did you decide to pursue research in this area?

Roger Fillingim: That's a good question. So I'm a clinical psychologist by training, and I was first exposed to chronic pain and the biopsychosocial model in graduate school when I worked in a chronic pain clinic. And this was back in the mid-'80s, and back then chronic pain treatment was one of the areas of medical intervention where psychologists were already well entrenched, and it was well appreciated that psychological factors and, in fact, psychological interventions for chronic pain could be particularly helpful. And so it was very impressive to me as a developing professional that what was traditionally considered very much a medical disorder was now incorporating the importance of psychological factors and getting patients more actively involved in their own rehabilitation. And so that sparked my interest in the biopsychosocial model and that became a theme of the work I continued to do throughout my career.

RELIEF: And so if there was this interest in psychological and social aspects when you were starting your career and moving in your career, does that mean that this approach has been there for a long time in the history of pain research, or has the focus been more on biological factors; where does this approach fit into the history of pain research?

Roger Fillingim: I had fortuitous timing because it was probably in the late '70s to early '80s when psychosocial factors were becoming integrated into our understanding of pain and into the management of pain, so I came along at the right time. Historically, as you might imagine, pain, like most other medical conditions, was viewed from a much

narrower biomedical focus, and the goal was to identify the underlying culprit, very much like an infectious disease model of thinking; if we identify the bug that's causing the disease and we can kill that bug, then the disease will go away. And the same sort of thinking was applied to pain; if we can identify the pathology or the tissue damage that's driving the pain and fix that pathology or tissue damage, then the pain will be resolved.

Unfortunately, as we now know, in tens of millions of cases here in the United States, such interventions to try to relieve the underlying so-called cause of the pain have been ineffective, leaving people with chronic pain, and so we need a broader model to be able to intervene more effectively when the more traditional biomedical approach has turned out not to be very helpful.

RELIEF: And do you think that this approach nowadays is accepted; do you think today there's still too much focus on biological, medical factors, or is this an approach, the biopsychosocial approach, that has gained more acceptance?

Roger Fillingim: I do think it has gained more acceptance, and I think most informed providers understand that chronic pain is a very complex experience that involves all aspects of the patient's life, and, in fact, I believe patients understand this increasingly. I think what we're falling short with is in integrating the more biomedical and psychological/psychosocial sides.

We still tend to think of them and almost treat them as they're occurring in parallel, and so we'll do the biomedical thing and maybe at the same time we'll do the psychosocial thing, but usually we'll do the biomedical thing and if that doesn't work then we'll do the psychosocial thing, whereas if we were to better integrate those approaches and understand more how they work together and how psychosocial processes affect biological mechanisms, and how biological processes affect psychosocial aspects of life, we would be much better off, but we're not quite there yet. So acceptance of the model is much better than it used to be, but we still have a ways to go in terms of better integrating the components of the model and how we care for patients.

RELIEF: So a major focus of your work is looking at individual differences in the experience of pain, so how one person differs from another in the pain experience. Can you talk a little bit about that: what are the main individual differences in the experience of pain, and why is this biopsychosocial model that you've just described useful in trying to understand these differences?

Roger Fillingim: Individual differences refers to the fact that the same painful stimulus can result in wildly different experiences of pain in different people, and that has been frustrating for us as researchers and clinicians for years because it's difficult for a particular surgery or a particular injury to understand how much pain a patient's going to have, because it depends on the patient. And when I say it depends on the patient, it depends on those many biological, psychological, and social factors that come together in a mosaic in each patient and sculpt a different pain experience in each patient, and we

usually have a relatively poor understanding of how those biopsychosocial factors are influencing pain in a given patient.

And so these individual differences are the rule, not the exception, and the biopsychosocial factors that we've been talking about, in my view, are what drive these individual differences. And so biopsychosocial model and individual differences research fit together beautifully because they both reflect the complexity of pain and the things that we need to understand better if we're going to more effectively assess and treat pain in people experiencing pain.

RELIEF: So let's talk about some of these biopsychosocial factors. Maybe we could start with the psychosocial factors. What are some of these factors that explain individual differences in pain, and how significant are they; how large an effect on the pain experience do these psychosocial factors have?

Roger Fillingim: That's a great question. There are a number of different psychosocial factors that have been studied; you can divide them up into various categories. For example, you can think of mood factors – depression, anxiety, anger – and those have been consistently associated with the severity of pain. In many studies, mood and emotion before the onset of pain can predict future development of pain, so it's not just that experiencing chronic pain can make one's mood more negative, it's that a negative mood before any pain experiences can increase the risk of future experiences of pain.

There are also cognitive processes – how we think about pain, how much pain we expect, and how individuals cognitively cope with pain; what sort of mental coping strategies or tricks they use to try to manage pain – those factors have been found to be very important. Certainly, psychological stress is a major driver of pain; not only is pain itself stressful, and when pain is present adding stress to a patient's life tends to exacerbate their pain. But very much like mood, if we measure your stress today and you're reporting high levels of stress, your risk for developing pain in the future is greater.

And so those are just some broad classes of psychological factors that are important. Maybe one other set of factors that's gaining a lot more attention now is psychological resilience factors. Historically, we've tended to focus more on negative factors or maladaptive psychological factors that make pain worse, but it's now well recognized that some individuals possess protective psychological characteristics that reduce their risk for pain or enable them to cope more effectively with pain. And these might be things like optimism, hope, positive coping strategies, positive affect, so these types of resilience factors are now becoming targets of treatment in order to help people manage their pain more effectively.

So those are some of the psychological factors that you can think about that contribute to individual differences in pain. The size of their contribution can be modest, depending on what the situation is, to really very robust effects and contributing to a large proportion of the variants in pain. There are studies kind of across a spectrum of effect sizes, if you

will, but it's well appreciated that these psychological factors are of substantial scientific and clinical importance in driving individual differences in pain.

RELIEF: In addition to these psychological factors, one of the things that you also study is, you look at demographic factors, so things like how old the person is, their sex, and their race, and how those factors impact the individual experience of pain. Can you talk a little bit about those as well, and, again, how important are they?

Roger Fillingim: Sure. We've been very interested in different demographic factors in our research over the years, and certainly others have, too, and gender differences have been widely examined in pain research; women are known to be at greater risk for a large number of chronic pain conditions, and so gender is an important factor. Some of these psychosocial factors that we just talked about may differ across gender, and that may be part of what drives the gender difference.

There are questions about how large the gender differences are in terms of pain, and gender differences vary depending on what kind of pain you're looking at, whether it's clinical pain or experimental pain, and if clinical pain the type of clinical pain. But these gender differences at a population level are incredibly important when you think of the excess female prevalence of many chronic pain conditions. So that's one example.

Ethnic differences, racial differences in pain are somewhat less well studied. There do appear to be some differences, but they're more in the direction of minority patients having higher levels of pain and disability in patients who already have chronic pain. There's less evidence that minority patients across the board are at increased risk for the pain itself; that is, they don't necessarily have higher prevalence of a variety of pain conditions, but when those pain conditions are present they tend to be more burdensome in minority patients.

And then, of course, age, and age is an interesting factor; it's not a categorical factor, it's a continuous variable of sorts. But it's true that for at least several types of pain, older adults are at increased risk. And that's particularly true of musculoskeletal pains – joint pains – and certain neuropathic pain states; those become more common with age. But actually some other pain conditions are not more common with age, some pain conditions become less common with age. So the relationship between age and pain is somewhat nuanced.

The one thing I would say about these demographic factors, we often refer to them as individual difference factors, but it's important to recognize that they're proxies for more proximal individual difference factors that are actually driving the pain. And the reason these group differences are important, for one thing, at a public health level, it helps you understand large population groups who may be at risk for certain conditions, and that may help you target your preventive strategies.

So that's one thing. But it also lets you know of natural experiments that might lead you or give you clues as to what some of the underlying individual difference factors are. For

example, if there are sex differences in pain, there must be factors that are driving those differences, and those factors must be sex-related in some way, and hormones, for example, would be a culprit that one might think is implicated in these sex differences in pain. So these demographic factors can start new lines of investigation that help you understand better the mechanisms or the individual difference factors that are driving pain.

And then, finally, one thing we need to remember about these group differences in pain is there can be qualitative differences; that is, a certain biopsychosocial variable, let's say, anxiety, might influence people in different groups differently, and so it may be more strongly pain-related in men than in women, or something like this. So that's the other part of these demographic factors that can be helpful; you can look at how different individual difference variables might influence pain differently in people who are in different demographic groups, and that can help you understand pain more clearly.

So that's a long-winded answer to the demographic factors, but I think the key is that they are really proxies for other individual difference variables, and understanding the group difference opens the door to doing more research to understand really what's underneath that group difference.

RELIEF: So it's very complicated. And to make things even more complicated, another area that you study is looking at genetic factors that underlie individual differences in pain. So how does that play into all of this; how important are genetic factors and are there maybe a couple of key findings from studies looking at the role of genetics in individual differences in pain that you could talk about?

Roger Fillingim: Sure. So genetics in pain, as in many other areas, are particularly important. If you look at the studies, mostly twin studies that have estimated heritability, or the amount of variance in a type of pain that's due to genetic variation, the estimates are 30 to 50% of that variance might be genetically determined, and so genes appear to be important. There have been many, many studies looking at specific genes, and now there are some studies coming out that are looking across the whole genome trying to identify new genes that might be important in pain. There are a handful of genes that come up time and time again as being important. Probably the most studied gene in pain research is the so-called COMT gene that encodes an enzyme that metabolizes catecholamines, and this gene is related to a lot of different pain conditions as well as to experimental pain sensitivity.

We've actually been involved in some research showing that, yes, this gene is important in pain, and it also interacts with psychological factors to influence pain. And so if you have a COMT gene that makes you pain sensitive plus you tend to catastrophize when you have pain – that is, you have high levels of negative thinking and feelings of helplessness, and you tend to magnify the experience of the pain – then that puts you at even greater risk than having either the gene or the catastrophizing alone. So the combined gene and psychology factors seem to influence pain more strongly than either

one alone, so that gives us an example not only of the importance of genetic factors, but also how these biopsychosocial factors interact with each other in complex ways.

So the COMT gene is a commonly studied gene. Another commonly studied gene has been the mu-opioid receptor gene, and there are a couple of studies now showing that there's a particular polymorphism of this gene that seems to be associated with pain perception, but may be associated with pain differently in men and women, and so this is another example of an interaction between individual difference factors. So this polymorphism in men in a couple of studies, one of which was ours, was associated with lower pain sensitivity, which is what we expect, but in women in our study and in one other, it was associated with higher pain sensitivity.

So understanding how in this instance a genetic factor is related to pain required that we take into account one of these demographic factors, which in this instance was gender. So it highlights the importance of trying to put the different factors together and understand their interactions in order to better appreciate how they're influencing pain.

RELIEF: And is that very complicated because there are so many different factors that are underlying individual differences in pain; is it very difficult to disentangle all of these factors that seem like they go together?

Roger Fillingim: Yes, I think at this point in time it's probably impossible; we can bite off what we can chew. Because I think it's difficult to measure all of the potential individual difference factors that might be important, but we can pick some. And we might have particular conceptual models or biological models that help us predict a particular interaction that might be important, and then we could study that interaction and ultimately we can cobble together the information and get a better understanding of how these processes work together. But you're absolutely right that given the sheer number of biological, psychological, and social factors that we could consider, putting them all together in one big model is overwhelming at this point in time.

RELIEF: One final area I wanted to ask you about was looking at how people respond, how they may respond differently to drugs, to analgesic drugs, drugs that relieve pain. We've been talking about individual differences in the experience of pain, but are there also significant differences in how different people with pain respond to different drugs, and what factors explain that variation?

Roger Fillingim: Yes, the individual differences that we see in pain are equally well represented in responses to pain treatment, which at least doubles the complexity of our task here. Opioid analgesics have probably been the most studied. There have been some studies showing sex differences in responses to opioid analgesics, ethnic group differences in responses to opioid analgesics, and, of course, we can alter people's responses to analgesics with contextual changes; for example, by changing how much analgesia they expect to experience. And so there are a variety of individual difference factors that could influence responses to medications.

Certainly, genetic factors are important; these could be the genes that encode enzymes that break down the medication, either clearing the medication from the system or breaking it down into active metabolites which makes the medication more effective, so genetic factors are important. And it could also be the genetics of the receptors that the medications are activating. So there are certainly pharmacogenomic factors that need to be studied.

Psychological factors are important. I have already mentioned people's expectations about the treatments. Other psychological processes, for example, anxiety or depression, might impact how somebody responds to a given medication. And then, as I already mentioned, some of the demographic factors are known to be associated with responses to medications. So all of the complexities of individual differences in pain apply to individual differences in treatment response, as well.

RELIEF: When you look at those differences in the response to treatment, and when you look at what we discussed earlier about differences in the experience of pain, what are the implications for patients, both in terms of treatment and also in terms of predicting what a person's risk of pain might be?

Roger Fillingim: I think in one sense, some of the implications for predicting risk of pain and for treatment overlap; that is, if we identify individual difference factors that predict risk for development of pain or risk for pain getting worse, those individual difference factors can then become targets of treatment if they are malleable.

So I'm thinking, for example, we've been involved in the OPPERA study that is designed to identify factors that put people at risk for development of orofacial pain, temporomandibular disorder, and we found a variety of psychological factors. We measured these factors in people who did not have facial pain, and over time some of them developed facial pain. And certain psychological factors before the development of pain were predictive of future development of pain, one of them, for example, being stress. And that might suggest that stress management could be an effective preventive approach or early intervention approach for this type of pain.

So some of the individual difference factors can be treatment targets. Of course, others, for example, gender, is not so malleable, but it does help you identify groups of individuals who might be at increased risk, and they might be the ones who are more strongly targeted for prevention or early intervention strategies. So that's one aspect of how these factors are related to treatment.

The other aspect, though, is that we need to move toward more effectively tailoring treatment to the mechanisms that are driving the pain in a given individual. And when I say mechanisms, I'm including all of the potential biological and psychosocial factors that we've been talking about. We tend to treat pain maybe to some degree based on algorithm or guideline, and guidelines tend not to be as well tailored to the individual as ultimately we'd like to be. And so to the extent that these individual difference factors are as important as we think they are, we'd like that to start dictating treatment a bit more.

And so I think that's another important implication for treatment is thinking toward better tailoring of treatment to the individual and the factors that are important in their pain.

RELIEF: The last question I wanted to ask you is about looking towards the future. What are the biggest questions that remain in terms of the biopsychosocial model of pain and using that model to understand individual differences in the pain experience and in the response to treatment? And I'm also wondering if you're optimistic that the pain research field will make progress towards answering these outstanding questions.

Roger Fillingim: I think this is a critical question. And I think one thing, as we talked about earlier, is the challenge of putting the individual difference factors together and understanding their interactions. And we already alluded to how complex that can be, but that really is one of the big questions that looms for the future is how do we build research models and clinical intervention models that appreciate these interactions and help us better understand these interactions among different individual difference factors? So I think that's a very big question.

And related to that is integrating across the different domains of factors. We still, I think because of our own limitations, our own scientific and conceptual limitations, we still tend to think, okay, there are these biological factors and then there are these other psychological factors, and we keep them artificially separate. But the psychological factors are, indeed, biological factors, and so stress can drive inflammation, and my thoughts and feelings are engaging brain networks that are also involved in processing pain-related information, and so on and so forth. And so achieving better integration across these domains so that we really actualize the biopsychosocial model which emphasizes these interactions.

And I am increasingly optimistic that we're going to move more toward these answers, partly based on how the field is evolving in its thinking – we appreciate these different issues now much more than we used to – but we also have technologies and approaches that will enable us to move toward this integration; for example, with brain imaging we can better understand some of the cerebral processes that are involved both in psychological modulation of pain and in fundamental pain processing. And so my optimism continues to increase that we're going to get answers to these questions, and, hopefully, answers that end up helping patients sooner rather than later.

RELIEF: Well, I think that is a great note to end on with lots to look forward to in this area of research. So, Roger, thank you so much for being here today, it's been really great to chat with you and to learn more about the biopsychosocial model of chronic pain, and we really look forward to following your research in this area in the future. So thanks so much.

Roger Fillingim: Thank you, Neil.