

# The Abnormal Central Pain Processing Mechanism In Patients With Fibromyalgia

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For the last five years at the University of Florida, we have been engaged in defining mechanisms that explain the pain of fibromyalgia and comparing them to those which apply to the general population. I will show you some data that we have found and explain how it plays out in terms of mechanisms that are centrally located in the brain and nervous system.

Pain is defined as an unpleasant sensory experience. That makes sense for people who don't enjoy pain--and there are actually some people who do. Pain is obviously subjective. It is something that you learn early in life, and early life experiences shape the way you experience pain.

Now what does pain actually mean, particularly fibromyalgia pain? Pain is really a continuum. Many people say: "Well, everybody has pain. What's so different about fibromyalgia?" This is really not a good argument. When you look at continuums, and I am speaking about biological continuums, there are many good examples. For instance, we have blood pressure. Blood pressure fluctuates in the population, but we have found that from a certain (measured) level on, it causes disease. Despite the fact that many people come very close to this level, they don't have hypertension, but after they cross that level they do. Blood sugar for diabetes is similar. Again, from a certain level on, high blood sugar causes disease. Other examples are fever (when our body temperature changes under certain circumstances) and something very simple, body height.

The continuum concept also applies to pain. From a certain level on, pain becomes a disease. I think that there is no question in the medical community and with health care providers that pain is a disease and can cause serious symptoms. But, pain is not just a biological phenomenon. As you can see, it has three components; it is a biological, psychological, and social phenomenon. What I will mostly focus on today is the biological aspect of fibromyalgia. The goal of such a discussion relates to therapies. I think it is important to remember that, despite the fact that our pain therapies are not optimally effective, we have therapies that can ameliorate pain.

Last but not least, we know that pain is related to nociception. Nociception means that there is a reason for pain. It is not just pain occurring "willy nilly". There is something in

your body that provides a signal to your central nervous system to cause the pain experience. Two specific areas I am going to focus on are pain specificity and neuroplasticity.

The assumption that was made until 20 years ago was that whenever you trigger pain somewhere in the body, the same experience will occur each time. What we have learned within the last 20 years is that our central nervous system actually can learn; it can change. This negates the assumption that pain, if it occurs, will always stay the same, regardless of time. In short, pain changes the central nervous system, and this phenomenon is called neuroplasticity.

Let me first show you how pain is distributed in the general population. When you look at chronic symptoms in the population, pain is really over-represented. It is the most frequent reason why patients seek medical attention. Fatigue leads to relatively less frequent physician visits. Usually, the reason for health care seeking is pain: widespread pain like in fibromyalgia, regional pain, and particularly tension headaches--the most common reason for doctor's visits. All of these syndromes are over-represented in women.

The distribution of pain in the population is also a continuum. Pain from the least to the worst severity is represented like a bell-shaped curve. This means that the worst pain afflicts relatively few as does the least pain, and most everybody is in between. For example, 20% of the population has chronic regional pain; 10% of the population has chronic widespread pain. This has strongly influenced the definition of fibromyalgia which is located at the end of the pain continuum. Many physicians really don't appreciate that this is the reason why they never see many patients who have few symptoms and are minimally affected by pain. In order to qualify for the definition of fibromyalgia, you have to have more pain than all of the other pain syndromes. The continuum ranges from transient pain in a few areas, to chronic widespread pain, and finally to fibromyalgia. The very last area, allodynia, is the worst of all pain experiences. This illness is present when even the lightest touch hurts. These patients can't lie down; they can't sit down because everything they do is perceived as painful.

Fred Wolfe, who has been involved in fibromyalgia research for a long time, looked at what pain actually does to people. He asked: Are fibromyalgia patients and non-fibromyalgia patients different in their response to pain? He looked at how distressed they are. He asked: Are they all depressed? Are they all at the end of a spectrum? How do these symptoms vary? He investigated rheumatoid arthritis (RA) patients, and he used something that he called the rheumatoid distress index (which ranges from patients who show little distress to patients who show a whole lot of distress). He found that there were few at the severe end and very few with very little distress; most everybody was in the middle. Then he applied similar criteria to fibromyalgia patients. Their ratings of distress were very similar to RA patients. Not all fibromyalgia patients are extremely distressed, and again, most everybody is in the middle.

What really makes someone have fibromyalgia? I don't think it really has to do only with pain. Fibromyalgia is really someone who reaches that level where they say, "Well, I've had pain for long enough. I want some explanation. I want something to be done about this." Although it is really not well worked out, people with pain tend to fall into the following categories. There are so-called normal subjects who have low pain sensitivity; they have no reason to ask any pain-related questions. Then there is the next population with medium pain sensitivity who experiences moderately severe pain episodes. They may have menstrual cramps. They have some body pains. They don't complain much either. But now come the people with high pain levels. They include those who either deal with the pain (they can move on with their lives and can function perfectly well) or start to show signs of dysfunction. Something goes wrong. They can't work as much as everybody expects them to--their family, their employers, etc. At this point, they may cross over into the area of fibromyalgia. These are the patients who have chronic widespread pain and who have dysfunction. They don't necessarily have to differ from people with high pain sensitivity. As for the ones who have really extreme pain--everybody will understand that they can't function because they are hurting under every circumstance.

The American College of Rheumatology has defined fibromyalgia as widespread body pain with tender points. I think tender points are one of the main reasons why fibromyalgia encounters such problems in the medical community. Tender points are areas of pain to light pressure at muscle insertion points. There are 18 of these, and 11 or more are required for diagnosis. But there are problems. One of the most important is that you can't correlate a tender point to pain. Everybody with fibromyalgia has tender points, but the number of tender points does not reflect pain level. Secondly, despite many people's assumption, the diagnostic examination of tender points is not easy. It requires skill. We have done evaluations of physicians and asked them to show us where they do their tender point exams, and everyone does them differently. Nobody ever goes back to the source and looks to see how tender points are actually defined. In order to do a tender point exam really well, you need to use a little machine called a dolorimeter that gives you a pressure reading. Last but not least, there are problems with validity if there are legal proceedings or disability claims.

Another study that discredited the concept of tender points in fibromyalgia was done by Don Goldenberg. He looked at fibromyalgia patients and individuals in the community who had tender points but had not sought medical attention. He did a very simple analysis to look at how they differed. When you look at what he measured, it was pain duration, tender points, pain intensity, and so on--even going down to Substance P and then lifetime psychiatric illness. The only area where the two groups differed was that fibromyalgia patients had more depression and more psychological abnormalities. It seemed like a simple correlation. These patients really differed in how they dealt with pain and in their abnormal psychological status. And that's probably what you've heard very frequently all along. Unfortunately, for many physicians, that's how they see fibromyalgia.

Going back to tender points, in a study that I have done evaluating over 200 patients with fibromyalgia, we looked at the distribution of tender points. These were patients whose tender points ranged in number from 11 to 18, but the distribution was not a bell-shaped curve. The curve completely shifted to the right, indicating that most patients with fibromyalgia have 18 tender points. I don't know how many of you have been tested, but this is really how it is. The majority of FMS patients have the maximal number of tender points. This is not their fault; that's just how tender points were defined in 1990. Tender points counts have no sensitivity for pain levels. In essence, this makes tender point counting useless, except maybe for the diagnosis of fibromyalgia.

I have looked at tender points over time using the proper equipment and technology. You all know your pain level changes. Do your tender points change? No, they don't. They always seem to stay the same. I followed the progress of seven patients over the period of one year. What I found is that they more or less stayed in the same tender point range. Nothing much really changes, again showing that tender points don't seem to be very helpful for the assessment of FMS patients.

Regarding the mechanisms that explain pain better in fibromyalgia, I have turned to the central nervous system. The evidence for peripheral pain generation is relatively weak. The real question is what happens in the structures that are important for pain modification? When pain experiences occur, they primarily occur in the dorsal horn of the spinal cord where the peripheral nerves enter.

Turning to the concept of pain memory, the creator of the pain specificity theory declared 20 years ago: When pain occurs, nerve cells signal through every step reliably from one to the next, so you have reproducibility. In short, it's as if the central nervous system is hard-wired. What we've found, however, is that when painful stimuli occur frequently enough or in rapid succession, suddenly the pain signals get rerouted. This means that, contrary to longstanding belief, the central nervous system can adjust or remodel itself. If there is a need for different modifications or different expressions, it will use different cells and now start to modify the incoming signals. This occurs at the spinal cord level, and it is here that some of the things you have frequently heard about are happening: Substance P, serotonin, neurokinins, biogenic amines. They all work here and modify the makeup of nerve cells. When these pain modifiers are present in changing concentrations, the signals that the nerves are supposed to transmit are now transmitted in a different fashion.

The transmission of pain signals from the spinal cord naturally has to go up to the brain because that's where you perceive the sensation and where you compute the sensation. For example, you might say to yourself: "I know where something is happening, but what does this mean? How do I have to respond?" This occurs involuntarily, particularly with chronic pain. In acute pain, everyone knows what to do--move away from the painful stimulus. That's the key. But in chronic pain, there are no detectable stimuli, and therefore people start to ruminate. "Is this bad for me? Is this going to get worse? Am I going to be disabled? Do I have to stop working?" All of these questions arise, and they are very normal.

In the area of the brain called the limbic system, negative connotations are added to these pain sensations: "I feel down. I don't feel good any more." All of these things happen when pain signals enter this brain circuit (i.e., the limbic system, the prefrontal cortex, and the somatosensory cortex). In addition, signals get transmitted back down to the spinal cord and again modify nerve cells. If you're doing well, if you're coping well, the signal at the spinal cord level gets down-regulated. If you're very worried and anxious, the signal gets up-regulated. So there's a clear reason why some of the therapies (i.e., cognitive behavioral therapy and exercise) work. They don't take all the pain away, but they work.

Last but not least, today we can see what patients are "thinking" using functional magnetic resonance imaging (fMRI). We have compared the brain images of patients with fibromyalgia to brain images of normal controls and found that fibromyalgia patients process pain differently. We are not the only ones to report these findings; this is evidence that has been repeated over and over again. fMRI scanning of pain gives us a lot of information about where the pain signals go and what brain areas are most involved in pain processing. There is biological evidence of a difference in central pain processing of chronic pain.

We are using physical stimuli (usually heat, mechanical, or electrical stimuli) to test pain-related systems so that we can really say what is wrong with the pain modification process at the spinal cord level and how these tests can be applied for diagnosis as well as therapeutic evaluation. That's very important. Always remember that pain studies are very difficult to do because if I enroll you all into a study and that reduces your anxiety, your pain goes down. This may have nothing to do with the medication I am giving you. In order to really get a better appreciation about the long-term changes that have occurred at the spinal cord level, we use experimental pain stimuli. We also ask pain patients about pain, and we have them rate their pain on scales--a sophisticated version of the 0-10 pain scale. There are better versions; 0-10 is not a great scale, but for many purposes it can make do.

The fact I want you to focus on is pain amplification. It works like this. With one painful stimulus, pain goes up, pain goes down--very predictable and very similar for everybody. Interestingly, if I apply the same identical stimulus repeatedly over time, things change. It's called windup. It's the same stimulus as before but repeated several times in a row. You respond, and your pain goes up. The more important fact is that with repeated stimulation, your pain doesn't come down as quickly as before. Now that would be fine if you just had more pain and came down the same way, but now your spinal cord starts to remember pain. The decay of pain experiences a less steep slope, so it takes more time to come back to the same level. If I administer repeated pain stimulations long enough or intensively enough, the memory is essentially burned in for a long time (i.e., central sensitization). We don't know for how long, but for a long time. These are patients who say, "I hurt myself, but I can feel the pain that occurred 10 minutes ago, half an hour ago, or whatever the time frame is." So that's really central sensitization, and that's pain memory.

The facts of windup and central sensitization are: First, this is a normal pain amplification mechanism. It occurs with every cut, bruise, or anything else painful. Our body uses this as a mechanism to warn us to stay away from a body area. That's the message that your body is sending you. Unfortunately, in chronic pain, it doesn't have the same meaning any more. You don't need this information, and then it becomes a medical problem. Windup occurs after repeated stimuli and can lead to central sensitization. Importantly, it leads to changes at the spinal cord level and also changes in gene transcription. Genes get activated, and they don't deactivate easily. Actually, nobody really knows how long it takes or if some of them ever deactivate.

Windup depends on stimulus frequency and intensity. You experience this in real life all of the time. You sit in your chair. You activate receptors in your muscles, and the sensation increases. That's why you shift your weight after a while. That's why you move. That's why you get up--because the repetitive stimulation causes pain. In our lab, we use a computer-activated device which provides heat stimuli to the palm of the hand. There are long intervals between stimuli, and what happens, as I mentioned before, is that the stimuli sensations don't return to baseline after each stimulus leading to an increase in pain sensation. Thus, if I increase the number of stimuli, I increase the general pain level that the patient experiences. The repetition and duration of stimulation is very important in the pain experience. It doesn't always have to be a single serious experience. Just a rapid number of smaller, repetitive experiences is enough.

So what does this mean for fibromyalgia? We have compared windup of normal control subjects to patients with fibromyalgia. Pain sensations of normal controls go up with repetitive stimulation, come down (slight delay), but they decay very nicely. If I use the same experiment in patients with fibromyalgia, it's dramatically different, and I think it is one of the best ways to prove that there is a biological mechanism.

As far as after-effects are concerned, once the stimulation has stopped, what happens in fibromyalgia patients versus controls? To share some of the scientific data with you, we found that 15 seconds after the stimuli were stopped, fibromyalgia patients still had pain. Sometimes there was still pain lingering 120 seconds after stimulation had ended, so it didn't decay as quickly as in a normal person. In contrast, the normal controls all returned to baseline and didn't experience pain more than 15 seconds after the stimulation had stopped.

Secondly, the quality of the sensation is also very important. Some qualities of pain are much easier to tolerate than others. Most people experience warmth as an after-sensation of pain, which is fine because nobody is bothered by a feeling of warmth. However, fibromyalgia patients often experience heat and burning, stinging, and sometimes numbness more than two minutes after the stimulus has been removed.

We have used and applied the same principles to muscles. We applied repetitive stimuli, all identical, to muscles of the forearm (i.e., extensor digitorum). A computer-activated device applied pressure to the muscle in a repetitive fashion. Again, the same separation

in pain augmentation of normal controls from fibromyalgia patients occurred. It was even more dramatic. Whereas all subjects started from the same baseline, the fibromyalgia patients went up much more dramatically at the long stimulus interval (one stimulus every 11 seconds), and they went up even more dramatically at the interval of one stimulus every three seconds.

What we also saw was how well normal controls are protected against muscle windup. When we used the same protocol in normal controls, we could hardly wind them up. We had to push so hard that we had to traumatize their skin; they got little bruises on their skin before they experienced any pain. Muscle in normal controls is very well protected, so unless you're traumatizing muscles badly, most "normal" persons will complain of pressure with repetitive stimuli, but they won't complain of pain. In fibromyalgia, windup was very easy, very reproducible.

We know that fibromyalgia was clearly associated with abnormal central pain processing mechanisms. Importantly, we wanted to know if any of our measures correlated with clinical pain. (As previously noted, tender points do not correlate with pain levels.) This is a very important question because it has a lot of implications as far as how to make prognostic statements as well as statements about the impact of therapy. We correlated clinical pain with windup sensations in fibromyalgia patients. We got a good correlation of 0.529, which for most intents and purposes shows that I can predict pain in a fibromyalgia patient with psychophysical testing. I can say where they are most likely going to end up. For example, if I do windup testing, the results will tell me how much clinical pain will likely be in a certain area. Therefore, this particular evaluation has a strong predictive value. This has been done with windup using thermal stimuli on the skin and with windup testing on the muscle which I think is the more relevant method for testing. Although I have only a few subjects enrolled so far, there was an excellent correlation of clinical pain and windup results.

In conclusion, we know that central pain processing is abnormal in fibromyalgia patients. We know that pain memory is clearly increased in this population and that fibromyalgia pain correlates with heat (thermal) windup. FMS pain also seems to correlate with mechanical windup. Part of the pain that you all experience and that we all know is happening in patients with fibromyalgia is due to clearly established biological mechanisms.

Let me just thank my collaborators at the University of Florida who include many scientists in the Neuroscience Department as well as several psychologists and dentists and the staff in my laboratory.

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include chronic musculoskeletal pain, fibromyalgia, systemic lupus, vasculitis, and several other conditions. Dr. Staud's research on abnormal central pain processing in fibromyalgia has generated a great deal of excitement in the research community.