IMMPACT XXIII - Central Sensitization/Somatosensory Amplification and Multiple Comorbidities

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A Matter of Record
(301) 890-4188

ACTTION

INITIATIVE ON METHODS, MEASUREMENT, AND PAIN ASSESSMENT IN CLINICAL TRIALS

IMMPACT-XXIII

Research Design Considerations for Chronic Pain Clinical Trials

Addressing Central Sensitization/Somatosensory Amplification and Multiple Comorbidities

Thursday, July 25, 2019

8:03 a.m. to 4:50 p.m.

The Westin Georgetown

Washington, DC

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:03 a.m.)

Introduction and Meeting Objectives

DR. TURK: Good morning. Thank you.

For those that don't know me, my name is Dennis Turk. I'm from the University of Washington. And I've had the honor of being the co-chair, I guess, whatever terminology we're using for IMMPACT and ACTTION for the last 23 years. I started out, and I had black hair and a nice beard, and it was very attractive. But people couldn't distinguish me from Bob Dworkin, who I've worked with for all these years, so I figured I had to do something different. So I made sure the beard went and my hair got a little lighter. But he's catching up on that, so I can't do that.

In case you're wondering, you are here for the 23rd IMMPACT meeting. I want to welcome all, and thank you for coming, some of you from great distances, and spending the time with us. Many of you have been to other IMMPACT meetings, so you're quite familiar with how things work.

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I'll go into some of the details about that, but there are some housekeeping details that we need to have. If we'd put them up on the screen, you can see them and I can see them. They are probably things you're very familiar with. When you got here, there was a sign-in a sheet at the front desk. Please make sure you do sign in each day, and then sign out, so that we'll know that you were here.

For those that don't know, this is called a cell phone, or an iPhone, or smartphone, whatever you call it. Please mute it. If you get some type of call that you must take, please leave the room with that. Don't try and whisper because, trust me, these microphones will pick you up if you're whispering.

The entire meeting is going to be audiotaped, but the morning session will be both audio and videotaped. So for the speakers, in the morning, especially, make sure that you don't wander around and stay by the microphone so that we can pick up your presentation. That's going to be

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something that you should be reminded of periodically because I know some of us have a tendency to wander away from the microphone. So please don't do that.

Notice the microphones in front of you. These are very sensitive. They are not only voice activated, but if you happen to hit the table, or if you happen to put your coffee cup down, they will light up, and someone will assume you have a question or something you want to say, so just be a little bit careful. Make sure you speak into the microphones because, remember, it's going to be recorded.

It is very helpful if at least the first, if not all the times, that you ask a question or you speak up, that you say your name so that we will be actually knowing who's speaking because often we don't have people do that, and it's very difficult to be able to know what that's going to be.

Restrooms, you know where they usually are. They're outside the meeting room to the left, my left or that way. Valorie is standing in the back

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and pointing, so that way. But if you get desperate, you could always ask somebody, Valorie or Julie, at the front desk to help you out on that.

For WiFi, if you want to use that, select Westin Meeting Rooms network on your browser, and the access code is ACTTION, A-C-T-T-I-O-N. Don't forget the double T's or you won't get it. Lunch is going to be at 12:00 in the Mayfair Court, and dinner is going to be in the same room, in the Mayfair Court.

So that's the logistical things. Behind me, standing by the door, waving her hand is Valorie Thompson. Valorie, you have all been involved with, whether through the emails filling you in. But if you have any questions, any problems, any concerns, anything that you need regarded to the logistics of the meetings, Valorie can handle all of those things. She also does our taxes, so if you need her to work for you in this other off season, she's happy to help you out with that.

Okay. So why are we here? Well it is the

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23rd meeting, and you know that the emphasis of this meeting has been something we're asked -- Bob and I were asked last night, how do we come up with these topics. For those that don't know, IMMPACT, as part of ACTTION, has an executive committee in which we have periodic calls, about three or four or five times a year, depending upon how things are going.

At those meetings, we discuss progress and what's been going on, and we always bring up for that committee to recommend topics for us that may be useful and valuable. Typically, we have several of those, and then as we plan ahead -- and if you don't realize it, we usually plan these meetings at least 9-10 months before we have them. That's identifying the topics, identifying the speakers, and finding background readings.

All of you should have been sent some background readings to help you understand if you're not familiar with some of the concepts and topics that we're going to be talking about. So that's how the topic comes up.

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If any of you, by the way, even though we say that the executive committee comes up with these topics, if you have certain topics or things that you think would be of interest, topics should all be related to some variation of doing clinical trials, or research, or research methods, or data analytic approaches that are not about specific drugs or products or treatments of any kind, though those may get considered as we start talking about these. But the emphasis is on how do you do the best job of designing clinical trials that are going to allow us to have the best information to essentially help patients, which are the end users of everything that we're trying to do.

As you'll hear from the meeting, from different presentations, sometimes we talk about some the high-level things, but, really, always keep in mind that the intent of this is that we can improve how well we provide some type of care or treatment for those individuals who have any one of a variety of different chronic pain conditions.

Now, at this particular meeting, the way

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it's going to be structured is you've got an agenda in front of you. There are moderators for each of the particular sessions. I will introduce the moderator for this morning session into the beginning of the afternoon. He, John Markman, who I'll mention later, will then introduce the different speakers, and then there will be plenty of time for discussions.

We emphasize and try to encourage you to not only asking questions during the sessions, but also when you're at coffee breaks, over dinners, we've intentionally tried to have as much of that time as possible so that you are able to interact, discuss -- I already heard about two manuscripts that are getting written based on people meeting this morning, so that's very interesting, and we're happy to encourage you to do that.

But think about what happens. We're over two days, and we intentionally have the meeting over two days because often what happens is after the first day, there's a lot of discussion and debate after people have left the room for the

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evening, and chatting, and having dinner with each other, and coming up with things that they then want to make sure we cover the next morning.

What's the objective of this meeting, of all of our meetings? The objective is that by the end of the meeting, there will be enough information to be able to construct a manuscript, which will be submitted to one of the regular journals -- depending upon the topic, it will vary -- that will make recommendations and considerations, things to consider in clinical trials, and research, and methodology related to the topic of interest, and some guidance that we hope will be useful. We have no ability to say you must do anything, but rather to get some recommendations about what you might consider if you're designing a clinical trial.

What I always put in the back of my mind is if in fact someone came to this meeting or read in the manuscript that we're going to come up with that you are going to all be authors on -- and I'll tell you about that -- and they were going to

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design a trial, what could they do then?

Not what can they do 5 years, 10 years when we have all the more data that everybody thinks we should always have, but they're going to go into their lab on Monday morning, or they're going to be writing their next grant for the next grant deadline, and they have to make some decisions.

So although it's nice to be able to refer to all the important research that needs to be done and what we need to know, what do you do now if you're going to design that study?

So the objective is that we will come up with information. They don't have to necessarily -- they're not guidelines in the sense of any formal guidelines, but there's some recommendations, things to consider, if you're planning to develop that type of trial.

Now, there has to be enough discussion and enough agreement, consensus if you will -- consensus, by the way, you realize is not a hundred percent agreement; consensus means the majority. There must be enough agreement so that

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there can be such a manuscript prepared, even if it has to say we couldn't decide but you need to consider the following kinds of things.

Now, we're scheduled to end this meeting tomorrow afternoon, but we've arranged that your rooms can be available for several additional nights after that. Just in case we can't come to any kind of decisions --

(Laughter.)

DR. TURK: -- we're happy to have the meeting go a little bit long because most of you want to spend your weekend in Washington, D.C., for those that are not of the area.

So that's available. This is not a threat, but it is a comment to you that we will encourage you to stay here until we end, and we have some information.

The process will be that information will be gathered together. There will be a manuscript draft developed -- it usually takes, 3, 4, or 5 months; it can take a longer, depends -- that will be circulated to all of you. And you have a

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choice. You can -- and we hopefully all will -- say, yes, in fact, I want to be and author of this particular manuscript, and we'll provide comments on this.

Now, if you look around the room and you see the number of people here, you can imagine what happens when everybody takes 2 or 3 weeks, and then somebody else takes another 3 weeks, and it drags out. So when we send you these drafts of the first version and all the subsequent versions, we hope and encourage you for some deadlines about when is it reasonable to get it to us because we want to then integrate and synthesize the comments.

You'll see another version of this. So when you leave this room, and even if it's the first draft, you're not agreeing a hundred percent to everything that's there, but you're basically helping to get to the point where we have some common consensus agreement, recommendations, guidances and considerations that we can put.

So don't feel if you see the first version that, "Hey, they forgot my favorite point," or "I

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asked the question about," and they left it out, because you'll have a chance, at least two and sometimes three -- and heaven forbid if it goes to a journal and it comes back with a gazillion revisions that we have to make. If they're minor, obviously, we won't burden you, but if there are things that require major attention, we may come back to you for that.

So this drags out, and it's a process, but you can expect that you will not be forgotten. You will be here. If for some reason, whether you have a personal lack of interest in the topic or you don't want to be involved in that manuscript, that's fine. We will acknowledge that you attended the meeting. So therefore, whether you're an author or not, there will be acknowledgement.

There's a website that's ACTTION, A-C-T-T-I-O-N.org. On that website, we list topics, the speakers. We ask permission from the speakers to put their slides up on the website so that you can have access to those, so if you couldn't copy everything down and you want to see

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that again.

A lot of people, I've been in meetings when they're taking photos on their cell phones of the slides. That could be really distracting and can really be difficult. So I encourage you not to do that and wait until these slides are up on the website.

Bob, that takes what, 3, 4, or 5 weeks to come up?

(Dr. Dworkin affirmatively nods.)

DR. TURK: Okay. So there will be a reasonable time. I know you're hot to get this information, but it can be when you're sitting in front of somebody and you're holding up, so I caution you about that.

What are we going to do? That's sort of where we're going. Any questions about either IMMPACT, or ACTTION, or this meeting? I'll direct all of those questions to Bob Dworkin because he's much more articulate than I am in handling these things. If there are any easy questions, I'll take care of those. But anything that requires any

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intense consideration, Bob will take care of that.
Bob, raise your hand for anybody that doesn't know you, Bob Dworkin from the University of Rochester.
So any about the logistics or about what we're going to be doing for the meeting?
(No response.)
DR. TURK: You're all in the right room? This is the IMMPACT meeting. Okay. In the past, some of you may remember, I used to have a slide that I decided not to put up about all the things that IMMPACT, I-M-M-P-A-C-T, could stand for. But it's Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. Clinical trials, that's sort of what we're all going to be about.
The topic for this particular meeting, it's a very challenging one, and it's going to cover a number of different issues from terminology and constructs that sometimes overlap, sometimes they're competing, and sometimes they're somewhat different. We'll be talking about things like sensory sensitization. We'll be talking about

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things like chronic overlapping pain conditions. We'll be talking about sensory physiology. We'll be talking about psychosomatic conditions. We'll be talking about somatization and autonomic perception.
We're going to be talking about a lot of different constructs and how they fit together. An important concept for me in thinking about this was the difference between comorbidity and multimorbidity. Comorbidity is going to be those conditions that occur frequently together, and it may or may not be something you consider bringing together in a clinical trial. Multimorbidity would be any combination of different symptoms and signs that may occur together but may not necessarily be highly prevalent in the population.
For example, fibromyalgia, which is one of our favorite topics that you'll be hearing a lot about, commonly co-occurs with IBS. So we will talk about should those be considered chronic overlapping pain syndromes and they are related to each other; or we could be saying, okay, well

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what's the index disease? In our clinical trial, what are we actually studying? Are we going to study chronic overlapping pain conditions?
In the past, what we've done is we've picked a specific disorder -- fibromyalgia, IBS, back pain, postherpetic neuralgia -- but the question then becomes what's the inclusion and the exclusion criteria? Do you leave people out of these studies who have these other conditions, and what are the implications of that? And what does that mean for when we want to do a clinical trial, and what does it mean when we want to talk about the interpretation?
So we'll be thinking about what are the inclusion and exclusion criteria they want to use in clinical trials. Are we going to be considering these different co-occurring conditions or are we going to be considering the comorbid conditions? They go together.
How do we design the study? What are the outcome measures, the appropriate outcome measures to use? If there's an underlying characteristic of

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pain as being the key characteristic of those patients, then we know what the outcome measures can be. But if in fact there's different anatomy and physiology that's involved, do we need to consider those or are those not going to be relevant? Does an IBS patient and a migraine headache patient have the same pathophysiology involved, and does that influence the outcomes that we think are going to be important?
These particular comorbid multimorbid conditions, are they in fact causally related or are they just co-occurrences? Is there some third factor that causes both of those that the treatment should focus? Perhaps depression causes both fibromyalgia and IBS. So is the treatment target the symptoms of depression or is it the symptoms of IBS and fibromyalgia? How are you going to handle that?
So those are the kinds of things that you'll be talking about, hearing about, debating, and discussing. There's agreement; there's disagreement. That's fine. That's why we're here.

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If there was all consensus and we all agree, we could have a very short meeting, and we'd all leave in the next hour. But since we don't think that's likely to be the case -- I don't think; I shouldn't say we; I don't want to speak for Bob -- those are the kind of things that we want to be focusing on.

We're not going to go around the room asking everybody who they are, to introduce themselves. It's too big a group. In the past we have done that, and then I had this grand idea, well, why don't we ask everybody to introduce the person on the left or the right of them, and therefore we'd get to know who knew who, and you'd find each other, but decided that's going to take too long; we're not going to do that.

So that's really what we're going to be doing. Any questions about the objectives, some of the topics, things that are going to be covered in this particular meeting, and anything that's not going to be covered in this meeting?

Do remember it's going to be videoed and audioed, so when you say something, people are

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going to know who you are. So if for some reason there's something that you're worried about somebody is going to hear -- Edward Snowden is listening in; who knows? -- then don't say it.

Lee?

DR. SIMON: So we're used to having a transcript come out of this meeting. Could you inform us as to why it's now being videoed as well as the transcript?

DR. TURK: The video is just the morning session, and Dr. Hertz from the FDA wanted it to be videoed because she wants to be able to present it to the people at the FDA. After this morning, I'm not sure exactly what the time is going to be, we will go straight to audiotape. That was the reason. It was a specific request to share it with the people at the FDA.

DR. SIMON: Just as long it wasn't the plaintiff's attorneys who were requesting that.

DR. TURK: Well, who knows? As I said, everything is up on the Web, so if anybody wants to see what happened at this meeting, it's going to be

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available, and we don't care. If the plaintiff's attorneys want to see it, good, more power to them. Maybe they'll learn something. It will be useful to them. So that's the reason for that.

Bob?

DR. DWORKIN: We are required to post the transcripts of the meetings, and that's why it's audiotaped because a transcript is being prepared. I don't think we're going to post this videotape. This was really at the request of the FDA to share with the people in Dr. Hertz's division.

DR. TURK: Thanks, Bob.

Another thing, let me remind you about the microphones. They are voice activated, but once 6 people or 6 noises have come in to any one microphone, it'll cut you off, anybody else who wants to be the 7th or the 8th persons, you have to wait. So if you see 6 lights and nobody's calling you. How come? It's because you're not getting -- once somebody stops speaking, that microphone then becomes active.

So don't feel we're cutting you off or we're

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not paying attention to you, but we're really tied to this voice activation. And it's interesting because I'm just noticing that the lights are going on and off all the time, so they are very sensitive. So if you want to whisper to your next-door neighbor, I strongly encourage you to either put your hand over your mic or move away from it. Do not move the mic -- I've taken some direction -- because they are set up and designed to work in a specific way.

Other questions about logistics, format, things that are going to happen, or who's here?

(No response.)

DR. TURK: Okay. Then what we're going to do is I will introduce the moderator for the first session. The moderator's job is really to introduce the speakers, and then enliven a discussion, lead a discussion and the panels that we have. I think the first one is this afternoon some time.

I'm delighted that the first chair we're going to have is Dr. John Markman. Most of you

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know him. I think for the introductions, we're not going to go into lengthy detail introductions about who all the speakers are. Pretty much, you know of each other. So the introductions will largely be just who you are, where you're from, and if you have some humorous anecdotes you want to say.

John, you're up first. Thank you all very much.

DR. MARKMAN: Good morning. Let me add my thanks to Bob, and Dennis, and the committee for bringing this together. My name is John Markman. It's a privilege to introduce our first speaker, who is a professor of neurobiology and neurology at Harvard Medical School. He launched his field in 1983 with his seminal paper on central sensitization when he was in the 7th grade.

(Laughter.)

DR. MARKMAN: And here, approaching a half century later, there's not a person in this room who doesn't engage with his ideas every day, and I can't think of any better praise than that.

Clifford?

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Presentation - Clifford Woolf

DR. WOOLF: It's a real pleasure to be here. I must admit this is a situation that is rather unusual for me. I tend to be someone who prefers to look forward rather than looking back, but I think it might be useful to you to give some context to the notion of what central sensitization is and how it was discovered.

For me, this began when I joined the lab of Patrick Wall at University College, London, in late 1979. The lab was in the mid-1980s. I had some hair then. Pat is sitting next to me. Between Pat and me is my graduate student, Allison Cook. Anne King at the back is my first post doc. Jakita Littleton was my first research assistant, so this was very fresh.

Sitting at the end is John O'Keefe, who was a member of our team who then got the Nobel Prize. And if anyone had told us at the time that he was going to win the Nobel Prize. I would have said, "Well, central sensitization will be discussed in a clinical context," as it is today. So unexpected

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things happen.

My first project at UCL was working with Maria Fitzgerald, who has become a very distinguished member of the pain community. We started exploring the circuits that we thought may contribute to the generational pain in the dorsal horn.

This was a time when electrophysiology techniques have improved such that we could now begin to record from individual neurons using intracellular recordings and identify the receptor field properties. In that way, we hope to put together some kind of circuit diagram as to how primary afferent input was processed and then would be transferred to the brain and contribute to the sensation of pain.

The work went technically well, however, I quickly appreciated that we had a major problem, and we called this the ADC, which is any damn cell. The reason for that was that we could only record from one cell at a time. Because we were trying to record intracellularly, we often had no cells

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preparation, and maximum, something like two or three. And frankly, we had no idea whatsoever what those were. We had no idea whether they were excitatory or inhibitory. We had no idea what connections they made.

Therefore, although we have characterized the properties of the cells, and we can say they have a particular receptive field property. They have a certain morphological appearance. We frankly had absolutely no idea how they work together as a circuit to drive the generation of pain.

We published this paper, but I decided it was time to do something different, and this led me to take an alternative approach. This is the FMN approach, which is the flexor motor neuron approach. This was actually driven by the work of Sir Charles Sherrington, who had been at Oxford and, again, another Nobel laureate, who had a profound impact on our understanding of reflex mechanisms. And he is the person that introduced the concept of nociception and nociceptors. His

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work was entirely based on looking at reflex responses and recognizing there were stereotyped responses to defined sets of stimuli.

The insight that I had is instead of recording from any damn cell in the dorsal horn, without knowing what it was and how it functioned, if I recorded from flexor motor neurons, I knew exactly what they do. Their reactivity led to the contraction of a flexor muscle, which would cause a certain pattern of movement.

So at least I could study neurons, whose function I could clearly define; and, to me, this was an extraordinary breakthrough as it were because instead of dealing with a black box with certain elements, I was dealing with the output of a black box and at least had some sense of the function.

So again, it's possible to record from these intracellularly to define their morphology, unlike with whole neurons, the morphology was much more stereotyped, and they resembled each other. At that time, the sense of motor neurons was they

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drove activity in muscles, and their major input were proprioceptive. But not surprisingly from anyone who had studied the flexor reflex, it turned out they had beautiful cutaneous receptive fields; in fact, almost better than those in the dorsal horn. So they would enable us to study the relationship between input to the spinal cord and its output.

This led to a paper that I did with John Swett, who was a visitor in our lab, studying the properties of these flexor motor neurons. Actually, this paper was published after the central sensitization paper, but this was definitely the proceeding work. The preparation we used was unanesthetized decerebrate rats and spinalized, so there was no anesthetic.

Up until that time, almost 99.9 percent of all papers were done in anesthetized preparations. We all know that the definition of an anesthetized preparation is no response to a noxious stimulus, so that was pretty crazy.

(Laughter.)

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DR. WOOLF: Here, we identified a model whereby by decerebrating the animals, we could remove the anesthetic and look at the function of the spinal cord without that confound. We studied the properties of individual motor neurons and discovered that the motor neurons have no spontaneous discharge. They were only activated by defined stimuli.

They all had mechanoreceptive fields, restrictions of ipsilateral foot or paw, and they required high intensity stimuli, noxious stimuli, to avert the response. As opposed to the dorsal horn neurons, each one of which was unique and different, these were very similar.

That was great, and I thought, now, when John Swett left, I could begin to study this more in a setting of actual pathology, so one of the first things I did was to do the effects of repeated heat stimuli and saw an elevation in the response of each stimulus. This reminded us and looked exactly similar to the work of Ed Perl, who was at the University of North Carolina, who had a

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longstanding, philosophical battle with Pat Wall.

Pat was interested in the patterns of activity and the famous mild gate control theory; whereas Ed was definitely of the labeled line notion. He felt that there were defined sets of nociceptors that had very particular problems, and it wasn't the pattern of activity but the activation of these labeled lines.

As part of his work, he discovered that exposure of nociceptors to inflammatory mediators, or inflammation, led to peripheral sensitization. I thought this would be a wonderful model of looking at the output of the CNS in the context of peripheral sensitization, and that's what I set out to do.

As I did this an accumulated my data, these are the receptor fields of individual flexor motor neurons that I studied. Something really struck me, and it was, as indicated here, a state of total confusion. That was that although I had started off with my study with John Swett, it was clear that the vast majority of flexor motor neurons had

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a cutaneous receptor field restricted to the ipsilateral paw that was high threshold.

As I recorded the total populations of neurons that I had from my studies, I found some that were bilateral. Somewhere, the thresholds were very low, and some in the tail. This was a real mess. I couldn't understand what was going on, and it took me a surprisingly long time to get resolution.

The resolution came when I realized that the receptive fields that were restricted to the hind paw and that were high threshold were those that I recorded at the beginning of the experiment, and the ones that had the very large receptive fields that were much lower, and that way you could activate the flexor motor neurons with light touch, for example, always occurred at the end of the experiment.

What is the difference? Well, during the experiment, I was doing repeated noxious stimuli. To characterize the receptive fields, I was exposing them to heat and to pinch, and by the end

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of the experiment, the hind paw was inflamed. So there had been a transition between these very restrictive receptive fields to these very broad ones over the course of the experiment, generated as a consequence of my producing tissue injury. That really was the moment that the penny dropped. I realized I was studying plasticity of the nervous system, something that I had not set out to do but was revealed by this analysis.

This then led to the publication of the first paper that discussed a central component to pain hypersensitivity, which was published as a single author paper in nature. The reason for that is that Pat Wall said he didn't believe a word of it --

(Laughter.)

DR. WOOLF: -- and he said sink or swim, and you're on your own here --

(Laughter.)

DR. WOOLF: -- which was very generous of him.

(Laughter.)

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DR. WOOLF: He ended up changing his mind, as you'll see in a moment.

One of the key findings of this paper was that the pain hypersensitivity as reflected by this expansion of receptive fields and the reduction of the intensity of stimulus required to evoke the flexion response was driven by an increase of excitability within the central nervous system.

This could be revealed by electrical stimulation; in other words, going beyond the tissue injury site, by just stimulating the peripheral nerve, you could now see, over time as a consequence of injury, you get a profound increase in the response to a standard input.

In the control situation, this particular motor neuron had no response. I now deliberately produced tissue injury, and you can see at 30 minutes, there's an increased response and gets even bigger at 60 minutes. If I produced a local anesthetic at the side of the peripheral injury, this persistence. So this indicated that there was some central hyperexcitability.

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These are some of the key points, and the conclusions that I made from this was that injury induced increases in excitability, and that was a consequence of changes within the spinal cord, and that noxious stimuli then had the possibility of producing plasticity within the nervous system. And as a consequence, the conclusion was that pain hypersensitivity had a central as well as a peripheral component.

Frankly, that was a new insight. Even though it may now seem quite obvious, at the time, there was no discussion. There was no thought of it. And as I said, there was the fact that Pat decided not to be a co-author on this because he thought this was impossible.

I then moved on with a study with Steve McMahon, another very distinguished graduates of the Wall lab, and we looked now deliberately at injury-induced plasticity in the flexion reflex and chronic decerebrate rats, and expanded out the nature of this central hyperexcitability state, and deliberately in these chronic decerebrate animals

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showed that different forms of injury produced very prolonged and very profound changes in the hyperexcitability reflexion reflex. It changed from being this high threshold of brief response to one where very low-intensity stimuli could evoke it. The response was greater, it was amplified, and it had a much longer duration. And these changes persisted for weeks on end.

Frankly, this really aligned itself, surprisingly to me, to the appreciation of what happens in patients. At that time, we began to interact with clinicians at the university college, and it was the time which I began to consider that these neurobiological mechanisms revealed in this preclinical model potentially may have clinical implications.

What Steve did as part of the study was to look at whether there were changes in primary afferents that may be driving these persistent changes. He found there weren't, that under those circumstances where the flexion reflex was hyperexcitable and had these profound changes,

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there were absolutely no changes in the properties of primary afferents, again suggesting this was driven by changes within the central nervous system.

We then did a series of papers, and this is where Pat decided he had made a mistake --

(Laughter.)

DR. WOOLF: -- and he was sufficiently a bigger man to say this was the biggest mistake in my career. He then joined us, and we started exploring some of the mechanisms underlying this. We teased out that the drivers of the central hyperexcitability differed depending on which sets of afferents were activated. The afferents from the muscles produced a much longer change than from the skin.

We discovered that this was not due to changes in the central terminal excitability. At that time, it part of the spinal gate control theory. There was a major focus on pre-synaptic inhibition, and we eliminated that as being a mechanism -- this was post-synaptic -- and the last

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paper with Pat and Steve, we went back to the dorsal horn and found that all the changes that we saw in the flexor motor neurons were captured by changes in the dorsal horn, showing that indeed was the primary site of this central hyperexcitability.

This paper in 1989 is the first time I think that at least in press, we used the term "central sensitization." From a historical point of view, I think the first time that I realized that this phenomenon could be compared with peripheral sensitization was in a discussion with Howard Fields, who had come to visit us in the early 1980's, soon after the original Nature paper was discussing.

Howard, thank you for introducing the term, which I then borrowed and used as my own.

(Laughter.)

DR. WOOLF: In the study, we also recognized that a major feature of the synaptic plasticity that was driving this central sensitization was heterosynaptic. This was important because this was exactly the same time that long-term

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potentiation had been discovered and proposed to be a major mechanism underlying memory. This argued that the retention of information in the central nervous system occurred by repeated use of a synapse, long-term potentiation of a synapse.

What we discovered was that if you drew a conditioning input, an input generated by a noxious stimulus, that would not only change the synapses activated by the noxious input, but would also change the input by neighboring afferents that haven't been activated by the conditioning input.

So this was heterosynaptic, that nearby synapses were changed by this conditioning input. This was very different from long-term potentiation, and this I think was one of the major mechanistic insights because it explains why a set of neurons that normally receive only input from nociceptors can now begin to fire in response to low threshold mechanoreceptive input. And the reason is that these low threshold mechanoreceptor inputs, their synaptic input can now be facilitated.

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This I think mechanistically was a big input, and this was captured in this study with Anne King, My first post doc, where we identified that normally most of the receptor fields in the dorsal horn had very large subliminal components. These were inputs that were too small to drive an output from the neurons normally.

But if the neurons became hyperexcitable, the subliminal inputs could be captured and completely transformed the receptor field properties of these neurons; so that neurons that were normally driven clearly by noxious inputs could now begin to be activated by per threshold or with noxious inputs. Neurons that have very small receptor fields could now expand to be larger.

All of these features captures some of the aspects of post-injury pain hypersensitivity, the reduction in the threshold for activation of pain, the spread sensitivity to non-inflamed areas, secondary hyperalgesia, et cetera.

What was particularly exciting is it took less than 10 years for Bob LaMotte and Eric

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Torebjork to show that this phenomenon could be generated in humans. What they did was to use intradermal injection of capsaicin, which at that time was not appreciated to activation of TRPV1, but it is a means of experimentally activating nociceptors.

What they revealed was exactly as we have shown in the flexor motor neurons and the dorsal horn neurons, that such brief input in nociceptors could produce an increase in sensitivity to pain and a spread of tactile sensitivity, an area of secondary hyperalgesia. This was exciting because it showed that there was shared neurobiological mechanisms between rodents and humans.

Another discovery that we made, quite early on, was the synaptic plasticity underlying this central sensitization included activation of the NMDA receptor. This in turn has led to -- I wouldn't go through them -- a whole series of studies that have indicated that, indeed, NMDA receptors do contribute, both in preclinical models but even more so in humans, the generation of the

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acute activity-dependent plasticity.

The kind of thing that Bob LaMotte and Eric Torebjork had shown, that capsaicin [indiscernible] secondary hyperalgesia was exclusively sensitive to NMDA receptor antagonists, and indeed, post-surgical pain hypersensitivity is also exquisitely sensitive. The trouble with NMDA receptor antagonists is that they are involved in long-term potentiation and memory.

Also, ketamine has psychotropic effects, so it's a therapy that is effective but has adverse effects, which make the balance of its use difficult; although it continues -- I'm surprised, when I was preparing for this, how many studies continue to use ketamine, and, at least in a postoperative setting, reduce the need for postoperative opioids, which is a positive thing.

As we explore this, we began to appreciate that there were enormous similarities between the post-injury hypersensitivity phenomenon, the central sensitization, in Eric Kandel had been doing on aplysia, where he was studying synaptic

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facilitation. His notion was this is all about the study of memory, but he was looking at the gill withdrawal reflex of aplysia, this preparation.

Terry Walters and I wrote an article in the early 1990s looking at the commonalities between the plasticity between mammals central sensitization and the phenomenon that Eric Kandel had described. This provoked an enormous response, one letter from Eric Kandel, that essentially said if we ever did repeat this, he would personally make sure that my career ended --

(Laughter.)

DR. WOOLF: -- that his work had nothing ever to do with pain; this was only about memory. And he was right because he got the Nobel Prize --

(Laughter.)

DR. WOOLF: -- the Nobel organization gave this for changes of function that are central for learning and memory. However, I am pleased to say that when I finally met Eric face to face, he did admit he had been studying pain after all, and that the phenomenon in aplysia was very similar to

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central sensitization.

So what were the clinical implications? As I began to explore these, I interacted with Lesley Bromley, who is an anesthesiologist at the University College hospital. One of the ideas that came up is if we potentially could prevent the development of central sensitization, what implications would that have for patients?

This led us to the concept of preemptive analgesia. If one treated early, prevented the establishment of heterosynaptic facilitation, would this be beneficial to patients in the sense that they would have less pain? The ideal setting we thought would be postoperative pain.

Frankly, at that time, the standard of care was that patients were anesthetized, and they were only given treatment after they woke up when their pain reached a certain level. PCA had been introduced. The doses they selected to control the pain were very high, and that was the notion. You only were treated when you had the pain. There was no sense of anticipating the pain.

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This study that we published in Lancet indicated that if you gave morphine before the operation, the amount of PCA, the choice that the patient made in terms of how much analgesic they selected postoperatively was significantly reduced, and this turned out to be quite a controversial issue.

There have been many studies, some of which claim that indeed there are benefits. In fact, again, in preparing for this lecture, I relooked at the literature, and actually in recent years, there have been a number of studies on the phenomenon of early treatment reducing the requirement for postoperative analgesic seems to be correct in certain settings.

Another aspect of this that is somewhat surprising is the whole focus initially that the mechanisms of central sensitization were on increases in excitability. As a result, work that include Joachim Scholz, who is in the audience here, we began to explore, particularly in the setting of neuropathic pain models, the possibility

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that in addition to increases in excitability, reduction in inhibition could contribute to the phenomenon.

Indeed, that's exactly what we found, that associated with peripheral nerve injury was a loss of GABAergic inhibition that included actual loss of some inhibitory neurons, and this contributed to a state of hyperexcitability so that this expanded the notion of central sensitization beyond purely being heterosynaptic facilitation to one that included disinhibition as well.

There have been many studies on the clinical manifestations. This clearly is the major theme of this talk. It includes surgery. That's been one of the biggest areas where it's easiest to detect. They started with an individual who has no pain, and you can then detect profound changes in their pain sensitivity and quantify that. But it also included a broad range of patients, patients with migraine, osteoarthritis, and neuropathic pain.

Each of them have the features. I think one of the issues that Dennis pointed out is how do we

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define central sensitization? How do we recognize it? What are the criteria for establishing where the patient has it? What are the implications for the patient if they do have it from a therapeutic point of view? And these are hopefully the kinds of issues we're going to touch on here. Clearly, it looks as if this is a phenomenon that could be widespread amongst a broad range of different individuals.

One of the issues as the concept evolved was should the term "central sensitization" be restricted to the initial discovery, which was a use-dependent hyperexcitability that lasted for tens of minutes, or could it capture all those expressions of an amplification of the nociceptor circuits?

This is something there has been some vigorous debate about. In the end, my feeling is that central sensitization includes all of those conditions where the central nociceptor circuits are altered such that there is a reduction in threshold and an amplification of responses, even

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if these are mechanistically or different from the original description.

So I think central sensitization should be a broad family of phenomena where the focus is on changes within the central nervous system, but again, this is something that we could discuss. At least for me, this is my definition of an amplification within the central nervous system, are those circuits that connect sensory input from the periphery to those cortical areas where pain -- and it drives the phenomenon of exaggerated response to noxious stimuli, hyperalgesia, and the response between noxious stimuli and allodynia, as well as changes in the summation and the spread of sensitivity to non-injured tissue, secondary hyperalgesia.

So to me these are some of the key features that I think represent this plasticity within the central nervous system.

What are the mechanistic underpinnings? How have they changed? Although I've worked very intensively on central sensitization in the decades

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after its discovery, after that time, I found that the technology available then was rather limited, so I diverted to other areas. However, as I'll indicate in a moment, there are some new technologies that I think are going to change things, and this has reintroduced me to begin to explore it.

This is a study I published last year with Zhigang He, where we found that the corticospinal tract in mice had a direct facilitatory effect on dorsal horn neurons and was a major contributor to tactile allodynia in the setting of nerve injury. This, again, was something completely unexpected, that there'd be a direct cortical input to the dorsal horn. My initial focus was entirely the changes driven from the primary afferents, but here was the brain itself contributing to the changes within the spinal cord.

That means this may be a means by which phenomena, again that Dennis has introduced, that our brains, our state, our mood, our attention, all of these could directly contribute to alterations

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in excitability in a real way; and that were originally thought to be psychosomatic manifestations are actually real neurobiological changes. So we're quite excited by that.

One of the other bits of work I've done recently, like many people, is to use optogenetics as a means to now be able to selectively activate or inhibit defined circuits. This happens to be a study where we have the express channel reduction in nociceptors. We can use a laser then to activate these nociceptors in a very defined way, in a very defined location, such that we can activate a single action potential from, we estimate, less than 10 afferents, a tiny, tiny input in the mouse.

What really surprised me, then, from this study was that this tiny input, one action potential in 10 afferents is sufficient to completely change the entire behavior of the animal. The animal not only has a withdrawal reflex; its whiskers start moving. It turns its head. If it's sleeping, there's a change in its

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EEG.

This completely changed by notion of how the nervous system works because what it reveals to me is that there are these circuits in the CNS that are waiting for a trigger to activate them, and that a tiny trigger, the smallest trigger you can imagine, is sufficient to invoke a very profound change.

I've always been looking for, in the context of input driving the system, profound discharges in many afferents. In fact, what it looks like is a tiny input, and a very few set of afferents is sufficient to provoke pain-related behavior. We think that this is likely to be part of the central sensitization patterns, where you do not need massive inputs; tiny inputs may be sufficient.

What are the diagnostic features of central sensitization? Again, I'm sure this is something that will be discussed through this meeting, but to me, it's all about how can you detect changes in amplification on nociceptor circuits, disproportionate pain, in the presence of dynamic

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tactile allodynia, temporal summation, and secondary hyperalgesia?

There's been the introduction of the central sensitization inventory. I'd be interested to know what people think of it. To me, the notion that you can use a questionnaire exclusively to try and capture something which is characterized by changes in sensitivity doesn't seem quite right, but it has become widely used. What's interesting now is that there are many studies using functional imaging that are capturing mechanistically changes in nociceptor circuits that correlate specifically with the presence of these disproportionate pain syndromes.

One of the other features of central sensitization is how it is revealed, mechanistically, how many analgesics work. In addition to the NMDA receptors, antagonists, which have a selective action on the heterosynaptic facilitation, there are now multiple papers illustrating that gabapentin and pregabalin both work on central sensitization, as does duloxetine,

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and indeed opioids. Some of the commonest currently available analgesics, at least some of their major mechanisms is the suppression of central sensitization.

Something else that current literature is beginning to imply is that central sensitization may be a contributor to the risk of development of chronic pain. This just summarizes the data for existing treatment. What's interesting is that two of the newest analgesic therapies, anti-NGF and anti-CGRP also have been suggested at having some action on central sensitization.

To come back to the risk of developing chronic pain, there are a number of papers, all published this year, which imply that the presence of central sensitization in individuals represents a risk factor for the development of chronic pain. This includes in the setting of persistent pain, after knee arthroplasty, the risks for the development of postherpetic neuralgia after acute herpes zoster, and cancer pain.

This is something that I think is pretty

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interesting. There clearly can be genetic drivers of the risk of individuals or the presence of individuals who have a greater degree of vulnerability for the development of central sensitization, and this may be a contributor to the risk of these individuals developing persistent pain; something to think about.

What next? As I said, after several decades of having left central sensitization to stew in its own juices as it were and to let people like Dan Clauw tease out how it manifests and some of its mechanisms, I've started to come back to it because there are now tools available to do the kinds of things that I wanted to do originally.

One of them is using GCaMP technology. It is now possible to measure activity in large populations of defined neurons. So instead of doing any damn cell, we can now look at the properties of neurons, the output neurons in the spinal cord, and the cortical neurons that are activated. Instead of one cell at a time, we can look at literally hundreds, if not thousands, and

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get a real sense of how the nervous system operates in the setting of defined inputs and the changes that occur.

We can optogenetically control these. We can switch these circuits on and off and see the changes of this. We can now use artificial intelligence and neural network based analyses to tease out both the changes in the circuits but also changes in behavior. We have recent data exploring how to measure behavioral signatures of pain, and these turn out to be much more sensitive than the reflex-evoked responses.

It's quite ironic that central sensitization was discovered by studying the reflex output of the spinal cord, but now I abhor it to say that the reflex response really doesn't reflect what the individual is feeling. We now have a technology to begin to measure that.

In addition, there's the possibility, which is extremely exciting, of using human stem cell based technology to recreate some of the key neural elements that are involved in nociception, both

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nociceptors but also using organoids. I think in the future, we will be able to model some of these changes in humans and begin to use them possibly in a precision medicine way to see which individuals are at risk.

We know, for example, in the setting of diabetic neuropathy work that Joachim has done, that there are individuals who have type 2 diabetes with absolutely no neuropathy or no pain, those who have neuropathy but no pain, and those who have painful diabetic neuropathy. We have absolutely no idea what is responsible; what are the susceptibility factors that drive a patient to have a particular clinical phenotype, and we may be able to capture that using this stem cell based technology.

I hope I've given you a flavor of the initial discovery of central sensitization. I certainly had no sense at that time that it would lead to this kind of meeting, which is extremely exciting. I am an MD-PhD, but my initial focus was in entirely neurobiological, but I am very excited

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now to begin to appreciate the clinical implications of this work. Thank you.

(Applause.)

Q&A

DR. BRUEHL: Clifford, I appreciate having you on the spot here to ask you this question. This is something that has bothered me conceptually for a while about quantitative sensory testing studies, is the temporal summation protocols that are supposed to tap into central sensitization are extremely explicit about the parameters of the stimulus. It has to be about 2 and a half seconds apart, it has to be very brief, and if you don't follow that, you get criticized.

We've done some work with some collaborators in Spain, where a 5-second long pressure stimulus spaced 30 seconds apart in fibromyalgia patients shows exactly the same pattern of increasing perceived pain over 10 trials, that looks exactly like temporal summation.

So my question to you is, based on the studies you've done and your understanding of

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central sensitization, what are the parameters, stimulus parameters, that would be expected to elicit central sensitization in an experimental setting?

DR. WOOLF: I think the challenge is, if we define central sensitization broadly as a state of amplification within the central nervous system, what tests and what parameters in those tests can reveal that amplification? I don't think it needs to be anything fixed other than it reveals a change within the process in the central nervous system.

If you are able to show that there's temporal summation with a certain set of conditions, what is revealing is that the same input, when given on repeated times, leads to a bigger and bigger response. That is one way of revealing the presence of amplification. And how you do it, frankly, is irrelevant. The goal should be is this test revealing the presence of an amplification within the central nervous system?

DR. MARKMAN: Steve, say your name. And please try and say your name first.

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DR. BRUEHL: That was Steve Bruehl, Vanderbilt University.

DR. SCHOLZ: Clifford -- I'm Scholz, Biogen -- thank you for this overview of the history of central sensitization. Central sensitization, the narrower sense, has mostly been studied in models of nociceptive pain. But it's also true for the work of Jurgen Sandkuhler on pordensation [indiscernible] of these signals in the central circuits.

Back in the days when I was at Columbia University, we conducted a study in the mouse model where we removed the NMDA receptor from the dorsal horn in the spinal cord. And to our surprise, we found after nerve injury, that there's no change in the development of pain during the first week, but that these animals do not develop chronic pain.

That's the complete opposite of what Jack Antareesey [ph], who has used the same model, finds in inflammatory pain. He basically reduces the initial period of pain development to a large extent, but the NMDA receptor in the spinal cord

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doesn't seem to play a role in chronic inflammatory pain.

So my question is, does central sensitization occur in conditions of nerve injury in neuropathic pain? Is it just that the timing is different or is the pharmacology different, and the NMDA receptor plays a different role?

DR. WOOLF: I think this was a key point. Again, I think Dennis raised it. If we use central sensitization broadly as the presence of amplification, I would say there's no question, it is present in -- you evoke it in healthy skin with capsaicin. You can reveal it in the presence of tissue injuries such as post-surgical pain, and it is a contributor to neuropathic pain by virtue of the presence of allodynia is an expression of amplification and a change within the central nervous system.

However, those may have different mechanistic underpinnings. Each of them may be operating in different ways with different pharmacologies. And the challenge is how to

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identify in an individual patient which is the responsible mechanism so that instead of regarding central sensitization as something where if the patient has it, there's a single treatment, but rather to ask the question very specifically, what is amplifying with or what is changing the nervous system?

In some settings, that may involve NMDA receptors, but I certainly accept that may not be present in others. That is exactly the difficulty. I think it's a broad notion of the involvement of the nervous system in the generation of pain, but that in no way implies that there's a single mechanistic underpinning.

DR. SIMON: Simon, Boston. As usual, a wonderful presentation, Clifford. Thank you. As a rheumatologist, I'm confronted by failure of clinical trials in lupus consistently because the heterogeneity of the disease is a problem, but we also have a group of patients who achieve inclusion in trials who have a painful syndrome, to a degree -- this is not a predominant part of

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lupus -- and yet, when we look to see if these people have inflammatory disease, they don't.

I was wondering within the inflammatory state, where you get pain and various different complications associated with that, do you believe that central sensitization takes a different pathway than if you just have a noxious stimulus that's nerve damage or something like that?

Do you think there is a difference in the way that that behaves, because certainly from a clinical perspective in doing trials, clearly these people are different, and why they're different seems to be a little hard to explain. Do you think inflammation does play a role?

DR. WOOLF: Yes, absolutely. Inflammation not only produces peripheral sensitization, which could constitute an input in nociceptors that could drive use-dependent synaptic plasticity, but also results in the production of signaling molecules such as nerve growth factor, which is retrogradely transported to the cell bodies, which changes the transcription of these neurons. These neurons

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start to produce peptides and other modulators that they don't normally do, and therefore have a different effect.

There are also centralized changes there as a consequence of the input to the CNS, and the CNS neurons start changing. So part of this dynamic plasticity is that in the disease setting, there may be profound changes. But to come back to a point that I made in terms of the risk of transition of pain, the presence in acute patients, or at least some measures, indicating heightened hypersensitivity or the presence of central sensitization as a risk factor of developing chronic pain, I think that may also be a factor. It's not just the presence of inflammation.

The reason I say that is there have been studies in OA, at least, where the chronicity of the pain and the failure of recovery after arthroplasty seems more to be associated with temporal summation rather than how much gab enhancement there is, as a measure of the degree of inflammation.

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In some patients, at least, there seems to be a heightened susceptibility. One of the big challenges in the setting of chronic widespread pain, as to why do individuals develop fibromyalgia, or temporomandibular joint disease, or irritable bowel syndrome, is a susceptibility of individuals to pathological amplification within the CNS, and maybe some of your SNE patients have that same risk.

DR. WASAN: Clifford, it's real interesting to hear from you the history of the initial observations of central sensitization in the sense that these were some of the observations of keen observed scientists. In most of the scenarios that you presented, the changes in the central nervous system were somewhat different in the peripheral input.

Are there any scenarios where de novo central sensitization occurs in the absence of any peripheral stimulus?

DR. WOOLF: Yes, and that's very difficult to study experimentally. Again, to come back to

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the chronic widespread pains that there's been repeated discussion of is this independent of peripheral input, again, with neuropathic pain, there's the argument of centralization such that there is no longer a requirement of ongoing input from the periphery to drive it.

In fact, our recent study with Zhigang He, corticospinal tract activation with the dorsal horn neuron, which was sufficient to produce tactile allodynia, indicates to us, the possibility at least, that there may be CNS autonomous circuits that at least can begin to drive this pathological amplification independent of a peripheral trigger, but it's the usual chicken and egg problem.

Most of the features of central sensitization are a reflection of the abnormal sensitivity to peripheral input. It's something worth considering and thinking about, but it actually is very difficult, I think, to formally prove.

DR. FARRAR: John Farrar, University of Pennsylvania. You suggested that in

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[indiscernible - too close to mic], and you will see the onset of a change in response to pain within seconds of the initial stimulus.

All of us, all humans, all animals are subject to this process that you very well described, and yet, there are clearly some patients in whom hypersensitivity or some degree leads to the potential for chronic pain, as you also suggested. I'm wondering if you might comment on what the components of this process are that might be more or less related to the likelihood of developing, as you were just describing, some change in the central system that leads to an ongoing process beyond the pain stimulus.

DR. WOOLF: Well, I can just share with you some unpublished work that is still ongoing. There's a long history in the setting of neuropathic pain that nerve injury results in ectopic activity and spontaneous firing of nociceptors. Certainly, all the early studies, largely driven by Marsha Devor showed very large waves of activity in injured nerve fibers, which

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could be the sustaining trigger for central sensitization.

With these new optical recording techniques, GCaMP recording, we've been looking both in the trigeminal and in dorsal ganglia after nerve injury with expectation we'd see this bursting ectopic activity, and frankly we don't. It's been a complete shock to me, completely and unexpected. We do see normally very low levels of spontaneous activity, and after nerve injury, we see similar levels, maybe a tiny bit higher, but not much.

This has at least opened up the possibility, again, that you need tiny inputs. It's not some massive convulsive discharge with thousands of neurons that is driving the pain, but actually activity in a handful of fibers that is sufficient to produce it, and maybe that's part of the element. And maybe as part of the centralization is that normally we are being bombarded by very low levels of input, and normally that is not sufficient to produce much of a pain, but in an amplified situation, it can.

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So I'm having to rethink the notion of what degree of input is sufficient to produce pain and maybe to trigger some of these changes, and it seems to be much, much lower than I had anticipated.

DR. MARKMAN: More questions?

DR. RATHMELL: Jim Rathmell from Brigham. Can you tie together mechanistically what we've learned about opioid-induced hyperalgesia with the concept of central sensitization, and then how might you approach those two, similarities or differences?

DR. WOOLF: Yes. Certainly, in the very acute setting with single use, opioids by virtue of decreasing transmitter release from nociceptors can reduce acute central sensitization. Presumably, its activity in the brain stem may also modulate some of the synaptic plasticity in the dorsal horn, and there have been preclinical studies of that.

I think the changes that occur chronically with chronic administration that lead to the development of opioid hyperalgesia are a reflection

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of pathological changes in opioid activity. Whether it has parallels to the phenomena of central sensitization, I'm not actually familiar of someone who's made a direct comparison mechanistically whether the chronic opioid induced changes, in terms of synaptic activity and membrane excitability are similar. I just don't know, but that's obviously worth thinking about.

DR. DWORKIN: We've gotten some feedback that people asking questions are coming too close to the microphone and that it's garbled. So if you ask a question, please leave reasonable room and space between your mouth and the microphone. Thank you.

DR. MARKMAN: So it's obviously a privilege to have that historical perspective. I hope that it has a chance to live on YouTube as a bootleg perhaps, so other people have the privilege of enjoying what we just had the privilege of hearing.

Our next speaker really reminds me of this idea that the eye cannot see what the mind does not know, and Dr. Clauw has given us the eyes to see

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central sensitization in many different clinical scenarios.

Dr. Clauw is a professor of rheumatology, anesthesiology, and psychiatry at the University of Michigan. Through his cogent descriptions of the clinical manifestations of central sensitization, I think it has changed how clinicians everywhere see patients who have pain that they cannot explain.

Presentation - Daniel Clauw

DR. CLAUW: Thanks so much, John, and thanks to Dennis, et al. for having this as a topic. This is exciting. And it's particularly exciting to talk after Clifford because I'm likewise am going to try to give a bit of historical perspective. I'll start a little bit later than Clifford. I was in my third year of medical school when he published his Nature paper.

But I'm going to talk about 30 years or so of clinical work, looking at all these overlapping concepts: central sensitization, chronic overlapping pain conditions, and now the new IASP term, nociplastic pain. I will be speaking rapidly

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because I have a lot to cover.

In the old days, there were two underlying mechanisms of pain, nociceptive and neuropathic pain. Almost all clinicians thought that all pain was caused by some problem out in the periphery, either damage, inflammation, or in some cases nerve damage. But as the biopsychosocial pain models began to come into favor in the pain field, the predominant central nervous system contributions to pain were really thought to be classic psychological concepts like anxiety, depression, or cognitive concepts like catastrophizing.

But as Clifford just really nicely outlined, animal studies were outlining both spinal and supraspinal mechanisms that were not depression, anxiety, catastrophizing that were capable of augmenting or amplifying peripheral nociceptive input or causing pain without any ongoing peripheral nociceptive input. So a number of us on the clinical side started to slog away and try to define what central sensitization might be in these clinical conditions.

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This is the first side of almost every talk I give. I am trained clinically as a rheumatologist. I don't act like a rheumatologist anymore; I'm a pain researcher. But there's actually three diseases I'm going to refer to over the course of my talk today: osteoarthritis, rheumatoid arthritis, and fibromyalgia, all of which I'm really going to use as metaphors rather than talking of those as stand-alone diagnoses.

When I was trained as a rheumatologist, I was taught that osteoarthritis was the classic peripheral pain condition; that what you saw in an x-ray is what that person would experience. If they had an x-ray like the one on the right, they would always hurt. If they had an x-ray like the one on the left, they would never hurt.

That turned out to be totally wrong. It turns out that 30 to 40 percent of people in population-based studies that have bone on bone in their knee do not have any pain whatsoever, and 10 to 15 percent of people that have severe knee pain have entirely normal radiographs.

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I'm using osteoarthritis as an example today. Our group studies probably 15 or 20 different chronic pain conditions, and I would like anyone to challenge me and say there is anything you can measure out in the periphery in any chronic pain condition that accurately predicts who is going to have pain or how severe the pain is going to be. There is always a tremendous disparity between what we can identify out in the periphery and whether someone's having pain or how severe the pain is going to be.

In osteoarthritis, this is a 30-year history of osteoarthritis. We went from it being a classic peripheral pain condition to realizing there was a terrible relationship between what you'd see on a radiographic and what people are experiencing. Then we started blaming the patients. We said anxiety, depression, catastrophizing were causing this.

It turns out, point of fact, very little of the variance between what you see on x-ray and what someone has experienced can be accounted for by

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classic psychological factors like anxiety, depression, and catastrophizing, and leads to smirking here because he lived through this as well.

The therapies that I was taught worked really well and in most all people with osteoarthritis -- NSAIDs, opioids, arthroplasty -- have very high failure rates. NSAIDs and opioids don't work any better in osteoarthritis than pregabalin and/or duloxetine work in fibromyalgia. These drugs all work about in 1 out of 3 people, and we even have failure rates of 20 to 30 percent with knee and hip arthroplasty even though it is the most successful surgery to do for chronic pain.

In rheumatoid arthritis, we said sort of a comparable thing happened in the field, and Lee was just alluding to this, is we have now incredible drugs to treat RA, lupus, ankylosing spondylitis, or biologics, but still 30, 40, 50 percent of people that are treated with those drugs -- and you can no longer identify any ongoing inflammation of

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these individuals -- these people still have widespread pain, fatigue, and have poor functional status.

So why is that? In these conditions, we really have been very effective at developing more and more peripherally directed interventions, but yet our patients often are not experiencing improvements in their pain.

I will talk about the F word, fibromyalgia. Regardless of what you think about fibromyalgia, I think it has taught us a lot about pain. I lived through the early days where fibromyalgia was defined on the basis of widespread pain and tender points. We helped teach the broader pain research community that tender points are stupid because what fibromyalgia patients in fact experience are allodynia and hyperalgesia. It doesn't matter where you push on someone with fibromyalgia, they are more tender.

But another set of studies that our group and others started to do in people with fibromyalgia were doing quantitative sensory

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testing for other types of non-painful sensory stimuli. And it turns out the fibromyalgia patients are just as sensitive to the brightness of lights or the loudness of noises as they are sensitive to pain.

So this was clearly something more than a spinal central sensitization mechanism, and, in fact, we didn't even know what terms to use as we started to write this. When we use the term "central sensitization," we would get criticized, but when we didn't use it, we would get criticized. In fact, right now we still have a lack of disagreement in the pain field about what to call this underlying construct.

I think in the broader pain field now, we think of fibromyalgia as sort of the poster child for diffuse hyperalgesia, allodynia, and central sensitization. Again, our group feels strongly that this should be defined more broadly than just on the basis of pain because these people have sensitivity to a number of other sensory stimuli, and they almost always have other CNS symptoms:

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fatigue, sleep problems, memory problems, and in many of them mood problems that we think are really part of that phenotype as well.

Now segueing back to a group of conditions where the individuals that would have had these conditions have suffered historically with credibility, conditions like fibromyalgia, irritable bowel. These have already been alluded. A couple of years ago, with a lot of help from Chris Veasley and a lot of patient advocates, the NIH came up with the term "chronic overlapping pain conditions." This term has stuck.

But we now acknowledge that a lot of these conditions -- irritable bowel, TMD, interstitial cystitis, low back pain, endometrius, dry eye disease -- if you don't know about it, dry eye disease, it's a really cool disease. It's basically the irritable bowel syndrome of the eye, where people feel their eyes are dry but their eyes are not really dry. This is the bane of ophthalmologists' existence like irritable bowel is the bane of gastroenterologists; existence, and

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like fibromyalgia is the bane of rheumatologists' existence.

But not only do we see the these features, these prominent central nervous system components to these classic chronic overlapping pain conditions, but you can identify these same mechanisms, these same symptoms in subsets of people with sickle cell disease, cancer pain; any other pain condition, if you look for the phenotype, you will find it. You will find people with more widespread pain than you would expect with memory problems, sleep problems, fatigue, and with sensory sensitivities other than sensitivity to pain.

In fact, the IASP a couple years ago voted and agreed that there was a third new category of pain; I hate the term, nociplastic pain. But be that as it may, we're now in the process of trying to define what nociplastic pain is. But again, I think we're really looking heavily to all these studies that have been looking both at chronic overlapping pain conditions, as well as when

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central sensitization is superimposed upon conditions like rheumatoid arthritis, or lupus, or some of our classic conditions where there is ongoing nociceptive input.

I started using this analogy a long time ago -- the basic science pain researchers heads will explode with this analogy -- but to try to teach clinicians and patients that the amount of pain that someone is experiencing was akin to the loudness of an electric tower. And all I was trying to do is to get people to add together what's going on in the guitar, i.e., what's the ongoing nociceptive input, and then what are the contributions from the central nervous system?

The central nervous system can clearly turn up or down the sensitivity to pain out in the periphery, and the studies that have been done have clearly shown that these people, these 40 percent of osteoarthritis patients that have bone on bone but don't have any pain, on quantitative sensory testing, they are way less tender or way less sensitive than people who do have pain.

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We can very clearly see with conditions like osteoarthritis that a lot of this sort of disparity between what you see on a knee radiograph and what the person's experiencing can be accounted for by differences in whether the central nervous system is facilitating or augmenting what's going on in the periphery, or whether it's inhibiting what's going on from the periphery.

There are a whole bunch of things that go on in the central nervous system that modulate what's going on out in the periphery, and there's bidirectional talk. I say this often. The distinction between the peripheral nervous system and the central nervous system is something that humans do. It's one nervous system, and that's really the way it behaves, as one contiguous nervous system, not as if it's dissociated.

A lot of different studies. Here are some studies done by Bill Maixner and others. You can see that if you take a group of people and phenotype them for how pain sensitive they are, and then you follow them for five years -- for example,

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as they did in the OPERA study, you'll find that the people who are more tender, who have less condition pain modulation are more likely to develop a new chronic pain condition over the next five years.

But the strongest predictor of developing new TMD and a number of other chronic overlapping pain conditions was a single self-report measure that was in OPERA called The Pill. The Pill really is looking at sensory and somatic amplification. It was originally developed, if I'm right, Roger, to study somatization. But the reality is what I'm talking about now is the biology of somatization.

Somatization, I hate using that term because it means there's no biological underpinning to this, but what I'm talking about is people who studied somatization were correct in pointing out all the clinical criteria. What they were incorrect about is that it didn't have a strong biological basis. Even the people that have historically studied somatization will acknowledge now that there's a neurobiology to somatization

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that's almost identical to what it is that I'm talking about.

Many of you that know the fibromyalgia literature would know that Fred Wolfe and I don't agree with about hardly anything. He still thinks that fibromyalgia patients are neurotic, middle-aged women that there's nothing wrong with. But I like giving him credit for he was the first one to say we shouldn't think of fibromyalgia as yes or no; we should think of it as the degree of fibromyalgia that people have, because he showed that in osteoarthritis, rheumatoid arthritis, and low back pain, the degree of fibromyalgia was more predictive of pain and disability than in rheumatoid arthritis, a sedimentation rate [indiscernible], a CRP, a joint count, some of the more objective measures that we hang our hat on.

I sometimes wonder whether it was a good idea to pull Fred out of fibromyalgia retirement because I think I poked a skunk.

(Laughter.)

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DR. CLAUW: But nonetheless -- Lee is laughing -- we now do have new criteria that don't require doing a tender point count, and we have used these criteria as a surrogate measure of the degree of central sensitization that people have. But I think these criteria are helpful because there are two components to them. They're looking at how widespread the pain is, and that probably is the most critical component of central sensitization. But they're also then probing people for these other CNS symptoms, fatigue, sleep problems, and memory problems that seem to travel along with this phenomenon and help you identify the people that have this phenotype.

To just to give you an example, imagine you're a well-meaning orthopedic surgeon and see someone with an x-ray like that one I showed on the right, bone on bone. They have bad knee pain. Are you going to offer them joint arthroplasty? Sure. But how much do you really think they would get if you operated on the knee in this person with fibromyalgia?

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So I'm showing this to show you that almost everyone would sort of intuitively say someone with fibromyalgia probably isn't going to do as well if they have knee or hip arthroplasty as someone without fibromyalgia. What I want to show you is that everything in between is important.

By looking at fibromyalgia as the end of the continuum, we've gotten a really distorted view of this phenotype. We think that all these people have prominent psychological comorbidities; they don't. The people that we label with fibromyalgia usually do, but when you see this in other settings, the psychological factors are really not nearly as important as this underlying neurobiology of amplification of what's coming from the periphery. You don't even need a psychologist. If people start crossing out words and putting in a new word, you can just use this.

(Laughter.)

DR. CLAUW: So I used to say that fibromyalgia was the tip of the iceberg and that there's a much larger number of people that have

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centralized pain that don't carry the label of fibromyalgia. Now since I'm part of the resistance movement, I say you've got to be really careful of what you might find underneath the rock.

(Laughter.)

DR. CLAUW: We have done a series of studies. By the way, Sharon, the PDF of this doesn't have the second part of the slide, so when it's posted, the second part of the slide won't come up, so we don't have to worry about that.

(Laughter.)

DR. CLAUW: I'm just going to present some data very briefly. These studies were led by Chad Brummett, where we've looked at the fibromyalgia measure as a predictor of differential outcomes in knee and hip arthroplasty, and we predicted that it would predict nonresponsiveness to opioids and nonresponsiveness to surgery.

We didn't just look at the fibromyalgia measure in all of these studies. We had the PainDETECT, catastrophizing, depression, and anxiety, but this is really the only thing that was

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innovative about the studies, is on the day of surgery, we gave people this measure to fill out, and we looked at how the scores on this measure influenced the opioid responsiveness on the first 24 to 48 hours after surgery.

This is acute opioid responsiveness, not chronic opioid responsiveness, as well as how well it influenced whether someone was going to get better if we replaced their knee or replaced their hip. This can be scored from 0 to 31 on this scale.

So Fred Wolfe was totally right. It doesn't matter where in the continuum someone is. Each 1-point increase in the fibromyalgia measure makes people less opioid responsive and less surgery responsive, and it doesn't matter if they're up by 13, which is the part of the scale that has said you have fibromyalgia, or if they move from a fibromyalgia score of 3 to 6. That 3-point increase in the fibromyalgia measure leads to an equal increase in opioid nonresponsiveness and surgery nonresponsiveness regardless of where it is

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on the continuum.

These phenomena are largely independent and certainly a lot stronger than classic psychological factors like anxiety, depression, and catastrophizing. In the final models in these papers, none of the psychological factors were in the final models. They didn't predict any of the variance.

I like showing this data slide. These are the 700 or so people in the knee and hip arthroplasty studies. You see that the most common fibromyalgia score was 5. The red line is 13. People on the right side of that red line would be said to have fibromyalgia based on the new fibromyalgia criteria.

There were 55 people out of 700 people in this study, that on the day of surgery when we gave them that questionnaire, we saw they had fibromyalgia. Guess how many of those 55 had anything in their chart that indicated that they had fibromyalgia or anything other than osteoarthritis?

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MALE VOICE: Zero.
DR. CLAUW: Zero. This is the problem here. Once people put a label like osteoarthritis on someone, they don't think of centralized pain. This is at the University of Michigan, which is arguably the epicenter for fibromyalgia research. I'm the one that gives the pain grand rounds for all of the departments. So if we're not seeing it, no one's seeing it.
But again, the more stark findings here -- look at these two people, patient A and patient B, neither of whom has fibromyalgia, but look at how different their opioid requirements are in the first 24 to 48 hours and how different they are with respect to likelihood of responding to knee and hip arthroplasty with improvements. Patient B needs 90 milligrams more of in the first 24 to 48 hours to control his pain and is 5 times less likely to get a benefit even though patient B doesn't have fibromyalgia, he has a higher fibromyalgia score.
Suzie As-Sanie is over there. She's an

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OB/GYN that studies pelvic pain, and we've replicated almost all of these findings in women that are getting hysterectomy for chronic pelvic pain, almost identical amounts of opioid nonresponsive. And I think it was 8 milligrams per fibromyalgia measure in your studies. But we've now replicated these findings in a different surgical cohort where surgery is being done to relieve pain.
So coming back to this diagram here, this third underlying representative of pain on the right, that any of the pain conditions on the bottom can have this superimposed. I think this is the point of emphasis, is all pain states are somehow mixed paints, and these central nervous system contributions occur across and often are superimposed regardless of what the main pain condition is that the person may have.
We study a lot of these different conditions; in fact, all the ones that are on the slide here, sickle cell disease, and Ehlers-Danlos syndrome patients have very high rates of

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centralized pain.
Now scoring high on the fibromyalgia measurement doesn't just tell you what isn't going to work; it tells you what is going to work. Lily started putting our body map in the duloxetine registration trials after duloxetine was already approved in the U.S. In fact, it was off patent in the U.S.
This is a reason duloxetine studied low back pain, and it showed that duloxetine works a lot better in the low back pain patients with multifocal pain. The more sites of pain on the Michigan Body Map that the person had, the more likely duloxetine was going to work. And it worked 60 percent better in people with low back pain plus 5 other sites of pain compared to people with one single site of low back pain.
I do consulting with a lot of different companies. This is a company, Samumed, that has a WNT inhibitor that's injecting into the knee. And I said to them early in their development program, "Put a body map in because this isn't going to work

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as well in people with osteoarthritis that have widespread pain as those without widespread pain."
Now, the only reason the company is still afloat is their development program now in phase 3 is only looking at osteoarthritis patients without widespread pain because that's the group the drug works in. It doesn't work in the people with osteoarthritis that have the more multifocal pain that a drug like duloxetine would probably work preferentially in.
This is CBD, systemic CBD. You may never see this trial, so I want to show it to you that it worked quite well in a recent study of knee osteoarthritis. In this study, it pointed out the difference between the males and females with respect to responsiveness.
Again, this is an over generalization, but if you look across clinical pain conditions, on average, because females have higher rates of any type of chronic pain, females have more prominent central nervous system contributions to their pain, what they found in the duloxetine studies is

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duloxetine worked better in a female compared to a male because it's working centrally, and a peripherally directed drug like CBD is probably going to work, on average, a little bit better in a group of males than a group of female because a higher proportion of a male's pain is coming from the periphery.

Almost all those people in the U.S. that have bone on bone, knee arthritis that don't have any pain are men because men are inherently less pain sensitive and sensory sensitive than women. So Vitaly and others are going to talk about functional neuroimaging.

I'm not going to really talk at this any length, but now there have been scores of studies that have shown the central nervous system contribution. This is the first fibromyalgia study that we did, fMRI, and this was done by Rick Gracely when he was still in our group.

You can see on fMRI, looking at connectivity measures, looking at the size and the shape of the brain, that there's a lot of objective

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underpinnings to what we're calling central sensitization. This is a series of studies done by Yvonne Lee. Ralph Edwards helped participate in these as well. This is just showing that these RA patients who have no ongoing inflammation but still have widespread pain responded to the drug milnacipran, one of the drugs that's approved for use in fibromyalgia.

We've gone on recently to publish studies that the brain imaging pattern of fibromyalgia superimposed on RA looks exactly like fibromyalgia, this classic default mode and insula hyperactivity. But the brain of someone with rheumatoid arthritis that has active inflammation -- this is a recent study in Nature Communication -- looks entirely different. When their pain is coming from active inflammation versus comorbid fibromyalgia, the patterns on connectivity look quite different.

Really quickly, the MAPP Network has been going on for 10 years, applying all of QST and all these different imaging techniques to groups of people with chronic pelvic pain. You can very

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clearly see in these groups of people with interstitial cystitis, there's three different phenotypes. About 20 percent of them will have pain confined to the bladder, about another 20 percent will have pain in the region of the pelvis and abdomen, and about 50 or 60 percent will have the more widespread pain phenotype.

But it's highly likely that those people are going to respond to different treatments. The people with the pain confined to the bladder probably will respond to a treatment aimed at the bladder, whereas the people that have the more widespread phenotype are probably going to be treated or need to be treated a lot more like someone with fibromyalgia would be.

We've published now about 60 manuscripts out of this MAPP network, and all of them, the main feature that differentiates people in any way is how widespread the pain is and whether they have this superimposed central sensitization.

I'm just going to end by showing a couple of slides because I think this is really important,

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and I don't think many groups are attending to this. I think there are two different types of central sensitization, and this is why I'm not sure we should use the term "central sensitization" for both types.

I think there is an activity-dependent central sensitization and those probably are the people with lupus, osteoarthritis, rheumatoid arthritis, sickle cell disease, where this is being driven by ongoing nociceptive input.

Then there's clearly a group that looks to be activity independent. The chronic overlapping pain conditions, those individuals you can't really identify much in the way of ongoing input that would be contributing to these symptoms.

The reason that I think that's important is that the people that have what we would call bottom-up central sensitization that's being driven by peripheral nociceptive input, I don't completely agree with Clifford. It may be that in many of those it's a tiny little bit of ongoing peripheral nociceptive input that is driving the CNS process.

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It may be that a drug for example, like a nerve growth factor antibody, that is able to entirely turn off that nociceptor would actually work better in a group of people with osteoarthritis that have central sensitization than it would in a group of people that don't.

I think it's an open question, but I think until then, it would be a mistake to lump these two subsets of central sensitization together because from a treatment standpoint, there's going to be profound implications of whether that central process is being driven by an ongoing peripheral process or whether that central process is a fundamental brain central nervous system process that we're going to always have to treat with more centrally directed drugs.

So when you look at the drugs that work for these centralized pain states, where you think primarily tricyclics, serotonin, norepinephrine reuptake inhibitors, and gabapentinoids, but you see that the drugs like opioids and NSAIDs don't seem to work in these pain conditions.

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If you look at the current treatment guidelines for the different product overlapping pain conditions, in virtually all of them, the people recommend strongly against the use of opioids. In some cases there are data supporting that, in some cases there are not. But it's almost unanimous, amongst the people treating these chronic overlapping pain conditions, that opioids are a bad idea.

It may very well be that this is because of some of the findings that we've identified in people with fibromyalgia, that it looks like the endogenous opioid system in fibromyalgia is actually hyperactive. People are releasing high levels of endorphins and enkephalins. Those are probably binding to their mu opioid receptor, and when that endogenous ligand binds to that opioid receptor, if you give someone an exogenous ligand, i.e., an opioid drug, it's not going to work as well because there's not as many unoccupied mu opioid receptors.

We clearly showed that in studies using PET with carfentanil and functional MRI at the same time, where it really looks as though the fibromyalgia patients have endogenous opioid-induced hyperalgesia, this is what we called it in this article. It really looked as though the endogenous opioid system might actually be participating in the pathogenesis of these conditions and why it might be a particularly bad idea to give these people on opioids.

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So even though we have a stable genius as a president, he didn't know that healthcare could be so complicated. In this editorial that I wrote a couple of years ago, I pointed out that one of the problems that I see with opioids is the opioid manufacturers have not been made to do trials in different pain states, so we don't really know what chronic pain conditions opioids might work in and might not work in because it's been a really narrow group of pain conditions.

So I'd love to see the randomized controlled trials if anyone had the stomach to do that these days. Those probably are never going to happen in most of the chronic overlapping pain conditions, but I think there are a lot of data suggesting that not all pain conditions are the same, especially chronic pain conditions with respect to their opioid and responsiveness.

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So I do think we are moving towards the era where if we know the underlying mechanism of someone's pain, we can more logically pick a drug and non-drug therapies. Our group is starting to do a lot of work with cannabinoids now.

We actually think that CBD might be a good cannabinoid for people with low grade inflammation in the periphery, i.e., something like osteoarthritis. But the recent studies that have been done, a couple that have been done suggesting a more centralized pain state, you're probably going to have to use a little bit of THC because that's a more centrally acting compound.

Finally, I just want to talk about how important the non-pharmacologic therapies across pain conditions, but especially for these chronic overlapping and central pain conditions, because it

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seems as though a lot of things that have happened to people as they have chronic pain for long periods of time, they become deconditioned and they stop moving. They start sleeping more poorly. They become more stressed. They develop bad habits.

These all then feed up to the brain, and I think that this is why, that in almost any chronic pain state, you can identify this subset of people, whether you want to call it central sensitization, chronification, whatever, but where these other factors, non-peripheral factors that are not coming exactly from the area of the body that the person's experiencing pain, play a prominent role.

Again, this is why I think the non-drug therapies are more broadly being used and emphasized with respect to the treatments, is that these therapies in fact are in many cases more effective than some of the current drugs that we have available. So I will stop there and take questions if people have them.

(Applause.)

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Q&A

DR. SIMON: Lee Simon, Boston. Again, great. I was wondering, you mentioned Ehlers-Danlos syndrome, which is a genetic disease, for those who don't know, of connected tissue with the idea that you've got hyperelasticity, hypermobile function. You don't think that this is related to the genetic abnormalities of collagen and elastin. You think it may be due to the hypermobile state, and thus -- I'm not sure I could ask anybody else but you because you're a rheumatologist.

So the hypermobile state, which then leads to premature OA and the symptoms associated with that, not because of the genetic abnormality directly.

DR. CLAUW: Exactly.

DR. SIMON: Okay.

DR. CLAUW: And in fact, that has been shown as -- a benign hypermobility has very high rates of comorbid fibromyalgia, and those people don't have the underlying genetic. We think that in

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hypomobility, it would be the repeated trauma from the hypermobility as sort of a chronic, nociceptive state that then drives -- I'm actually giving the keynote next week at the Ehlers-Danlos meeting, because this is a huge problem for them.

If you look at any of their literature, this is a tremendous problem for people with Ehlers-Danlos or hypermobility. They almost all look a lot more like fibromyalgia patients than they do like someone with just nociceptive pain in a single location.

DR. MARKMAN: Roger?

DR. FILLINGIM: Dan, you talked about these two different flavors of central sensitization. Do you think these are independent populations? Is this a progression? Do you go from bottom up to top down? Do people stay stable in their phenotype?

Could you talk a little more about that?

DR. CLAUW: Yes. I mean, I can tell you a lot more in two or three years. We're doing a series of studies now that's being funded by a

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center grant from NIAMS, where we take people with rheumatoid arthritis that are getting a new biologic, osteoarthritis that are getting hip arthroplasty, and carpal tunnel syndrome that are getting carpal tunnel repair. We fix the peripheral problem, and then we look at whether those people have resolution of their widespread pain of their central sensitization.

So far, we do see two quite different patterns; that some people when you fix a peripheral problem, everything melts away, the pain in the knee and the more widespread pain. Then there's another group that it doesn't seem to make much of a difference; and, in fact, those are the people that don't respond very well to knee or hip arthroplasty. They have a transient improvement and for about a month or so it's more like a placebo effect, and then they almost go back to the way they were before.

But we don't know of any other way to sort out right now the difference between those two. It's not until we study those people at baseline,

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and then we see how they do after the surgery, and then we can put them in the category of top-down and bottom-up based on how they respond to that peripherally directed intervention.

But I don't know any other way to study this phenomena. The only thing right now that we are seeing, that we hypothesize and that we are seeing that is different from those two groups is it doesn't seem as though the bottom-up people have sensitivity to other sensory stimuli, which would sort of make sense. There wouldn't necessarily be any reason you would -- that if this was being driven by the kinds of mechanisms that Clifford talked about, there isn't any reason that those people would start to be more sensitive to auditory stimuli or visual stimuli, which are cranial nerves that are coming directly into the brain.

Yes, John?

DR. FARRAR: John Farrar, University of Pennsylvania. Is there any evidence that using the drugs that you suggest might reduce the fibromyalgia, the central sensitization; that use

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of those in anticipation of an upcoming insult, surgery or otherwise, might actually reduce the likelihood of the chronic persistent pain? Let's say in the arthritis, which honestly would be a great model to look at.

DR. CLAUW: Yes. I think the data are mixed. The two classes of drugs that have been most widely used in this setting -- I guess three; Clifford talked about ketamine, but it would be the gabapentinoids or the SNRIs. And some of the data suggest that those are helpful and some suggest they aren't.

No one has done the study that I think needs to be done, is only treat the subset of people that score high on the fibromyalgia measure because I think the problem with the studies that have been done is you treat everyone, and not everyone needs it. You can identify -- it's probably in most cohorts about a third of the patients with osteoarthritis that clearly have this superimposed central sensitization. The trials would be better if done looking just at that subset rather than

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giving the drug to a bunch of people that you don't think really need it or are going to benefit from it.

Ajay?

DR. WASAN: Ajay Wasan from University of Pittsburgh. You dissed a lot of the psychological factors --

DR. CLAUW: No, I --

DR. WASAN: -- and that's okay.

DR. CLAUW: I just want to deemphasize them because they've been talked about forever as those are the central factors. And I'm not saying they're not important. I'm just saying that they're not the same as this.

DR. WASAN: I get that, and that makes sense. But would you agree that at least in the patients that have, say, prominent psychological factors, that at the very least you could say that those factors are amplifying or worsening the same mechanisms of sensitization or maybe creating their own mechanisms of sensitization?

DR. CLAUW: Yes.

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DR. WASAN: Okay.

DR. CLAUW: So again, when someone has those features in addition to chronic pain, they should be treated. I'm just saying that if you look at how this all evolves -- and we're starting to look now in data sets of children, like 10-11 year olds as they start to develop pain, and as soon as they start to develop pain, you see the fatigue, memory problems, and sleep disturbance, the more CNS contributions.

The earlier that you do these studies, a lot of times you see the psychological factors occur because of the pain rather than are the root cause. But of course, in a lot of clinical cohorts, these psychological factors are front and center. They're a big component of what we have to treat.

So I'm not trying to minimize the importance of them clinically. I'm just saying that don't think that they're the same thing as what I'm talking about, because I think the biggest mistake people have made is if you think of a fibromyalgia patient, you think of prominent psychiatric

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comorbidities because most of them have it. If you then take that and infer that that means that the biology of fibromyalgia has prominent psychological/psychiatric underpinnings, I'm not necessarily agreeing at that point. I think you have to be a little bit careful about what caused what.

DR. WASAN: Yes. I think it's the issue of teasing out the independent and shared variants --

DR. CLAUW: Right.

DR. WASAN: -- and that's the tricky part.

DR. CLAUW: Yes.

John?

DR. MARKMAN: Dan, that was excellent. Can I just some questions as a clinician. As you said, the hallmark of these syndromes is the widespread distribution of symptoms. So in a patient who has widespread pain or widespread noxious, or however you want to characterize unpleasant symptoms, for whom you feel like you can exclude peripheral causes -- so they don't have OA, and they don't have some other inflammatory syndrome that Lee

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talked about.

Can you just talk about what your differential diagnosis of widespread pain is in those patients? What are the other possibilities?

DR. CLAUW: That's a really good question. I think a big part of it depends on how long they've had the symptoms. If you see someone in clinical practice that's starting out at age 13, had painful menstrual periods, and then they had irritable bowel, and functional abdominal pain a little bit later in their life, and then in their 20s they had regional pain and interstitial cystitis, and then finally their pain becomes so widespread, I don't think there is a differential.

If you have like a 15-20-year history of the classic chronic overlapping pain conditions occurring together in the same individual, I think in that individual, I'll do some regulars, some simple screening tests, thyroid function, those, but I'm not really looking that aggressively for anything else.

I think that if someone presents subacutely

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with those same symptoms, I'm doing a really extensive diagnostic workup because early autoimmune diseases look a lot like fibromyalgia. So clinically, a lot of it depends on the history I get from that person, the workup that they'd have to date, and what already has been excluded versus what still in play.

DR. MARKMAN: Just as a follow-up, as you pointed out with your initial OA slide and the certain catechism that was central to rheumatology training, in neurology training there's a catechism that everywhere is not a pattern.

DR. CLAUW: Right.

DR. MARKMAN: And again, we have things like epilepsy monitoring units where we monitor people for 7 days to see if they have electrographic correlates to their seizure activity and use that as a basis for deciding whether they get therapy or not.

So again, I would just like you to react to that notion because I think that some of us are -- as you know, these are professional belief

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systems which are inculcated in people, and I'm happy to jettison it. But I want to hear how you respond to that idea that everywhere is not a pattern.

Also, what would be your epilepsy monitoring unit analog? Is there any other way to tease out? I think maybe that's part of the question that Ajay's getting at, how do you -- again, other than this longitudinal historical view, which you just proposed, how else do you -- what is the diagnostic enterprise look like?

DR. CLAUW: Just to be clear, is what you're questioning is when someone has widespread pain, how do I know whether that's real or not and whether it's credible? Because I'm not really following you.

DR. MARKMAN: Well, it's always real. I don't think anybody's disputing whether it's real, but I do think that as a clinician, I'm sure we all have a sense of -- again, whether it's conscious or unconscious to the patient, there's a lot of volitional and self-report, which we are asked to

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interrogate and more deeply understand.
So I guess it's not a question of whether it's real for the patient. Of course it's real for the patient that is reporting; pain is an experience. So nobody's questioning that piece. But I do think we do feel this pressure to say, well what's the neuroanatomical correlate in a patient -- because at the onset of these syndromes -- I remember your writing from the '90s when we were talking about Gulf War syndrome, and this was called poorly explained medical illness. I believe that was the terminology used then. I always thought, well, okay, but what do you have to do to characterize poorly explained? What's the work that needs to be done to say that this is in this other bucket?
DR. CLAUW: Other than taking people and put them in a scanner, which we can only do on a research basis, I don't think there's any way we can look at, if you will, the veracity of the symptoms. But I would challenge this notion that people with widespread pain, that I worry about

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that any more than, for example, regional pain. Over the course of my career, I found the biggest factor of volitional components is in low back pain where it's often occurring in an occupational setting, and that's regional pain. But I don't have any better way of figuring out the degree to which that regional pain is real versus unreal in low back pain than I do in fibromyalgia, and I just live with that.
I just don't think that -- and I think that is problematic when people are trained that there's always going to be this sort of hardwired diagram, where you can trace where the pain is coming from, because I think in these conditions where the central nervous system is playing a prominent role, it's just like the whole brain's on fire in these individuals, and they have a lot of different CNS manifestations.
It is difficult. Again, if we have to wonder or worry about the veracity, I don't think I have anything right now that I can use in clinical practice. But I think that's a broader problem

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with any chronic pain state. I don't think we should call out this group of people, that this is a bigger problem in this group of people than it is in any other --
DR. MARKMAN: That's fair. This is why I think we're going to go toward a mechanism-based treatment, which is what Dr. Woolf and others have called for. My question would be, do you need to get CSF on every one of these patients just to ask the question, so you can begin to say -- because we'll never know if we never ask. If we just say the brain is on fire, and we don't image people, and we just treat them symptomatically, we'll never get any further. We'll never do the phenotypic work to solve the question.
I guess one of the questions I think for this group is what do you do to include or exclude this diagnosis other than self-report?
DR. CLAUW: Again, I would say that this patient-reported outcome that we use functions pretty well, and we've done a lot of work showing that it correlates nicely with QST. It correlates

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nicely with brain imaging. That paper in Arthritis & Rheumatology that showed the default mode network insula, the specific hypothesis was the degree of fibromyalgia on that fibromyalgia measure would correlate strongly in rheumatoid arthritis patients with that specific connectivity pattern, and that's exactly what we found.
So we actually are proposing that that patient-reported outcome for now does a pretty good job of identifying this subset of people, and we'll keep making it better and better with more data and things like that. We use a PHQ-9 to screen for depression, and we don't care that we understand the neurobiology of depression in that individual with depression. When we see depression on a PHQ-9, we treat it.
We're literally trying to develop something short and brief like a PHQ-9 to say if you see this, and it's elevated, think of this pain as being different and gravitate towards the more centrally directed treatments rather than the more peripherally directed treatments. I think that, by

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and large, that will work right now.
DR. ARNOLD: Hi. Lesley Arnold from Cincinnati. So getting back to your top-down/bottom-up, I know you're still working on the study, so you don't have all the information yet about that. But it just seems difficult for me to understand why they would be so different, and why the central sensitization process would present differently, so I'm interested to see with time how that turns out for you.
If it's true that it just takes tiny input to drive this pain, as we heard earlier, maybe in the top-down group, it really isn't just top-down, that there are peripheral inputs. And as you pointed out, the peripheral and central nervous system, we artificially separate them, but they are really one in the same. And I worry that what you're doing is, again, going back to that mind versus body; that really they're one in the same. And I don't want you to think that top-down is influenced by the periphery as well, and vice versa.

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DR. CLAUW: No, I'm not. I'm not saying -- again, in fact, there is a study in fibromyalgia that suggests that people with fibromyalgia have comorbid myofascial pain or osteoarthritis, and that treating that makes the hyperalgesia, allodynia better.
So I'm saying that all of these are mixed pain states --
DR. ARNOLD: Right.
DR. CLAUW: -- that most people with fibromyalgia have some myofascial pain, or some osteoarthritis, or some ongoing nociceptive input, and clinically, I try to identify those problems and treat those problems because I think those are -- I'm just looking for anything I can get a foothold to treat.
This is more of a conceptual model. I think that there are different people that have more sort of brain, central nervous system contributions versus people that it's more being driven by ongoing nociceptive input.
DR. MARKMAN: We've got time for two more

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questions. Nat and John.
DR. KATZ: Nathaniel Katz from Boston. Hi, Dan.
DR. CLAUW: Hey, Nat.
DR. KATZ: You propose that there might be two separate phenotypes, one with pure pain and hypersensitivity and another with hypersensitivity to both pain and to other types of sensory stimuli like light, and sound, and things like that.
Could you expand more on what we know about the extent to which those two phenotypes are really different; and in particular, whether anybody has looked at whether that predicts a response to any type of treatment?
DR. CLAUW: No. No one to date has looked at that. And again, the only way we know to look at it is the way we're doing it, which is very laborious, is to take a group of people, treat them with a peripherally directed treatment and follow them for 6 months and see what their longitudinal course is of their central sensitization after that.

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I don't know any other way to tease this out. I'd love to hear ideas about other ways that we could get at -- and then the other thing that makes this even more confusing, if you think about it, is let's say that you have a group of people with rheumatoid arthritis or osteoarthritis. Some of those people are going to be top-down people because they just happened to be the 6 percent of the population that was born with fibromyalgia. Those people are not protected from osteoarthritis later in life.
So in a group of osteoarthritis or rheumatoid arthritis patients, there will certainly be some top-down and some bottom-up. And to what Lesley said, I don't think those are mutually exclusive. I think there's a lot -- we can't tell the difference between them right now on any kind of brain imaging. The only thing, again, that we're finding that looks different is the sensory sensitivity in the one group and not in the other.
So again, right now, I treat them clinically almost as if they are identical because I don't

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have any way of dissecting them, nor do I know that there would be a different -- again, except the thing that's really important, I think, is that if it's being peripherally driven, then peripherally directed treatments might work really well. That's where I hope people don't miss the central message that the peripheral drive might be still incredibly important for what's going on in the CNS.

DR. KATZ: There's some evidence that your prediction is correct. I'll tell you about it in the break.

DR. CLAUW: Yes.

DR. FARRAR: The one example I know of where a local truly can reduce or eliminate a spreading pain syndrome is certainly in some patients with Morton's neuroma in their foot, they get a whole foot, whole ankle, whole knee pain. And if you can find the single point that hurts and inject it with local anesthetics, sometimes the whole thing goes away. Akin to what Mithcell Max used to do, injecting capsaicin under the skin, getting widespread pain. As soon as you numb the area

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where the capsaicin was injected, the whole syndrome goes away.

The question I actually wanted to ask, though, is that all of us have seen patients who have undergone a surgery and end up with chronic regional pain syndrome, a bunionectomy with a foot that ends up being problematic, and it's an acute event that occurs 6 weeks after.

Would you presume that there could be, as opposed to the development of this slowly over a period of years, from age 13 to whatever, an acute onset of this central process that you're describing?

DR. CLAUW: Oh, absolutely, and that's been looked a lot at in fibromyalgia and irritable bowel. Let me talk about something that you're not used to hearing me talk about; irritable bowel. In irritable bowel, there are 6 different infections of the GI tract: salmonella, shigella, campylobacter; that if someone has those infections, 6 to 8 percent of those people, after that infection clears, will be left with irritable

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bowel, just like 6 to 8 percent of people that are in motor traffic accidents develop something like fibromyalgia.

So it's very clear that different stress or trauma -- and this was Gulf War. A lot of our early working looking at his phenotype is people that were deployed to war. After war, any war in the U.S. goes to, there will be a group of people that come back looking like this. After the first Gulf War, it was just this; and after Iraq and Afghanistan, it was this superimposed on PTSD and the polytrauma triad right now. But I think this can often be triggered by different types of stressors, or events, or things like that, and then come on much more subacute than this indolent onset that I was talking about.

That's two questions. Am I done, John?

DR. MARKMAN: You're done.

(Applause.)

DR. MARKMAN: We'll take about an half-hour break.

(Whereupon, at 10:08 a.m., a recess was

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taken.)

DR. MARKMAN: Our next speaker comes to us from the Brigham and Women's Hospital. He is an associate professor of anesthesiology and has taught most of us about psychophysics and psychosocial modulation of pain intensity, and explaining variability with his work on catastrophizing and other constructs.

Dr. Edwards, thanks for taking the time

Presentation - Robert Edwards

DR. EDWARDS: Good morning, everyone. Thanks very much for having me, and thanks especially for including me in the morning session. I noted this is the only part of the session that will be videotaped, from which I can only conclude that the most physically attractive, intelligent people were invited to speak in the morning --

(Laughter.)

DR. EDWARDS: -- so thank you. I'm flattered. I'm happily married, but still flattered nonetheless.

I'm going to spend the next 30 minutes or so

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talking to you about somatosensory amplification, a term I thought I knew quite a bit about, but what, somewhat surprisingly to me, appears only relatively rarely as a specific term in the pain literature. A recent PubMed search turned up just over 40 articles that used that term, and this is in sharp contrast to other terms like central sensitization, or pain modulation, or catastrophizing, which will get you thousands of hits.

So I think what's happened is over the years, a number of different terminologies have been applied to this set of interrelated constructs, and I'm going to try and unpack some of that over the next 28 minutes or so.

The term "somatosensory amplification" seems to pass into the literature in the late '70S and early '80s. Arthur Barsky, who's a psychiatrist, and some others begin writing about things like amplification, and somatization, and hypochondriasis. Out of that comes the term somatosensory amplification, which gets defined as

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the tendency to experience somatic sensations as intense, noxious, and disturbing.

It's presumed to include both lower level sensory and higher level cognitive and emotional processes. And out of this work comes the SomatoSensory Amplification Scale, which is developed and validated through the '80s. You can see some of the items up there. It's a set of items that ask people about their tendency to respond to environmental or proprioceptive perturbations; so things like sudden loud noises really disturb me.

Over the next decade or two, this construct gets linked to all sorts of clinical conditions, many of them pain related; so fibromyalgia, migraine headache, low back pain, and that sort of thing, and a number of non-pain related conditions as well: chronic fatigue syndrome and some others that often would go under the heading of psychosomatically influenced conditions.

In the conceptualization of somatosensory amplification, it is conceived of as being a factor

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that is related to but distinct from other factors that we'd all consider overlapping; things like catastrophizing, and central sensitization, and hypervigilance. This distinction is made on the basis of theory rather than on the basis of data. I actually don't find the distinctions at all convincing.

Just for example, I'll quote from a recent review article. "Somatosensory amplification is distinguished from sensitization on the basis that sensitization represents always an acquired characteristic, never an innate one. Sensitization doesn't include non-pain related sensations, and sensitization is not related to cognitive and emotional factors." And I would disagree strongly with all of those things, and hopefully I can present some data that disputes that notion.

I'm going to wind up talking about a number of different components, or elements, or aspects of somatosensory amplification. At various times, the question is going to come up, can we measure and talk about these things separately and uniquely?

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Is it even possible? Should we try?

At IMMPACT meetings like the phenotyping meeting, we have recommended and proposed that people measure some of these things separately in the context of clinical trials. So things like somatic focus, and hypervigilance, and catastrophizing, and anxiety and pain facilitation, we recommend should all be measured separately, even though we know they overlap to a fairly substantial degree, and maybe to an extreme degree in certain pain conditions.

So my take-home message from this talk, if you need a nap over the next 25 minutes or so, is that we really can measure these things separately. We have the validated tools to do it. But man, do these things all overlap quite a bit with one another, and it is an open question whether it's worth trying to put in the effort to individually and uniquely measure each of these things and look at them as specific unique predictors.

With that in mind, we're going to spend the next few slides talking about somatization, or

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somatic focus, or somatosensory amplification, and we're going to do it in the context of the OPPERA study, which is widely considered one of the premier prospective cohort studies of risk factors for the development of chronic pain; thousands of people very carefully phenotyped, followed for years, to look at what predicts the development of temporomandibular joint disorder.

The analyses are done in a couple of ways, and perhaps Roger Fillingim will tell us more about the OPPERA study later on. But no matter how you do the analyses, a couple of factors that are defined by symptom inventories are the somatization subscale of the symptom checklist, and The Pill, or the Pennebaker Inventory of Limbic Languidness.

Both of these are symptom checklists, so how frequently do you experience things like muscle pain, and itching, and watery eyes, and that sort of thing? Those come out as some of the most important predictors of the development of temporomandibular joint disorder in the OPPERA study even when you control for other related

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factors, which is an important thing to keep in mind.

I'm going to tell you a little bit more about The Pill, and I'll just read from Roger's nice description of some of the outcomes of the OPPERA study. "Two of the most important risk factors for elevated TMD incidents were greater number of comorbid pain conditions and greater extent of nonspecific orofacial symptoms. Other important baseline risk factors were preexisting bodily pain and heightened somatic awareness."

So we vary the terms a little bit, but this is the data from the pill, which emerges as the single most important psychosocial predictor of the development of TMD in the OPPERA study. You can see one of the curves there, the higher The Pill score, the greater the incidence of TMD. And on the right, you can see some of the items from The Pill, which is 54 items long and ask people about the frequency with which they experience a number of unpleasant bodily sensations.

As we're talking about symptom counts and

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somatosensory amplification, we of course are going to have to talk about sensitization. Since we've had talks by Clifford Woolf and Dan Clauw, you don't need me to give you a definition of sensitization. So I'll jump right into talking just a little bit about the processes by which we measure it.

A lot of us do quantitative sensory testing in some of our work. Many of us, even those who don't, are familiar with it. This comprises a set of techniques that uses standardized laboratory-based stimulation to measure individual differences in responses to pain. There have been some really neat functional neuroimaging studies that suggest that this individual variability is strongly related to central nervous system processing of pain in the brain.

I'd just like to highlight using Roger's slide -- you can see his picture up there, so I made sure to give him credit. I'd like to highlight the individual variability that you get with any of these quantitative sensory tests.

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This is data just from the general population, and what you might be able to see here are pain ratings in response to a standardized heat stimulus. The same stimulus some people will rate as a zero, that stimulus will also get rated at the top of whatever scale you give people, 100, intolerable pain, et cetera, so a wide variation in pain sensitivity even in the general population.

There are some nice predictive studies that show the relevance of this sort of individual difference. A lot of these are surgical studies. This is just data from one, which is a nice large study of herniorrhaphy, almost 500 patients followed for 6 months after hernia repair. They're tested preoperatively with a heat pain stimulus. Those who rate that heat stimulus as more painful are much, much, much more likely at 6 months postoperatively to continue to have chronic postsurgical pain; so a predictive relevance of this sort of pain sensitivity.

Now, in addition to just measuring straight up pain sensitivity in the laboratory, no one here

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will be surprised to hear that it's also important to measure pain modulatory processes; so endogenous pain inhibition, endogenous pain facilitation, all of the signals entering the nervous system, of course, unmodulated at a variety of levels of the neural axis.

We can get at some of this, at least to some degree, with noninvasive QST in the laboratory. And as many of you know, some of the best validated and most commonly used methods for assessing endogenous pain modulation are CPM, or conditioned pain modulation, to measure pain inhibition, and temporal summation in order to measure pain facilitatory processes.

These are considered two distinct types of pain modulation and two distinct psychophysical procedures, although as we'll see later, these systems are probably interrelated to some degree. And just like people vary in their pain sensitivity, there's wide variation, both in groups of chronic pain patients and in the pain-free population in general, in the amount of CPM or the

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amount of temporal summation that they evidence.

This is some nice data presented recently by Serge Marchand in fibromyalgia patients, as well as healthy controls. What you can probably see from those distributions is that no matter what group you're studying this in, some people have very good condition pain modulation, so potent pain inhibition, and some people show facilitation or hyperalgesia instead of pain inhibition with this 2-stimulus CPM testing paradigm.

That's true both in the normal population and in chronic pain patients. It's just the distributions differ, and those without chronic pain are more likely to show inhibition. Those with chronic pain conditions like fibromyalgia are more likely to show facilitation or hyperalgesia.

There have been a number of prospective and cross-sectional studies that evaluate CPM as a predictor of all sorts of other important outcomes. We know that CPM is reduced or absent in lots of chronic pain conditions. Many of them could fall under the umbrella heading of centralized chronic

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pain conditions like fibromyalgia.

Even within groups of chronic pain patients, variability in CPM has been shown to predict how severe people rate their daily pain, how little physical function they have, and the degree of postoperative pain in some surgical studies. It's been shown to predict analgesic responses and the magnitude of exercise-induced analgesia as well; so a clinically relevant and important to measure factor.

David Yarnitsky and others have popularized the notion of a pain modulatory profile. In theory, you can measure these sorts of processes using QST in the lab, and then assign people to a point on a pain modulatory spectrum. Are they more prone nociceptive, more facilitatory in nature, or more antinociceptive, or inhibitory in nature?

Given the size of the screen, you have no chance at all of seeing what data I have up there, so you'll have to trust me when I say these are some forest plots from a recent meta-analysis of CPM in temporal summation, in patients with

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fibromyalgia. There are a couple of dozen studies, and very reliably, the results suggest that fibromyalgia patients show elevated temporal summation and reduced CPM relative to pain-free demographically matched controls, and these are quite large effect sizes.

This is just a visual example of some data from our own laboratory, controls knee OA patients, and fibromyalgia patients. All of them get the same train of 10 identical noxious mechanical stimuli. What you can see is that pain ratings from the first to the 5th to the 10th stimulus summate to a greater degree, so elevated temporal summation, in the fibromyalgia patients relative to both other groups.

Now, we've looked at relationships between temporal summation and CPM. Interestingly, when you give patients with chronic pain opioids, it doesn't seem to affect their temporal summation, but it does suppress their CPM. When you look in samples of patients -- I probably won't be able to figure out how to use this thing effectively, so I

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won't try.
But when you look in samples of patients, if you look at that scatter plot on the bottom right, there's a nice inverse -- it's modest. It doesn't explain a ton of the variance, but there's a highly significant inverse correlation between CPM and temporal summation. The more effective your CPM pain inhibitory mechanisms are, the less temporal summation that you have, and this is in a group of patients with chronic musculoskeletal pain.
All of these processes like temporal summation and CPM are situated within the context of the biopsychosocial model of pain, which I suspect we all subscribe to, and which posits that dozens, or hundreds, or maybe even thousands at this point, of factors affect people's experience of and report of their responses to pain.
I'm going to spend just a handful of slides or so focusing on one small component of the biopsychosocial model of pain, a commonly studied risk factor for chronic pain. You heard in Dan Clauw's talk some discussion of catastrophizing.

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This is one cognitive and emotional element of the biopsychosocial model Thanks, Ajay, for letting me borrow this slide.
I do need to emphasize that catastrophizing is really strongly interrelated with all sorts of other measures of negative affect like anxiety, and depression, and neuroticism. So it's not as though this is a perfectly unique labeled line style factor that predicts all on its own. It occupies a space in which it overlaps moderately or more with all of these other factors that we measure generally via questionnaire.
But that said, there are a number of predictive studies that suggest that catastrophizing uniquely can predict things like the future onset of chronic back pain. This study is almost 20 years old now, a prospective epidemiologic study. If you take people who are initially chronic pain free and split them according to their baseline level of catastrophizing, those who catastrophize most are at 3 or 3 times greater risk for developing chronic

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or disabling low back pain over the next year relative to those who are low in catastrophizing.
Within samples of patients who already have chronic pain, catastrophizing is also an important predictor. These are some data from a recent study of neuropathic pain treatment. In this particular study, the researchers look at pretreatment levels of catastrophizing and their relationship with how much analgesic benefit people get from medications like amitriptyline, and nortriptyline, and gabapentin, and pregabalin.
What you can hopefully see from that scatter plot is the higher the catastrophizing score, the less the reduction in neuropathic pain with these treatments. In the figure on the right, the higher the catastrophizing score, the more likely people are to discontinue treatment, presumably because of a greater experience of adverse side effects, which I'll show some additional data on later.
So what I'm going to argue and hopefully conclude is that catastrophizing as part of this biopsychosocial model is really strongly linked

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with a variety of other elements of somatosensory amplification and centralized chronic pain. Dan Clauw's presentation was terrific and touched on a number of aspects of centralized chronic pain.
What I hope to show you over the next handful of slides or so is that catastrophizing probably influences a lot of those centralized chronic pain elements. I'm going to go through these slides fairly quickly just to make sure that I can finish on time and because they're fairly straightforward in nature.
Our group, as well as a number of others, has studied things like the relationship between catastrophizing and pain sensitivity in the laboratory in chronic pain conditions.
These are some data from a large recent study of patients with chronic low back pain. Those patients are more mechanically pain sensitive, they're hyperalgesic relative to controls, and they have higher levels of catastrophizing, and those things are related. When you run a mediational model, you see that,

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statistically, the higher catastrophizing in the patient group explains a substantial proportion of their increased pain sensitivity.

Temporal summation, which I mentioned before, is also influenced by catastrophizing, or since a lot of this stuff is a cross-sectional, we could also suggest that catastrophizing is influenced by temporal summation. It is very likely that there are bidirectional reciprocal influences here, but in this case I'm going to talk about it as catastrophizing influencing temporal summation.

What you can see from that graph is that the high catastrophizing musculoskeletal pain patients show elevated temporal summation relative to the low catastrophizers. This is a finding that has shown up in dozens of studies in all sorts of samples: chronic back pain, headache, healthy controls; it is very consistent.

Catastrophizing is also related to reduced CPM in a number of chronic pain conditions. This is some data from a recent systematic review and

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meta-analysis of CPM in irritable bowel syndrome. The researchers find that CPM is reduced in IBS, and I'll just quote from the discussion section here.

"In addition, reduced CPM responses were significantly correlated with higher anxiety, stress, and pain catastrophizing." The correlation coefficient R is around 0.4 or so, and it's noteworthy that the researcher showed that group differences in CPM responses were no longer significant when psychological factors were accounted for in the analysis.

Catastrophizing, anxiety, stress, other sorts of indices of psychosocial distress seem to be strongly contributing to the reductions in pain inhibition in some of these chronic pain samples.

We see a more subtle link between catastrophizing and impairment or reduction in CPM. These are some nice data collected by Ajay Wasan, oral opioid treatment of patients with chronic radicular low back pain. They're split into patients who have low and high levels of negative

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affect, so the high NA group has high catastrophizing, high anxiety, high depression.

They don't differ from one another in CPM at baseline, but once you give them opioids, which we've shown in a previous slide can suppress CPM, only the high negative affect group, only the high catastrophizing group, only the high anxiety group shows a reduction in CPM with oral opioid administration.

A number of groups have also shown that widespread pain, which is a hallmark of these centralized sorts of pain syndromes, is strongly influenced by catastrophizing. You can take patients with OA, or headache, or back pain, and the highest catastrophizing of those patients are more likely to report pain in pain sites other than the primary location of their initial pain.

There are even some nicely done laboratory studies. This one is from Mick Sullivan's group up in Canada. He uses an exercise procedure in the lab, isometric or eccentric exercise that produces DOMS or are delayed onset muscle soreness. The

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exercises target the right pectoral muscle and the deltoid. Healthy subjects come in and do these exercises in the lab. They measure them 24 and 48 hours later for the presence of post-exercise pain.

What you might be able to see from that color plot there is that the high catastrophizers on the right report pain to a greater degree, or a higher percentage of them report pain in a variety of sites that weren't directly targeted by the exercise; so their other shoulder, their other arm, their forearm, their hand, et cetera. The high catastrophizers in response to this targeted exercise stimulus develop more widespread pain complaints.

It is also true that high catastrophizers experience the most side effects from all sorts of treatments. I showed you the Corey Toth study earlier. This will just be some data from a recent study of ours at Brigham and Women's. Bob Jamison is one of the leaders in this area in terms of looking at opioid-related side effects in patients with chronic pain who are maintained on opioid

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therapy.
What you may be able to see highlighted there is that the patients who report the highest levels of side effects from oral opioid treatment have much higher levels of catastrophizing than the patients who report low side effects, which presumably is one of the reasons that the highest catastrophizers are most difficult to treat and most often drop out of treatment.
I'm going to spend just a couple of slides muddying the waters a little bit on whether catastrophizing is consistently a unique predictor of some of the most important pain-related outcomes that were all focused on. In some studies, this has turned out to be true. What I mean is when you measure a handful or more of psychosocial factors and look at all of their predictive influence, sometimes catastrophizing comes out as the most important predictor or even the sole significant predictor.
In this study, trying to predict acute postsurgical pain after hysterectomy, the

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researchers measure a number of psychosocial factors, including catastrophizing and anxiety. They're all significant at a univariate level, but when you plug them all in, only catastrophizing remains a unique predictor, and when you run mediational models, catastrophizing mediates the effect of anxiety on acute postoperative pain. So catastrophizing emerges as the primary, or most important, or sole unique predictor.
This is absolutely not the case in all studies, and particularly when you measure a wider variety of potential predictors, as we happen to do in this study predicting acute outcomes after total knee replacement, which you can hopefully see from this table is that when you measure catastrophizing in its univariate association with acute pain after total joint replacement, the p-value for that is 0.002. It's a highly significant predictor.
So catastrophizing measured before surgery predicts the severity of acute postoperative pain. But when you include a number of other predictors in the model, including psychophysical predictors

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like temporal summation, which you can maybe see at the far right of that yellow or gold line, is that catastrophizing is no longer a significant predictor. That p-value is over 0.9, and temporal summation of pain, again measured before surgery, remains the single most important predictive factor determining patient-reported severity of acute pain after this surgery.
So sometimes catastrophizing emerges as a sole predictor, particularly when it's in a mix with just other psychosocial factors, but once you include other overlapping elements, whether it's temporal summation or other sorts of potential predictive variables, catastrophizing can absolutely lose some of its predictive ability, and that is probably just the nature of the interconnected biopsychosocial model of pain.
I'll come back to the OPPERA study briefly. The pill, Pill, this symptom checklist, which is the most important psychosocial predictor in terms of the OPPERA study's models that predict the development of temporomandibular joint disorder,

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The Pill remains a significant predictor in one of the of the top 10 predictors overall, even when you control for things like clinical history, and comorbidities, and autonomic function, and pain sensitivity measured by QST, and every other psychosocial factor that you care to throw into the mix.
Some of these things can remain unique predictors, and it's very likely that different elements of somatosensory amplification might uniquely predict different outcomes. So perhaps temporal summation is the best predictor of acute outcomes after surgery. Perhaps a measure like The Pill, or somatic focus, or somatization, whatever we want to call it, is among the best predictors of long-term outcomes, really long-term outcomes, like the development of a chronic pain condition.
Not surprisingly, as you'd expect I hope, based on the biopsychosocial model, there's a huge amount of overlap between these different risk factors or mechanisms. Probably all of them share some neurobiological substrates, which is what I'm

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going to talk about over the next 3 or 4 minutes or so before I wrap up.

I should emphasize now, and hopefully will again, that the discussion of neurobiological substrates is of course very appropriate, but in some ways a little bit misleading because it implies that the neurobiology comes first and then drives all the other stuff. And I really suspect -- and I bet many of us in this room do as well -- that there are bidirectional relationships here; that you can alter someone's cognitions and emotions and change their neurobiology just like you can alter their neurobiology and change their cognitions and emotions.

So I'm not going to spend much time talking about functional MRI studies of brain networks and their potential maladaptive properties that characterize patients with chronic pain, in part, because Vitaly Napadow, my colleague and neighbor in the back, is going to do a much better job of that later this afternoon. But I do want to emphasize just a couple of recent findings that

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have come out of some of our collaborative studies.

In general, what these studies do is use functional MRI and connectivity analysis to look at patterns of connectivity among different brain networks that probably link to different aspects of the pain experience. We'll look at networks like the somatomotor network, the salience network, the default mode network; and you heard Dan nicely mention a few of these.

In general, what a lot of these studies suggest is that these networks are maladaptively interconnected or hyperconnected in patients with chronic pain relative to demographically matched pain-free controls. I want to just focus on two of these networks, the somatomotor network and the salience network, the somatomotor network as exemplified by primary somatosensory cortex, and the salience network as exemplified by anterior insula.

One of our recent findings in this area suggests that for patients with fibromyalgia, these two networks are linked in a way that they're not

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in healthy controls. Furthermore, when we put people in the scanner and apply a standardized painful stimulus to them, mechanical stimulus applied to the lower leg, the connectivity between those networks increases to an unusual and probably maladaptive degree in patients with fibromyalgia, and this is compared to healthy controls.

So those networks are already interconnected. In healthy controls, they're unconnected. Put patients in the scanner, apply experimental pain to them, and the connectivity goes up quite a bit. There's variability in how much that connectivity increases, and really what I want to show you here is what that variability is related to.

The amount of connectivity between the anterior insula and primary somatosensory cortex, when we apply pain to fibromyalgia patients in the scanner, is correlated with how much clinical pain severity they report in day-to-day life. It's correlated with our pain catastrophizing scale scores. It's correlated with how much attention

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they say they paid to the cuff pain when they're in the scanner. This is the experimental stimulus we apply; so think of this as a measure of hypervigilance to pain. And it's correlated with how much temporal summation we measure psychophysically while they're in the scanner.

So all of these things, and probably all elements of somatosensory amplification, probably all moderately inner correlated with one another, are also all moderately intercorrelated with what we might think of as this neurobiological substrate for pain measured as maladaptive degrees of hyperconnectivity in these networks.

There are all sorts of other neurobiological processes, way too many to get into, and I would be way out of my depths with lots of them. But I want to mention very briefly a bit of the recent emerging story related to microglia and activated microglia in the context of chronic pain.

Animal studies have suggested for a long time that microglial activation plays a crucial pathophysiologic role in all sorts of a chronic or

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long-lasting pain conditions; for example, after nerve injury in rats. It's only recently become possible to noninvasively measure microglial activation in humans using a fairly newly developed PET ligand as PBR-28.

Vitaly and my colleague, Marco Loggia at Mass General, are leading many of these studies. And what you might be able to see from this cut-out on the lower right of the screen there is a comparison of fibromyalgia patients and healthy controls at two different sites. One's at Mass General and one's at Karolinska Institute in Sweden.

At both sites, what they're looking at is the PET evaluated degree of microglial activation in pain-relevant brain regions. In a whole bunch of regions -- anterior cingulated cortex, sensory cortex -- these regions span -- all of those networks I was just talking about, the fibromyalgia patients have more microglial activation than the controls, which seems reasonable.

We might conclude that there's a

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pathophysiologic role for microglial activation in fibromyalgia, and that seems all fine and good. But I just want to emphasize that in a number of studies, these micro activations are pretty strongly linked to psychosocial factors reflecting emotional distress or other elements of somatosensory amplification.

In this study of healthy controls compared to patients with chronic back pain, what we see, and what you can see in those scatter plots, is there is a really tight relationship between patient's BDI score, so how distressed they are, and how much microglial activation they have in brain regions like the anterior and midcingulate cortex.

If you split up patients, it is only the patients who have elevated psychological distress who show increases in microglial activation in those areas. The chronic back pain patients with low BDI scores look just like the controls when you look at their levels of microglial activation.

This is cross-sectional. I don't know what

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drives what. Maybe microglial activation comes first, maybe depression comes first, or maybe, more likely, you can get to this final spot via either pathway, and depression, and distress, and catastrophizing, and anxiety create microglial activation. It's also the case that if you activate people's microglia and produce neuronal inflammation, you get a lot of those psychosocial factors as well. I suspect, but can't prove, that you can get there in either direction.

To wrap up -- because I'm about a minute over here -- these various elements of somatosensory amplification that I've talked about -- somatization, sensitization, pain facilitation, catastrophizing -- all interrelate, at least moderately, with one another. They might all be both final, common pathways, as well as specific mechanisms getting to those final common pathways by which people can develop chronic pain conditions, as well as maintain those conditions.

I just want to remind people that when we're talking about things like sensitization, there's a

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really broad array of manipulations that we could apply that have been shown to change people's sensitivity to pain; gender reassignment surgery. We can give people insomnia. We can inject LPS. We can make them catastrophize

We can give them remifentanil and opioid-induced hyperalgesia. We can give them the flu. We can make them depressed. We can give them surgery. We could socially isolate them. We could refuse to let them be physically active, and we could decondition them. And we could set up a nocebo paradigm that increases their pain sensitivity. I kind of ran out of room and breaths, but there are 200 other things we could put on that slide that influence, robustly, people's pain sensitivity and their measured levels of sensitization.

Final slide, somatosensory amplification, a neat historical term that hasn't really been well defined. The term itself isn't widely used, but variations of that term are, and are clearly important. That construct or phenomenon shares a

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lot of space with other more commonly used terms that have proven to be important predictors of pain-related outcomes; all of these things strongly interrelated with one another.

It seems likely to me, particularly based on data, that these things share neurobiological substrates, which Vitaly and other presenters will probably talk more about. It may be that different elements of somatosensory amplification differentially predict different outcomes, although we need quite a bit more work in that area.

Really, the one question of interest for me is whether we should be trying to uniquely measure and analyze all of these elements separately. So for our clinical trials, should we be giving everyone a pill, and a PCS, and an anxiety measure, and doing a full QST battery, and doing fMRI, and doing PET, and doing everything else we can think of to measure these different elements, or does the overlap mean that we can just take a few of these and consider them as representative of the construct of somatosensory amplification?

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I don't know the answer to that myself, but I bet with the collective brain power in this room, we are smart enough to figure it out. So I will leave you with that, and thanks very much to my colleagues at Brigham, and Mass General, and to Ajay Wasan in Pittsburgh who really provided all of the data and work that went into collecting these findings. Thanks very much.

(Applause.)

Q&A

DR. BRUEHL: This is Steve Bruehl; a quick question for you. In looking at the literature, have you ever encountered large sample studies that have used multiple of these options and applied something agnostic like cluster analysis to see if there's evidence for them all reflecting some underlying construct?

DR. EDWARDS: The OPPERA study does probably as good or better a job of that relative to any other study I can think of. I'm not sure they did cluster analysis. Roger will know better. Yep, they may have done both cluster and factor

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analysis, and been able to derive sort of sets of these variables that tend to be most interrelated or hang together.

Whether we can then take that data and select out specific elements of those clusters or factors, and just measure those things and consider them representative, I don't know for sure, but it might be beneficial for the field if we all went back and took a closer look at all those OPPERA papers because that's probably the best in the sense of that sort of thing being done.

DR. FARRAR: John Farrar, University of Pennsylvania. I'm clearly pointing out something that you are aware of, but I think it may not be general, which is that you suggested that there were differences in terms of which was most important, catastrophizing or temporal summation, whereas in both studies, both of them had univariate effects.

Now, which one stays in is going to be dependent on a host of factors that may have nothing to do with the relationship between them,

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and it may be the variability with which each is measured and the quirks about the population. And as many of us are familiar with, the Framingham study made a huge mistake when it put diastolic pressure into the model first, and then systolic pressure fell out. And all of a sudden somebody said, "Well, let's go look at the other way around," and it turned out that both are important.

So I'm not sure that the data actually contradicts itself. The question, though, that I wanted to try and get to is what do you think catastrophizing is measuring in terms of brain function? Every psychosocial process is a transmitter, mediated, connection-involved, frequency and pattern process. I'm quite willing to accept that it's measuring something that is important and is part of this process, but I don't know that it argues that it is more or less important than some of the other things that we're measuring.

So what do you think, from a brain perspective, we're actually measuring with

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catastrophizing?
DR. EDWARDS: That's a terrific question. I agree with your premise that the predictive capacity of any of these things is going to vary quite a bit depending on the subtleties and nuances and quirks of any individual study, and that's why it's going to be really challenging -- although hopefully we're up to the challenge -- to come up with a list of definitive recommendations that sound something like, "For all trials of X, we should absolutely be measuring these 5 factors as particularly important." So that's probably what we'll spend some time working on tomorrow.
If you need me to put my nickel down right now and identify the fMRI assessed neurobiological substrates of catastrophizing, I would probably ramble for a minute or two about alterations in default mode network function and alterations in default mode network connectivity with other networks of interest like the salience network.
I'll put in a plug here for Vitaly, who may touch on some of those issues in his talk. If he

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wasn't planning to, now he probably has to, so sorry, Vitaly.
(Laughter.)
DR. EDWARDS: But some data that is emerging from some of our studies. And I'd suggest that some of the MAPP related data and some of Dan Clauw's data as well I think seems to identify the default mode network particularly as being influential in some of these centralized chronic pain syndromes, whether it's fibromyalgia patients or whether it's pelvic pain patients with widespread pain.
In general, those are the patients who report the most catastrophizing, as well as the most temporal summation, as well as the most other physical symptoms, and all of those other things together.
Clifford?
DR. WOOLF: How do you deal with the problem of the difference between correlation, which is strong in some cases, and causality? You're making an assumption that these are driving the risk

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factor or driving the disease phenotype, whereas they may just be correlated.
DR. EDWARDS: Very true. The one-word answer to your good question about how I deal with that problem is poorly. However, the longer term answer is we're currently engaged in a number of studies of non-pharmacologic treatments that specifically target elements of patient's presentation like catastrophizing, and we take all sorts of measurements at various time points over the course of those treatments, including our admittedly crude measurements of pain neurobiology using fMRI, PET, and other sorts of things.
Presumably, those longitudinal studies in which we're systematically manipulating one of the cognitive and emotional factors and measuring changes in that, as well as changes in neurobiological outcomes, will at least help us to shed some light on the temporal dynamics of those relationships.
There are no studies like this yet, but I wouldn't be surprised if everything turns out to be

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bidirectional. And if you make people catastrophize by, for example, giving them information about their chronic pain syndrome and how it can never be cured, it's going to ruin their life, they better quit their job, probably their marriage is going to fall apart, that sort of thing, and you make them really anxious and catastrophic about their pain, I'm quite confident that that changes the dynamic interrelationships between default mode network and some of these other networks. I have no doubt that changes brain function and probably eventually structure.
I suspect it's also true that if you had really specific techniques, which we don't yet, and you could do TDCS, or TMS, or a technique like that, and selectively manipulate the default mode network and its activity and its relationship with other brain networks, you could produce a catastrophizing state that way.
So I strongly suspect that either path can influence the other, and how that happens most often in patients, I don't know, and is to me a

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fascinating and open question.
John?
DR. MARKMAN: Can I just ask, to the extent that you think this maladaptive connectivity between the anterior insula and the primary somatosensory cortex kind of correlates or fits with this narrative, what I'm missing here is the role of the spinal cord in modulating pain intensity.
I think many of us think that the cord probably plays some important role in the up or down regulation of pain signaling, and I just don't understand how you can ask these questions unless you're assuming that's somehow neutralized or nullified. How do you deal with that complexity?
DR. EDWARDS: Also poorly.
(Laughter.)
DR. EDWARDS: That's a fantastic question, and it would be foolish and short-sighted of me to say that I don't think the spinal cord is an important player in these sorts of relationships and how they unfold in the nervous system.

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Clearly, it is hugely important.
Probably like a lot of us, I'm a little bit limited by the availability of tools for these human studies. It's really easy to give people a bunch of questionnaires and measure things like catastrophizing, and hypervigilance, and somatic focus.
It's harder, but not so hard, to put them in a scanner and measure patterns of brain function. But it gets really difficult, at least for someone like me, to do reasonable assessment of what's happening in the spinal cord in patients with chronic pain or when we apply standardized QST style stimulation in the laboratory.
So the true answer to your question is that I, when pressed, try to always emphasize how important the spinal cord is but never include it in our studies because I don't have the capacity to measure the function or even structure of what's happening at that level.
DR. MARKMAN: Fair enough. Thanks. We have time for one more question. Yes, Dan?

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DR. CLAUW: A great talk, Rob. I just wanted to almost respond to what Clifford said. I think we finally are with human studies in this, that we're identifying models that help us unpack the temporal relationship between some of these things. I agree with almost everything Rob said, except I think that in many cases, catastrophizing is more of a state than a trait.
In some recent studies, for example, in hip and knee arthroplasty that Jeff Katz did, dramatic reductions in catastrophizing that are highly related to the amount of pain control that someone got after they're getting their knee replaced.
So I think sometimes when we see catastrophizing, especially in these people with chronic overlapping pain conditions, I think that way of thinking is because for 20-30 years, these individuals who've had pain, they've sought medical attention, and no one's done anything that has helped their pain, and they develop this way of thinking, and you see that that way of thinking is clustered with the QST findings and things.

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So in order to dissociate, we're going to have to do these studies where longitudinally you can look at someone, you see catastrophizing take a huge drop, and you look at brain imaging, you look at everything and say, okay, what led to what? Because we similarly see fairly impressive improvements in depression that are a factor of pain relief after arthroplasty.
But I couldn't agree more that these things are all interconnected and intermixed. We're just now, I think in the human studies, starting to try to unpack these things.
DR. EDWARDS: Dan is now my favorite question asker of all time, and I totally agree with everything you just said.
(Laughter.)
(Applause.)
DR. MARKMAN: Our last speaker this morning batting cleanup is Dr. Hertz, who is the division director for Anesthesia, Analgesics, and Addiction Products. She is obviously a clinician as well as federal public service.

Presentation - Sharon Hertz

DR. HERTZ: Hi, everyone. I got here a little late, so I haven't had a chance to say hello to everyone. I'm just going to talk about indications a little bit. It's a very different, sort of a left turn, from this morning talk. When we're thinking about these different processes, hopefully eventually we're going to end up with targeted treatments and how do we translate that into an indication.

I'm going to talk a little bit about some of the guidances that we've had, which try to define how to study different aspects of pain. It's kind of funny. I've been at the agency now, at the Food and Drug Administration, for a little over 20 years, and we've been writing a pain guidance for a little over 19.

(Laughter.)

DR. HERTZ: We've had a couple drafts. I remember Bob Rappaport saying he was just insistent that we get this thing done before he leaves, so I'm not so hopeful.

(Laughter.)

MALE VOICE: He's left.

(Laughter.)

DR. HERTZ: Yes.

The '92 guidance was in place for a long time, and it was an interesting document. It described a number of different things. This I thought was interesting, the state of the art of the controlled evaluation for effectiveness of chronic analgesic administration, i.e., more than 2 to 3 days.

That's an interesting definition of chronic, but I think, really, what it was distinguishing was multiple dose versus single dose and how well the models for single dose analgesic trials had been established, and we were still trying to develop additional models to study other, approaches to drug administration, because clearly these pain populations were not 2-to-3-day populations.

This was also very interesting. I focused on the chronic part of this because acute pain has always been a little bit easier to discuss. In the

'92 guidance, it talked about how we should study peripherally acting products for 6 months, but centrally acting for at least a month because of safety issues. I think it just reflects 1992 and the time prior was just such a very, very different time in this work.

Some of you may know that the history of analgesic products at the agency has been interesting. For a number of years, it was split between two divisions. One division had the Schedule 2's, and the other division had NSAIDs and some Schedule 3 and 4's. The approach to development kind of started separating, and they were brought back together around 2005 or '06 when we were reorganized, and we've been trying to clean things up ever since. For those of you who consult, I'm sure there's a variety of opinions on how well we've done that.

One of the approaches that we used to try and understand how to develop indications was to have a scientific workshop. Bob was the first author writing up the proceeds of that workshop.

It talked about what we could do in terms of extrapolating efficacy across different conditions and some of the factors and what the considerations were to do so.

I'm here five years later. That's super quick by federal agency standards. We published for comment a draft guidance, the 2014 draft guidance, taking into consideration some of the things we learned in the scientific workshop. And the guidance, which by the way is also now off the website, talked about what do we need to know about an NME versus something that was not an NME, or something that was new class versus not a new class.

We were really focused on avoiding these supraspecific or pseudospecific indications as a way to get a product out in use but not have the kind of information we need, particularly the safety information, in the kind of populations in which it would actually be used. So we to find where we thought very, very narrow indications would be appropriate, so if it only was going to

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work in a narrow population or if safety concerns would necessitate restricting it.

We had a menu, effectively, of what it would look like to develop products for different conditions. We actually did have central neuropathic pain in there as opposed to peripheral neuropathic pain. Nobody has ever actually filled the menu items for general chronic pain indication, nor have we seen much in the visceral pain area for acute pain. We did talk about some subgroups of indications.

So we're working on some more guidances now because I like working on guidances, to some extent, and we're going to be covering a number of things. You'll be seeing these hopefully -- well, you'll be seeing them depending on how long you stay active in the literature.

(Laughter.)

DR. HERTZ: What do we currently have in terms of indications? This is all fairly pragmatic. Indications are generally reflected, the underlying clinical studies, with some

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extrapolation. But our approach to study design has changed, therefore if you look at the range of indications out there in analgesic products across the span of the last couple of decades, it's pretty diverse.

We've been working on harmonizing indication language to the extent that we have the information to do so. Another reason why indications may be changing is because of new information that becomes available, the opioids. Everything has to say the word "opioid" in it these days.

The opioid indications are something that we've spent a lot of time working on. Labeling is the number one communication tool for FDA. This group is probably not a good group to survey in terms of who's actually read a label, but when I talk in front of a group of people who have MDs or other prescribing related degrees and I ask them who writes it, have you ever read one, it's pretty low numbers.

So anyway, what we've done with the opioids -- this is the example of the current

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extended-release, long-acting indication -- is we've tried to combine both risk and benefit. Traditionally, indications tell you what something works in. Here, we seem to have a need to emphasize if you're going to use it to treat pain, don't forget the rest of the baggage that comes along with them. So we have the indication, which says if you use these products, other products that may have different or lesser risks aren't going to be suitable.

We have a similar type of that for the IR products. Here's transmucosal immediate-release fentanyl label. In contrast to the ER/LA label, which is just pain severe enough to warrant the drug, this one is narrow, and this was narrowed based on safety concerns. The range of fentanyl doses in these products is pretty expansive, and the pharmacokinetics really made us concerned about what it would look like if these were widely used in a general way.

The fact that the first one was a raspberry flavored lozenge, also referred to as "the

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lollipop," really made us worried about what would happen if these got into a very popular wide use without an understanding of the safety concerns, so this was very narrow.

Here's a recent one, not controversial at all, the first sufentanil product that is not a parenteral or is not an ID formulation. Here, it's for pain, but again, heavy emphasis on the safety aspect of it being in a supervised setting, and we listed a whole lot of other things that people were worried about in the limitations of use.

Going back to some of the non-opioids in older products, again, this was very much pragmatic what was studied, signs and symptoms of a variety of arthritides and pain. It's interesting that we have this signs and symptoms concept even though in some of these, there was no sign actually being measured; it was all symptoms for a number of them, but people seemed to understand how to use Naprosyn pretty well.

Then we have another nonspecific, non-selective NSAID, which turned out it had a big

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problem with bleeding. So it got limited to a shorter duration, and by some miracle people have actually respected this one in contrast to anyone here who's ever prescribed bromfenac, which had to come off the market because the limitation on duration wasn't being respected there were bad outcomes.

Here's this centrally-acting drug, and the indications that it currently has. Again, it's indicated for the treatment of diabetic peripheral neuropathy based on two studies of our standard 12-week duration, double-blind, placebo-controlled fixed dose in this case in adults with diabetic peripheral neuropathic pain.

For the fibromyalgia indication, again, two studies using a CR criteria. I don't remember what year these are from, but it's a few years old. It's not the most current version. I'm glad that we used a history of widespread pain in addition to the tender points sites, which we know should be more leery of, and of course chronic musculoskeletal pain. This one was interesting

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because it actually was a combination of different clinical trials that resulted in some measure of extrapolation. We had studies in low back pain. We had studies in OA. Boom. That's musculoskeletal pain.

Another example would be Lyrica, which has a number of interesting indications. The DPN, diabetic peripheral neuropathy, is a common target. Lots of people have it. It's easy to recruit, and there's a big market.

Postherpetic neuralgia and fibro we also have here, and also neuropathic pain associated with spinal cord injury, which was interesting. Does this constellation of indications suggest we should be broadening this in some way? So far, the company hasn't asked for it, so we don't go poking bears if we don't need to, but that's how that labeling stands.

So what would a truly novel indication be in this current environment and referable to this meeting? Could we indicate something for the management of pain due to central sensitization? I

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think, Cliff, you might like that. You've long supported the concept of mechanism-based drug development. But what does that mean and how would that be interpreted and used? Should it be somehow narrower? Management of some aspect of what is manifest in what could be coming from central sensitization, or hyperalgesia or allodynia in the setting of widespread pain, or specifically due to that process?

Is the science ready to support that type of clinical drug development? This is going to depend on a number of factors to get to this type of an indication, How do we define the population is very much the topic here. What's the range of manifestations? What's most important to the patients? Can diagnostic criteria be translated into a study population, and more importantly, can it be translated into an indication or a way that clinicians can apply a strategy with at least some way of matching what was done in a clinical trial?

What about the measurements? For those of you who've participated in our qualification

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process, first, I apologize --

(Laughter.)

DR. HERTZ: -- and second, we need to have validated measures. I like the idea of putting somebody through an fMRI, a PET scan, or a QST battery, and the other things that were just mentioned to define the population, but clearly that's not going to translate into clinical practice. So we need to have some way of defining the population using reliable measures that can then support a reasonable indication.

As we think about what the implications are of what we know, once a lot of these questions get better defined answers, I think we can start looking at how to translate that into indications. That's all I have.

(Applause.)

Q&A

DR. CLAUW: Thanks very much, Sharon. I'm just wondering if we could use the drug duloxetine as an example of, knowing what we know now rather than what we knew 7 or 8 years ago when that drug

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was being developed, how one might be able to approach, for example, an indication of chronic musculoskeletal pain with a certain score on the body map or the fibromyalgia measure.

In hindsight, that has almost certainly -- we certainly know in low back pain -- Lily did the study subsequently, and it was the people with the higher score that were the ones that duloxetine worked in. And that almost certainly would be the case with the osteoarthritis group as well. There's a lot of data that would suggest that it would have been the people with OA with either the more diffuse pain on body map or the higher fibromyalgia score.

So I'm just wondering now if a company approached you now and said we have a drug that we think works across a number of different chronic musculoskeletal pain indications in the subset of people that have central sensitization, and we're going to use this PRO that's been widely used and shown in these different studies, and we even know what this PRO relates to on fMRI and quantitative

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sensory testing.

What would be the reception that one would get at the agency, and what types of things would you be concerned about, worried about, so that we could help move the field in that direction? Because I think we all think that would be good for the field if we could move in that direction.

DR. HERTZ: That's a great question, and it's actually quite layered in terms of what implications of that approach could be.

First of all, in the context of somebody simply wanting to do that, conceptually if you screen your patients and use that as a selection criteria, you can improve your assay sensitivity. You can see what the effect is in the population that's going to respond. And presumably, a PRO could even be useful for clinicians who are dealing with pain patients in terms of drug selection. Yes, as long as the PRO has adequate validation, I think that it is certainly an approach that could be considered.

What I wonder, though, is what percent of

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the population that would reflect, and then what are the implications if we indicate the drug for musculoskeletal pain in patients who are characterized by this somehow? Because the reality of the environment that we're in right now is what about the other people who don't necessarily meet those criteria but who might respond for other reasons perhaps, and what about access to it? Is being more focused going to create some type of barriers?

I mean, aside from the practical aspects of it, I think it would be great to have mechanisms to evaluate patients that match them with the drugs they're getting treated with as opposed to trial and error. So instead of a number needed to treat of 3, or 6, or whatever to find a person who responds well, if you can get that down to 1 or 2, well, that's terrific.

DR. RATHMELL: Jim Rathmell from Brigham and Women's. I just want you to expand on that because how does that differ from what's happening today where we have these run-in periods where you enrich

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the population for responders before you do the first treatment, and then you're analyzing the data?

So just expand on how you approach the current trial paradigm that increases the chances of success, but then as you're evaluating the compound, you know that the user, the end user, the clinician, is going to completely ignore that the trials that got it approved were enriched.

DR. HERTZ: Well, they're ignoring it because they don't read our darn labels. We describe that if a hundred people are run-in and 50 get to the next level because of meeting criteria, then they already start to know that half the population didn't respond. In fact, I think it's higher.

Then surprisingly, in spite of enriching the population, we still get a bunch of dropouts. I mean, the whole point of the enrichment was to avoid having so many dropouts. We're basing our analysis on imputed data, which doesn't serve anybody well, but then we still lose another 30

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percent.
So using a gross enrichment scheme just to have enough people in the study, to keep them in the study long enough to get outcomes, because they either tolerate it or respond with some measure of efficacy, how does that compare to this?
Well, I suspect that the -- because then we've cut out the risk of a number of dropouts early because we're removing some of the people who can't tolerate the drug. We've potentially excluded a number of people who might drop out for lack of efficacy. We still have, at the end of the day, only a portion of the population that responds.
Enrichment, the way it's currently being done -- which by the way is primarily being done in opioid studies, not in some of the other drugs, and I'll talk to that point in a minute -- it's a sledgehammer. The potential PRO is much more of a tweezer, picking people more appropriately as opposed to just kind of whacking other people out of the way.

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The reason why the approach was adopted for opioids -- and this is a method that's been used in other centrally-acting drugs for a variety of different reasons. We actually borrowed this. Just for the record, this was not created by IMMPACT or ACTTION. This was brought to IMMPACT or ACTTION by us because we saw this method being used in other cases with somewhat low response rates as a way to improve assay sensitivity; for instance, depression.
So if you have a fixed-dose trial, and it takes weeks and weeks for people to tolerate the drug, and you don't have weeks and weeks to titrate them and get them used to it -- plus, even with enough time, there's a bunch of people who just aren't going to like that particular drug for a variety of reasons -- and then you force them to get into the study to stay on a fixed dose for a long period of time -- we were having dropout rates of 50-60 percent. How do you analyze that?
Then you have to start powering your study to be a responder, yes or no, and then you're

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increasing the size, and you're losing information. That's a situation which a drug is not readily tolerated in a method of use that doesn't necessarily reflect clinical practice. With duloxetine, that had a fixed-dose design. That was more of a standard clinical trial design, and it didn't run into the problem.
So I think you have to look at what the enrichment is trying to achieve. In one case, it's just trying to make the study feasible in the context of you have data to analyze, and you don't have a missing data problem. In the other hand, and in this situation, it's actually trying to select the right population. I still don't know in the opioid study who is going to be a responder at the end of a 12-week period. It's still not going to be a 90 percent response rate. It's still going to have a higher number needed to treat.
DR. DWORKIN: Sharon, I'm going to go back to Dan's question. Let's say we have a PRO that we predict identifies which patients treated with duloxetine are going to respond robustly. Do you

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also want to see in the clinical trial that the patients who score low on that PRO don't respond to duloxetine? So are you really predicting that one subgroup -- are you going to need to see data that one subgroup responds robustly but another subgroup doesn't, or is it sufficient to just show the robust response and the high scores?
DR. HERTZ: That's the kind of question I don't like to answer --
(Laughter.)
DR. HERTZ: because it kind of sounds like advice about specific things. So I would say the way in which you define the population should reflect what you think will be acceptable labeling and an acceptable way of defining your indication. You don't have to prove drugs don't work. If you enrich the population and a whole bunch of people said it didn't work, you don't have to keep them in the study; you can enrich them out, or let them leave as part of the enrichment program. You don't have to still prove it doesn't work in them because that initial enrichment period, it's very blunt.

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So I would say to you, or to whomever, what do you want to do? How do you want to define your population and how do you want to define your indication? Because there are going to be implications to how you use any instrument or any set of inclusion/exclusion criteria to define an indication.

DR. WOOLF: Could I ask another theoretical question? Assuming that Dan's correct, and we can identify who's at risk and that potential therapeutic, and prevent the evolution to chronicity, how would you manage that as a preventative rather than a symptom control?

DR. HERTZ: How would you manage that?

(Laughter.)

DR. HERTZ: I'm trying to think of specific examples. There is some interest in the setting of chemo-induced neuropathic pain to perhaps try to prevent it as well as to try and manage it. The questions I would ask are how well can you define the at-risk population? What are the risks and benefits of treating that population with whatever

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your product is, and what is the appropriate time to decide whether or not it's actually preventative? Do you have to stay on the drug or not indefinitely? Does it prevent it and you're good to go, or is it just an ongoing therapy?

Those are the kinds of questions that would have to be considered. But yes, there's prevention stuff all over the FDA, perhaps more in other divisions. But yes, I think prevention is something that can be considered.

Lesley?

DR. ARNOLD: Yes. Hi. Lesley Arnold, Cincinnati. When we're talking about an indication for central sensitization, we are talking symptoms beyond pain because when someone has that condition, as we've heard about, they have other symptoms in addition to pain.

One of the challenges that we've faced over the years is how to get a labeling for these other important symptoms that these patients experience: pain, fatigue, sleep disturbance. And we've worked to develop different outcome measures that

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incorporate these symptoms, but they've never really been used yet as a primary outcome in these trials.

For example, Lyrica, pregabalin, works very well on sleep disorders related to fibromyalgia, but it never really reached a level of getting on a label even though we know that it works. I think it's just been very challenging for us to know how to present this information to the prescribing doctors so that they know about it and can take advantage the drug's capabilities, but also just addressing all these multiple symptoms that these patients experience so that they get a better effect from their treatment.

DR. HERTZ: Well, it sounds like you're talking about fibro. I'd have to go back and look at the exact language for the products that have fibro indications, but I think if your drug is going to treat multiple aspects of a disease, then we can think about a broad indication. We need to know what's important, how you're going to define it, and then you need good tools.

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If you ask a patient in the morning did they sleep well at night, the answer is that's not an adequate tool. That's what we get a lot of the time, and that's a lot of why we don't see stuff in labeling because we don't have a validated measure. I think that you can think about what are validated measures, and then you can design your study to incorporate them with your statistical plan, taking that into consideration.

DR. MARKMAN: Time for two more questions.

DR. CLAUW: This is a question I think you can answer. I'm going to try and ask it.

(Laughter.)

DR. CLAUW: Is the process the same for qualifying a PRO that we would, for example, try to use for a label change, a PRO that matches sleep with objective measures, and the same for the PROs that we might use to enrich for a study? You already apologized. I think many of us have found that the process that is necessary to create the former kind of PRO that would be used for a label change is quite onerous.

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But I'm just sort of wondering if the PROs we might use to segment -- something as simple as a body map, if that would have to go through that same process or if that could just be considered this is what we're going to use, here's the data, and we don't have to go through that.

DR. HERTZ: That's a nice technical question, and I can --

(Laughter.)

DR. CLAUW: It's a yes/no. I've been trying to ask you a question that you could answer.

DR. HERTZ: The qualification is intended for outcome measures. So if a tool is being used to help define the population, that's not an outcome measure.

DR. CLAUW: Okay. Great. Thank you.

DR. MARKMAN: John?

DR. FARRAR: John Farrar, University of Pennsylvania. Thank you for the talk. One of the things that becomes clear in the opioid era is that the extension of risk and benefit goes beyond the population that may use the drug for therapeutic

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purposes to a larger issue. I'm not going to ask you that question.

I think, though, what it suggests is that there is a reason for people developing new agents and things that they want to use to clearly demonstrate safety, safety not only in the population who might have a therapeutic benefit but safety beyond.

It also suggests that trying to come up with some mechanism for predicting which patients are most likely to respond to that therapy, as you suggest, not with MRIs and very expensive tests, but with some patient-reported outcome or something else, is going to be key issue trying to get products to market.

It seems to me the question that I wanted to ask is whether there has been thinking about the concept of actually encouraging people who were submitting analgesics in particular but drugs in general, to add to studies measures that might help in understanding later which population is most likely to respond.

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In particular, I'm talking about Rob Edwards' discussion of catastrophizing. It would seem like if we had more clinical trials where we had those measures included, it would benefit all of us in terms of trying to think about it later.

I'm just wondering whether -- I know that there are lots of issues involved in that, but what I'm really asking is whether you think that's a good idea and leave it at that.

DR. HERTZ: Scientifically, I think it's a great idea. What it means in terms of an application and all of that is a completely different question. What goes in a label and what goes in a study are going to overlap. You can't put something in a label that wasn't in a study. But you can have a boatload of stuff in the study that doesn't go in a label, and publish it, and that's informative and useful. We can't put a complete study report in a label. We've got to just kind of focus on stuff.

If I take your question a little further -- well, I'm not going to take it further.

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(Laughter.)

DR. HERTZ: So, yes. I think that a lot of that would be really helpful because I think, first of all, the more you have, especially early in development, the easier it is to figure out who to put in a phase 3 study. The more you have early in development really can give you a much clearer sense of what at least the initial use of the drug can be in a much more meaningful way than the sort of shotgun approach we see more often than not.

Particularly -- I have to sort of anonymize this -- I had an interaction under an IND for a drug, and the phase 2 study, which was going to enroll 400 patients, was based on a complete experience of 65 patients previously, and we knew nothing about the behavior. The results of the 65-patient study was highly encouraging enough to go from that into a 400-patient study.

How many people have seen 65-patient studies potentially mislead a program? So I think the key is when and where you want to put that extra information, those tools, in. If it's informative

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early on and helps you create a better targeted phase 3, great. Then if you want to include it as either inclusion criteria or as an outcome measure that sounds like that's more of an inclusion criterion, sure that can be reflected in describing the patient population that benefits.

DR. MARKMAN: One last question, and then we'll break for lunch.

MS. VEASLEY: Thanks. Chris Veasley, Chronic Pain Research Alliance. Sharon, last summer there was a first FDA-focused patient -- what's it called? FDA patient-focused drug development meeting.

DR. HERTZ: Patient-focused drug development meeting.

MS. VEASLEY: Yes. So the conclusions of that meeting are very similar to what we've just been discussing, the impact that patients express, the impact that pain has on their life, problems with sleep, mood, so on and so forth, widespread pain, and a lot of the things we've already discussed today.

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So my question to you is what influence does the findings of that report have, either on the guidance -- so the question is, does that affect the guidance that you provide to people doing clinical trials and manufacturers, or do you simply take that information into account when you're reviewing applications or approvals, to say that it lines up with.

Do you understand the question?

DR. HERTZ: I might need to sort of narrow what I'm trying to answer with you a little bit. Are you asking about how many of those endpoints, or symptoms, or signs should be included in the clinical trial, should be included in labeling, or should be required by us?

MS. VEASLEY: As John just mentioned, the difference that I'm asking is, are you simply taking what the patients have said into account when you're reviewing something that's already being submitted to you, or are you saying or making recommendations to the clinical research community and manufacturers around what patients are saying

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to you, so on and so forth?

So it's not just the severity of pain, but the fatigue and the sleep, so you're actually giving guidance to the community on how they should be looking at this when they're researching the efficacy and outcome measurements for these trials.

DR. HERTZ: We are not going out and saying we had this meeting and here's what was conveyed to us to people in drug development. What we've done is make that information available. It's on the Web. We have summaries and we actually have a transcript.

When somebody is coming in with a symptomatic treatment, what's important to the patient should be the first question. A lot of times with analgesics, we just kind of skip to pain intensity, and part of the reason for that is an inability to convince people that these other important domains -- going back to one of the original papers produced by IMMPACT, the 6 domains that are important in analgesic clinical trials I think reflect very well what we've heard from

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patients recently, and this goes back many, many years. It's good reinforcement.

If we go to sleep, for instance, though, when we tell people you need to have a reliable sleep instrument, not the did you sleep well last night rated on a 0 to 10 scale, it often goes away.

Is that answering your question at all?

MS. VEASLEY: It does. It's kind of like the cat and mouse here because when we talk to companies who are doing trials for let's just say low back pain, but they're not taking into count multisite pain, they're not able to recruit enough patients with just low back pain, so they're recruiting a diverse set of patients into the clinical trial.

We're saying, as Dan showed in the data that he showed, multisite pain, widespread pain is an important indication in terms of whether a patient may or may not benefit from this.

They oftentimes will come back and say, okay, that's interesting, but the guidance doesn't reflect this or the FDA doesn't require it, so

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we're not going to do it. Do you see what I'm saying? So if the communication comes from you that this may be an important aspect to look at --

DR. HERTZ: It will have no -- I don't think we can -- what can be required is negotiable and difficult to state in an absolute way. We certainly would entertain any useful way -- so what these people are effectively doing is shooting themselves in the foot by enrolling a diverse population that has characteristics that may make them particularly not just heterogeneous, but really major subpopulations. Therefore, if it's only going to work in one population and not the other, you're going to lose your signal.

So it's expedience over logic, and you've got to power it, that's great. But why you would enroll that population without defining it better and using inclusion/exclusion criteria likely to define a successful population is a question I can't -- I don't know why that's done, but it's certainly not something we've said don't do.

(Applause.)

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DR. MARKMAN: We're going to break for lunch. We'll be back here around 1 p.m.

(Whereupon, at 12:09 p.m., a lunch recess was taken.)

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A F T E R N O O N S E S S I O N

(1:20 p.m.)

Panel and Audience Discussion

DR. MARKMAN: We have a chance for the next hour to have some live counterpoint between this morning's speakers and also some additional speakers here, Dr. Fields among them. So I'm just going to start by opening up for questions from people here, and then if not, I've got a few of my own.

DR. COLLOCA: I have a question.

DR. MARKMAN: Dr. Colloca?

DR. COLLOCA: Yes. Luana Colloca from the University of Maryland. This question is for the panel. I don't know who I'd like to address. No one mentioned, the nocebo effects, the power of expectancy, how this patient looks like in terms of what they expect, what they wish, and how much you do to try to take into the neurobiology of expectancy.

If you can comment on that, including the FDA representative, how expectancy can be involved

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with in designing a clinical trial and interpretation of the outcomes. Thank you.

DR. MARKMAN: Sharon, do you want to start?

DR. HERTZ: No.

(Laughter.)

DR. MARKMAN: Contestant number 2. Dan, would you like to start?

DR. CLAUW: No.

(Laughter.)

DR. CLAUW: Let me just say, I agree. It's a really good question. I don't think it's been very well studied at all with any of the techniques, like with functional MRI and things like that.

DR. COLLOCA: Clinically.

DR. CLAUW: Right. That's what I'm saying, is I think, experimentally, that's been well studied, and we certainly know it to be the case, but I likewise wouldn't know the answer to your discrete question.

DR. FIELDS: Well, expectancy is an inevitable part of every pain experience. It's a

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very clear variety of studies, and it's new, or it's not necessarily pathological.

I thought this morning's talks were immensely informative. I certainly learned a lot. I was surprised that the word "expectancy" was not used.

Some things that stood out to me from looking over the material that was sent before the talks, and then the talks, one of them is that central sensitization is normal. If you have a noxious stimulus, if you have a nociceptive input, by and large, you're going to get central sensitization. I'd like to know if there are examples of peripherally generated pain in which there is no central sensitization.

Are there? Clifford, where are you?

DR. WOOLF: Where am I?

(Laughter.)

DR. FIELDS: No more questions.

DR. WOOLF: I think bringing up the notion of what is the protective function of pain is crucial here. In the setting of acute, transient,

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noxious stimuli that are non-tissue damaging, I think most of them do not generate central sensitization. There's not sufficient input to produce a detectable change.

But the minute you cross that threshold and you actually get tissue injury, then that is the adaptive function of central sensitization because now it shifts from the need to protect the body against damage from now protecting the damaged part of the body again, and enabling healing to occur. That almost certainly has been the evolutionary drive for why we develop central sensitization.

DR. FIELDS: So it's a good thing.

DR. WOOLF: So that's a good thing. But the question there becomes pathologically, why in this setting of patients with fibromyalgia, or why in this setting of patients that have peripheral nerve injury does this adaptive pro-healing mechanism become pathologically present when there is no healing that occurs. And the same thing for [indiscernible - mic distortion] arthritis.

It's one of those things where an adaptive

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response has been corrupted in a pathological setting. And I think the challenge for us is to try and tease out that -- and that again is, is that general or are there some individuals that have a very high risk of that for whatever reason.

The question I've always struggled with is what is this massive gender imbalance? What is the driver? Is this completely genetic or are there some other factors that make women so much higher at risk? When you say that almost all the individuals with arthritis with no pain are male, if you could tease that out, would that provide us some claim to mechanism of pain and even potentially introduce a therapeutic means by which we can convert -- [indiscernible] at least as far as the central sensitization is concerned.

DR. MARKMAN: Is any of that gender imbalance borne out in the central imaging data where you would expect to see some differential network activation in men versus women? Do you see that?

DR. CLAUW: Yes, you do. And in fact,

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usually when you're doing functional imaging, you're analyzing the males and females separately if you have big enough data sets and cohorts because they really are quite different, and I think we're learning that in a lot of the studies that we and others are doing.

This is a really interesting question. When you look at the sex and gender differences, I think there's a couple of things we know and a bunch that we don't know. It's clearly not estrogen and progesterone. It may be testosterone. It may be a lack of testosterone. There's a lot of emerging data in animals that testosterone is analgesic, and that may protect males.

But if you go all the way back to just sort of basic sensory physiology, women are more sensitive to almost all of these sensory stimuli. And if they're unfortunate enough to be actively menstruating, they often get even more sensitive in the premenstrual phase of their cycle.

So there's just something about being a female that makes them more pain sensitive and

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sensory sensitive. I think we understand that fairly well now. I don't think we've yet figured out how to tailor treatments differently to chronic pain patients, based on their sex or gender.

DR. MARKMAN: Roger?

DR. FILLINGIM: If we're thinking that this initial central sensitization is adaptive and that it gets sort of hijacked and becomes pathological, do we think that that's because the ongoing pathological processes fail to stop or some more adaptive resolution mechanism fails in certain populations?

DR. WOOLF: I think at least there are hints that has been [indiscernible]. I think part of the issue also comes back to this mechanistic thing, that the adaptive central sensitization is largely this use-dependent transient [indiscernible] reversible, whereas, at least in the neuropathic pain setting, where the disinhibition is transient [indiscernible], and there seems to be a loss of inhibitory neurons, where irreversible changes in the CNS participate.

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The big unknown is the fibromyalgia, in the absence of any clear trigger, why in those individuals is there this heightened amplification, which is not restricted just to somatosensory inputs, and is that mechanistically quite different from either of those other two extremes.

DR. CLAUW: I think it is. I think some of the animal models that purport to be animal models of fibromyalgia, whether it's the swim stress model, which I think is a pretty good model. That's really more of a stress model of developing central sensitization. In fact, there are a number of models of central sensitization.

A lot of the work that -- at Kansas -- Julie Christensen's done with visceral pain models, the neonatal separation models, again, they're not nociceptive input models. They're stress models that lead to the development of these kinds of conditions. So I think it's pretty clear that in both animals and humans, people can develop pain and other symptoms without clear, nociceptive input.

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We did studies recently because we have been arguing with people about what small fiber neuropathy means, and that forced us to go into preclinical models and do some -- and we showed that by just increasing glutamatergic activity in the brain, we could get all the pain behaviors that you get in any of the animal models of pain.

So I think that -- and by the way, you also get the exact same thing that looks like small fiber neuropathy, which we think is just structural reorganization of the peripheral nervous system in any chronic pain state, not a specific finding that tells you anything about the pain, but that's a different conference for a different debate.

But literally in that preclinical model, with Eva Feldman's group reading the biopsies, which is a credible group that knows about small fibers, we literally found that just by increasing glutamatergic activity in the CNS, that we got, quote/unquote "small fiber neuropathy."

But again, I think this is where we all have to just -- it's all one nervous system. It's not

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peripheral or central. What happens in the central nervous system profoundly impacts the tone or the gain on what's going on in the periphery, and vice versa. What's going on in the periphery, to a great extent, can trigger central sensitization.

DR. MARKMAN: Dan, this is a follow-up to that point, and you said in your talk that this dichotomy between central and peripheral is a human made or manmade distinction. So just for my own clarification, why are we talking today about central sensitization? Why aren't we just talking about sensitization? Why are we trying to make this split point between central sensitization?

DR. CLAUW: That's a good point. I probably should do what I say people should do. But the conference, to be fair, is on central sensitization. And you can differentiate the difference clinically between peripheral sensitization and central sensitization.

Those papers that I alluded to that Yvonne Lee did in rheumatoid arthritis, she found that the amount of ongoing inflammation in a rheumatoid

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arthritis patient was very highly related to peripheral sensitization: tenderness at the joints or over the areas involved by the rheumatoid arthritis. But she found that there was no relationship at all between the amount of inflammation and tenderness at a site like the mid trapezius region or the sites that are tender in people with more central sensitization.

So she could pretty clearly, in a series of longitudinal studies, identify both peripheral sensitization and central sensitization in rheumatoid arthritis. To the extent that we can experimentally do that, again, I am critical about thinking of the nervous system as two different nervous systems, but I think it's helpful from a mechanistic standpoint to try to localize where the sensitization is occurring. So there may be differential treatment implications.

DR. MARKMAN: Just as a clarification -- because tomorrow I think we're going to be forced to think about inclusion/exclusion criteria and considerations -- are you

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suggesting that perhaps as part of a way to define a study population, we would need to look for a range of peripheral inflammatory markers and exclude them in a study population where we're asking questions about central sensitization?

DR. CLAUW: I think it just depends on the study question, but I wouldn't say as a blanket statement that that would be necessary, especially when you're looking at central sensitization superimposed on an inflammatory state. The last thing I'll say is the kind of inflammation, the kind of low-grade inflammation that seems to track with central sensitization is different than the kind of inflammation we see in a classic autoimmune disease. Andrew Schrepf has done a lot of this work in the MAPP network.

But really, you don't see it unless you take whole blood and stimulate with LPS or some other way. It looks like the immune system is primed in these individuals. The more widespread the pain is in interstitial cystitis, the more of this low-grade inflammation that you see.

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I want to contrast that as a rheumatologist that treats inflammation clinically. That kind of inflammation doesn't seem to go away with cortical steroids or with the biologics that we use to treat RA. It may be more neurologically driven inflammation, and it may be that not all inflammation is the same just like not all pain is the same. It's a fundamentally different kind of low-grade inflammation that's not going to respond to our classic anti-inflammatory drugs we use to treat autoimmune disease.

DR. FIELDS: I want clarification of what Dan just said. When you say low-grade inflammation, low-grade inflammation of what?

DR. CLAUW: All we know right now, in several different studies, you can bring out this difference between the people with central sensitization versus those without by taking whole blood and stimulating with LPS, and then seeing the big increase in proinflammatory cytokines that occur after 24 hours of stimulation.

The baseline measure --

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DR. FIELDS: In the central nervous system --

DR. CLAUW: No, it is peripheral blood. These are peripheral blood --

(Crosstalk.)

DR. FIELDS: So you're saying that there is a peripheral inflammatory process in what you're calling widespread pain.

DR. CLAUW: I'm saying that the immune system is different, and it seems to be primed in people with widespread pain. It does not look like the same of inflammation we see like in an autoimmune disease, where you could see a biopsy and see inflammatory cells or anything like that. It really seems to be a fundamentally different type of inflammation.

DR. FIELDS: So it's inflammation, but it's not autoimmune inflammation.

DR. CLAUW: Correct.

DR. FIELDS: Okay. I'm not a rheumatologist. I'm having difficulty following what you're saying.

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DR. CLAUW: Well, I'm having trouble following what I'm saying.
(Laughter.)
DR. CLAUW: I'm just saying that because it doesn't get better when we give -- when you take someone with rheumatoid arthritis or lupus and you treat them with these really powerful drugs that we now have, you will see that a sizable subset of them, the inflammation goes entirely away. But this, what they were talking about today, doesn't change at all. This central sensitization doesn't change at all
The inflammasome, if you will, that is associated with this is entirely different than the kind of inflammation you see as a consequence of autoimmunity.
DR. FIELDS: Okay. So we're saying that there is a peripheral real abnormality that's secondary to what's going on in the central nervous system, and there is some sort of different kind of inflammatory process from, say, rheumatoid arthritis or lupus that's also going on. But what

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makes you think that pain is centralized or originates in the CNS or is independent of what's going on in the periphery, or am I misinterpreting what you're saying?
Because it seemed to me that before today's session, I was pretty clear that there was this thing called centralization, which stated that to a certain extent, that pain is independent of what's going on in the periphery, and I don't see any direct evidence for it. Now what I'm hearing is that maybe there is something going on in the periphery as well, in which case we're back to square one.
DR. CLAUW: No, I don't think so.
DR. FIELDS: Square two.
DR. CLAUW: We don't know that what's going on in the periphery -- what I'm talking about, i.e., inflammation that can only be brought out if you stimulate cells with LPS for 24 hours, but otherwise, at baseline, all the different proinflammatory cytokines are the same at baseline in these different individuals.

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So I don't think that because that finding has been identified, that that means that that is the peripheral nociceptive input that drives fibromyalgia. It's just one of the many things that we're identifying, and we have to go, again, deconstruct which of these are causal and which are epi phenomenon. But I don't think that that low-grade inflammation that we're finding is driving the pain. I don't in any way think that is responsible for the pain these people are having.
DR. WOOLF: Again, to throw some comments in, just because we use the word "sensitization" as coming to peripheral and central doesn't mean they are linked. I think they are mechanistically quite different. Peripheral sensitization is a consequence of the reduction in the threshold of nociceptors, usually as a result of post-translational changes in TRPV-1, and TRPA-1, and other transducer [indiscernible]. And that post-translational process is driven by the activation by immune mediators over receptor tyrosine kinases.

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The mechanism is pretty well known, and it's highly defined. It's at [indiscernible], where there is exposure to those immune mediators, and because it's post-translational, it's usually temporary and short-lived. It has certain features. Usually at the site of inflammation, because of TRPV1, it's often got a reduction in the noxious heat threshold as opposed to central, which often has much more of a tactile component and include secondary hyperalgesics.
While I agree, that in the end, we should not artificially separate peripheral and central -- they do operate together -- actually, I think these are quite distinct, and we shouldn't lump together as best we can. The fact that NSAIDs act, to a large extent, on peripheral sensitization in many settings and has no effect whatsoever on many of the diseases as a case in point, it still raises the question of whether the degree which central sensitization is fully autonomous, if ever, or whether there will always be some need.
If it's a normal level of activity, a normal

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individual would not drive it, but in someone who has a heightened responsiveness of CNS, some very low level input may be sufficient to retain the -- or whether in some conditions you truly can have a fully centralized -- I think that has been theoretical. I've never seen evidence that has completely supported it.

DR. FIELDS: If anybody interpreted what I said as a way of confusing central and peripheral sensitization, I apologize. That was certainly not my intention, and I'm fully aware of the differences between the two. On the other hand, there's some evidence in the literature that damage primary afferents can become lower threshold and fire spontaneously, and there's some evidence that at least in some patients with fibromyalgia, there's a process in the peripheral nervous system that looks like damage.

DR. WOOLF: Right. One of the features that has always suggested that is if someone has particularly a neuropathic pain a rising from a neuroma, and you put a local anesthetic, the

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surprising features of that observation is that the local anesthetic immediately blocks the pain. But that very often has relief from pain that lasts for 6 weeks, whereas the local anesthetic only lasts for an hour or so.

So again, that's showing that this peripheral trigger is having very prolonged effects --

DR. FIELDS: Absolutely.

DR. WOOLF: -- and that by regressing the peripheral trigger, you can have very prolonged relief as well.

DR. FIELDS: Sure. I don't have a problem with that.

DR. MARKMAN: That's good. We have a couple of questions. I'll start with Simon, who's been waiting patiently, and then Mike.

DR. HAROUTOUNIAN: Hi. Simon Haroutounian, Wash U. It was really interesting to hear the morning sessions about different surrogate measures of central sensitization in terms of constellations of symptoms and signs, patient-reported outcome

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questionnaires, psychophysics, imaging, et cetera. I was really wondering -- I want to hear the panel's thoughts about should we sort of fight which of the surrogate measures performs better and stick to it, or we might want to think more broadly in terms of combining several different modalities in developing some sort of more sophisticated overall measure that would represent central sensitization, which could be, again, specific to particular conditions.

DR. CLAUW: Let me take a crack at that. One thing that I think everyone in the room would agree, or most everyone, is that there should be a body map in every clinical trial of a pain condition because I think in its essence, the best way to discriminate centralized from non-centralized pain is by how widespread the pain is, if you just look across all the studies.

If you then take some of the individual questionnaires or PROs, whether our group says it's the fibromyalgia measure or Charlie Cleeland says it's his measure, or whatever, I don't know

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what -- we now have those in studies at the item level. We're looking to see which other items would best discriminate central sensitization from not central sensitization. But I don't think the studies have been done yet to say that one is superior to another.

I think the fibromyalgia measure has been used in more studies by our group to show that it leads to differential treatment outcomes, whereas the CSI that Charlie's developed has not been validated or used in that same way.

So I like the measure we're using, but to be more neutral, I would say that the starting point should be to put a body map in the trial because that will tell you a lot, and you can be a little bit more agnostic to which of the specific measures you then want to use above and beyond a body map.

DR. MARKMAN: So if I could just take the liberty of putting someone on the spot, Nat, I know you have some experience in terms of operationalizing body map information, and if you don't want to answer this, that's fine. But I just

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thought you could speak to this from a study conduct issue. How simple do you think this would be, how easy to interpret, could this be managed at the site level? Again, do you think it separates in terms of assay sensitivity in any studies that you've seen conducted, and so forth?

DR. KATZ: I don't know about assay sensitivity, but it's not hard to operationalize. There are lots of studies that have used e-diaries or whatever, and have used body maps, and it's easy to collect the data and make it work at the clinic.

DR. MARKMAN: Is your a priori hypothesis that in some conditions it would be useful in terms of segregating or predicting responders from non-responders?

DR. KATZ: Well, hearing all the presentations this morning and seeing the data on the relationship between widespread pain and this concept of centralization and it's predictive validity for the response to analgesics, at least in some circumstances, it certainly seems worth pursuing. It's easy enough to collect the data.

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I think, Dan, you and I were talking at lunch that it may be worth collecting even some additional information beyond that. We have a lot of experience operationalizing a sensory testing kit, if you will, by the bedside in a large multicenter, U.S. based and global studies. If there were value to that, even that is not hard to do.

DR. MARKMAN: Great. Thank you.

DR. WOOLF: I was just going to say that I think the accurate clinical phenotyping of patients, as a non-clinician, is absolutely crucial. It seems to me that one of the problems has been the assumption that certain measures are going to be important; in other words, a bias selection of the phenotype.

With Jurgen some years back, we tried to do an unbiased screen of all of the possible measures that may predict the presence of different kinds of pain, what we call the standardized evaluation of pain step. It was an incomplete study; that the thrust was we don't know which of those phenotypic

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measures are going to be important and relevant.

In fact, what turned out for us in that initial trial to be the most sensitive measure was that the presence of neuropathic pain wasn't a single positive symptom, even though I think 90 percent of what we measured were positive symptoms. But it was not too surprising, the loss of sensation, the actual clinical evidence of some nerve damage, and that was the most sensitive measure.

So I would just say that to try and collect as much information in an unbiased way because some of our hypotheses may be rather imprecise, and we don't always know what it is that's going to turn out that's going to be able to identify the patients or responders, or none.

DR. EDWARDS: One more quick follow-up. Simon, it's a great question. By way of deliberately putting words in your mouth, it sounds like your question is implying that if we have all of these various domains measured in different ways -- QST, self-report, imaging, whatever it

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might be -- and they all interrelate and overlap, but none of them anywhere near perfectly, which means possibly they're all conveying important, unique information, wouldn't it be an interesting idea if we could develop a brief multimodal screen for centralization or tendency toward fibromyalgianess, or whatever we might want to call it, and maybe that screen would incorporate things like a body map and some self-report questions on emotional distress, and a brief measure of temporal summation, and some assessment of sensitivity to other physical symptoms or different sensory modalities.

Maybe if we had a multimodal screen like that, that you could do in 10 or 15 minutes, and that captured, to at least some degree, all of those various overlapping elements, and that got validated and used in a number of trials, we'd wind up with something that would be easy and convenient to recommend for pretty much all future trials of any kind of treatment in any pain condition.

I'd be delighted if we got to a spot like

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that, and maybe that's a project you'd be interested in working on. And if so, sign me up as a collaborator, but we'll probably have a little ways before we get there.

DR. MARKMAN: Mike?

DR. ROWBOTHAM: Mike Rowbotham. I just wanted to get some data out there and get some comments from the panel. When I was studying postherpetic patients back 2000-2010, publishing a lot on the capsaicin response test, patients who had long-standing postherpetic neuralgia of what we were calling the allodynic type, very exquisitely sensitive to touch, if you kept touching them -- so temporal repeated stimulation -- the area of pain would just get bigger and bigger and bigger, and become more and more excruciating.

You put capsaicin, just over-the-counter capsaicin, on a small square of skin, it would greatly aggravate their pain. So then when we looked at a cohort of acute zoster patients and followed them, some up to 8 years, as they got better, once their capsaicin response normalized,

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meaning it felt like it did in contralateral, unaffected skin, they were basically out of the woods. They no longer had pain, and their pain ever came back again.

So the question is how would you take a very crude but easy to administer test like that and use it to distinguish between central and peripheral sensitization? Could that even be done? How would you modify it?

DR. FIELDS: That's a great idea. I think one of the ways that occurred to me -- and I was thinking about that last night -- that what you could do is you could look at the time course of the expansion of the allodynic area outside the site where you injected the capsaicin.

DR. ROWBOTHAM: This is topical.

DR. FIELDS: Yes.

DR. ROWBOTHAM: It's over-the-counter cream.

DR. FIELDS: Or you could do a capsaicin injection and look at the spread. Albeit the intensity of the allodynia, there will be an extent of the allodynia. That has to be central because

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it's outside the area where you injected the capsaicin, so the fibers in that area won't be directly affected.

Plus, since they're low-threshold mechanoreceptors, they don't express the capsaicin, the vanilloid receptor. So they're not going to be activated; they don't get sensitized. So there, at least in normal skin, you have a measure of central sensitization, whatever the mechanism. That could distinguish between patients with widespread pain or not. It could distinguish between males and females, so you have a lot of data, and you can use that test as a way to evaluate drugs because they could reduce the spread of the allodynia, the extent of the allodynia.

So it seems like it might be a great way to get preliminary data on drugs, the extent to which they affect the capsaicin pain itself versus the spreading pain.

DR. MARKMAN: We can even ask that question now, potentially, because patients are receiving --

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DR. WOOLF: Just to ask, as part of your studies, you differentiated the irritable nociceptor group from those -- so how did they fall within the spectrum? Did those who were non-irritable, did they respond with the --

DR. ROWBOTHAM: It didn't bother them. It didn't provoke their pain. Some were so deafferented, they barely even felt it, whereas the other ones, what we call the irritableness receptor subtype, it didn't take very long before -- because it was just topical, so it wasn't a sudden all or none phenomenon like when you do injection. It would just build up, and it wouldn't take very many minutes before they would start modest sensations, and then the area of pain would start to expand.

So there's definitely a central component because we could make the area of touch-evoked pain expand into a very, very large extent with this test, in many inches, actually, outside the area where we'd applied it.

DR. MARKMAN: Do you think putting on an 8 percent high-dose capsaicin patch on a patient

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with postherpetic neuralgia -- where obviously in clinical practice, many of us do that. Some patients sit there and read the New Yorker calmly with no spike in their blood pressure, and other patients are weeping and need everything, including an epidural, potentially.

DR. ROWBOTHAM: When those studies were done, they weren't doing that kind of profiling, I don't think.

DR. MARKMAN: But in clinical practice now, we see -- I'm just wondering, we have an opportunity now to ask that question. We have patients every day, all around the country, who are getting high-dose capsaicin patches, who've had previous bouts of zoster. So perhaps there may be an opportunity to actually ask that question in a regular -- even in a clinical setting.

DR. ROWBOTHAM: It's an easy test to do. It's a little scary in the sense that once it starts -- I mean, you can ice the area down, you can remove the capsaicin, and you can do those other things. You could even inject local

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anesthetic, but you don't really have a way of completely turning it off. I mean, it is a provocative test that can be quite painful and in some patients.

DR. MARKMAN: Joachim?

DR. SCHOLZ: Could the panel comment on assay validation? The measures that you discussed here, temporal summation, the capsaicin test, and all those phenotypical measures, how would you determine that they truly reflect central sensitization? Are you assuming that in a patient with chronic pain, if they correlate with the existence of this chronic pain, that's enough; that's demonstration of central sensitization?

How do you separate from other mechanisms of pain? And within central sensitization, if you used a broad definition, how do you separate from the increase in the excitatory pathway from the lack of inhibition in a clinical context? What would be a path forward? Because otherwise, we have no way of assessing sensitivity and specificity of these assays. Then working at Biogen, it becomes

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useless in terms of proof of concept.

DR. MARKMAN: Rob, is CPM the answer to that?

DR. EDWARDS: Probably not, but it might be one component of a multimodal answer. That is also a terrific question, and I am doubtful I'll have any sort of definitive answer, and in fact I'll wind up deferring to my basic science colleagues on the panel who will know better.

It seems pretty clear that we won't, for example, be recording from wide dynamic range neurons in the dorsal horn in humans anytime soon. But even if we did, would we really be able to distinguish between -- let's call it differences between bottom-up sensitization and top-down effects?

So if we were trying to, in humans, determine whether temporal summation really is a perfect analog of wind-up in animal models, we would have to record from those WDR neurons, and I think we'd have to exclude the possibility of top-down influences, correct? And we're probably

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not spinalizing people either, I would guess for the purposes of doing that.

I have trouble wrapping my head around how it would be possible to even come close to meeting the standard of perfectly precisely identifying those mechanisms, underpinning, things like CPM and temporal summation in humans. I think it can't be done. Even if fMRI gives us a little bit of insight into what the brain is doing, the spinal cord in humans is going to be a little bit of a black box in most of these questions.

So I wonder if I might eventually be able to talk you into adopting a different and perhaps less stringent standard for considering some valid measure of an important phenotypic characteristic of patients.

DR. FIELDS: Can I add to that?

DR. MARKMAN: Yes.

DR. FIELDS: I'll put on my basic science hat. One thing we might be able to do -- and I don't know the literature. Maybe Clifford knows some current stuff, but you could, say, a capsaicin

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application on one arm, and then look at pressure pain thresholds or continuous thresholds on the contralateral leg and see if you have a lowering of threshold or if you have an enhancement of, let's say, wind-up on the contralateral side. Then it seems to me that it's peripheral -- I mean, it's a central effect, and it reflects at least one form of sensitization.

I kind of don't like the general term, "sensitization." I like the specific term that refers to a specific synapse of the dorsal or ganglion cell on to the second order of cell in the dorsal horn.

We know, for example, that if you block all the myelinated fibers in your arm with a blood pressure cuff, and even light touch produces burning pain, and you get much greater spread of sensation from the sight of stimulation, and that happens immediately with no increase in glutumate transmission, all it is a removal of some sort of large cyber inhibitory effect, is that sensitization?

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I don't know, but it would come under the global sensitization. Loss of gabaergic neurons in the dorsal horn, that would come under the general term "sensitization." I kind of like the term "amplification" a little bit better as a general term than sensitization to do specifically with the enhancement of transmission between the primary afferent and the second-order neuron.

DR. BRUEHL: I'll kind of piggyback here on this conversation here. Cutting across the talks in the first part of today, one of the things that I think about is Clifford's talk seems quite clear that that true central sensitization happens after something that causes nociceptive input. It's a response to something. It's an adaptation to that.

But we look more broadly in the humans and these supposed markers like temporal summation, which are supposed to be tapping into the same thing, are correlated with catastrophizing, and depression, and these other things. And you look at other literature, and it shows prospectively that depression and catastrophizing predicts onset

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of new chronic pain, which to me suggests if it's a sensitization of some kind, it's a preexisting sensitization.

Maybe this is back to the top-down/bottom-up idea, but it seems like you've got some people that may be predisposed to a sensitizing response and other people have that as a reaction to an insult. I think if we're trying to assess that, it'd be really important to make sure we have measures of both of those aspects, although I'm not sure exactly which those would be.

DR. MARKMAN: Is CRPS-1 a natural vehicle to ask these questions in, given the lack of clarity about a peripheral insult, or no?

DR. BRUEHL: I don't know the answer to that. It's too complex. It's a messy condition. I don't know if that would be ideal.

DR. MARKMAN: Does anyone have a response?

DR. FIELDS: CRPS-1 includes a condition that used to be known as reflex sympathetic dystrophy, which was easily diagnosed and had objective changes in the periphery, including

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osteoporosis, swelling, and changes in sweating. CRPS-1 includes that if it doesn't get better, plus a whole lot of other things.

As a neurologist, I'm much more of a splitter than I am a lumper. I'd rather look for subcategories and figure out what's the underlying biology and group conditions together that might have different causes and different underlying mechanisms. I feel like if you do that, you're kind of setting yourself up to fail in clinical trials.

DR. BRUEHL: You're saying if you lump --

DR. FIELDS: If you're a lumper, yes.

DR. BRUEHL: That is potentially what we're doing with the broad terminology of somatic amplification and central sensitization if it's two entirely different processes that we're lumping together.

DR. FIELDS: That's kind of what I'm saying, yes.

DR. MARKMAN: If you could react to that, that would be great.

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DR. WOOLF: I think to go to Joachim's point about how to get sensitivity and specificity in the assays, I don't think we vary [indiscernible], whether provocative or whether as part of our -- I think it comes back to Simon's question as well of how to phenotype patients and which measurements are going to have that sensitivity and specificity to reflect the presence of disinhibition versus increased excitation.

I think we've got to actively explore that. I think there's been too much reliance on very crude measures such as temporal summation of heat, yes, which wind up as present, but, boy, it's only a tiny component of the full range of synaptic plasticity that occurs, and it's very temporary. So it may capture some elements, but there are almost certain -- you mentioned putting on the cuff and now getting pain in response to activation of low threshold C fibers. Putting on the cuff also eliminates tactile allodynia in patients with neuropathic pain, so there are two sets of inflammation you can get from that.

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So I'm completely with you avoiding the lumping. We've got to try and distinguish what are the specificities of the pain that is present.

DR. MARKMAN: I think what I'm hearing you say is that sort of a PRO only or PRO driven methodology is not going to have the horsepower to get us where we want to go in terms of this sort of sensitivity and specificity of different mechanisms.

Dan, I just would like you to react to that because I feel like with the studies that you've done, especially in the perioperative period and other windows, I feel like what I hear is that the PRO methodology actually gets you 80 or 90 percent of the way there. So I think one of the challenges is we have to reconcile those two points of view, unless I'm misinterpreting those studies.

DR. CLAUW: No. I think that the PRO method is as good as it gets right now. I think that the studies that are likely to be funded as part of the HEAL initiative, the backpack HEAL initiative, the low back pain studies where people, you do

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basically everything to them. You do all the omics, you do imaging, you do QST, and then you expose them to a series of different treatments with underlying mechanisms of action and look at them longitudinally.

That will start to allow us to separate the wheat from the chaff here. But I still think that even right now, this widespread pain and non-widespread pain thing has worked in a lot of different studies of analgesics. So I don't think that we shouldn't use that waiting for a better more granular way.

There's probably a hundred different central mechanisms that can cause central sensitization. I think of central sensitization as a term like hypertension, which doesn't in any way tell me how someone got there. It just tells me sort of like a final common pathway. But I'm okay with at first just being able to measure someone's blood pressure before I figure out is that a kidney problem, is that a cardiac problem, is that a brain problem.

All the different ways someone can get to a

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final common pathway of hypertension, that's going to take another couple of decades. But I think that right now with PROs, we can in a very crude way say this looks to be a more centrally driven process because the people that have more widespread pain respond better to it, or this looks at the other end of the continuum. I don't think we shouldn't start now doing this with what we have available.

DR. SCHOLZ: The risk is that we measure increased pain sensitivity, not central sensitization, just to rule out, to some extent, the peripheral mechanism. Would that be satisfying to the FDA if it considers a label for central sensitization? Because that's not the original definition of central sensitization, right? It was a specific mechanism.

DR. HERTZ: I'm not answering that.

DR. SCHOLZ: I did not expect it. I just wanted to point it out that the way we define it and the way we operationalize it has implications, obviously, on the development of treatments.

DR. EDWARDS: Can I just follow up on that

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for one second? I'll make it quick, although perhaps I should take a page out of Sharon's and Bob Mueller's playbook --

(Laughter.)

DR. EDWARDS: -- and Todd and others playbook and have no comment more often. It's way too late.

I want to follow up because I'm really enjoying mentally chewing over Joachim's good question about separating peripheral from central sensitization and Howard's very nice response, which involved a theoretical experiment where you apply capsaicin, topical or injected, intradermal capsaicin, to the left arm, and then you measure I think the right leg, temporal summation or some equivalent of that.

I think if I were so inclined, I could cite some literature suggesting that any noxious stimulus you apply produces a physiological stress response that has manifestations in the periphery, and I could site some very specific literature that suggests that capsaicin application is associated

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with a quick and brief systemic inflammatory response.

I don't actually know the time course of that, but I know it happens pretty quickly and goes away pretty quickly. But I could use that, I think, to argue -- I don't know if it would be perfectly persuasive, but I could use that to argue that any changes you see subsequent to that intradermal capsaicin on the left arm are all peripheral in nature and driven by a stress response or a circulating inflammatory response, and that's the reason you get the increase in temporal summation or wind-up.

I wouldn't personally believe that, although I'm perfectly willing to argue things that I don't believe if it seems like fun.

DR. FIELDS: You've done that repeatedly.

DR. EDWARDS: I have. So that's part of why I say I wonder if it might be an unfair standard. And this is just going to sound like special pleading coming from a psychologist, but it might be possible that we can't ever a hundred percent

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precisely separate central from peripheral sensitization, and it might just be that we wind up having to live with some degree of that uncertainty and adopt measures that we can't characterize precisely but that we find are predictive on the basis of empirical data.

DR. MARKMAN: John, and then Jim, and then --

DR. FARRAR: Seeing that the time is getting a little bit later, I wanted to switch gears just a little bit, but not too far, which is that from my perspective, any place in the nervous system where there's a synapse, there's the potential for feedback loops and an effect on the threshold which the firing will take place. Most of those occur north of the peripheral nervous system. One could argue all of them do, but I'm having it open if people want to argue something else. The point I'm trying to make is that, clearly, this is a very complicated system.

Rob, what you presented, you talked about catastrophizing, and I asked you the question about

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where is catastrophizing. It seems to me reasonable, in what we've heard today, to differentiate between a upregulation, an activation, a sensitization, whichever term you like, of the connections in the brain that monitor and do something about pain, which I think leads to the widespreadness and the other things that we're talking about, and, if you like, the super cortical, the cortical phenomenon that then impact that in terms of depression, catastrophizing, et cetera.

To get at what Sharon was discussing before, that in order to get approval for or to think about even, in experimental settings, drugs that might affect this process, whatever it is, we need to have a measure that somehow gets at that, and that is not going to be overly responsive to some of the things that we're not interested in.

So this question is for both you and Dan, which is, with the fibromyalgianess, if you would treat a fibromyalgia patient who's severely depressed, my guess is that their overall pain and

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symptoms get better. Maybe they don't go away. Maybe they still have widespreadness. But if I'm doing a clinical trial, and even if I'm measuring those things, it's going to get very messy in terms of trying to differentiate the effect of the change in mood, and depression, and catastrophizing, and other pieces, to the actual changes to that central pain processing center or units, and I wonder what your thoughts are.

DR. EDWARDS: I'm not at liberty to respond to that question, and I defer to Dan.

DR. CLAUW: I'm going to use the Sharon-Bob Mueller answer --

(Laughter.)

DR. CLAUW: -- the "I work in D.C." answer. I guess I could try to answer it. No, I don't even want to try to answer it.

DR. FARRAR: Let me ask you differently. If patients get treated for depression, does their score on the fibromyalgianess questionnaire, that you use widely, change?

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DR. CLAUW: In some cases when you treat people's depression, their pain gets better, and I think there's more evidence for the converse. Because again, we have better interventions like knee arthroplasty and biologics in RA that can make pain better in a subset of people very rapidly. We don't have drugs that make depression better so rapidly, except ketamine or something like that.

I think there's a lot of evidence that making people's pain better makes their depression and their catastrophizing better, and there's some evidence that making their depression or catastrophizing better makes their pain better. There's no question these are bidirectional, but I actually think that if you look longitudinally in the course of the life of a pain patient, I think that, in many instances, the pain comes first, and a lot of these other things sort of pile on afterwards.

I think in those individuals, treating their mood disorder, in my clinical experience, hasn't been as likely to make their pain better because a

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lot of these other things have occurred as a consequence of their pain, and I'm going to try to target making their pain better.

DR. HERTZ: What's interesting, though, is when you look at some of these patients, let's take fibromyalgia with a fairly high frequency of comorbid depression, what are you going to treat them with? An antidepressant. So it gets even more complicated because you may not be able to establish what can you do first. You may not be able to establish what's being treated. All you know is at the end of the day, they're getting better.

One of the things we did with one of the drugs was we asked them to specifically look at responses with and without depression to see if it was really more a matter of treating the depression. In that particular case, it wasn't, but sometimes it's very hard to tease that out.

DR. CLAUW: But I think that is true. The two classes of drugs we use most commonly that are both antidepressants and analgesics, tricyclics and

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SNRIs, have in general not shown that the presence of depression makes someone more likely to respond to that drug as an analgesic.

That's why I made the statement that I made, is that I don't think there's as much evidence for treating depression and making pain better as there is for the converse. Although again, of course it's important. Of course if a chronic pain patient is depressed, they're anxious, or catastrophizing, I think that needs to be addressed. But again, I think that the clinical trial data are pretty clear with tricyclics and SNRIs that it's not the case that you're treating subclinical depression, and that somehow is circling back to make the pain better. These are directly analgesics.

(Crosstalk.)

DR. MARKMAN: I think maybe [indiscernible] an attempt to design those trials, though, to show their analgesic benefit. Just to make the point the trials with the tricyclics, what I think the attempt was in the design was to discern their

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analgesic benefit from their antidepressant benefit. Again, the fact it didn't show that may just be a function of how they were set up and designed.

DR. WOOLF: Something I think we need to keep in mind -- we're talking here about depression and pain, but comorbidity has been a big feature of the discussion, but sometimes they may be mechanistically linked. We recently had a study on sleep deprivation, which was discussed, and we found that if you start off with a healthy mouse and you deprive it of sleep by just letting it play with toys over the night every time the EEG indicates it's about to fall asleep, after 5 days, the animal has heightened pain sensitivity and a reduced response to standard analgesics.

So that is part of the link between the two, as you've kept on saying, and we perhaps should not artificially separate them because they are part of the same package.

DR. MARKMAN: We're in the final 5 minutes, so I just want to let Jim and Ian ask their

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question.

DR. RATHMELL: Jim Rathmell. Not to beat it too death, but as a clinician, the idea that you're going to be able to clinically, even in the context of a very carefully constructed trial, differentiate peripheral from central sensitization, it doesn't seem, to me, to matter that much.

What I want to know is -- mechanistically, it matters a lot, but at the bedside, if you've got a patient with either chronic widespread pain or heightened pain sensitivity on testing, those are the things that probably allow you to lump them easily at the bedside, and it's hard to get that underlying mechanism. So be pragmatic as we come up with what is the paradigm that we're going to test.

DR. GILRON: I've been following the peripheral/central discussion, and I'm just wondering if there's a need to distinguish between sensitization as a facilitative state or condition and the presence and location of the pain

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generator.

Is there actually a source of ongoing nociception versus -- well, I don't know, someone who's purely fibromyalgia 100 percent and apparently has no source of nociception, or osteoarthritis, or anything, as sort of a separate beast to someone who had shingles or has diabetic neuropathy and happens to have pain or the OA situation?

DR. MARKMAN: I'm not sure what the question was, Ian.

DR. GILRON: Okay. If we were going to define an inclusion criterion, do we want to exclude people who have -- I mean, you can have OA of your shoulder, and gout in your toe, and low back pain, so you've got chronic widespread pain, but you've got a pain generator in those situations. Would that person fit into a clinical trial of central sensitization?

DR. CLAUW: Well, I think they were put in all the trials of fibromyalgia patients because if you look at the average age of the fibromyalgia

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patients in the registration trials, they were 50-ish. Almost certainly, a lot of those people had some incident OA, and myofascial pain, and things like that; it's hard to imagine they wouldn't have.

So I think that the registration trials that were done in fibromyalgia were probably not done in pure -- because although all those trials did exclude like rheumatoid arthritis, and lupus, and things like that -- and they may have said we exclude OA -- they were never screening for away and really excluding OA because there probably would be no one in the trial.

So I think that those trials did end up including a bit of a mix. I think the people had to have widespread pain, but many of them probably had something above and beyond that. But maybe that would account for that the average effect would be better if we could look at the people who don't have those peripheral drivers, and thus, don't respond to a pure peripheral therapy.

DR. FIELDS: I just wanted to say there's

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really good animal evidence that supports what Dan kind of said earlier about depression seeming to respond to the treatment of pain. More often, the treatment of depression helps with the pain. One of the measures that people are using consistently in animal models of chronic pain is the allodynia, which is a feature of depression. So I feel like the animal literature is consistent with that clinical observation.

DR. KATZ: I might have missed this earlier, but I've heard that there are some people who have a lifelong history of central sensitization. They've got migraine, and irritable bowel, and bad menstrual cramps or whatever for years or decades before they show up. Then I've heard that there are other people who are seemingly normal, and they show up, and if you give them some kind of noxious stimulus like say an arthritic knee or a surgical stimulus, then they react with this rush of central sensitization.

Do we know whether those are the same people or different people?

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DR. CLAUW: No, we don't because, again, what you would need is long-term longitudinal studies from people when they're in their childhood to adulthood. The long-term longitudinal studies in the United States have not generally included any useful pain outcomes, other than just like a pain score, but nothing that we would need to in any way unpack or dissociate -- other than OPPERA, but again that wasn't -- I'm now talking about NHANES and some of the other longitudinal studies.

OPPERA I think was the only exception to that rule, that it was epidemiologically derived cohorts. They were more population based. They followed them longitudinally. And they did look at a lot of things, and it was a really great exercise in identifying the things that were strongly associated versus were not. But I think that's about all we have. We don't have that in the general population.

DR. KATZ: You could also imagine, in one of these many experimental studies that you've heard, where somebody shows up and they get intradermal

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capsaicin or what-have-you, and you separate the ones with this massive central sensitization response versus ones that don't, to just ask them about their life history.

Wouldn't that be another way of getting at that? It surprises me that that has not been done. Has it not?

DR. CLAUW: You do. We often do. We're asking people about a history of pain. We're asking about cumulative trauma and giving them a questionnaire to try to get a trauma. But people's ability to retrospectively report these kinds of things is pretty abysmal. If you don't collect it prospectively, the veracity of the data are really suspect.

We did a study with John Warren in interstitial cystitis where we thought we had an inception cohort of 300 women who had new interstitial cystitis, and we published 6 papers on it before we went back and got their medical records, and found that 40 percent, we found their medical records had a clear case before that, or

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several cases; that they just forgot.

They didn't remember that they presented, and it was diagnosed as an UTI, but if you looked at the records you saw -- and I think that this is a big problem when we study the transition from acute to chronic pain because a lot of those people that we say are pain free, they didn't have pain at the time we put them in the study, but they had dysmenorrhea and all this other stuff over the course of their lifetime, and we haven't historically done a good job of tracking that, and then looking at how it predicts differential outcomes.

DR. KATZ: The reason why I asked, or one reason why I asked, is that if there's more than one phenotype that we're talking about here, if it's the people with lifelong central sensitization versus the people that just have it now, then if we're going to put together some kind of battery to phenotype these patients, then it's going to have to somehow try to sort out whether they have a lifetime history of central sensitization or not.

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DR. MARKMAN: That's great.
Well, good. I want to thank the speakers and Dr. Fields. It was a great session. Thank you all.
(Applause.)
DR. TURK: That was a great session, and I want to thank John Markman for being the moderator all morning and into that session. We're now going to be switching to another moderator, so you can get the chance for John to relax. The next moderator is going to be Ajay Wasan from the University of Pittsburgh. Ajay is going to basically be the introducer of the speakers, as well as the moderator of the session.
Ajay, you're up.
DR. WASAN: Thanks, everyone. That was a lively session. I'm not as witty as Dr. Markman, so I want to set the expectations a little lower for the quality of the wit and the insightful questions that may come from me. Secondly, as a psychiatrist, I'm more of a lumper.
My only reaction to some of Dan's comments,

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which are wonderful, is that there actually is a pretty good substantial literature in patients with pain and depression, that if you only treat their depression, both their depression and pain get better. Probably Lesley can chime in later about that as well, but that's just something to keep in mind as we're going forward.
Our first speaker's next session will be Dr. Kleykamp. She's a psychologist, and she's an associate professor at the University of Rochester. She is part of the ACTTION and IMMPACT brain trust, along with Shannon Smith and Jennifer Gewandter. What they do is they do a lot of the really important foundational work for all the different topics that we take on as a group.
So, Annie, please come up and glad to hear from you.
Presentation - Annie Kleykamp
DR. KLEYKAMP: Hi, everyone. Thank you for that introduction. I joined ACTTION full-time last year, and today I'll be talking with you about a systematic review that we've worked on this year

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focused on fibromyalgia and temporomandibular disorders. I have to say my background is in addiction. This is my first chronic pain meeting, so I'm learning a lot.
What I'm bringing to the table is my experience with conducting systematic reviews. But I say all that because I was very naive going into this review. I know a little bit about fibromyalgia only through anecdotal stories, family members diagnosed. I didn't know much. I thought, this is a very clear concrete topic, and generally, I haven't dealt with epidemiology; I like this idea. Then as we dug in, and as I'm learning today, the complexity of these disorders really played out in the literature.
So my goal was to give you all really clear prevalence and incidence estimates at the end of this presentation for each of these comorbidities, chronic pain and psychiatric in these index disorders, and I don't feel comfortable doing that. You'll learn about that and what is out there, the challenges and actually trying to group it, and how

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we can move forward with that.
I mentioned I'm with ACTTION, and just wanted to point out that I was with a consulting firm in Bethesda for about four years before I started at ACTTION. We did have clients in the pharmaceutical industry, and I worked on harm reduction in e-cigarettes. None of that work is related to what I'll talk about today.
Everybody in the room has already heard a lot about these index disorders. These are what we focused on for our review, and we used only those studies that had a clear criteria-based diagnosis for these disorders. And that comes up again and again because there's a lot of literature out there where it's either self-report or documented in a chart, but not necessarily using these criteria.
I know and I'm learning they've evolved very much since the 90s, and that's another issue that we ran into because the literature we ended up collecting spans '90s through the present, and the diagnostic criteria were evolving during that time, which can impact prevalence estimates.

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Generally speaking, what I saw in the literature are varied estimates of fibromyalgia, as you might imagine, sometimes well above 11 percent, depending on the sample, just showing it's hard to get that general estimate. Similar with temporomandibular disorders -- I did want to point out this paper, and I don't think anyone's brought it up -- Wolfe and colleagues noted that although we've considered fibromyalgia a really female or women focused disorder, they did a study in Germany looking at rheumatoid arthritis patients and determined that depending on how you sampled, you actually get a much greater number of men diagnosed with fibromyalgia than previously thought, which adds to the challenges in this review, because I'd say most of the studies we located were women only or majority women.

Just to bring it back to the main topic of today, central sensitization, fibromyalgia and temporomandibular disorders, lying among many of those that we'll talk about, we had to narrow this systematic review, or I would have never finished

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it. So we focused on these two. It was new to me to learn that they, too, are related.

Why do this? Why is an effort like this -- it took us many hours. Ewan and McKenzie, I'll point them out at the end of the talk so you can direct the really difficult questions their way. But three of us dug into this months and months of trying to figure out how do you best estimate these comorbidities and how you look at them in the literature. But it's important given that, as we've discussed, these comorbidities -- depression, psychiatric, all of these things -- can influence patient's symptoms. Their report of pain and quality of life also can very much inform the diagnosis of the index disorder, can allow us to talk about mechanisms, piece apart better what's going on, and refine treatments.

Two main goals give you an overview. What's out there? So we ask ourselves what's been published on these comorbidities in these index disorders and can we give you estimates of

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incidence and prevalence? We registered our systematic review in PROSPERO. We set forward with ambitious search strategy. We had three databases. We completed that in late April with the guidance of a librarian. Inclusion criteria, like I mentioned, we focused on those studies that used ACR, RDC, or DC. I'm learning as these evolve, the acronyms.

An important distinction as far as psychiatric comorbid outcomes. We only focused on the buckets of data related to mood, anxiety, and personality disorders, so we didn't look at substance use and schizophrenia. We also only included those studies that diagnosed these psychiatric disorders using a structured interview by a trained professional and a standardized assessment tool, which was most often the DSM.

I cite this study here. I unfortunately don't know how to pronounce the last name, but they did a really interesting analysis where they pulled apart depression in fibromyalgia patients and looked at rates of depression when it was

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self-reported versus when it was expert diagnosed. As you might imagine, self-reported rates of depression were much higher in fibromyalgia patients compared to expert guided.

What that means, it could of course be a reporting bias. The point from that paper was to lean more towards more structured ways to diagnose these psychiatric outcomes in studies looking at comorbidities, so that's what we did.

Our initial search -- sorry this is so small -- 806 articles were retrieved from that. I found another 49 looking at reference lists. So we had 683 after duplicates were removed, just meaning same article pulled from separate databases. We did a title and abstract review and excluded a bunch more, and we arrived at 169. We did a full-text review. You'll see here 125 were excluded at that stage, which is a pretty high number, and I'll go on the next slide into details on that.

Our final count, if I pull you down to the very bottom, are 41 studies. We did have 6 studies

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that overlapped, so they had been published in separate journals but reported on the exact same data and patient sample, so I combined all those. I didn't want redundancy there.

We did have two studies that looked at fibromyalgia and temporomandibular disorder patients in the same study and did head to head comparisons, so they counted as two studies even though they were only one citation. The main point there is if you try to sum across a lot of my slides with the counts, you can drive yourself mad because the counts don't always add up because there's a lot of multiple findings in each study.

Like I said, we had a lot of excluded studies. The main reason I would say, 75 percent of studies, were that the diagnostic criteria for our psychiatric disorders and for our index disorders, they didn't meet what we required. I do want to point out for chronic pain comorbidities, we had no restrictions on that except that they had to be chronic pain, but we didn't require that they had to be assessed a certain way. We tried to keep

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those requirements liberal.

Most 47 of these were excluded due to self-report psychiatric disorders or survey instruments that weren't standardized or administered by a trained professional; 33, fibromyalgia wasn't diagnosed using criteria as specified, and then 15 for TMD. If you go on down, these next two bullets mainly just didn't meet our really broad criteria, so they didn't present data on prevalence or incidence, and it wasn't a research study, and so on.

There was one study we identified I cited here that specifically noted that the TMD patients they are looking at, it was the acute phase. I wanted to flag that because it was very helpful and important. I am learning about this shift from acute to chronic pain, but that definitely, if that hadn't been specified, is a way that our results when reporting them in a systematic review can get a little messy because then the patients aren't exactly consistent if they are in an acute phase, so we excluded that.

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We had 41 studies like I said. Although we were looking for cohort studies that were trying to specify incidence, we didn't locate any published studies that reported on incidence of these comorbidities in the index disorders, so all studies' report on prevalence were cross-sectional. Publication years, I mentioned the '90s to the present, so '92 to 2018. Most studies were in the U.S. and Italy, and scattered throughout some other countries.

Consistently, patients or participants were recruited from outpatient clinic settings using convenience sampling, and a subset, so I'm categorizing consecutive sampling as a type of convenience sampling here. So they were a subset that just as patients came in, they recruited. We'll talk a little bit about that once I show the figures how that can isolate the findings to various specific patient populations and possibly contribute to bias in estimating prevalence.

Sample sizes, a really wide range, a very small sample, 22 up 70 some thousand. However, the

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median was 100, so rather small. Mean participant age, as you might imagine, middle age, this didn't differ between the temporomandibular disorder studies and fibromyalgia, which I'll break down further on the next slide.

Most studies were majority women, so over 50 percent I'd say it was rare -- there was only one study that had more men, and nearly half of the studies included only women. So this was definitely a female dominated population of studies. Disease duration was most often reported for fibromyalgia, not for temporomandibular disorders. However, when reported, they were about the same with a median of a little over 7 years.

Because there are so many buckets of data, I've tried to use some parallel construction on this slide and our figures so I don't lose you as I present. What we've got here is 4 main categories of the data. This sort of maps on to, you've got fibromyalgia and temporomandibular disorders on the left, so we ended up including 37 studies that focused on fibromyalgia and only 10 with TMD, and

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then our comorbid disorders, and we had about an equal split there.

So what I'm going to do is show you findings starting in the upper left with the chronic pain fibromyalgia studies and move through there. I'll try to do this each time so I don't lose you. I found myself getting confused just giving this presentation, so slow me down if talk to fast here, please.

Lifetime and current prevalence were reported in different studies, so I'll always start with lifetime prevalence. For fibromyalgia and chronic pain, there were 4 studies. So what you see on the Y-axis are the different types of chronic pain comorbidities that we identified. These were dictated by the literature, so we weren't specifically looking for, say, interstitial cystitis. We would just let the research dictate that.

Then you have the bars representing percentage, so prevalence there. And you'll notice these, if you can see them, the black bolded

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numbers at the end of each bar. Those are cases or counts that correspond to that percentage. I wanted to give you a sense of the sample size of some of these studies. For example, for this lower back comorbidity, the purple bar, it's getting up close to 70 percent of that population, but there were only 14 of those people in that study.

What you see here, I'll give you a brief idea, and I'll try to summarize it. But we haven't used any quantitative statistics to combine these. In fact, everything I'll do is narrative or descriptive today. But the idea is to show you it's very difficult to combine these findings, especially when you only have four studies represented across all these bars. So what that means is it was often the case that one study would look at migraine, irritable bowel syndrome, lower back pain, and TMD.

So only four studies are represented across here. You get some outliers. Irritable bowel syndrome was often measured in these studies, and you see those are hovering around lifetime 50.

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Here's current prevalence. More studies measured current prevalence, and this is, again, fibromyalgia and chronic pain. What I noted here was TMD, or temporomandibular disorders, were rather high in two of the studies. You have multiple studies looking at an irritable bowel but not necessarily consistently finding things and also quite variable in the number of participants.

I've tried to group at the top the head related pain, analgesic overuse, trauma related, or all headache type pains. U There was one study that measured multiple types of headaches in the same sample of participants, so you also get that type of bias.

To walk you down to the next one, here we have 9 studies that looked at chronic pain in TMD. Again, if you try to sum across, as I present each slide, it doesn't necessarily equal the 13 or 9 because some studies reported current and lifetime prevalence; just so you don't drive yourself mad in that regard. Only two studies looked at lifetime prevalence of chronic pain comorbidities in TMD.

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I think the most obvious thing was that the percentages were much lower. The prevalence was considerably lower than fibromyalgia, but, again, there could be multiple reasons for that, not necessarily the true existence of those comorbidities. For example, is it true that fibromyalgia patients tend to over-report certain health conditions, or maybe they're seeking out health care more than this population. Here, we have current prevalence for TMD and chronic pain, a few more studies.

I was surprised I didn't see more headache related assessments there. I guess the main finding I saw on here is, if you remember, current prevalence in fibromyalgia and chronic pain, these blue bars at the bottom represented TMD, and they were up near 80. You're just not seeing that same -- but only in two studies -- increased prevalence of fibromyalgia in TMD patients.

Next, is the most common comorbid morbid disorder assessed, and that's in fibromyalgia studies. This one gets even more complicated.

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Because there were so many, I've split anxiety disorders separate from mood disorders. There was one personality finding, and I just realized I didn't include it on the slides, but, actually, there was only one study that looked at personality disorders, so I've only focused on anxiety and mood disorders.

Here we've got fibromyalgia and anxiety and lifetime prevalence, 10 studies. At the top, we start with different types of phobias in the purple, going down to lighter. Then you've got obsessive compulsive disorder, panic disorder, all the way down to generalized anxiety disorder. Sometimes titles change depending on the studies.

On the next slide, you'll see a whole category of studies that just labeled it anxiety. It's not even clear if this was generalized anxiety disorder. One other thing I'd like to point out making this challenging is PTSD in the most recent revision to the DSM got moved out of anxiety disorders into a separate category. I still included it because there was a lot of talk, at

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least in the background of these papers, the role of PTSD in fibromyalgia.

Many studies looking at panic disorder here. I don't feel confident making any conclusions from this. This is lifetime prevalence. It looks like panic disorder appears higher than others, but again, you're getting really small sample sizes of 12-20 in some of these studies. I was surprised to not see more studies looking at generalized anxiety.

This is what I'm mentioning, the red bars at the bottom, different types of anxiety, panic disorder. This is current prevalence. More studies looking at PTSD, that was one that stood out at me as a signal. But again, I didn't have a lot of confidence giving sample sizes of some of them.

I would say that -- I'll be showing you the mood disorders on the next slide, and I do those bars in blue. It was interesting how higher the prevalence was of these. Here you have lifetime prevalence of mood disorders, so major depressive

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disorder and general depression as labeled by the studies, and those are rather high compared to the other figures we've seen.

Now, whether or not, again -- and we've been talking about depression -- what's fueling this, including whether researchers -- maybe more studies are focusing on depression than other psychiatric disorders, we can't really say, but we can describe what's out there. So similarly, for current prevalence of mood disorders, you're getting higher levels or higher prevalence compared to anxiety.

There is a systematic review out looking at major depressive disorder. It's the one I cited earlier that was talking about self-report versus expert diagnosed depression. They do a meta-analysis and actually do suggest that there is an increased prevalence. We can talk about that, too.

One other surprised finding was that there were so few studies that were included that look at psychiatric outcomes in temporomandibular disorders, so I just broke this one down on one

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slide. This was published in 2007. The sample size was 63 and looked at current psychiatric comorbidities, from 17.5 percent for depression and a little lower for the others.

Basically, a quick snapshot of what I found before I dig into some lessons learned. All studies were cross-sectional. We only retrieved 41 that met criteria. They all included adult patients from outpatient clinics. Most included middle-aged women and most focused on fibromyalgia. Perhaps I'm not familiar with the funding situation, maybe that's a reason, or maybe it's just a fact that there's more people diagnosed with fibromyalgia. I'm not sure if that's true either, but it certainly is taking up more space in the published literature.

If forced, I felt bad coming here not telling you all some sort of prevalence summary. I looked and used my own criteria, so if there were at least two studies that we included for review with a prevalence estimate of over 30 -- I was being very generous here -- what could I give you

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as a take home? What we were seeing is IBS and TMD were most likely in fibromyalgia as chronic pain comorbidities, and depression and PTSD, but PTSD, a very limited number of studies. I would say double that for depression.

TMD, the best I could do is headache disorders, but there really weren't a lot of studies, and it makes sense given where TMD pain takes place, and of course there was only one study for psychiatric outcomes for TMD.

Where would we go from this? Obviously, I wouldn't feel confident giving someone these sides so they could cite in a paper the prevalence of this or make the argument confidently that there's a particular comorbidity more common in one index disorder or the other. But we know that it's very difficult to measure incidence in these chronic type conditions, so that isn't in the literature as we reviewed it.

Potential for selection bias, we've got small sample sizes. Patients were recruited through convenience sampling. They were already

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in, say, rheumatology clinics or pain clinics, so that self-selects them. This was a methodological trade-off, large sample population-based studies. I'll just say database studies that didn't specify diagnostic criteria were not included, but that could be a nice comparison in a review like this to see what type of information that gives us.

Like I said, all or majority of studies focused on women in fibromyalgia. I've noted the Wolfe paper, which is suggesting maybe we need to rethink this idea that women are the focus of fibromyalgia, and it may be arising from our bias and sampling and the way we determine prevalence.

Also, you can't deny that as we have gained understanding and as we're here today to try to understand these disorders so has diagnostic criteria evolved. I know ACTTION has a couple of working groups that have published specifically on fibromyalgia and TMD diagnostic criteria and really refining this process. Our literature span this whole time, so as those criteria were changing, it's certainly added error to how we estimate

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prevalence.

Another topic -- and we haven't talked a lot about it here. I am not that familiar with it, but we didn't include juvenile fibromyalgia, but I see in the literature that's a topic that's come up a lot, and almost a different beast, in a way, if we were to include them in the review.

Temporal order of co-occurring index in comorbid conditions is an obvious problem with cross-sectional studies, and it's coming up. We just talked about depression and fibromyalgia, and the idea of what contributes to what. Known relationships between comorbidity, so we know that anxiety and depression are more likely to be diagnosed in the same person, and that also influences their relationship with index disorders, so we can't ignore that.

I wanted to mention sleep. I heard it come up a couple times. This was another outcome or a comorbid issue that we were thinking about including. Our review is getting so large, we decided to leave it out, but a recent paper from a

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working group through ACTTION noted sleep issues are a key symptom of fibromyalgia.

I did try to see what's been done. There are two systematic reviews looking at sleep quality in populations like FM or TMD, but I have to say I didn't see sleep being measured very often. Of course, we weren't looking for it. It's not something I commonly saw. I guess it's a variable that's very important for all of these outcomes.

Well, special thanks to my co-reviewers, McKenzie and Ewan, thank you. Any questions?

(Applause.)

DR. WASAN: Thanks.

DR. KLEYKAMP: Are we waiting?

DR. WASAN: I think maybe in the interest of time, we'll do all the questions at the Q&A. Maybe that will help us make up a little bit of time. Next, we have one more speaker, and then we'll have a break, and then we'll have another speaker, and then a Q&A.

Our next speaker is Dr. Roger Fillingim, which almost all of us know here. He's done so

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much important work in actually most of everything we're talking about today, so he's going to be a great contributor here. As I said, we all know him well. He's a distinguished university professor at the University of Florida in the College of Dentistry. He's a pain psychologist by training, and he also is director of the Center for Pain Research and Intervention, Center of Excellence at the University of Florida within the College of Dentistry.

Roger, please go ahead.

Presentation - Roger Fillingim

DR. FILLINGIM: Great. Well, thanks, Ajay. I meant to talk about central sensitization and overlapping pain conditions, which is a bit daunting since I now realize we don't know what central sensitization is.

(Laughter.)

DR. FILLINGIM: I felt somehow like consensus would be more clarifying, but first let me just talk about the fact -- and we just heard about this nicely from Annie -- that pain

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conditions certainly overlap. Chris Veasley and the Chronic Pain Research Alliance has really moved this forward quite a bit. One thing I might bring up is osteoarthritis. We heard Dan talk about osteoarthritis a bit; I'll talk about it, and where that fits in with these other commonly overlapping pain conditions is not clear.

I'll show you some data from the OPPERA study. And that looks like I have 4 minutes left, so that's a little daunting as well.

(Laughter.)

DR. FILLINGIM: Here are some early data from the OPPERA study. We have a bunch of controls and a smaller number of TMD cases. What you see is the prevalence of 0 to 4 other idiopathic pain conditions in these two groups. If you have zero other pain conditions, your odds of TMD are 1 here, so that's a reference group. If you happen to have all four of the other overlapping pain conditions, you're 170 times more likely to also have TMD than if you have no overlapping pain conditions. So the presence of other pain conditions in this

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particular analysis increases the risks that you're also a TMD case.

Some more recent data that you may not be able to read, but this is from our OPPERA-2 study, and what you see are the index conditions in the bolded letters here. If we take fibromyalgia, for example, fibromyalgia right here on the upper, your left, the little cutout is the proportion of fibromyalgia cases who didn't have any other of the pain conditions, and the other pain conditions are headache, irritable bowel syndrome, low back pain, and TMD.

So 10 percent of fibromyalgia cases had fibromyalgia alone. The rest of them had some combination of these other conditions; whereas if you move over here to the right to headache, you see fully half essentially of the headache cases had headache alone and none of the other conditions. So that's an interesting way to look at this.

Then when you get the slides and can look at them in your own time, we have the different

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combinations that are available here. For fibromyalgia there, you see T, H, I, B, and F, that is a quarter of the fibromyalgia cases had all of the pain conditions, and then you can see the other combinations there. So this is a fairly detailed look at the overlap that occurs across these different pain conditions, and you can see it's quite substantial.

What does this have to do with central sensitization? Of course, we've heard very nicely from Clifford about what central sensitization is and where it came from. This quote from his 2011 paper, in which he summarized a lot of this work, says, "central sensitization is amplification of neural signaling within the CNS that elicits pain hypersensitivity." He identifies several clinical signs that we might see in patients that might reflect central sensitization.

We can also think about risk factors that are common to these sort of prototypical overlapping pain conditions, which include female sex. We've heard a lot about today widespread pain

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sensitivity, which is what I'm primarily talking about; psychological factors, somatic symptom burden, and familial and genetic factors. I note that one of these is pain sensitivity, and the others have been associated with pain sensitivity. So all of these risk factors might have a common link to central sensitization.

If we talk about sex for a moment, not only are females at greater risk for each of these conditions individually -- again, some more OPPERA data -- the female predominance increases as the number of overlapping pain conditions increases here. So you see that it's getting close to almost exclusively females who have essentially all of the overlapping pain conditions that we studied in OPPERA.

Family history, here we have the TMD bars. In purple, you see cases of TMD. The height of the bar reflects the proportion of those TMD cases who also report that they have a family history of TMD, and the same for headache, family history of headache. And in yellow, you see the proportion of

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cases who report no family history of that particular index condition, and you can see that for everything, except for, surprisingly, low back pain here. There's a strong, at least self-reported, familial history of that particular condition.

What about psychological factors? We've heard quite a bit about this. These again are OPPERA data, and the text is intentionally small enough to where you can't make anything out of it. But the heat map here, the darker the shade of orange would be a stronger association of, for example, TMD in the first column with that particular psychological measure.

The first two psychological measures are measures of somatic symptoms, and you see that they seem to be more strongly associated with each of the index pain conditions, particularly for fibromyalgia, low back pain, and TMD.

Then as you go down, you see there are some weaker associations. There are coping strategies at the bottom. Catastrophizing is in the middle

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and so on and so forth. But you don't see so much a smoking gun; that is this psychological factor is associated with this pain condition, whereas this other psychological factor is associated with this other pain condition.

The psychological factors maybe to some degree are agnostic to the pain condition, and you see that the strongest associations between psychological factors and any of the pain conditions seem to occur around somatic symptoms, at least of the psychological factors we've studied in OPPERA.

Maybe a little more impressive is this heat map, which shows the association of the same psychological factors with the number of pain conditions somebody is reporting, and the comparison here is always to people who don't have any of the pain conditions. So the further right you go, the darker colors indicate a stronger association of that psychological factor with more idiopathic pain conditions.

The message here is very straightforward;

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that is the more idiopathic pain conditions you have, the stronger the psychological burden or the association with psychological symptoms, maybe not terribly surprising.

So for another ACTTION initiative, we put together some ideas about mechanism-based pain assessment, if you will. On the left you see pain related factors that might tell us a little something about mechanisms, although not specifically, and then on the right some other techniques that are primarily research-based that can also give us mechanism-based information.

I'll give a few examples of at least some of these: pain distribution and qualities, QST findings, and I'll hint at neuroimaging, but I'll let somebody who actually knows about this, Vitaly, talk about this after the break.

One thing in terms of the widespreadness of pain -- this is some data from Chung Jung Mun, who is now working with Claudia at Hopkins, I believe. They recently published this paper where they had a large cohort of people who were known, who were

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recruited to have chronic pain, and they looked at the different conditions that people reported and the number of body sites at which people reported pain.

You can see, for example, people with cluster headache, the blue bar indicates that they reported having 4 and a half on average pain conditions. I'm not sure what half of a pain condition feels like to somebody. So you see there's a lot of comorbid pain conditions, which we already know, and there are even more pain sites at which people are experiencing non-transient pain.

Again, here's some data from OPPERA here, and these are heat maps based on an OPPERA version of a body map. On the far left there you see what controls were reporting; that is these are people who had no idiopathic pain conditions, and the other heat maps show you where people are reporting pain on the front and the back, and not surprisingly, the heat map is much stronger for people with fibromyalgia. People with low back pain are reporting pain in the low back, but a lot

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of people are reporting a large amount of pain in the head, especially posteriorly.

It looks like overlapping pain conditions are not agnostic to the location of pain. These are some data from OPPERA that Gary Slade published recently. This is the odds of TMD based on where other comorbid pain conditions were, and people with headache had a much higher prevalence or odds of TMD. Next was neck pain, and next was pain below the neck.

These are the figures for OPPERA data. Gary also looked at two large data sets, national data sets, and really showed the same pattern, so there may be some segmentality to this, although your odds of TMD are still significantly higher than the general population, even if your other pain conditions are below the neck.

So if we turn to quantitative sensory testing as maybe the most common method for assessing something like central sensitization, there are any number of papers out there now that have used quantitative sensory testing to show that

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people with a variety of chronic pain conditions respond differently on QST than people without those conditions, whether you want to call this pain sensitivity or altered pain modulatory balance.

An example is the OPPERA study here where we were looking at pressure pain thresholds at sites across the body. In the blue bars, you see the threshold for controls; the red bars for TMD cases. What we see is that no matter where we're poking TMD cases, they're more sensitive than controls, and this has been a common finding for TMD but also for many of the other conditions that we're talking about here.

We've done some of this work in osteoarthritis, which, as Dan talked about, has historically been viewed as the classic peripherally-based regional pain condition. Chris King looked at our data, and we broke it down -- our OA group, we broke into those who had a high degree of knee pain versus a low degree of knee pain. This was a community based sample based

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on the characteristic pain intensity score. When we start looking at quantitative sensory testing measures, essentially the high pain OA group was always more sensitive than the other two groups, and the low pain OA group was somewhat intermediate between controls in the high OA pain group.

These are pressure pain thresholds. Medial and lateral are on the joint line of the affected knee, the quadriceps of the ipsilateral leg, and then the trapezius and the arm on the ipsilateral side. So whether we're, again, poking people where their clinical pain is or we're poking them in non-painful sites, our high OA pain group is more sensitive.

If we look at temporal summation of mechanical pain using a von Frey hair, after one trial, the high OA pain group reports higher pain, but then that slope is much deeper after we've poked them 10 times once a second. That slope is representing what we think is some kind of mechanical temporal summation, and that slope is steeper in our high pain OA group than in controls;

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again, whether we're poking them on the knee or an unaffected area, which is the hand.

Similar findings with temporal summation of heat pain, both more pain and a steeper slope to that summation of pain across trials in the high pain group with OA. I mentioned earlier, in terms of mechanism-based pain assessment, that features of the pain, qualities of the pain might matter, so we had the pain detect to examine neuropathic like symptoms in our knee osteoarthritis group. Roughly, 17 percent of our osteoarthritis group reported or exceeded the standard cutoff on the pain detect for classifying neuropathic pain.

These were more likely to be non-white, obese, and were slightly younger actually. So we controlled for these factors when we were making the other comparisons. First of all, they just report more pain in general. Their knee pain is more severe, the people who reported neuropathic features. This is on the McGill Pain Questionnaire short form. All of the subscales are higher for the neuropathic like group than the

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non-neuropathic.

When we looked at movement evoke pain, this is a short physical performance battery where we have them do a balance task, a chair standing task, and a walking task. When we ask how much each of those things hurt, that pain was higher in the people who reported neuropathic features.

Then when we look at our quantitative sensory testing results, we see that it's really only temporal summation. Of the many quantitative sensory tests that we did, only temporal summation distinguished the neuropathic pain like group from their non-neuropathic counterparts.

This is mechanical temporal summation, and we see the same effect with -- I'm sorry. That was heat pain, temporal summation, and we see the same effect with mechanical temporal summation. So this sort of heightened pain facilitation but not conditioned pain modulation distinguished these two groups. So some of the features of neuropathic pain might be mechanistically relevant in this sample.

If we look at quantitative sensory testing

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measures back to the OPPERA study using these same heat maps, the top QST measure there is pressure pain threshold measured on the temporalis muscle. Maybe not surprisingly, that's strongly associated with TMD because those muscles hurt in TMD cases. Moderately associated with fibromyalgia, we see a little more darkness in the fibromyalgia and TMD compared to the other groups, but not terribly strong associations between QST and individual index pain conditions.

However, again, when we look at the number of idiopathic pain conditions, the heat map gets more darker shading as we go to the right here. If you have all of the idiopathic pain conditions, you're fairly sensitive to however we choose to hurt you here.

(Laughter.)

DR. FILLINGIM: So this is, again, an example of QST connected to different idiopathic pain conditions. Here are some of the same data shown in graphical form. You see on the X-axis the number of idiopathic pain conditions; on the

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Y-axis, the Z score for that particular pain measure. If we look at the top- left there, pressure pain on the temporalis, there's a pretty linear relationship between the number of idiopathic pain conditions and one's pressure pain threshold on the temporalis.

But if you look at a couple of these after sensation measures on the bottom panels, it looks like there's sort of a break point where once you hit three or maybe for idiopathic pain conditions, that's where you're more likely to have after sensations; that is we've applied mechanical pain stimuli, or heat pain stimuli. We stopped, and 15 seconds later it still hurts you.

So there's again some links, but the associations between QST measures and the number of idiopathic pain conditions seem to vary somewhat, depending on which QST measure we're looking at.

These are all cross-sectional data that I've been showing you, so an obvious question is, is central sensitization a predictor, or consequence, or epi phenomenon of chronic overlapping pain

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conditions? This was the original OPPERA incidence study that Joel Greenspan published, and what you see here are the hazard ratios; that is what is the risk of developing TMD in the future based on what your QST responses were before you had TMD.

We see a few -- they're all weak, but a few significant findings in the heat pain area here. A couple of the pressure pain sensitivity measures, particularly those on the head, predicted future development of TMD. But these are quite modest associations compared to some of the psychological factors and clinical factors we've looked at.

More impressive from the OPPERA study are findings that as people are developing TMD pain, their pressure pain sensitivity is changing. This is the baseline value. At that point, nobody in the study has TMD. At some point, some people are developing symptoms of TMD, and we bring them back to the clinic to determine whether they actually have TMD with a standardized exam.

There are two groups of people who developed TMD. One group we later classified as persistent

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TMD because when we re-examined them 6 months later, they still met criteria for TMD. Another group 6 months later no longer met criteria for TMD, so we called them transient TMD, and then here we have controls who never developed TMD.

What you see is that from the time that we first met them to the visit at which we classified them as having TMD, their pressure pain thresholds decreased significantly. You see that in the transient cases, there's a trend toward their pressure pain thresholds renormalizing, whereas in those whose TMD persisted, their pressure pain thresholds stayed low, suggesting that pressure pain threshold is more of a consequence or a co-occurrence with the development of TMD than a predictor of future development of TMD.

On the other hand, Tuhina Neogi's group at Boston recently published this study, so they had a large group of individuals who didn't have knee OA but were at risk for developing knee OA in the MOST study. They identified 4 clusters of people in their sample based on quantitative sensory testing

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profiles. One cluster had high pressure pain sensitivity and moderate facilitated temporal summation.

So this was the most pathological pain sensitivity profile, and they had about double the risk of developing a way over the follow-up period compared to the low to moderate proportion of pain sensitivity; essentially the low pain sensitivity group. In this study, baseline measures of quantitative sensory testing were predictors of future risk for developing, in this case, osteoarthritis and a fairly strong effect here.

I'm not going to get too much into neuroimaging. There is some work looking at whether brain structure is associated with one's pain sensitivity, and that's inconsistent. Some findings show a relationship between reduced either cortical thickness or gray matter volume and pain sensitivity measures. Other studies find no such associations.

But I did want to at least mention this study of structural brain alterations before and

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after knee arthroplasty. What they showed is that after knee arthroplasty, patients show significant increases in gray matter in several brain regions, and actually decreases in gray matter volume and bilateral somatosensory cortex.

This was also accompanied by QST changes; that is, their temporal summation profile decreased significantly, and their pain inhibitory response improved significantly, suggesting that this corrective treatment or pain-reducing treatment normalized both quantitative sensory testing responses, as well as brain volumetric measures.

So we come to this. This is the original OPPERA model that's been modified over the years, which is based on the notion that a variety of genetic factors combined with environmental contributions would drive changes in two intermediate phenotypes, high psychological distress and a high state of pain amplification, and those intermediate phenotypes are associated with increased risk of painful, chronic overlapping pain conditions.

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One thing we need to think about, we've heard a lot about somatic symptoms, somatosensory amplification, and central sensitization. In the original OPPERA model, we classified this as psychological distress, although one could easily put it in the pain amplification bucket. So we need to think about how some of these constructs are related and what the mechanisms are.

In conclusion, chronic overlapping pain conditions seem to exhibit multiple signs of central sensitization. As we increased the number of pain conditions, that is associated with significantly increased pain sensitization, if you will. Sensitization could be a risk factor or could be a consequence. There's evidence for both depending on the study.

These various domains that we measure with different methods, that may all reflect to some degree mechanisms associated with central sensitization, we need to somehow reconcile these and develop models as to how to put them together, as we've talked about already. I'll certainly

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acknowledge my many colleagues and funding agencies, and that's all I have.

(Applause.)

DR. WASAN: That' great. Actually, both speakers helped us make up some time.

Dennis, do you want to go to break now or should we actually -- we made up a little time. Should we go to break instead of questions. Okay. Do you want to do the full 30 minutes or 20-minute break? What would you like?

DR. TURK: Use your discretion. Surprise us.

DR. WASAN: Okay. Surprise, surprise. We'll do a 20-minute break. That will pick us up and get us closer to be on track.

(Whereupon, at 3:18 p.m., a recess was taken.)

DR. WASAN: Thanks, folks. This will be our last talk, and then we'll have the Q&A. I think Vitaly probably feels under a lot of pressure because he's had a lot of buildup. People keep referring to the talk of Vitaly, the talk of

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Vitaly; what's going to happen?

Dr. Napadow is one of my closest colleagues for many years. He's a biochemical engineer and an acupuncturist. He's an associate professor of radiology at the Harvard Medical School and Massachusetts General Hospital, and he's director of the Center for Integrative Pain Neuroimaging there at the Martinos Center, which is a large neuroimaging center that is part of MGH. So he's going to speak to us today about a lot of the pain imaging findings in the brain, and then we'll have a Q&A after that.

Presentation - Vitaly Napadow

DR. NAPADOW: Thank you very much. It's a real pleasure to be here and get the chance to present to you. For my talk today, I've been tasked with an overview of central sensitization and neuroimaging, and neuroimaging applications to try to better understand central sensitization and some of the markers and some of the metrics that we've been talking about in the last few talks.

I'm not really going to go too much into

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this, we've already had a lot of discussions, but just the general idea that there is this ontology that I think still needs to be develop around the term "central sensitization," and I think is an evolving discussion that I guess we're all having. But strictly defined, central sensitization refers to a controlled stimulus that is imparted, and then measuring some sort of neuronal event that is happening in response to that controlled stimulus.

Clinically, obviously, there are certain limitations in what we can do in humans versus animal models, but clinically, sensitization can be inferred indirectly from phenomenon such as hyperalgesia and allodynia, but there's also other phenomenon that are associated with this central sensitization such as temporal summation of pain, reduced conditioned pain modulation, reduced habituation, cortical amplification, increased receptive field size, and sort of plasticity and cortical representations.

So all of these concepts I'm going to try to overview in my talk.

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The question is how do we assess this with neuroimaging? I know we're a multidisciplinary crowd here, so I wanted to take just a very brief step back and talk about just the general idea that functional neuroimaging actually involves multiple different modalities that can get at different aspects of brain structure and function.

If we think of a neuronal event that's happening somewhere in the brain, there's an electromagnetic response that's imparted in response to these neuronal events. This type of activity can be picked up with technologies such as EEG and MEG. There's a neurotransmitter response. Glutamate and GABA concentrations, for example, can be assessed with magnetic resonance spectroscopy, whereas endorphins and receptor binding can be assessed with positron emission tomography, PET.

Then there's a hemodynamic response. When you have an neuronal event, you have this concomitant increase in blood flow, and that can be picked up with optical techniques, imaging techniques, as well as a variant of MRI called

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functional MRI or fMRI, and that's principally what we're going to be focusing on in this talk.

With fMRI, there's a contrast called BOLD, or blood oxygenation level dependent. With this contrast, basically you can think of a basal state of brain activity where there's a basal amount of activity, there's a basal amount of blood flow to these capillary beds, and a basal relative concentration of oxygenated and deoxygenated hemoglobin, and then a basal MRI signal.

When that area of the brain becomes activated, and there's an activated state, you now have an increase in blood flow, an increase in oxygenated hemoglobin because basically what happens is there's a decrease in oxygenation very locally, but then there's an in-rush of new blood, which then brings more oxygenated hemoglobin and a decrease in deoxygenated hemoglobin. And it's actually this decrease in concentration of deoxygenated hemoglobin that leads to lower field gradients around the vessels that it's feeding, which then leads to an increase of the MRI signal

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because there's lower field gradients.

So in review, an activation somewhere in the brain leads to an increase in the ratio of oxygenated to deoxygenated hemoglobin, leading to an increase of this MRI parameter called T2-star, which then leads to an increase in the MRI signal, and that's ultimately what we're tracking with this technology.

What does fMRI data look like? Well, it kind of looks like MRI data. You take an image of the entire brain every, say, 1 to 2 to 3 seconds, and then you can get a time course by just looking at the brightness of any voxel or volume element anywhere in the brain over time. If you have a typical experimental design where you have -- this is called a block design where you're not doing something and you're doing something. Let's say you're stimulating with a painful stimulus over here and then stop stimulating.

You are then calculating a statistical test to see how the MRI signal time series everywhere in the brain relates to what it is that you are doing,

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and the result of that test can then be appreciated by these color-coded maps over the brain. So when you see these pretty pictures, all they really are is the results of a statistical test, or a series of statistical tests, corrected from multiple comparisons of course, where you see this signal either increasing, such as red and yellow over here, in response to some sort of stimulus, or decreasing such as blue and cyan over here in response to that stimulus.

So hopefully we're generally on the same area now in terms of understanding some of these imaging modalities. One good place to start I think, because they're actually has been quite a lot of work that's done in the pain imaging field, is to look at a meta-analysis. So you're probably familiar with clinical trials meta-analyses.

You can do something similar with functional imaging, where basically a lot of these papers have tables published where you have locations of activations and deactivations in response to pain stimulation, and you can take those

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locations -- these are kind of like the little red dots over here -- and you can feed those into meta-analytic algorithm called ALE for activity likelihood estimation; they called it in ginger ale as the software

Basically, there's a series of these, but I happen to choose this one because they talked about sensitization. In this study, you can see there's more than 200 studies that went into this meta-analysis. Over 150 papers were with healthy controls; 32 papers in chronic pain patients, and about 9 studies that were there looking at hyperalgesia. I'll talk about this in a little bit of detail.

First of all, looking at the response in healthy controls, this is basically just response to -- in this case it was cutaneous. This particular meta-analysis focused on cutaneous pain stimulation, principally heat pain. What you see here is activation in a lot of the brain areas that are modeled and from review papers we know to be important for nociceptive processing.

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You have the thalamus over here; we have the thalamus over here. We have both anterior insula, posterior insula. We have S2, or secondary somatosensory cortex; ACC or anterior cingulated cortex that are activated in response to these pain stimulations in healthy subjects, and also some pain modulatory areas, importantly to note, such as ventrolateral prefrontal cortex and VTA, ventral tegmental area.

How about in induced sensitization, induced hyperalgesia, with these studies, it's a smaller number of studies, but typically in these studies, it's a model in healthy subjects where you inject or use some sort of capsaicin intervention to induce a secondary hyperalgesia, which is thought to be reflective of central sensitization.

While he localization between the normalgesia and the hyperalgesia in healthy controls actually did not differ, and the regions that were activated in this state did not differ between injecting capsaicin versus not injecting capsaicin, the strength of the activation did

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differ. They show greater activation in regions such as the anterior insula, posterior insula, secondary somatosensory cortex, and the anterior cingulate.

Basically, this can be inferred only from studies that actually did a direct contrast of hyperalgesia versus normalgesia, so then those coordinates can be passed up to this meta-analytic level. That's something important to understand.

Basically, there's a generalized upregulation of pain and salience processing area such as the insula, secondary somatosensory cortex, and the cingulate in this capsaicin-induced hyperalgesic state. This is very much consistent with EEG.

I'm not going to talk a lot about EEG, but it's very much consistent with EEG studies that have used this kind of model with this capsaicin-induced central sensitization, where you basically generally get this elevation of what's called the N2 peak over here, around 180 to 200 milliseconds after the stimulus. They induce

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capsaicin injection in the hand, only in one hand, not the other, and then do a punctate probe and look at EEG response. So you see this elevation of the N2 peak as kind of a marker of central sensitization.

What about chronic pain patients? This is where it gets interesting, and this is a quote from the review. Remarkably, similar activation patterns in healthy controls in chronic pain patients, there was no significant differences in the spatial localization of nociceptive processing between healthy subjects and chronic pain patients; no significant differences in the intensity of activation.

Those studies that directly calculated the chronic pain versus healthy control contrast also did not find any differences. No significant differences for subgroup of fibromyalgia versus healthy. This is all chronic pain patients. If we just look at subgroups, let's say just widespread pain, just fibromyalgia, there was also no differences found there. And this is in cutaneous

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pain, so what's going on here.
So maybe it's just continuous pain. We did a study where we used deep-tissue evoked pain where we have this a cuff that's inflated over the lower leg from outside of the scan room, and we looked at response to this deep-tissue evoked pain; nice activation pattern in healthy controls; nice activation pattern in fibromyalgia patients. Contrasting the two, no significant differences whatsoever.
There's definitely hyperalgesia. This is the pressure. This was a percept-matched study. This is the pressure that was used to evoke an equal amount of pain in the fibromyalgia patients and in the healthy controls, a very significant difference there, but yet no differences in brain response.
Why no difference? I don't know, but one potential reason is that most of the studies in that meta-analysis, and our study in particular, used percept-matched stimulation. If you look at a stimulus-matched condition -- this was a nice study

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out of a Tor Wager's lab -- they used both a percept-matched and a stimulus-matched condition, and what they found is that when both fibromyalgia patients and healthy controls receive an -- this is a thumb-squished pain -- equal amount of pressure on the thumb, the fibromyalgia patients report that as a significantly greater pain stimulus than do the healthy control subjects; whereas they also induced a higher input, higher pressure, in the healthy controls that readily matched the amount of pain that was reported between the fibromyalgia patients' healthy controls.
If you look at the brain response in these two different conditions, what you see is that it's completely following the perception of pain in these subjects, be they chronic pain patients or healthy controls. The amount of activation in the match, in the stimulus-matched condition with 4.5 kilograms, was significantly larger in the chronic pain patients, and that was the case for all of these regions. Be it the anterior insula, the cingulate cortex, posterior insula, they all showed

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the same general pattern, whereas if you matched the amount of pain that the healthy controls are feeling by having a larger input, now you don't have a significant difference between the brain response. So that's, I think, pretty interesting.
We also know that this is not just a case for pain stimulation. This is a pain-sensory effect, and Dan very nicely talked about this earlier. This was from the Clauw group where they had a visual stimulation and they looked at different lux or different intensities of this alternating checkerboard. These things were rated as more and more unpleasant as the lux increases, and fibromyalgia patients were hypersensitive to this. At any given lux, they were rating the unpleasantness of the stimulus as more.
Basically, if you then compare this very intense condition, which is what they did here with the brain imaging, you find an elevation of response specifically in the anterior insula cortex, and I'll come back to this region in a little bit. I think what was actually really

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interesting is that the amount of response in the anterior insula cortex was correlated with the amount of clinical pain that the patients happened to be in at the time of the scan.
How about some other fMRI metrics of central sensitization? Actually, this has not been talked about very much. There was some talk about this I think in Clifford Woolf's talk, the idea of receptive field size, and the correlate from a neuroimaging standpoint of that might be considered cortical representations in the primary somatosensory cortex.
We've known for a long time that S1, or primary somatosensory cortex, is organized in a somatotopic fashion over here. This is from the early studies with Penfield. We can use neuroimaging and functional MRI noninvasively. We don't have to open up the skull in these epileptic patients and map out their homunculus. We can actually do this noninvasively with functional MRI.
For example, this is the response masked for the primary somatosensory cortex, which is over

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here in the postcentral gyrus. This is the response to the stimulation of the second finger, the third finger, and the fifth finger. And I think if you can imagine the center of mass of these little activation clusters, you go up the gyrus as you go from 2 to 3 to 5, and that's exactly what Penfield found back in the 1930s, that as you go up the gyrus, you can track out these different fingers.

So what we did is we mapped out these finger representations in neuropathic pain patients, specifically carpal tunnel syndrome patients, where we also looked at the nerve conduction velocities at the wrists, so electrophysiological findings at the local peripheral median nerve. What we found is that patients suffering from carpal tunnel syndrome have wider cortical representations and board cortical representations.

This is the normal separation in healthy subjects from digits 2 to 3 to 5, and only those digits that are innervated by the median nerve in these patients show contracted representations.

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The representations are closer to one another in the postcentral gyrus, whereas digit 5, which is ulnar nerve innervated, the pinky, is nicely separated from those other digits in both healthy subjects and in CTS patients.

This was a finding back in I think 2006, and then we were able to replicate that with a much larger study in 2014. The interesting thing that we found, at least in an earlier study, was that the separation distance, the more contracted the D2/D3 separation distance here on the Y-axis, the greater the median nerve latency.

This is a measure of median nerve pathology, or pathology at the peripheral nerve at the wrist is correlated with this cortical representation remapping or this maladaptive neuroplasticity that we see in the brain. That's a nice way to get from the peripheral effect to the central effect, because I think that's actually been talked about lot here, is what are the limitations of functional neuroimaging in looking at the brain responses versus some of the cord responses that has been the focus of a lot of animal research.

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What about other fMRI metrics of central sensitization such as temporal summation and conditioned pain modulation? This has also been brought up a few times here. There are issues. It is not so straightforward to assess these phenomenon in a neuroimaging setting. For example, with temporal summation, which is assaying a pain facilitation, the stimulus frequency is such that it makes it difficult to really track this nicely with functional MRI.

So it's less amenable to these fMRI event related designs because of the slow hemodynamic response to any neuronal event, which is peaking roughly 5 to 6 seconds after a neuronal event. So it makes it difficult to assess this with a repeated series of stimuli as you would like to do.

One thing that we've been working with to try to get over some of these barriers is to look at not just evoked response with these kind of block designs or event related designs, but to look at other metrics such as a brain connectivity.

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Functional brain connectivity has actually kind of started to dominate the functional imaging field I would say in the last 10 years. Just a little bit about this, this is the idea that even in a resting state, if you just collect data, not have any sort of block design, but you just have the subject lying there in a scanner and you're collecting functional MRI data, you see these fluctuations.

Here, this is kind of a video of the MRI signal over time, and red and yellow is when, on average, the signal rises, and blue and cyan is on average when the signal drops below some mean level. What you can see here is that these fluctuations are not chaotic, they're not random. They actually follow in these kind of distinct networks. When this particular part of the brain activates, this other particular part of the brain also activates.

So the idea here is that if you do, say, an independent component analysis or some other time frequency analyses, you can actually pick out these

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distinct networks, and these networks are kind of like assemblies that rise and fall over time. So when one network is activated, another network is deactivated.

Our brain is constantly cycling through this. We're never completely at rest. The brain is always doing something if we're alive. These networks have been described, and some of the canonical networks include networks that are very important for pain and nociception processing. These include the somatomotor network where S1 and primary somatosensory cortex is located for intensity and location and discrimination of pain.

Also, the salience network, which has previously been partially dubbed the pain neuromatrix, which is a term that which fallen significantly out of favor in the pain neuroimaging community. The salience network is looking at nodes such as the anterior cingulate cortex, the anterior insula, temporoparietal junction.

These are brain areas that respond to salient stimuli, be there painful or non-painful.

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These are stimuli that are defined as something that stands out from the background and stands out from other stimuli. That's why it's called the salience network, so you can see that a lot of these brain areas are also involved here in reviews of nociception processing in the brain.

They're highly relevant. One set of experiments that we've done is to take our cuff pain provocation, or cuff pain device, and one nice thing about this is that we can actually -- it's not like a heat pain device where you don't want to burn somebody, so there's a limitation of how much time you can keep this on. With the cuff pain, you can inflate this cuff, and you can keep it on there for four minutes, sometimes even tens of minutes in some labs.

So we were able to then keep it on for, say, 6 minutes, a period of time of 6 minutes, and this is kind of a sustained deep tissue pain. We can contrast that with a resting state, where it's a more usual way of running these kinds of connectivity analyses, where you just have the

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subjects lying there at rest.

What we found, at least in healthy subjects over here, is that these networks shift their connectivity in a sustained pain state versus a resting state. In a sustained pain state, the areas that are activated, primary somatosensory cortical areas that were known to be activated by the stimulus, because they're in the representation of the leg over here in S1, are shifting from their quote/unquote, "home network," which is this sensory motor network, to the salience network.

So we have a decrease over here for pain versus rest in this area to the sensory motor network, and the same exact area is also increasing its connectivity to the salience network. Now this location mapping, this area in your body, has become more salient to you because you're feeling the stimulus in that area. It kind of makes sense but hadn't been shown before.

If we then look at this in chronic pain patients, in fibromyalgia patients, we see something very, very similar, that if we take a

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seed in the S1 leg area and we see what that's connected to, and we contrast that for a sustained pain state versus a resting state, we see that there's an increase between S1 leg connectivity and other key nodes of this salience network such as the anterior insula over here. That's the case for both the right and the left anterior insula.

But interestingly enough, you can also measure temporal summation during this period. This is a little bit different than temporal summation as it's measured with, say, pinprick probes or something like that at once a second. But if you ask subjects how much pain were you in the last 2 minutes of that 6-minute period versus the first 2 minutes of that 6-minute period, you can get this assessment of a temporal summation, sort of an increase or habituation, or a decrease in the amount of pain that they're in towards the end of the scan versus the beginning of the scan.

We look at this as a temporal summation index, and we see that fibromyalgia patients report a larger sort of summation of pain during the last

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2 minutes versus the first 2 minutes. If we then look at that summation index and we see how that relates to S1 leg connectivity, we find that the greater the S1 leg connectivity specifically to the anterior insula, the greater the temporal summation that was reported by the patients.

This is kind of looking at the circuitry underlying temporal summation. It clearly involves not just salience and anterior insula processing areas, but also primary somatosensory processing areas. I think that's one interesting thing that we found in these studies.

What about conditioned pain modulation? Here, we also have a lot of problems. There have been very few studies that have been published trying to assess conditioned pain modulation in the scanner, and this is problematic for, a host of reasons. But in looking through this literature, one study that did I thought kind of a nice job of this was out of -- I think this is a group out of Hamburg.

First of all, what was nice is that they

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actually found the group effect for conditioned pain modulation. Many of the studies that have been published look at just individual subject variability and don't actually find a main effect of group, so a main effect with the conditioning stimulus versus without the conditioning stimulus.

This study actually did do that and had a pretty straightforward design. I'm not going to talk much about this naloxone part of this, but they also included an opioid blocker here as well to try to better understand the mechanisms.

In this study, what was interesting is that they actually tried to replicate some of the cold CPM studies for conditioning stimulus, where they put one of the subjects legs into this wooden kind of crate, and then took ice bags and put a bunch of ice bags around the leg in order to induce the condition stimulus, a continuous stimulus of the cold pain. And they counteracted that with saline at room temperature as a control.

What they found, first of all, was a very nice effect of CPM. With the cold over here, you

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get a very nice and significant reduction in the pain rating reported by the sub [indiscernible]. These are healthy controls by the way. Also, if you look at the brain response with the cold pain versus without the cold pain, you see a very nice reduction -- this is actually coding for reduction; it's red -- a reduction in areas such as the thalamus, the insula, S2, midcingulate cortex. These are all kind of nociceptive processing areas. This was I think a really nice result for CPM is also affecting this kind of common pathway of nociceptive processing areas in the brain.

One question is, let's talk about where is the central sensitization happening? If it's from peripheral to central, is it something that's specific in the cord, or is it something that also could be in the brain, or is it potentially both? Do chronic pain patients, for example, show amplification at the primary synapse, such as the dorsal horn over here, or is it higher up in the brain, or both?

One way to get at this, as we were thinking

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of how to do this, is to look at facial pain and facial stimulation, because with facial stimulation, this is an example of just raw fMRI data that we're able to collect. You can see here that not only can you acquire data from the cortex and subcortical supraspinal regions, but you can also collect data from the brainstem. If you impart stimuli over the trigeminal pathways on the face, you can also assess activity in the spinal nucleus of the trigeminal nerve, over here, Sp5, in the medulla and the pontomedullary junction.

What we did is that we used a stimulation design where we had a facial stimulus. In this case, it was kind of an aversive air puff stimulation, and we looked at migraine patients and healthy controls. These were interictal episodic migraine patients.

The air puff stimulation was at a frequency that we thought was high enough to induce some sort of summation effect as well to be more aversive in the patients. What we did is that we had a series of 14-second long stimulation periods interspersed

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with 20-second duration resting periods. We had 11 of these stimuli, and I'll come back to why that's important.

If we combine the brain response across patients in healthy controls in terms of both brainstem and brain response, we see that there was nice activation in Sp5, or spinal trigeminal nucleus, in the brainstem, which is right around the pontomedullary junction over here. There was also nice activation in S2 and posterior insula regions, as well as the hypothalamus over here, which is kind of interesting. You don't always see hypothalamic response, but perhaps this was due to the fact that we were studying migraine patients.

One interesting thing that we found is that there was actually no difference between migraine patients and healthy controls in response at the primary synapse. This is kind of the analog of the dorsal horn. In this case, these were episodic migraine patients. There was an equal amount of response activation in Sp5 across different groups.

However, when we then calculated an

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amplification ratio, which is the amount of activation in these other regions such as posterior insula and S2 and hypothalamus relative to the amount of Sp5 activation, sort of this analog of the dorsal horn, that's where we saw this very nice difference between migraine patients and healthy controls. We see this elevation or this ratio that we refer to as kind of a cortical amplification ratio, which is relative to the gain that you have. It's the gain from the primary synapse in the brainstem up to the cortex.

Another interesting thing that we did is that we looked at habituation. Instead of analyzing all of the stimulation blocks equally, as is typically done in fMRI experiments, one nice thing about pain and evoked pain, actually, is that it's a very strong -- it's a very high SNR stimulus in terms of fMRI response.

You can actually look at individual blocks of stimulation and assess brain response to individual blocks of stimulations. It's very hard to do this for cognitive tasks for example, by the

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way, which is typically why you have multiple repetitions, and you're averaging, averaging, averaging. But you can do this for pain stimuli because the SNR is nice.

What we did is that we calculated brain response to each of these individual stimuli independently, and we looked to see what happened over time, and we could fit, basically, regression lines to each individual subject's response to seeing these tracks over time.

What we found is that whereas in healthy controls, these are the open circles, you see this nice kind of habituation as you go from the first stimulus down to the 11th stimulus, and that was less so the case for migraine patients. Migraine patients tended to have a flattened response and a lower slope of this habituation from time to time.

One potential marker of central sensitization might also be this reduction in habituation in repeated stimuli as you see over time. In fact, there was a correlation between the amplification ratio that I showed you previously

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and the habituation slope such that the more they amplify, the more the subjects amplify in regions such as posterior insula cortex, the more they also have sometimes even a positive habituation slope. This means that there's a facilitation, an increase, in response as they go from the 1st to the 11th stimulus.

Now, a little of summary. Differentiating central sensitization metrics in the brain with functional MRI, we showed you elevated or altered fMRI response in chronic pain patients specifically when the stimulus was stimulus matched between groups, between patients and healthy controls in areas such as the thalamus, S1, S2, anterior insula, which was also there for visual stimulation sensory stimuli, by the way, posterior insula, and ACC.

Temporal summation was encoded not just by insula response but also connectivity between the insula and primary somatosensory cortex. Also, brain amplification and reduced habituation were noted in specifically the posterior insula in

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migraine patients. So this is another potential nice approach to look at more specific brain-based central sensitization metrics in patients.

I don't mean to say that these are the only areas where centralization is to occur and these are the only circuitry for central sensitization, because these responses might actually be mediated by other brain regions. If you look at the original description of pain processing, nociception processing, and chronic pain, there are other areas here such as the prefrontal cortex, which I haven't talked about at all, and posterior cingulate cortex.

So how do these regions come into play? Well, a recent study that we completed is we actually had fibromyalgia patients induced to catastrophize. So we had them in the scanner, and during specific periods of time, we told them to reflect on some of the pain catastrophizing statements that are in the PCS scale.

So the degree to which different patients identified with these catastrophizing statements

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were correlated with the amount of activation response in areas such as the ventral PCC. You see, basically, the posterior cingulate cortex and medial prefrontal cortex over here as kind of encoding the catastrophizing portion of what the subjects were doing, and the degree to which they were internal -- because not all fibromyalgia patients catastrophize; but the degree to which they reported that they were able to encapsulate these catastrophizing statements was nicely correlated with the activation in specifically ventral PCC.

In conclusion, central sensitization, once considered purely a spinal cord phenomenon, is clearly noted in multiple brain responses, including primary somatosensory cortex. Different aspects of central sensitization, such as CPM, temporal summation, gain habituation, all these receptive fields sizes, can be assessed by different fMRI methods and support different brain circuitries. I think in the future, we need to spend more time in developing novel experimental

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designs to better assess these different aspects of central sensitization.

I thank you for your attention, and I thank the funders for a lot of this research and my colleagues, specifically Jeungchan Lee, and Jieun Kim, who did a lot of the imaging analyses in these studies, and Rob Edwards, my close collaborator at Brigham.

(Applause.)

Q&A and Panel Discussion

DR. WASAN: Why don't we have the rest of the panel come up, and then we'll have the Q&A. We're also going to be joined by Christin Veasley, who is the director of the Chronic Pain Research Alliance in Rhode Island, and also a Shannon Smith, who's assistant professor in the Department of Anesthesiology at the University of Rochester and part of the IMMPACT-ACTTION group as well, who does a lot of systematic reviews and does a lot of foundational work that I mentioned.

I thought maybe I would just start out with one question, and then we'll get the ball rolling.

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I don't need to intentionally start this off with a hard question, but it got me thinking from this morning, this issue of association versus causality. We know that applies to any of the things we're looking at, whether it's QST, or fMRI, et cetera.

This is really a question for all of us here, but also, I'd like to hear what the biostatisticians in the room think, which it seems to me that in a lot of our literature, there's very little use of causal inference statistics, so things like Bayesian network analysis, CART, things like that, which might get at some of this association versus causality kind of questions.

I just want to get some reactions from the panel what you all think about that; have you thought about it in your work; is there a next step forward using those other type of statistical approaches? Would they have any advantages? So come up with all the stuff you've done.

DR. NAPADOW: From a statistical modeling approach to get at issues of causality, it depends

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if you consider mediation modeling to be causal in nature. With some of the other methodologies, Bayesian modeling, and predictive coding, and stuff like that, the problem is that you need a lot of stimuli, and you need a lot of repetitions to really adequately use some of these models, and that can be difficult with pain stimuli, especially with chronic pain patients. For getting at issues of central sensitization in chronic pain patients, those are some of the limitations of those kinds of approaches.

DR. FILLINGIM: I don't understand any of those statistics, so I probably shouldn't comment on those. Some of the folks in OPPERA have used some causal modeling, in particular looking at sleep and stress over time and how that predicted first onset TMD. But I think we also need to think about our experimental designs and collecting prospective data, really, and ultimately doing experimental manipulations, whether those are clinical trials or other types of manipulations, in order to make true causal inferences, with all due

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respect to all the statisticians in the audience.

DR. WASAN: If there are any statisticians who want to chime in on this, we have a couple of here. Is anyone here? Is Scott here, or someone in the back as well? Go ahead, John.

DR. FARRAR: I wanted to ask another question, but I'll chime in on the comment. I think the comment made is the key one, which is that there isn't anywhere near enough data to do it. These studies are all less than a hundred people, probably less than 20, and many of them are 30, which is wonderful because you get statistically significant changes. But it's only one 30 people, so all you can comment on is the 30 people. Whether that 30 people are representative of the population is a completely different issue. So I think we're not there yet, and maybe we'll get there at some point.

What I wanted to ask, actually, was just a specific question about the imaging data. All the data you presented was BOLD. ASL obviously has a whole different set of features. One of the things

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that has intrigued me about the differences between the two is that you might be able to superimpose the BOLD and the ASL.

For instance, ASL is very good at looking at -- as in any mechanism, you really have to look at chronic pain, and there is some disagreement about that. But in general that's, I think, an acceptable statement. One of the thoughts would be if you initially imaged with ASL to get a sense as to how much pain the patient seemed to be experiencing that day, and then tried some of the stimuli on top of that, where then you might gain additional information about the state of the brain and then its response to stimulation. I wonder what your thoughts were.

DR. NAPADOW: I won't take the bait in arguing with you about chronic pain in ASL --

(Laughter.)

DR. NAPADOW: -- or maybe I will. I've published with ASL. I mean, ASL certainly has some advantages. It's not as sensitive to large draining veins as BOLD is. One problem with ASL is

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that the SNR is much lower than with BOLD. There's also controversy about what type of ASL we should be using, peak ASL versus ASL.

I think ASL kind of has its uses, but it's not going to be a panacea. I guess my quibble with your statement is that that's part of what connectivity analyses can be used with BOLD data, and BOLD is much better for connectivity analyses because you get much better temporal resolution with BOLD than you do with ASL. The temporal resolution with ASL is like 9 seconds. The temporal resolution with BOLD can be as low as a second and a half, 2 seconds, or something like this.

DR. FARRAR: To push back a little bit, I completely agree with in terms of your assessment of ASL, in terms of its sensitivity, but it does give an absolute value for blood flow. And it would be, I think, useful in interpreting the stimuli data, to know that a particular part of the brain has already got a higher level of blood flow to start, and to see whether that might in some way

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influence its ability to respond.
The other piece of it that is very interesting to me is that there have been a couple of studies where they've applied chronic pain using a blow-up cuff on an arm. Actually, the study I'm thinking about was an injection of hypertonic saline into the muscle, which hurts. They maintained the level of and reported the patient the same, but over time, the blood flow to the brain in the areas involved actually returned to normal.
One of the arguments there is that what we're measuring here is blood flow. Blood flow is 2 or 3 steps removed from the actual thing we're interested. And it may be that blood flow basically exceeds what is needed, and then slowly returns to a more normal. And it raised the question of what happens when you do those kinds of studies, the BOLD studies, over a period of 4, 5, or 10 minutes because maybe the brain has a differential response over time.
All of that to say that this is still very

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interesting stuff. I'm worried that we need to take some of that with a grain of salt before we go --
DR. WASAN: Just to clarify, folks, ASL refers to arterial spin labeling.
DR. FARRAR: I'm sorry, yes.
DR. WASAN: It captures the magnetic moments related to the arterial flow versus the magnetic moments related to the BOLD signal, which is the draining venous flow. Vitaly is underplaying his hand a little bit. He has a whole bunch of ASL studies that have been done, and looked at that carefully, and looked at the overlap, and, clearly, there's a role.
Does anybody else have any other comments on John's question, Dr. Farrar's question? Yes?
DR. WOOLF: Related to that, I find it difficult to deal with a technology that operates at seconds, whereas ACTTION's potential lasts milliseconds, and that measures your voxel at 100,000 neurons -- something like that; maybe that's an underestimate -- but a mixture of

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excitatory, inhibitory projection locally, et cetera.
So in the end, what is it that you're measuring? Yes, you're measuring changes in blood flow that perfect activity, but in a very crude way, especially n temporally, when you say these are measures of the function of the nervous system, I would say, no they aren't. They are an integrated set or changes at a very gross and crude level, and we've got to be extremely careful about what they mean, and what the connectivity map actually means in terms of the actual function of the node [indiscernible] system.
DR. NAPADOW: I can't argue with that. The types of tools that we have for looking at rats, and mice, and other animal models are orders of magnitude better, but we have certain tools that we are able to use in humans. What I'm trying to argue is not that I'm able to pick out inhibitory, versus excitatory, versus specific neurons, or types of neurons, but that there is some rationale in what we're looking at.

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By looking at the strength of the response, by looking at relative strengths of responses between different brain areas, and looking at things like amplification ratios, I think it's highly relevant, and we're seeing these things in somatotopically toxic defined areas. So it's not just like a big wash over the entire brain.
DR. FIELDS: Actually, Bob [indiscernible - too close to mic] that particular point, the last point that you made is crucial, novel, and important. It is this idea of the amplification [indiscernible] -- draining starts with a known stimulus. You can actually show that the BOLD signal correlates with the intensity of the stimulus, or with the intensity of the reported pain, or both.
Then there's reason to believe that the information that gets to the cortex has to go through the trigeminal nucleus caudalis, where you have sufficient spatial resolution; if not good enough temporal resolution. But the idea that for a given signal in the trigeminal nucleus to show an

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enhanced response in the cortex in a subset of patients is, in my mind, direct evidence that there is a specific central component of amplification. It's in the cortex.

Well, actually I don't know that because there's no direct projection from TNC to insula. So there, the question is, is it there in the thalamus; is it via the parabrachial nucleus; is it via the amygdala? In theory, you could determine that.

So the question I have -- now that I'm getting to a question -- is could you vary the analysis with respect to the stimulus in such a way that you could see whether there's a delay in the onset of activity between the TNC and the insula? Then, you should be able to do that.

DR. NAPADOW: In theory, yes. In reality, there are certain assumptions that are made with fMRI data analysis about the hemodynamic response function that I mentioned before, about 5 or 6 seconds peaking after a neuronal event. That's an assumption, and actually there is variability

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across the brain and probably what the hemodynamic response function actually is.

So I personally have always been very skeptical with causality types of analyses with fMRI data because if you see that, say, the insula is peaking before the secondary somatosensory cortex, you don't know if that's really because of an actual neuronal event that happened preceding the somatosensory cortex or whether the hemodynamic response function in the insula happens to be a little bit faster because the arteries that are feeding that area are maybe a little bit larger for any number of reasons.

So that's why I've always been -- signal processors will go in, and they'll run their algorithms on anything, but the neurophysiology behind all this is such that I kind of am a little bit hesitant about causality types of analyses, and the question that you just asked about what's peaking first.

DR. SRINIVASA: It's a question for both Roger and Vitaly. Both of you have demonstrated,

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with both quantitative sensory testing measures or imaging, that there are measures that clearly differentiate normal subjects with central sensitization disorders suggestive of amplification or central sensitization, but clinicians are often dealing with single individuals.

Do any of these measures diagnose abnormality of central sensation in a given patient? If so, what would be the sensitivity and specificity of these measures?

DR. FILLINGIM: I think for QST, we don't know. There is probably a QST profile that everybody would say is abnormal. How far down the continuum you have to go in order to have a QST profile, I don't know. They haven't been really applied diagnostically. They've been much more used as research tools based on their continuous values, and so on and so forth.

I think if we ever want to move this into more practical use, there's a lot of work to be done in terms of the psychometrics and validation of at least QST types of tools for the clinical

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setting.

DR. BRUEHL: I've got another assessment type question. Vitaly, your data nicely showed that there is some central amplification above the spinal cord, and it got me thinking about the measures. So what we were looking at in the overlapping conditions was qualitative; yes or no, do you have a diagnosis there? A lot of times, like in Dan's work, we're talking about multiple pain locations but, again, it's yes or no; do you have them?

I'm wondering if we're talking about amplification, wouldn't the intensity of the stimulus at each of those locations make a difference as well? I don't know if people who use pain drawings or variants of the Michigan Body Map actually get stimulus or pain intensity in each of those areas, but I wonder what the value of that would be if indeed what's going on is an amplification, because it would imply you get bigger effects for people. Like for someone who had 8 out of 10 pain in 5 locations is very

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different than someone who has 8 out of 10 in one location and then a 1 in all the other locations.
DR. NAPADOW: I'll let Dan answer, but I think that's exactly why Dan advocates not just using the map but using intensity values at all those different locations that they're reporting.
DR. CLAUW: I wouldn't say, and John can acknowledge the fact, that it will make your head explode if you collect intensity at every single point. So that's what we decided to do in the map, and I think that's a really bad idea.
What we do in our studies is the digital body map, if you check the region of the head, you get a drop-down thing that you have to rate the pain in that region, but we only make people rate in each of 7 regions, the 2 arms, the 2 legs, the front of the trunk, the back of the trunk, and the head. We found that when you start asking people to rate at up to 35 sites, which is what the body map has, then big question that we grapple with in the map is what would be a checkbox? Because we used to just say yes/no, but what do you count like

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a pain level of 1 in a site? Do you say that's, yes, pain?
So anyway, the way we tried to do it really granularly in the map I think is overkill.
DR. FARRAR: Actually, if I could just add to that. In the current map, we used the CHOIR map, which is 64 spaces. Each space gets a rating.
(Laughter.)
DR. FARRAR: To put it mildly, the patients get tired of it after awhile. And in analysis of that data, the best cutpoint is between 0 and 1, maybe between 1 and 2; so pain, yes or no on a site. And whether you reduce it to 7 or to 14, one can argue about, but certainly not 64, so I think a much simpler map.
Then a question this morning to Nat about the usability of a body map, we've actually spent some time developing an app that allows a patient to click on 7 sites and actually rate those 7 sites. It can be completed in 30 seconds. So it can be used and used regularly over time if you wanted to use it in a measured study.

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DR. FILLINGIM: If I can just jump on that, in order to make this just completely ridiculous, intensity is not the only and maybe not the most important thing we should measure. What about the duration of pain? What about the temporal features? Do they have pain 24 hours a day or does it fluctuate? What about the sensory qualities, and so on and so forth.?
So depending on what our question is, I think it's a fair message we need to do better with pain assessment. Epidemiological studies are still, do you have chronic pain; yes or no? That's almost completely uninformative. So we can do better, but we can also go to the point of no return and impossibility in terms of assessment.
DR. WASAN: To follow up on that, one thing we were talking about a little bit at the break is that so far we've talked a lot about how somatosensory amplification, one of the best clinical indicators is the extent of widespread pain. But then there also of course many other pain conditions, which have some somatosensory

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amplification components but are focal pain conditions; the data on abnormal QST responses in patients with back pain who do not have fibro, who have more isolated pain.
So maybe some question to follow up on this, which is what the panel thinks about are there other of indicators of somatosensory amplification clinically besides just the pain and number of body regions, or other things people would chime in with.
DR. FILLINGIM: Do you want to respond to that, Penney?
MS. COWAN: No, I don't, but I want to respond to something you just said about measuring the pain. For people living with pain, it's more than just the intensity of the pain; it's the impact it has on their life. I know that's not part of that, but it's huge for that person living with pain.
I don't want to you to forget that it's not just about the measure of pain. There are so many other factors that are involved in that when you're

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actually looking at a person living with pain and their ability to function and actually live a full life in spite of the pain.

DR. WASAN: I think that's a good point, too, that one of those bidirectional relationships perhaps related to somatosensory amplification is the impacts on life. That's a big broad term for a lot of things. But as well, that may impact the degree of amplification, and the amplification may impact the degree of impacts on life. So it's another one of those bidirectional things.

I think that's another issue maybe for us to address tomorrow when we talk about a manuscript, which is what are all the different possible clinical indicators of somatosensory amplification, suggestive of such a process going on?

DR. FILLINGIM: I think, certainly, as Dan talked about that there are not a lot of non-pain sensory experiences, they don't have to be somatosensory. They can be other senses but within the somatosensory system. Things like The Pill, which we've used a lot, and OPPERA, assess a wide

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range of bodily symptoms from itchy throat, to runny nose, to breathing problems, to whatever. And those are some of our best predictors of who's at risk for developing TMD in the future.

So it certainly goes beyond the pain space. I think if at this meeting we can come to some consensus about what's central sensitization, and what's other stuff, and where do they overlap, and if they're separate constructs, how and what should we measure, I think it would be a huge contribution to the field.

DR. WASAN: Yes, Simon?

DR. HAROUTOUNIAN: I have a question. Do we know which among those different sensitization symptoms that we discussed are more bothersome for patients, or which are considered more key ones from a patient's perspective rather than ours, or a researcher, or a clinician perspective if we're thinking about sensitivity to noises, to light, to touch? Or are there particular conditions in which patients tend to express more concern with specific sets of symptoms or signs?

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DR. WASAN: There's actually good data on lumbar radicular pain, that the radicular component of pain is one of the most bothersome aspects of chronic low back pain. And the same would apply to neck and arm radicular pain in terms of how you measure it and comparing it to all the other impacts related to pain. There are a lot of studies on that, so definitely with bothersomeness, really, the radicular pain seems to be one of the most distressing that people have.

Other questions or comments? Nat?

DR. KATZ: Has functional neuroimaging shed any light on the relationship between mood disturbances and chronic pain, whether there is any common circuitry?

DR. NAPADOW: Yes, I think there is a lot of common circuitry there. A lot of depression research is also pointing to some of these kind of salience processing brain areas.

Also, this whole idea -- I was recently going through the literature on some of our findings linking cross kind of connectivity between

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default mode network and salience processing areas as underlying chronic pain severity. Looking through the depression literature, there's a lot of evidence for cross-correlation between default mode network and insula salience processing areas in the depression space.

So yeah. I think there's a lot of overlap there. In fact, our most recent publication was actually very interesting. I didn't talk about this at all, but we have this marker of DMN and insula connectivity as a potential marker for pain, for chronic clinical pain. We identified this in different cohorts. I think Dan talked about it a bit in fibromyalgia, as well as low back pain populations.

In the most recent low back pain study that we ran, which was fairly large, almost over a hundred patients, we did not find it, and I was very surprised about that. Originally, we wrote up the paper and we sent it in. The paper was rejected, and the reviewer said, "How come you're not talking about DMN and insula connectivity?

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I've seen all your papers about it." So I said, "It's very strange."

So we went back, and we actually looked at catastrophizing. One thing we noticed is that compared to our previous studies, the catastrophizing intensity, or the catastrophizing load [ph] on the PCS scale was significantly lower in our newer, larger study. These were healthy, fairly active low back pain patients.

When we then stratified by catastrophizing -- we divided it into thirds. When we looked at the just high pain catastrophizing, we saw exactly the same result, where a DMN and insula connectivity was related to pain intensity in these subjects, but only for the high catastrophizing group.

So there's this very interesting influence of negative affect and catastrophizing in these markers that are associated with pain intensity.

DR. FILLINGIM: I think this brings up a broader point, and I think Annie spoke about this in her talk, our recruitment biases. Whether we're

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doing a neuroimaging study, or whether we're doing a clinical trial, the OPPERA study, or we're recruiting from the clinic, well, that's going to bias us towards certain conclusions about depression and maybe bias us toward certain neuroimaging findings versus community-based samples, and so on and so forth. And how we generate a representative sample we can still make sense of, I just think that's a critical issue.

DR. WASAN: There were some other -- Rob? Go ahead, Dr. Dworkin.

DR. DWORKIN: Vitaly, if I gave you -- and you'd be blinded -- 10 fMRIs, you could tell me how to capture them, of patients with kind of classic fibromyalgia, and 10 MRIs of patients with classic postherpetic neuralgia matched for age and sex, would you be able to sort them accurately into two piles?

DR. NAPADOW: Maybe if I got really lucky.

(Laughter.)

DR. DWORKIN: I think that's a no.

DR. NAPADOW: I think that's a no.

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DR. DWORKIN: So does that mean that we are nowhere near being able to use fMRI for diagnostic phenotyping purposes?

DR. NAPADOW: Yes, clinical applications, we are nowhere near that. We do not have a painometer. I do not think we will ever have a painometer. Applying these kinds of technologies, I'm very much -- I'm not against sensitivity and specificity analyses, and these kinds of things, and trying to find biomarkers and all this kind of thing. But in terms of actually applying these in the clinic, I don't see us getting there.

DR. WASAN: Yes, Clifford?

DR. WOOLF: A couple of points for you. Sorry to be picking at -- you haven't mentioned AI machine learning analyses. I'm a bit surprised about it. It seems like that at least is one way to remove the bias from the analysis.

The other one is when you're talking about amplification with the trigeminal system, how much of that is due to true increased activity or progressive [inaudible - coughing] more and more

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neurons as you go up the pathway towards the cortex from the trigeminal nucleus of the -- the spinal nucleus of the trigeminal?

DR. NAPADOW: I'll hit the second point later. But that's why we're comparing of patients to healthy controls, unless you think that there's a vast difference in the number of neurons in healthy controls versus migraine patients or vice versa, and that's why we're seeing it.

So, yes. I'm sure there is a difference in the number of neurons that we're capturing in Sp5 versus in the cortex, but that would be the case for healthy controls and for patients. So the amplification ratio we're looking at is cross-comparing these two groups, so in theory we should be able to equate for that.

DR. WOOLF: Machine learning.

DR. NAPADOW: Machine learning.

So yes, there has been AI types of analysis that have been applied and multivariate pattern analyses in these kinds of things because it's such a large -- we're talking about 40 to 80, depending

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on the spatial resolution, thousands of voxels that we're assessing.

We've done some of this to try to take these markers that we're finding, either with connectivity or in that case actually with ASL, and other markers to see if we can predict clinical pain intensity. So these things have been done with evoked pain. There was a Tor Wager's paper in New England Journal of Medicine. That was for heat pain. We just published something in Pain with clinical pain, where we exacerbated patient's pain similar to Ajay's model of pain exacerbation of low back pain.

So we've applied machine learning in those types of cases to try to better predict clinical pain intensity. But in terms of -- so yes, there's been a lot of this kind of work done; less so I think in the pain field. I think pain lags sometimes some of the other larger analyses, larger applications in terms of like mental health and other applications of fMRI. But I think it's coming, and there are definitely a lot of groups

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that are applying these tools.

DR. WOOLF: We don't have a painometer, so you don't think this represents a potential pain biomarker then, a way of measuring presence of pain or its response to analgesic interventions?

DR. NAPADOW: I mean, it could. I'm not saying that we shouldn't try to apply these methods. I'm giving you, I guess, my prediction. My educated prediction is that our area under curve, our sensitivity, specificities, and accuracies that we're going to be able to get at are probably not going to be to the case that a random clinician or a family practice doc somewhere is going to be able to send somebody to do an fMRI and tell them -- when I'm in a cab or in an elevator with an MD, and they ask me what I do, and I tell them, they said, "Oh, I would love to have this objective test. You've got to figure something out," because, ultimately, a lot of them don't trust their patients, so they want this objective clinical test because there's no way that Mrs. Smith is really a 10 out of 10 pain. I don't

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think she's showing that.

So that's why they want it, and I don't think that's the best rationale for why we should be doing this.

DR. COLLOCA: I would like to comment on this last thing because today we saw from Daniel that some patients with osteoarthritis come with radiographic changes, and some not radiographic changes.

First, we don't have, with fMRI, the specificity for the single participant yet. We do that analysis of a big number of participants, and the larger the number, the better ability to be precise with our estimation of the pain.

But also once we will have this sense of greater, more activation, still the patient's going to say, this painful stimulation doesn't bother me. And that is what we observe, at least in my experience, people with wonderful activation in the brain, in the area that we expect, and they don't feel that intensity as something that is high or unpleasant to them.

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So we don't have to forget that pain can't be reduce to a number, a numerical rating scale, that drove [indiscernible], neither to a bold activation, even if we will end up being able to study bold responses in each single participant.

DR. WASAN: Yes? Go ahead, Mike.

DR. ROWBOTHAM: I have two questions. One is about the migraine diagnoses. Are you including the classic migraine with aura [indiscernible - off mic]? The other is, can somebody comment about primary pain, what's going into ICD-11? Because it's hard to distinguish how that difference [indiscernible - mic fades] -- overlapping pain syndrome --

DR. FILLINGIM: Just really quickly, it's a relatively small sample. Some of the subjects had aura, some did not, but they were all interictal.

DR. ROWBOTHAM: Okay. I'm thinking about all of the studies that were presented today because [indiscernible - mic fades] a lot of them included migraine along with -- sort of what they call common migraine or tension migraine

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[indiscernible].
DR. FILLINGIM: In OPPERA, it would have been anything that met ICHD criteria for any kind of migraine.
DR. KLEYKAMP: And for the epi studies, most often -- I don't remember exactly, but I don't remember logging anything related to aura. It was very general, and they didn't break down the different migraine types. They did sometimes have chronic tension type separate from migraine, but they were generally grouped, so you couldn't be very precise.
DR. WASAN: And the ICD-11 issue, I don't if anybody --
DR. ROWBOTHAM: [Indiscernible - off mic].
(Crosstalk.)
DR. ROWBOTHAM: [Indiscernible - off mic]. There's an elephant in the room.
DR. DWORKIN: I was going to start off tomorrow afternoon by talking about this. After our lunch break, I looked at the criteria for chronic primary pain, and it's interesting.

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There's three criteria longer than 3 months. And second is associated with significant emotional distress or functional disability. And the three criterion is not better accounted for by another condition.
So I don't think what we've really been talking about for the last hours is this. This is a waste basket category. There's nothing about central sensitization, centralized pain. It's just longer than 3 months, kind of functional and emotional disability, and no other explanation. But we can revisit this tomorrow at 1:00, but I'm not sure it's a problem for us.
DR. WASAN: I don't know if anybody here was actually on the IASP task force that advises --
MALE VOICE: No [indiscernible - off mic].
DR. WASAN: So that's why I was going to ask about that.
On the artificial intelligence question, we talk about that a lot, and it's emerging. I think it's important, too, that we keep in mind that even that has its own biases, too, because you can

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adjust all sorts of parameters and creating these algorithms for how you're going to identify patterns, and then the unbiased part is applying and seeing if that pattern fits a new chunk of data that you have. But there are all sorts of processes involved in adjusting the parameters to actually come up with the AI algorithm you're going to apply; so just something to keep in mind, too.
Dan, yes?
DR. CLAUW: I just want to talk a little bit about how functional imaging may creep into clinical care in a meaningful way. I completely agree with Vitaly it's not on the horizon that we're going to have a painometer, that we're going to be able to look in someone's brain and say that's a 3, that's a 5, that's a 7. But I actually think there are things, that in the not too distant future we will be able to use functional imaging.
Regular 3T scanners can do kind connectivity fairly well and do proton spectroscopy fairly well. I think proton spectroscopy, we are doing a study with a company now that we thought their drug would

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work a lot like pregabalin, and we had a whole number of a priori hypotheses about the high glutamate, and the insula was going to predict the people who responded to the drug, and it would change connectivity, and everything that we hypothesized happened.
That was really helpful during drug development for that company because they would have otherwise closed down this program if not for the incredibly strong, functional imaging signal that we had. Those early trials were only 4-week trials, and we said to them, "Please don't close this down." And Irene said the same thing when she was consulting, is that it really looks like the drug is working, but you probably haven't given it enough time to work.
So I think that looking in individuals, looking for patterns that predict responsiveness to different types of drugs, I think that will occur well before we have a painometer, but I don't want to in any way say that functional neuroimaging won't creep into clinical practice in a meaningful

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way because I actually think that it can, and it will the next 5 to 10 years.

DR. WASAN: Emerging technologies, too, so functional near-infrared spectroscopy, which is a portable unit. You can get a little bit of the cortical activation, some more on the surface areas. But you can take it from room to room when you're doing a clinical trial, and you can apply it. And that's being developed, too, and looked at.

DR. CLAUW: And all these technologies are better at looking at an individual longitudinally and looking at change in individual, but cross-sectionally, they're all abysmal as far as just looking at someone at a single point in and say they have this diagnosis or they don't. But longitudinally, I think they tell us a lot more.

DR. WASAN: Any other comments?

(No response.)

DR. WASAN: Okay. Any other comments or questions people have? We can actually finish five minutes early.

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(No response.)

Adjournment

DR. WASAN: Okay. Great. See you all at dinner. Thank you.

(Applause.)

(Whereupon, at 4:50 p.m., the meeting was adjourned.)

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