

*IMPACT XXIII - Central Sensitization/Somatosensory
Amplification and Multiple Comorbidities*

July 25, 2019

*A Matter of Record
(301) 890-4188*

Page 1	Page 3
<p>1 ACTTION</p> <p>2</p> <p>3</p> <p>4</p> <p>5 INITIATIVE ON METHODS, MEASUREMENT, AND</p> <p>6 PAIN ASSESSMENT IN CLINICAL TRIALS</p> <p>7 IMPACT-XXIII</p> <p>8</p> <p>9 Research Design Considerations for</p> <p>10 Chronic Pain Clinical Trials</p> <p>11 Addressing Central Sensitization/Somatosensory</p> <p>12 Amplification and Multiple Comorbidities</p> <p>13</p> <p>14</p> <p>15</p> <p>16 Thursday, July 25, 2019</p> <p>17 8:03 a.m. to 4:50 p.m.</p> <p>18</p> <p>19</p> <p>20 The Westin Georgetown</p> <p>21 Washington, DC</p> <p>22</p>	<p>1 C O N T E N T S (continued)</p> <p>2 AGENDA ITEM PAGE</p> <p>3 Comorbidities in Chronic Pain:</p> <p>4 A Systematic Review</p> <p>5 Annie Kleykamp, PhD 262</p> <p>6 Central Sensitization and Chronic</p> <p>7 Overlapping Pain Conditions</p> <p>8 Roger Fillingim, PhD 285</p> <p>9 What Has fMRI Revealed About</p> <p>10 Sensitization and Chronic Pain?</p> <p>11 Vitaly Napadow, PhD 307</p> <p>12 Q&A and Panel Discussion 339</p> <p>13 Moderator - Ajay Wasan, MD</p> <p>14 Adjournment 374</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p>
Page 2	Page 4
<p>1 C O N T E N T S</p> <p>2 AGENDA ITEM PAGE</p> <p>3 Introduction and Meeting Objectives</p> <p>4 Dennis Turk, PhD 4</p> <p>5 Neurobiology of Central Sensitization</p> <p>6 Clifford Woolf, MD, PhD 26</p> <p>7 Q&A 58</p> <p>8 What is "Centralized Chronic Pain" and</p> <p>9 How Can It Be Assessed?</p> <p>10 Daniel Clauw, MD 71</p> <p>11 Q&A 102</p> <p>12 Somatosensory Amplification and the</p> <p>13 Development and Maintenance of</p> <p>14 Chronic Pain (including assessment)</p> <p>15 Robert Edwards, PhD 124</p> <p>16 Q&A 158</p> <p>17 Regulatory Perspective on the</p> <p>18 Introduction of New Analgesic Indications</p> <p>19 Sharon Hertz, MD 169</p> <p>20 Q&A 180</p> <p>21 Panel and Audience Discussion 203</p> <p>22 Moderator - John Markman</p>	<p>1 P R O C E E D I N G S</p> <p>2 (8:03 a.m.)</p> <p>3 Introduction and Meeting Objectives</p> <p>4 DR. TURK: Good morning. Thank you.</p> <p>5 For those that don't know me, my name is</p> <p>6 Dennis Turk. I'm from the University of</p> <p>7 Washington. And I've had the honor of being the</p> <p>8 co-chair, I guess, whatever terminology we're using</p> <p>9 for IMMPACT and ACTTION for the last 23 years. I</p> <p>10 started out, and I had black hair and a nice beard,</p> <p>11 and it was very attractive. But people couldn't</p> <p>12 distinguish me from Bob Dworkin, who I've worked</p> <p>13 with for all these years, so I figured I had to do</p> <p>14 something different. So I made sure the beard went</p> <p>15 and my hair got a little lighter. But he's</p> <p>16 catching up on that, so I can't do that.</p> <p>17 In case you're wondering, you are here for</p> <p>18 the 23rd IMMPACT meeting. I want to welcome all,</p> <p>19 and thank you for coming, some of you from great</p> <p>20 distances, and spending the time with us. Many of</p> <p>21 you have been to other IMMPACT meetings, so you're</p> <p>22 quite familiar with how things work.</p>

Page 5

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

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

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

Page 6

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

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

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

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

Page 7

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

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

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

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

Page 8

1 23rd meeting, and you know that the emphasis of
2 this meeting has been something we're asked -- Bob
3 and I were asked last night, how do we come up with
4 these topics. For those that don't know, IMMPACT,
5 as part of ACTION, has an executive committee in
6 which we have periodic calls, about three or four
7 or five times a year, depending upon how things are
8 going.

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

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

Page 9

1 If any of you, by the way, even though we
 2 say that the executive committee comes up with
 3 these topics, if you have certain topics or things
 4 that you think would be of interest, topics should
 5 all be related to some variation of doing clinical
 6 trials, or research, or research methods, or data
 7 analytic approaches that are not about specific
 8 drugs or products or treatments of any kind, though
 9 those may get considered as we start talking about
 10 these. But the emphasis is on how do you do the
 11 best job of designing clinical trials that are
 12 going to allow us to have the best information to
 13 essentially help patients, which are the end users
 14 of everything that we're trying to do.
 15 As you'll hear from the meeting, from
 16 different presentations, sometimes we talk about
 17 some the high-level things, but, really, always
 18 keep in mind that the intent of this is that we can
 19 improve how well we provide some type of care or
 20 treatment for those individuals who have any one of
 21 a variety of different chronic pain conditions.
 22 Now, at this particular meeting, the way

Page 10

1 it's going to be structured is you've got an agenda
 2 in front of you. There are moderators for each of
 3 the particular sessions. I will introduce the
 4 moderator for this morning session into the
 5 beginning of the afternoon. He, John Markman, who
 6 I'll mention later, will then introduce the
 7 different speakers, and then there will be plenty
 8 of time for discussions.
 9 We emphasize and try to encourage you to not
 10 only asking questions during the sessions, but also
 11 when you're at coffee breaks, over dinners, we've
 12 intentionally tried to have as much of that time as
 13 possible so that you are able to interact,
 14 discuss -- I already heard about two manuscripts
 15 that are getting written based on people meeting
 16 this morning, so that's very interesting, and we're
 17 happy to encourage you to do that.
 18 But think about what happens. We're over
 19 two days, and we intentionally have the meeting
 20 over two days because often what happens is after
 21 the first day, there's a lot of discussion and
 22 debate after people have left the room for the

Page 11

1 evening, and chatting, and having dinner with each
 2 other, and coming up with things that they then
 3 want to make sure we cover the next morning.
 4 What's the objective of this meeting, of all
 5 of our meetings? The objective is that by the end
 6 of the meeting, there will be enough information to
 7 be able to construct a manuscript, which will be
 8 submitted to one of the regular
 9 journals -- depending upon the topic, it will
 10 vary -- that will make recommendations and
 11 considerations, things to consider in clinical
 12 trials, and research, and methodology related to
 13 the topic of interest, and some guidance that we
 14 hope will be useful. We have no ability to say you
 15 must do anything, but rather to get some
 16 recommendations about what you might consider if
 17 you're designing a clinical trial.
 18 What I always put in the back of my mind is
 19 if in fact someone came to this meeting or read in
 20 the manuscript that we're going to come up with
 21 that you are going to all be authors on -- and I'll
 22 tell you about that -- and they were going to

Page 12

1 design a trial, what could they do then?
 2 Not what can they do 5 years, 10 years when
 3 we have all the more data that everybody thinks we
 4 should always have, but they're going to go into
 5 their lab on Monday morning, or they're going to be
 6 writing their next grant for the next grant
 7 deadline, and they have to make some decisions.
 8 So although it's nice to be able to refer to
 9 all the important research that needs to be done
 10 and what we need to know, what do you do now if
 11 you're going to design that study?
 12 So the objective is that we will come up
 13 with information. They don't have to
 14 necessarily -- they're not guidelines in the sense
 15 of any formal guidelines, but there's some
 16 recommendations, things to consider, if you're
 17 planning to develop that type of trial.
 18 Now, there has to be enough discussion and
 19 enough agreement, consensus if you
 20 will -- consensus, by the way, you realize is not a
 21 hundred percent agreement; consensus means the
 22 majority. There must be enough agreement so that

Page 13

1 there can be such a manuscript prepared, even if it
 2 has to say we couldn't decide but you need to
 3 consider the following kinds of things.
 4 Now, we're scheduled to end this meeting
 5 tomorrow afternoon, but we've arranged that your
 6 rooms can be available for several additional
 7 nights after that. Just in case we can't come to
 8 any kind of decisions --
 9 (Laughter.)
 10 DR. TURK: -- we're happy to have the
 11 meeting go a little bit long because most of you
 12 want to spend your weekend in Washington, D.C., for
 13 those that are not of the area.
 14 So that's available. This is not a threat,
 15 but it is a comment to you that we will encourage
 16 you to stay here until we end, and we have some
 17 information.
 18 The process will be that information will be
 19 gathered together. There will be a manuscript
 20 draft developed -- it usually takes, 3, 4, or
 21 5 months; it can take a longer, depends -- that
 22 will be circulated to all of you. And you have a

Page 14

1 choice. You can -- and we hopefully all
 2 will -- say, yes, in fact, I want to be and author
 3 of this particular manuscript, and we'll provide
 4 comments on this.
 5 Now, if you look around the room and you see
 6 the number of people here, you can imagine what
 7 happens when everybody takes 2 or 3 weeks, and then
 8 somebody else takes another 3 weeks, and it drags
 9 out. So when we send you these drafts of the first
 10 version and all the subsequent versions, we hope
 11 and encourage you for some deadlines about when is
 12 it reasonable to get it to us because we want to
 13 then integrate and synthesize the comments.
 14 You'll see another version of this. So when
 15 you leave this room, and even if it's the first
 16 draft, you're not agreeing a hundred percent to
 17 everything that's there, but you're basically
 18 helping to get to the point where we have some
 19 common consensus agreement, recommendations,
 20 guidances and considerations that we can put.
 21 So don't feel if you see the first version
 22 that, "Hey, they forgot my favorite point," or "I

Page 15

1 asked the question about," and they left it out,
 2 because you'll have a chance, at least two and
 3 sometimes three -- and heaven forbid if it goes to
 4 a journal and it comes back with a gazillion
 5 revisions that we have to make. If they're minor,
 6 obviously, we won't burden you, but if there are
 7 things that require major attention, we may come
 8 back to you for that.
 9 So this drags out, and it's a process, but
 10 you can expect that you will not be forgotten. You
 11 will be here. If for some reason, whether you have
 12 a personal lack of interest in the topic or you
 13 don't want to be involved in that manuscript,
 14 that's fine. We will acknowledge that you attended
 15 the meeting. So therefore, whether you're an
 16 author or not, there will be acknowledgement.
 17 There's a website that's ACTION,
 18 A-C-T-I-O-N.org. On that website, we list
 19 topics, the speakers. We ask permission from the
 20 speakers to put their slides up on the website so
 21 that you can have access to those, so if you
 22 couldn't copy everything down and you want to see

Page 16

1 that again.
 2 A lot of people, I've been in meetings when
 3 they're taking photos on their cell phones of the
 4 slides. That could be really distracting and can
 5 really be difficult. So I encourage you not to do
 6 that and wait until these slides are up on the
 7 website.
 8 Bob, that takes what, 3, 4, or 5 weeks to
 9 come up?
 10 (Dr. Dworkin affirmatively nods.)
 11 DR. TURK: Okay. So there will be a
 12 reasonable time. I know you're hot to get this
 13 information, but it can be when you're sitting in
 14 front of somebody and you're holding up, so I
 15 caution you about that.
 16 What are we going to do? That's sort of
 17 where we're going. Any questions about either
 18 IMMPACT, or ACTION, or this meeting? I'll direct
 19 all of those questions to Bob Dworkin because he's
 20 much more articulate than I am in handling these
 21 things. If there are any easy questions, I'll take
 22 care of those. But anything that requires any

Page 17

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

Page 18

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

Page 19

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

Page 20

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

Page 21

1 If there was all consensus and we all agree, we
2 could have a very short meeting, and we'd all leave
3 in the next hour. But since we don't think that's
4 likely to be the case -- I don't think; I shouldn't
5 say we; I don't want to speak for Bob -- those are
6 the kind of things that we want to be focusing on.
7 We're not going to go around the room asking
8 everybody who they are, to introduce themselves.
9 It's too big a group. In the past we have done
10 that, and then I had this grand idea, well, why
11 don't we ask everybody to introduce the person on
12 the left or the right of them, and therefore we'd
13 get to know who knew who, and you'd find each
14 other, but decided that's going to take too long;
15 we're not going to do that.
16 So that's really what we're going to be
17 doing. Any questions about the objectives, some of
18 the topics, things that are going to be covered in
19 this particular meeting, and anything that's not
20 going to be covered in this meeting?
21 Do remember it's going to be videoed and
22 audioed, so when you say something, people are

Page 22

1 going to know who you are. So if for some reason
2 there's something that you're worried about
3 somebody is going to hear -- Edward Snowden is
4 listening in; who knows? -- then don't say it.
5 Lee?
6 DR. SIMON: So we're used to having a
7 transcript come out of this meeting. Could you
8 inform us as to why it's now being videoed as well
9 as the transcript?
10 DR. TURK: The video is just the morning
11 session, and Dr. Hertz from the FDA wanted it to be
12 videoed because she wants to be able to present it
13 to the people at the FDA. After this morning, I'm
14 not sure exactly what the time is going to be, we
15 will go straight to audiotape. That was the
16 reason. It was a specific request to share it with
17 the people at the FDA.
18 DR. SIMON: Just as long it wasn't the
19 plaintiff's attorneys who were requesting that.
20 DR. TURK: Well, who knows? As I said,
21 everything is up on the Web, so if anybody wants to
22 see what happened at this meeting, it's going to be

Page 23

1 available, and we don't care. If the plaintiff's
2 attorneys want to see it, good, more power to them.
3 Maybe they'll learn something. It will be useful
4 to them. So that's the reason for that.
5 Bob?
6 DR. DWORKIN: We are required to post the
7 transcripts of the meetings, and that's why it's
8 audiotaped because a transcript is being prepared.
9 I don't think we're going to post this videotape.
10 This was really at the request of the FDA to share
11 with the people in Dr. Hertz's division.
12 DR. TURK: Thanks, Bob.
13 Another thing, let me remind you about the
14 microphones. They are voice activated, but once
15 6 people or 6 noises have come in to any one
16 microphone, it'll cut you off, anybody else who
17 wants to be the 7th or the 8th persons, you have to
18 wait. So if you see 6 lights and nobody's calling
19 you. How come? It's because you're not
20 getting -- once somebody stops speaking, that
21 microphone then becomes active.
22 So don't feel we're cutting you off or we're

Page 24

1 not paying attention to you, but we're really tied
2 to this voice activation. And it's interesting
3 because I'm just noticing that the lights are going
4 on and off all the time, so they are very
5 sensitive. So if you want to whisper to your
6 next-door neighbor, I strongly encourage you to
7 either put your hand over your mic or move away
8 from it. Do not move the mic -- I've taken some
9 direction -- because they are set up and designed
10 to work in a specific way.
11 Other questions about logistics, format,
12 things that are going to happen, or who's here?
13 (No response.)
14 DR. TURK: Okay. Then what we're going to
15 do is I will introduce the moderator for the first
16 session. The moderator's job is really to
17 introduce the speakers, and then enliven a
18 discussion, lead a discussion and the panels that
19 we have. I think the first one is this afternoon
20 some time.
21 I'm delighted that the first chair we're
22 going to have is Dr. John Markman. Most of you

Page 25

1 know him. I think for the introductions, we're not
2 going to go into lengthy detail introductions about
3 who all the speakers are. Pretty much, you know of
4 each other. So the introductions will largely be
5 just who you are, where you're from, and if you
6 have some humorous anecdotes you want to say.
7 John, you're up first. Thank you all very
8 much.
9 DR. MARKMAN: Good morning. Let me add my
10 thanks to Bob, and Dennis, and the committee for
11 bringing this together. My name is John Markman.
12 It's a privilege to introduce our first speaker,
13 who is a professor of neurobiology and neurology at
14 Harvard Medical School. He launched his field in
15 1983 with his seminal paper on central
16 sensitization when he was in the 7th grade.
17 (Laughter.)
18 DR. MARKMAN: And here, approaching a half
19 century later, there's not a person in this room
20 who doesn't engage with his ideas every day, and I
21 can't think of any better praise than that.
22 Clifford?

Page 26

1 Presentation - Clifford Woolf
2 DR. WOOLF: It's a real pleasure to be here.
3 I must admit this is a situation that is rather
4 unusual for me. I tend to be someone who prefers
5 to look forward rather than looking back, but I
6 think it might be useful to you to give some
7 context to the notion of what central sensitization
8 is and how it was discovered.
9 For me, this began when I joined the lab of
10 Patrick Wall at University College, London, in late
11 1979. The lab was in the mid-1980s. I had some
12 hair then. Pat is sitting next to me. Between Pat
13 and me is my graduate student, Allison Cook. Anne
14 King at the back is my first post doc. Jakita
15 Littleton was my first research assistant, so this
16 was very fresh.
17 Sitting at the end is John O'Keefe, who was
18 a member of our team who then got the Nobel Prize.
19 And if anyone had told us at the time that he was
20 going to win the Nobel Prize. I would have said,
21 "Well, central sensitization will be discussed in a
22 clinical context," as it is today. So unexpected

Page 27

1 things happen.
2 My first project at UCL was working with
3 Maria Fitzgerald, who has become a very
4 distinguished member of the pain community. We
5 started exploring the circuits that we thought may
6 contribute to the generational pain in the dorsal
7 horn.
8 This was a time when electrophysiology
9 techniques have improved such that we could now
10 begin to record from individual neurons using
11 intracellular recordings and identify the receptor
12 field properties. In that way, we hope to put
13 together some kind of circuit diagram as to how
14 primary afferent input was processed and then would
15 be transferred to the brain and contribute to the
16 sensation of pain.
17 The work went technically well, however, I
18 quickly appreciated that we had a major problem,
19 and we called this the ADC, which is any damn cell.
20 The reason for that was that we could only record
21 from one cell at a time. Because we were trying to
22 record intracellularly, we often had no cells

Page 28

1 preparation, and maximum, something like two or
2 three. And frankly, we had no idea whatsoever what
3 those were. We had no idea whether they were
4 excitatory or inhibitory. We had no idea what
5 connections they made.
6 Therefore, although we have characterized
7 the properties of the cells, and we can say they
8 have a particular receptive field property. They
9 have a certain morphological appearance. We
10 frankly had absolutely no idea how they work
11 together as a circuit to drive the generation of
12 pain.
13 We published this paper, but I decided it
14 was time to do something different, and this led me
15 to take an alternative approach. This is the FMN
16 approach, which is the flexor motor neuron
17 approach. This was actually driven by the work of
18 Sir Charles Sherrington, who had been at Oxford
19 and, again, another Nobel laureate, who had a
20 profound impact on our understanding of reflex
21 mechanisms. And he is the person that introduced
22 the concept of nociception and nociceptors. His

Page 29

1 work was entirely based on looking at reflex
2 responses and recognizing there were stereotyped
3 responses to defined sets of stimuli.
4 The insight that I had is instead of
5 recording from any damn cell in the dorsal horn,
6 without knowing what it was and how it functioned,
7 if I recorded from flexor motor neurons, I knew
8 exactly what they do. Their reactivity led to the
9 contraction of a flexor muscle, which would cause a
10 certain pattern of movement.
11 So at least I could study neurons, whose
12 function I could clearly define; and, to me, this
13 was an extraordinary breakthrough as it were
14 because instead of dealing with a black box with
15 certain elements, I was dealing with the output of
16 a black box and at least had some sense of the
17 function.
18 So again, it's possible to record from these
19 intracellularly to define their morphology, unlike
20 with whole neurons, the morphology was much more
21 stereotyped, and they resembled each other. At
22 that time, the sense of motor neurons was they

Page 30

1 drove activity in muscles, and their major input
2 were proprioceptive. But not surprisingly from
3 anyone who had studied the flexor reflex, it turned
4 out they had beautiful cutaneous receptive fields;
5 in fact, almost better than those in the dorsal
6 horn. So they would enable us to study the
7 relationship between input to the spinal cord and
8 its output.
9 This led to a paper that I did with John
10 Swett, who was a visitor in our lab, studying the
11 properties of these flexor motor neurons.
12 Actually, this paper was published after the
13 central sensitization paper, but this was
14 definitely the proceeding work. The preparation we
15 used was unanesthetized decerebrate rats and
16 spinalized, so there was no anesthetic.
17 Up until that time, almost 99.9 percent of
18 all papers were done in anesthetized preparations.
19 We all know that the definition of an anesthetized
20 preparation is no response to a noxious stimulus,
21 so that was pretty crazy.
22 (Laughter.)

Page 31

1 DR. WOOLF: Here, we identified a model
2 whereby by decerebrating the animals, we could
3 remove the anesthetic and look at the function of
4 the spinal cord without that confound. We studied
5 the properties of individual motor neurons and
6 discovered that the motor neurons have no
7 spontaneous discharge. They were only activated by
8 defined stimuli.
9 They all had mechanoreceptive fields,
10 restrictions of ipsilateral foot or paw, and they
11 required high intensity stimuli, noxious stimuli,
12 to avert the response. As opposed to the dorsal
13 horn neurons, each one of which was unique and
14 different, these were very similar.
15 That was great, and I thought, now, when
16 John Swett left, I could begin to study this more
17 in a setting of actual pathology, so one of the
18 first things I did was to do the effects of
19 repeated heat stimuli and saw an elevation in the
20 response of each stimulus. This reminded us and
21 looked exactly similar to the work of Ed Perl, who
22 was at the University of North Carolina, who had a

Page 32

1 longstanding, philosophical battle with Pat Wall.
2 Pat was interested in the patterns of
3 activity and the famous mild gate control theory;
4 whereas Ed was definitely of the labeled line
5 notion. He felt that there were defined sets of
6 nociceptors that had very particular problems, and
7 it wasn't the pattern of activity but the
8 activation of these labeled lines.
9 As part of his work, he discovered that
10 exposure of nociceptors to inflammatory mediators,
11 or inflammation, led to peripheral sensitization.
12 I thought this would be a wonderful model of
13 looking at the output of the CNS in the context of
14 peripheral sensitization, and that's what I set out
15 to do.
16 As I did this an accumulated my data, these
17 are the receptor fields of individual flexor motor
18 neurons that I studied. Something really struck
19 me, and it was, as indicated here, a state of total
20 confusion. That was that although I had started
21 off with my study with John Swett, it was clear
22 that the vast majority of flexor motor neurons had

Page 33

1 a cutaneous receptor field restricted to the
2 ipsilateral paw that was high threshold.
3 As I recorded the total populations of
4 neurons that I had from my studies, I found some
5 that were bilateral. Somewhere, the thresholds
6 were very low, and some in the tail. This was a
7 real mess. I couldn't understand what was going
8 on, and it took me a surprisingly long time to get
9 resolution.
10 The resolution came when I realized that the
11 receptive fields that were restricted to the hind
12 paw and that were high threshold were those that I
13 recorded at the beginning of the experiment, and
14 the ones that had the very large receptive fields
15 that were much lower, and that way you could
16 activate the flexor motor neurons with light touch,
17 for example, always occurred at the end of the
18 experiment.
19 What is the difference? Well, during the
20 experiment, I was doing repeated noxious stimuli.
21 To characterize the receptive fields, I was
22 exposing them to heat and to pinch, and by the end

Page 34

1 of the experiment, the hind paw was inflamed. So
2 there had been a transition between these very
3 restrictive receptive fields to these very broad
4 ones over the course of the experiment, generated
5 as a consequence of my producing tissue injury.
6 That really was the moment that the penny dropped.
7 I realized I was studying plasticity of the nervous
8 system, something that I had not set out to do but
9 was revealed by this analysis.
10 This then led to the publication of the
11 first paper that discussed a central component to
12 pain hypersensitivity, which was published as a
13 single author paper in nature. The reason for that
14 is that Pat Wall said he didn't believe a word of
15 it --
16 (Laughter.)
17 DR. WOOLF: -- and he said sink or swim, and
18 you're on your own here --
19 (Laughter.)
20 DR. WOOLF: -- which was very generous of
21 him.
22 (Laughter.)

Page 35

1 DR. WOOLF: He ended up changing his mind,
2 as you'll see in a moment.
3 One of the key findings of this paper was
4 that the pain hypersensitivity as reflected by this
5 expansion of receptive fields and the reduction of
6 the intensity of stimulus required to evoke the
7 flexion response was driven by an increase of
8 excitability within the central nervous system.
9 This could be revealed by electrical
10 stimulation; in other words, going beyond the
11 tissue injury site, by just stimulating the
12 peripheral nerve, you could now see, over time as a
13 consequence of injury, you get a profound increase
14 in the response to a standard input.
15 In the control situation, this particular
16 motor neuron had no response. I now deliberately
17 produced tissue injury, and you can see at 30
18 minutes, there's an increased response and gets
19 even bigger at 60 minutes. If I produced a local
20 anesthetic at the side of the peripheral injury,
21 this persistence. So this indicated that there was
22 some central hyperexcitability.

Page 36

1 These are some of the key points, and the
2 conclusions that I made from this was that injury
3 induced increases in excitability, and that was a
4 consequence of changes within the spinal cord, and
5 that noxious stimuli then had the possibility of
6 producing plasticity within the nervous system.
7 And as a consequence, the conclusion was that pain
8 hypersensitivity had a central as well as a
9 peripheral component.
10 Frankly, that was a new insight. Even
11 though it may now seem quite obvious, at the time,
12 there was no discussion. There was no thought of
13 it. And as I said, there was the fact that Pat
14 decided not to be a co-author on this because he
15 thought this was impossible.
16 I then moved on with a study with Steve
17 McMahon, another very distinguished graduates of
18 the Wall lab, and we looked now deliberately at
19 injury-induced plasticity in the flexion reflex and
20 chronic decerebrate rats, and expanded out the
21 nature of this central hyperexcitability state, and
22 deliberately in these chronic decerebrate animals

Page 37

1 showed that different forms of injury produced very
2 prolonged and very profound changes in the
3 hyperexcitability reflexion reflex. It changed
4 from being this high threshold of brief response to
5 one where very low-intensity stimuli could evoke
6 it. The response was greater, it was amplified,
7 and it had a much longer duration. And these
8 changes persisted for weeks on end.
9 Frankly, this really aligned itself,
10 surprisingly to me, to the appreciation of what
11 happens in patients. At that time, we began to
12 interact with clinicians at the university college,
13 and it was the time which I began to consider that
14 these neurobiological mechanisms revealed in this
15 preclinical model potentially may have clinical
16 implications.
17 What Steve did as part of the study was to
18 look at whether there were changes in primary
19 afferents that may be driving these persistent
20 changes. He found there weren't, that under those
21 circumstances where the flexion reflex was
22 hyperexcitable and had these profound changes,

Page 38

1 there were absolutely no changes in the properties
2 of primary afferents, again suggesting this was
3 driven by changes within the central nervous
4 system.
5 We then did a series of papers, and this is
6 where Pat decided he had made a mistake --
7 (Laughter.)
8 DR. WOOLF: -- and he was sufficiently a
9 bigger man to say this was the biggest mistake in
10 my career. He then joined us, and we started
11 exploring some of the mechanisms underlying this.
12 We teased out that the drivers of the central
13 hyperexcitability differed depending on which sets
14 of afferents were activated. The afferents from
15 the muscles produced a much longer change than from
16 the skin.
17 We discovered that this was not due to
18 changes in the central terminal excitability. At
19 that time, it part of the spinal gate control
20 theory. There was a major focus on pre-synaptic
21 inhibition, and we eliminated that as being a
22 mechanism -- this was post-synaptic -- and the last

Page 39

1 paper with Pat and Steve, we went back to the
2 dorsal horn and found that all the changes that we
3 saw in the flexor motor neurons were captured by
4 changes in the dorsal horn, showing that indeed was
5 the primary site of this central hyperexcitability.
6 This paper in 1989 is the first time I think
7 that at least in press, we used the term "central
8 sensitization." From a historical point of view, I
9 think the first time that I realized that this
10 phenomenon could be compared with peripheral
11 sensitization was in a discussion with Howard
12 Fields, who had come to visit us in the early
13 1980's, soon after the original Nature paper was
14 discussing.
15 Howard, thank you for introducing the term,
16 which I then borrowed and used as my own.
17 (Laughter.)
18 DR. WOOLF: In the study, we also recognized
19 that a major feature of the synaptic plasticity
20 that was driving this central sensitization was
21 heterosynaptic. This was important because this
22 was exactly the same time that long-term

Page 40

1 potentiation had been discovered and proposed to be
2 a major mechanism underlying memory. This argued
3 that the retention of information in the central
4 nervous system occurred by repeated use of a
5 synapse, long-term potentiation of a synapse.
6 What we discovered was that if you drew a
7 conditioning input, an input generated by a noxious
8 stimulus, that would not only change the synapses
9 activated by the noxious input, but would also
10 change the input by neighboring afferents that
11 haven't been activated by the conditioning input.
12 So this was heterosynaptic, that nearby
13 synapses were changed by this conditioning input.
14 This was very different from long-term
15 potentiation, and this I think was one of the major
16 mechanistic insights because it explains why a set
17 of neurons that normally receive only input from
18 nociceptors can now begin to fire in response to
19 low threshold mechanoreceptive input. And the
20 reason is that these low threshold mechanoreceptor
21 inputs, their synaptic input can now be
22 facilitated.

Page 41

1 This I think mechanistically was a big
2 input, and this was captured in this study with
3 Anne King, My first post doc, where we identified
4 that normally most of the receptor fields in the
5 dorsal horn had very large subliminal components.
6 These were inputs that were too small to drive an
7 output from the neurons normally.
8 But if the neurons became hyperexcitable,
9 the subliminal inputs could be captured and
10 completely transformed the receptor field
11 properties of these neurons; so that neurons that
12 were normally driven clearly by noxious inputs
13 could now begin to be activated by per threshold or
14 with noxious inputs. Neurons that have very small
15 receptor fields could now expand to be larger.
16 All of these features captures some of the
17 aspects of post-injury pain hypersensitivity, the
18 reduction in the threshold for activation of pain,
19 the spread sensitivity to non-inflamed areas,
20 secondary hyperalgesia, et cetera.
21 What was particularly exciting is it took
22 less than 10 years for Bob LaMotte and Eric

Page 43

1 acute activity-dependent plasticity.
2 The kind of thing that Bob LaMotte and Eric
3 Torebjork had shown, that capsaicin [indiscernible]
4 secondary hyperalgesia was exclusively sensitive to
5 NMDA receptor antagonists, and indeed,
6 post-surgical pain hypersensitivity is also
7 exquisitely sensitive. The trouble with NMDA
8 receptor antagonists is that they are involved in
9 long-term potentiation and memory.
10 Also, ketamine has psychotropic effects, so
11 it's a therapy that is effective but has adverse
12 effects, which make the balance of its use
13 difficult; although it continues -- I'm surprised,
14 when I was preparing for this, how many studies
15 continue to use ketamine, and, at least in a
16 postoperative setting, reduce the need for
17 postoperative opioids, which is a positive thing.
18 As we explore this, we began to appreciate
19 that there were enormous similarities between the
20 post-injury hypersensitivity phenomenon, the
21 central sensitization, in Eric Kandel had been
22 doing on aplysia, where he was studying synaptic

Page 42

1 Torebjork to show that this phenomenon could be
2 generated in humans. What they did was to use
3 intradermal injection of capsaicin, which at that
4 time was not appreciated to activation of TRPV1,
5 but it is a means of experimentally activating
6 nociceptors.
7 What they revealed was exactly as we have
8 shown in the flexor motor neurons and the dorsal
9 horn neurons, that such brief input in nociceptors
10 could produce an increase in sensitivity to pain
11 and a spread of tactile sensitivity, an area of
12 secondary hyperalgesia. This was exciting because
13 it showed that there was shared neurobiological
14 mechanisms between rodents and humans.
15 Another discovery that we made, quite early
16 on, was the synaptic plasticity underlying this
17 central sensitization included activation of the
18 NMDA receptor. This in turn has led to -- I
19 wouldn't go through them -- a whole series of
20 studies that have indicated that, indeed, NMDA
21 receptors do contribute, both in preclinical models
22 but even more so in humans, the generation of the

Page 44

1 facilitation. His notion was this is all about the
2 study of memory, but he was looking at the gill
3 withdrawal reflex of aplysia, this preparation.
4 Terry Walters and I wrote an article in the
5 early 1990s looking at the commonalities between
6 the plasticity between mammals central
7 sensitization and the phenomenon that Eric Kandel
8 had described. This provoked an enormous response,
9 one letter from Eric Kandel, that essentially said
10 if we ever did repeat this, he would personally
11 make sure that my career ended --
12 (Laughter.)
13 DR. WOOLF: -- that his work had nothing
14 ever to do with pain; this was only about memory.
15 And he was right because he got the Nobel Prize --
16 (Laughter.)
17 DR. WOOLF: -- the Nobel organization gave
18 this for changes of function that are central for
19 learning and memory. However, I am pleased to say
20 that when I finally met Eric face to face, he did
21 admit he had been studying pain after all, and that
22 the phenomenon in aplysia was very similar to

Page 45

1 central sensitization.
2 So what were the clinical implications? As
3 I began to explore these, I interacted with Lesley
4 Bromley, who is an anesthesiologist at the
5 University College hospital. One of the ideas that
6 came up is if we potentially could prevent the
7 development of central sensitization, what
8 implications would that have for patients?
9 This led us to the concept of preemptive
10 analgesia. If one treated early, prevented the
11 establishment of heterosynaptic facilitation, would
12 this be beneficial to patients in the sense that
13 they would have less pain? The ideal setting we
14 thought would be postoperative pain.
15 Frankly, at that time, the standard of care
16 was that patients were anesthetized, and they were
17 only given treatment after they woke up when their
18 pain reached a certain level. PCA had been
19 introduced. The doses they selected to control the
20 pain were very high, and that was the notion. You
21 only were treated when you had the pain. There was
22 no sense of anticipating the pain.

Page 46

1 This study that we published in Lancet
2 indicated that if you gave morphine before the
3 operation, the amount of PCA, the choice that the
4 patient made in terms of how much analgesic they
5 selected postoperatively was significantly reduced,
6 and this turned out to be quite a controversial
7 issue.
8 There have been many studies, some of which
9 claim that indeed there are benefits. In fact,
10 again, in preparing for this lecture, I relooked at
11 the literature, and actually in recent years, there
12 have been a number of studies on the phenomenon of
13 early treatment reducing the requirement for
14 postoperative analgesic seems to be correct in
15 certain settings.
16 Another aspect of this that is somewhat
17 surprising is the whole focus initially that the
18 mechanisms of central sensitization were on
19 increases in excitability. As a result, work that
20 include Joachim Scholz, who is in the audience
21 here, we began to explore, particularly in the
22 setting of neuropathic pain models, the possibility

Page 47

1 that in addition to increases in excitability,
2 reduction in inhibition could contribute to the
3 phenomenon.
4 Indeed, that's exactly what we found, that
5 associated with peripheral nerve injury was a loss
6 of GABAergic inhibition that included actual loss
7 of some inhibitory neurons, and this contributed to
8 a state of hyperexcitability so that this expanded
9 the notion of central sensitization beyond purely
10 being heterosynaptic facilitation to one that
11 included disinhibition as well.
12 There have been many studies on the clinical
13 manifestations. This clearly is the major theme of
14 this talk. It includes surgery. That's been one
15 of the biggest areas where it's easiest to detect.
16 They started with an individual who has no pain,
17 and you can then detect profound changes in their
18 pain sensitivity and quantify that. But it also
19 included a broad range of patients, patients with
20 migraine, osteoarthritis, and neuropathic pain.
21 Each of them have the features. I think one
22 of the issues that Dennis pointed out is how do we

Page 48

1 define central sensitization? How do we recognize
2 it? What are the criteria for establishing where
3 the patient has it? What are the implications for
4 the patient if they do have it from a therapeutic
5 point of view? And these are hopefully the kinds
6 of issues we're going to touch on here. Clearly,
7 it looks as if this is a phenomenon that could be
8 widespread amongst a broad range of different
9 individuals.
10 One of the issues as the concept evolved was
11 should the term "central sensitization" be
12 restricted to the initial discovery, which was a
13 use-dependent hyperexcitability that lasted for
14 tens of minutes, or could it capture all those
15 expressions of an amplification of the nociceptor
16 circuits?
17 This is something there has been some
18 vigorous debate about. In the end, my feeling is
19 that central sensitization includes all of those
20 conditions where the central nociceptor circuits
21 are altered such that there is a reduction in
22 threshold and an amplification of responses, even

Page 49

1 if these are mechanistically or different from the
2 original description.
3 So I think central sensitization should be a
4 broad family of phenomena where the focus is on
5 changes within the central nervous system, but
6 again, this is something that we could discuss. At
7 least for me, this is my definition of an
8 amplification within the central nervous system,
9 are those circuits that connect sensory input from
10 the periphery to those cortical areas where
11 pain -- and it drives the phenomenon of exaggerated
12 response to noxious stimuli, hyperalgesia, and the
13 response between noxious stimuli and allodynia, as
14 well as changes in the summation and the spread of
15 sensitivity to non-injured tissue, secondary
16 hyperalgesia.
17 So to me these are some of the key features
18 that I think represent this plasticity within the
19 central nervous system.
20 What are the mechanistic underpinnings? How
21 have they changed? Although I've worked very
22 intensively on central sensitization in the decades

Page 50

1 after its discovery, after that time, I found that
2 the technology available then was rather limited,
3 so I diverted to other areas. However, as I'll
4 indicate in a moment, there are some new
5 technologies that I think are going to change
6 things, and this has reintroduced me to begin to
7 explore it.
8 This is a study I published last year with
9 Zhigang He, where we found that the corticospinal
10 tract in mice had a direct facilitatory effect on
11 dorsal horn neurons and was a major contributor to
12 tactile allodynia in the setting of nerve injury.
13 This, again, was something completely unexpected,
14 that there'd be a direct cortical input to the
15 dorsal horn. My initial focus was entirely the
16 changes driven from the primary afferents, but here
17 was the brain itself contributing to the changes
18 within the spinal cord.
19 That means this may be a means by which
20 phenomena, again that Dennis has introduced, that
21 our brains, our state, our mood, our attention, all
22 of these could directly contribute to alterations

Page 51

1 in excitability in a real way; and that were
2 originally thought to be psychosomatic
3 manifestations are actually real neurobiological
4 changes. So we're quite excited by that.
5 One of the other bits of work I've done
6 recently, like many people, is to use optogenetics
7 as a means to now be able to selectively activate
8 or inhibit defined circuits. This happens to be a
9 study where we have the express channel reduction
10 in nociceptors. We can use a laser then to
11 activate these nociceptors in a very defined way,
12 in a very defined location, such that we can
13 activate a single action potential from, we
14 estimate, less than 10 afferents, a tiny, tiny
15 input in the mouse.
16 What really surprised me, then, from this
17 study was that this tiny input, one action
18 potential in 10 afferents is sufficient to
19 completely change the entire behavior of the
20 animal. The animal not only has a withdrawal
21 reflex; its whiskers start moving. It turns its
22 head. If it's sleeping, there's a change in its

Page 52

1 EEG.
2 This completely changed by notion of how the
3 nervous system works because what it reveals to me
4 is that there are these circuits in the CNS that
5 are waiting for a trigger to activate them, and
6 that a tiny trigger, the smallest trigger you can
7 imagine, is sufficient to invoke a very profound
8 change.
9 I've always been looking for, in the context
10 of input driving the system, profound discharges in
11 many afferents. In fact, what it looks like is a
12 tiny input, and a very few set of afferents is
13 sufficient to provoke pain-related behavior. We
14 think that this is likely to be part of the central
15 sensitization patterns, where you do not need
16 massive inputs; tiny inputs may be sufficient.
17 What are the diagnostic features of central
18 sensitization? Again, I'm sure this is something
19 that will be discussed through this meeting, but to
20 me, it's all about how can you detect changes in
21 amplification on nociceptor circuits,
22 disproportionate pain, in the presence of dynamic

Page 53

1 tactile allodynia, temporal summation, and
2 secondary hyperalgesia?
3 There's been the introduction of the central
4 sensitization inventory. I'd be interested to know
5 what people think of it. To me, the notion that
6 you can use a questionnaire exclusively to try and
7 capture something which is characterized by changes
8 in sensitivity doesn't seem quite right, but it has
9 become widely used. What's interesting now is that
10 there are many studies using functional imaging
11 that are capturing mechanistically changes in
12 nociceptor circuits that correlate specifically
13 with the presence of these disproportionate pain
14 syndromes.
15 One of the other features of central
16 sensitization is how it is revealed,
17 mechanistically, how many analgesics work. In
18 addition to the NMDA receptors, antagonists, which
19 have a selective action on the heterosynaptic
20 facilitation, there are now multiple papers
21 illustrating that gabapentin and pregabalin both
22 work on central sensitization, as does duloxetine,

Page 54

1 and indeed opioids. Some of the commonest
2 currently available analgesics, at least some of
3 their major mechanisms is the suppression of
4 central sensitization.
5 Something else that current literature is
6 beginning to imply is that central sensitization
7 may be a contributor to the risk of development of
8 chronic pain. This just summarizes the data for
9 existing treatment. What's interesting is that two
10 of the newest analgesic therapies, anti-NGF and
11 anti-CGRP also have been suggested at having some
12 action on central sensitization.
13 To come back to the risk of developing
14 chronic pain, there are a number of papers, all
15 published this year, which imply that the presence
16 of central sensitization in individuals represents
17 a risk factor for the development of chronic pain.
18 This includes in the setting of persistent pain,
19 after knee arthroplasty, the risks for the
20 development of postherpetic neuralgia after acute
21 herpes zoster, and cancer pain.
22 This is something that I think is pretty

Page 55

1 interesting. There clearly can be genetic drivers
2 of the risk of individuals or the presence of
3 individuals who have a greater degree of
4 vulnerability for the development of central
5 sensitization, and this may be a contributor to the
6 risk of these individuals developing persistent
7 pain; something to think about.
8 What next? As I said, after several decades
9 of having left central sensitization to stew in its
10 own juices as it were and to let people like Dan
11 Clauw tease out how it manifests and some of its
12 mechanisms, I've started to come back to it because
13 there are now tools available to do the kinds of
14 things that I wanted to do originally.
15 One of them is using GCaMP technology. It
16 is now possible to measure activity in large
17 populations of defined neurons. So instead of
18 doing any damn cell, we can now look at the
19 properties of neurons, the output neurons in the
20 spinal cord, and the cortical neurons that are
21 activated. Instead of one cell at a time, we can
22 look at literally hundreds, if not thousands, and

Page 56

1 get a real sense of how the nervous system operates
2 in the setting of defined inputs and the changes
3 that occur.
4 We can optogenetically control these. We
5 can switch these circuits on and off and see the
6 changes of this. We can now use artificial
7 intelligence and neural network based analyses to
8 tease out both the changes in the circuits but also
9 changes in behavior. We have recent data exploring
10 how to measure behavioral signatures of pain, and
11 these turn out to be much more sensitive than the
12 reflex-evoked responses.
13 It's quite ironic that central sensitization
14 was discovered by studying the reflex output of the
15 spinal cord, but now I abhor it to say that the
16 reflex response really doesn't reflect what the
17 individual is feeling. We now have a technology to
18 begin to measure that.
19 In addition, there's the possibility, which
20 is extremely exciting, of using human stem cell
21 based technology to recreate some of the key neural
22 elements that are involved in nociception, both

Page 57

1 nociceptors but also using organoids. I think in
2 the future, we will be able to model some of these
3 changes in humans and begin to use them possibly in
4 a precision medicine way to see which individuals
5 are at risk.
6 We know, for example, in the setting of
7 diabetic neuropathy work that Joachim has done,
8 that there are individuals who have type 2 diabetes
9 with absolutely no neuropathy or no pain, those who
10 have neuropathy but no pain, and those who have
11 painful diabetic neuropathy. We have absolutely no
12 idea what is responsible; what are the
13 susceptibility factors that drive a patient to have
14 a particular clinical phenotype, and we may be able
15 to capture that using this stem cell based
16 technology.
17 I hope I've given you a flavor of the
18 initial discovery of central sensitization. I
19 certainly had no sense at that time that it would
20 lead to this kind of meeting, which is extremely
21 exciting. I am an MD-PhD, but my initial focus was
22 in entirely neurobiological, but I am very excited

Page 58

1 now to begin to appreciate the clinical
2 implications of this work. Thank you.
3 (Applause.)
4 Q&A
5 DR. BRUEHL: Clifford, I appreciate having
6 you on the spot here to ask you this question.
7 This is something that has bothered me conceptually
8 for a while about quantitative sensory testing
9 studies, is the temporal summation protocols that
10 are supposed to tap into central sensitization are
11 extremely explicit about the parameters of the
12 stimulus. It has to be about 2 and a half seconds
13 apart, it has to be very brief, and if you don't
14 follow that, you get criticized.
15 We've done some work with some collaborators
16 in Spain, where a 5-second long pressure stimulus
17 spaced 30 seconds apart in fibromyalgia patients
18 shows exactly the same pattern of increasing
19 perceived pain over 10 trials, that looks exactly
20 like temporal summation.
21 So my question to you is, based on the
22 studies you've done and your understanding of

Page 59

1 central sensitization, what are the parameters,
2 stimulus parameters, that would be expected to
3 elicit central sensitization in an experimental
4 setting?
5 DR. WOOLF: I think the challenge is, if we
6 define central sensitization broadly as a state of
7 amplification within the central nervous system,
8 what tests and what parameters in those tests can
9 reveal that amplification? I don't think it needs
10 to be anything fixed other than it reveals a change
11 within the process in the central nervous system.
12 If you are able to show that there's
13 temporal summation with a certain set of
14 conditions, what is revealing is that the same
15 input, when given on repeated times, leads to a
16 bigger and bigger response. That is one way of
17 revealing the presence of amplification. And how
18 you do it, frankly, is irrelevant. The goal should
19 be is this test revealing the presence of an
20 amplification within the central nervous system?
21 DR. MARKMAN: Steve, say your name. And
22 please try and say your name first.

Page 60

1 DR. BRUEHL: That was Steve Bruehl,
2 Vanderbilt University.
3 DR. SCHOLZ: Clifford -- I'm Scholz,
4 Biogen -- thank you for this overview of the
5 history of central sensitization. Central
6 sensitization, the narrower sense, has mostly been
7 studied in models of nociceptive pain. But it's
8 also true for the work of Jurgen Sandkuhler on
9 pordensation [indiscernible] of these signals in
10 the central circuits.
11 Back in the days when I was at Columbia
12 University, we conducted a study in the mouse model
13 where we removed the NMDA receptor from the dorsal
14 horn in the spinal cord. And to our surprise, we
15 found after nerve injury, that there's no change in
16 the development of pain during the first week, but
17 that these animals do not develop chronic pain.
18 That's the complete opposite of what Jack
19 Antareesey [ph], who has used the same model, finds
20 in inflammatory pain. He basically reduces the
21 initial period of pain development to a large
22 extent, but the NMDA receptor in the spinal cord

Page 61

1 doesn't seem to play a role in chronic inflammatory
2 pain.
3 So my question is, does central
4 sensitization occur in conditions of nerve injury
5 in neuropathic pain? Is it just that the timing is
6 different or is the pharmacology different, and the
7 NMDA receptor plays a different role?
8 DR. WOOLF: I think this was a key point.
9 Again, I think Dennis raised it. If we use central
10 sensitization broadly as the presence of
11 amplification, I would say there's no question, it
12 is present in -- you evoke it in healthy skin with
13 capsaicin. You can reveal it in the presence of
14 tissue injuries such as post-surgical pain, and it
15 is a contributor to neuropathic pain by virtue of
16 the presence of allodynia is an expression of
17 amplification and a change within the central
18 nervous system.
19 However, those may have different
20 mechanistic underpinnings. Each of them may be
21 operating in different ways with different
22 pharmacologies. And the challenge is how to

Page 62

1 identify in an individual patient which is the
2 responsible mechanism so that instead of regarding
3 central sensitization as something where if the
4 patient has it, there's a single treatment, but
5 rather to ask the question very specifically, what
6 is amplifying with or what is changing the nervous
7 system?
8 In some settings, that may involve NMDA
9 receptors, but I certainly accept that may not be
10 present in others. That is exactly the difficulty.
11 I think it's a broad notion of the involvement of
12 the nervous system in the generation of pain, but
13 that in no way implies that there's a single
14 mechanistic underpinning.
15 DR. SIMON: Simon, Boston. As usual, a
16 wonderful presentation, Clifford. Thank you. As a
17 rheumatologist, I'm confronted by failure of
18 clinical trials in lupus consistently because the
19 heterogeneity of the disease is a problem, but we
20 also have a group of patients who achieve inclusion
21 in trials who have a painful syndrome, to a
22 degree -- this is not a predominant part of

Page 63

1 lupus -- and yet, when we look to see if these
2 people have inflammatory disease, they don't.
3 I was wondering within the inflammatory
4 state, where you get pain and various different
5 complications associated with that, do you believe
6 that central sensitization takes a different
7 pathway than if you just have a noxious stimulus
8 that's nerve damage or something like that?
9 Do you think there is a difference in the
10 way that that behaves, because certainly from a
11 clinical perspective in doing trials, clearly these
12 people are different, and why they're different
13 seems to be a little hard to explain. Do you think
14 inflammation does play a role?
15 DR. WOOLF: Yes, absolutely. Inflammation
16 not only produces peripheral sensitization, which
17 could constitute an input in nociceptors that could
18 drive use-dependent synaptic plasticity, but also
19 results in the production of signaling molecules
20 such as nerve growth factor, which is retrogradely
21 transported to the cell bodies, which changes the
22 transcription of these neurons. These neurons

Page 64

1 start to produce peptides and other modulators that
2 they don't normally do, and therefore have a
3 different effect.
4 There are also centralized changes there as
5 a consequence of the input to the CNS, and the CNS
6 neurons start changing. So part of this dynamic
7 plasticity is that in the disease setting, there
8 may be profound changes. But to come back to a
9 point that I made in terms of the risk of
10 transition of pain, the presence in acute patients,
11 or at least some measures, indicating heightened
12 hypersensitivity or the presence of central
13 sensitization as a risk factor of developing
14 chronic pain, I think that may also be a factor.
15 It's not just the presence of inflammation.
16 The reason I say that is there have been
17 studies in OA, at least, where the chronicity of
18 the pain and the failure of recovery after
19 arthroplasty seems more to be associated with
20 temporal summation rather than how much gab
21 enhancement there is, as a measure of the degree of
22 inflammation.

Page 65

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

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

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

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

Page 66

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

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

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

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

Page 67

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

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

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

Page 68

1 could be the sustaining trigger for central
2 sensitization.

3 With these new optical recording techniques,
4 GCaMP recording, we've been looking both in the
5 trigeminal and in dorsal ganglia after nerve injury
6 with expectation we'd see this bursting ectopic
7 activity, and frankly we don't. It's been a
8 complete shock to me, completely and unexpected.

9 We do see normally very low levels of spontaneous
10 activity, and after nerve injury, we see similar
11 levels, maybe a tiny bit higher, but not much.

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

Page 69

1 So I'm having to rethink the notion of what
2 degree of input is sufficient to produce pain and
3 maybe to trigger some of these changes, and it
4 seems to be much, much lower than I had
5 anticipated.
6 DR. MARKMAN: More questions?
7 DR. RATHMELL: Jim Rathmell from Brigham.
8 Can you tie together mechanistically what we've
9 learned about opioid-induced hyperalgesia with the
10 concept of central sensitization, and then how
11 might you approach those two, similarities or
12 differences?
13 DR. WOOLF: Yes. Certainly, in the very
14 acute setting with single use, opioids by virtue of
15 decreasing transmitter release from nociceptors can
16 reduce acute central sensitization. Presumably,
17 its activity in the brain stem may also modulate
18 some of the synaptic plasticity in the dorsal horn,
19 and there have been preclinical studies of that.
20 I think the changes that occur chronically
21 with chronic administration that lead to the
22 development of opioid hyperalgesia are a reflection

Page 70

1 of pathological changes in opioid activity.
2 Whether it has parallels to the phenomena of
3 central sensitization, I'm not actually familiar of
4 someone who's made a direct comparison
5 mechanistically whether the chronic opioid induced
6 changes, in terms of synaptic activity and membrane
7 excitability are similar. I just don't know, but
8 that's obviously worth thinking about.
9 DR. DWORKIN: We've gotten some feedback
10 that people asking questions are coming too close
11 to the microphone and that it's garbled. So if you
12 ask a question, please leave reasonable room and
13 space between your mouth and the microphone. Thank
14 you.
15 DR. MARKMAN: So it's obviously a privilege
16 to have that historical perspective. I hope that
17 it has a chance to live on YouTube as a bootleg
18 perhaps, so other people have the privilege of
19 enjoying what we just had the privilege of hearing.
20 Our next speaker really reminds me of this
21 idea that the eye cannot see what the mind does not
22 know, and Dr. Clauw has given us the eyes to see

Page 71

1 central sensitization in many different clinical
2 scenarios.
3 Dr. Clauw is a professor of rheumatology,
4 anesthesiology, and psychiatry at the University of
5 Michigan. Through his cogent descriptions of the
6 clinical manifestations of central sensitization, I
7 think it has changed how clinicians everywhere see
8 patients who have pain that they cannot explain.
9 Presentation - Daniel Clauw
10 DR. CLAUW: Thanks so much, John, and thanks
11 to Dennis, et al. for having this as a topic. This
12 is exciting. And it's particularly exciting to
13 talk after Clifford because I'm likewise am going
14 to try to give a bit of historical perspective.
15 I'll start a little bit later than Clifford. I was
16 in my third year of medical school when he
17 published his Nature paper.
18 But I'm going to talk about 30 years or so
19 of clinical work, looking at all these overlapping
20 concepts: central sensitization, chronic
21 overlapping pain conditions, and now the new IASP
22 term, nociplastic pain. I will be speaking rapidly

Page 72

1 because I have a lot to cover.
2 In the old days, there were two underlying
3 mechanisms of pain, nociceptive and neuropathic
4 pain. Almost all clinicians thought that all pain
5 was caused by some problem out in the periphery,
6 either damage, inflammation, or in some cases nerve
7 damage. But as the biopsychosocial pain models
8 began to come into favor in the pain field, the
9 predominant central nervous system contributions to
10 pain were really thought to be classic
11 psychological concepts like anxiety, depression, or
12 cognitive concepts like catastrophizing.
13 But as Clifford just really nicely outlined,
14 animal studies were outlining both spinal and
15 supraspinal mechanisms that were not depression,
16 anxiety, catastrophizing that were capable of
17 augmenting or amplifying peripheral nociceptive
18 input or causing pain without any ongoing
19 peripheral nociceptive input. So a number of us on
20 the clinical side started to slog away and try to
21 define what central sensitization might be in these
22 clinical conditions.

Page 73

1 This is the first side of almost every talk
 2 I give. I am trained clinically as a
 3 rheumatologist. I don't act like a rheumatologist
 4 anymore; I'm a pain researcher. But there's
 5 actually three diseases I'm going to refer to over
 6 the course of my talk today: osteoarthritis,
 7 rheumatoid arthritis, and fibromyalgia, all of
 8 which I'm really going to use as metaphors rather
 9 than talking of those as stand-alone diagnoses.
 10 When I was trained as a rheumatologist, I
 11 was taught that osteoarthritis was the classic
 12 peripheral pain condition; that what you saw in an
 13 x-ray is what that person would experience. If
 14 they had an x-ray like the one on the right, they
 15 would always hurt. If they had an x-ray like the
 16 one on the left, they would never hurt.
 17 That turned out to be totally wrong. It
 18 turns out that 30 to 40 percent of people in
 19 population-based studies that have bone on bone in
 20 their knee do not have any pain whatsoever, and 10
 21 to 15 percent of people that have severe knee pain
 22 have entirely normal radiographs.

Page 74

1 I'm using osteoarthritis as an example
 2 today. Our group studies probably 15 or 20
 3 different chronic pain conditions, and I would like
 4 anyone to challenge me and say there is anything
 5 you can measure out in the periphery in any chronic
 6 pain condition that accurately predicts who is
 7 going to have pain or how severe the pain is going
 8 to be. There is always a tremendous disparity
 9 between what we can identify out in the periphery
 10 and whether someone's having pain or how severe the
 11 pain is going to be.
 12 In osteoarthritis, this is a 30-year history
 13 of osteoarthritis. We went from it being a classic
 14 peripheral pain condition to realizing there was a
 15 terrible relationship between what you'd see on a
 16 radiographic and what people are experiencing.
 17 Then we started blaming the patients. We said
 18 anxiety, depression, catastrophizing were causing
 19 this.
 20 It turns out, point of fact, very little of
 21 the variance between what you see on x-ray and what
 22 someone has experienced can be accounted for by

Page 75

1 classic psychological factors like anxiety,
 2 depression, and catastrophizing, and leads to
 3 smirking here because he lived through this as
 4 well.
 5 The therapies that I was taught worked
 6 really well and in most all people with
 7 osteoarthritis -- NSAIDs, opioids,
 8 arthroplasty -- have very high failure rates.
 9 NSAIDs and opioids don't work any better in
 10 osteoarthritis than pregabalin and/or duloxetine
 11 work in fibromyalgia. These drugs all work about
 12 in 1 out of 3 people, and we even have failure
 13 rates of 20 to 30 percent with knee and hip
 14 arthroplasty even though it is the most successful
 15 surgery to do for chronic pain.
 16 In rheumatoid arthritis, we said sort of a
 17 comparable thing happened in the field, and Lee was
 18 just alluding to this, is we have now incredible
 19 drugs to treat RA, lupus, ankylosing spondylitis,
 20 or biologics, but still 30, 40, 50 percent of
 21 people that are treated with those drugs -- and you
 22 can no longer identify any ongoing inflammation of

Page 76

1 these individuals -- these people still have
 2 widespread pain, fatigue, and have poor functional
 3 status.
 4 So why is that? In these conditions, we
 5 really have been very effective at developing more
 6 and more peripherally directed interventions, but
 7 yet our patients often are not experiencing
 8 improvements in their pain.
 9 I will talk about the F word, fibromyalgia.
 10 Regardless of what you think about fibromyalgia, I
 11 think it has taught us a lot about pain. I lived
 12 through the early days where fibromyalgia was
 13 defined on the basis of widespread pain and tender
 14 points. We helped teach the broader pain research
 15 community that tender points are stupid because
 16 what fibromyalgia patients in fact experience are
 17 allodynia and hyperalgesia. It doesn't matter
 18 where you push on someone with fibromyalgia, they
 19 are more tender.
 20 But another set of studies that our group
 21 and others started to do in people with
 22 fibromyalgia were doing quantitative sensory

Page 77

1 testing for other types of non-painful sensory
 2 stimuli. And it turns out the fibromyalgia
 3 patients are just as sensitive to the brightness of
 4 lights or the loudness of noises as they are
 5 sensitive to pain.
 6 So this was clearly something more than a
 7 spinal central sensitization mechanism, and, in
 8 fact, we didn't even know what terms to use as we
 9 started to write this. When we use the term
 10 "central sensitization," we would get criticized,
 11 but when we didn't use it, we would get criticized.
 12 In fact, right now we still have a lack of
 13 disagreement in the pain field about what to call
 14 this underlying construct.
 15 I think in the broader pain field now, we
 16 think of fibromyalgia as sort of the poster child
 17 for diffuse hyperalgesia, allodynia, and central
 18 sensitization. Again, our group feels strongly
 19 that this should be defined more broadly than just
 20 on the basis of pain because these people have
 21 sensitivity to a number of other sensory stimuli,
 22 and they almost always have other CNS symptoms:

Page 78

1 fatigue, sleep problems, memory problems, and in
 2 many of them mood problems that we think are really
 3 part of that phenotype as well.
 4 Now segueing back to a group of conditions
 5 where the individuals that would have had these
 6 conditions have suffered historically with
 7 credibility, conditions like fibromyalgia,
 8 irritable bowel. These have already been alluded.
 9 A couple of years ago, with a lot of help from
 10 Chris Veasley and a lot of patient advocates, the
 11 NIH came up with the term "chronic overlapping pain
 12 conditions." This term has stuck.
 13 But we now acknowledge that a lot of these
 14 conditions -- irritable bowel, TMD, interstitial
 15 cystitis, low back pain, endometrius, dry eye
 16 disease -- if you don't know about it, dry eye
 17 disease, it's a really cool disease. It's
 18 basically the irritable bowel syndrome of the eye,
 19 where people feel their eyes are dry but their eyes
 20 are not really dry. This is the bane of
 21 ophthalmologists' existence like irritable bowel is
 22 the bane of gastroenterologists; existence, and

Page 79

1 like fibromyalgia is the bane of rheumatologists'
 2 existence.
 3 But not only do we see the these features,
 4 these prominent central nervous system components
 5 to these classic chronic overlapping pain
 6 conditions, but you can identify these same
 7 mechanisms, these same symptoms in subsets of
 8 people with sickle cell disease, cancer pain; any
 9 other pain condition, if you look for the
 10 phenotype, you will find it. You will find people
 11 with more widespread pain than you would expect
 12 with memory problems, sleep problems, fatigue, and
 13 with sensory sensitivities other than sensitivity
 14 to pain.
 15 In fact, the IASP a couple years ago voted
 16 and agreed that there was a third new category of
 17 pain; I hate the term, nociplastic pain. But be
 18 that as it may, we're now in the process of trying
 19 to define what nociplastic pain is. But again, I
 20 think we're really looking heavily to all these
 21 studies that have been looking both at chronic
 22 overlapping pain conditions, as well as when

Page 80

1 central sensitization is superimposed upon
 2 conditions like rheumatoid arthritis, or lupus, or
 3 some of our classic conditions where there is
 4 ongoing nociceptive input.
 5 I started using this analogy a long time
 6 ago -- the basic science pain researchers heads
 7 will explode with this analogy -- but to try to
 8 teach clinicians and patients that the amount of
 9 pain that someone is experiencing was akin to the
 10 loudness of an electric tower. And all I was
 11 trying to do is to get people to add together
 12 what's going on in the guitar, i.e., what's the
 13 ongoing nociceptive input, and then what are the
 14 contributions from the central nervous system?
 15 The central nervous system can clearly turn
 16 up or down the sensitivity to pain out in the
 17 periphery, and the studies that have been done have
 18 clearly shown that these people, these 40 percent
 19 of osteoarthritis patients that have bone on bone
 20 but don't have any pain, on quantitative sensory
 21 testing, they are way less tender or way less
 22 sensitive than people who do have pain.

Page 81

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

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

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

Page 82

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

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

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

Page 83

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

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

19 I sometimes wonder whether it was a good
 20 idea to pull Fred out of fibromyalgia retirement
 21 because I think I poked a skunk.
 22 (Laughter.)

Page 84

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

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

Page 85

1 So I'm showing this to show you that almost
2 everyone would sort of intuitively say someone with
3 fibromyalgia probably isn't going to do as well if
4 they have knee or hip arthroplasty as someone
5 without fibromyalgia. What I want to show you is
6 that everything in between is important.
7 By looking at fibromyalgia as the end of the
8 continuum, we've gotten a really distorted view of
9 this phenotype. We think that all these people
10 have prominent psychological comorbidities; they
11 don't. The people that we label with fibromyalgia
12 usually do, but when you see this in other
13 settings, the psychological factors are really not
14 nearly as important as this underlying neurobiology
15 of amplification of what's coming from the
16 periphery. You don't even need a psychologist. If
17 people start crossing out words and putting in a
18 new word, you can just use this.
19 (Laughter.)
20 DR. CLAUW: So I used to say that
21 fibromyalgia was the tip of the iceberg and that
22 there's a much larger number of people that have

Page 86

1 centralized pain that don't carry the label of
2 fibromyalgia. Now since I'm part of the resistance
3 movement, I say you've got to be really careful of
4 what you might find underneath the rock.
5 (Laughter.)
6 DR. CLAUW: We have done a series of
7 studies. By the way, Sharon, the PDF of this
8 doesn't have the second part of the slide, so when
9 it's posted, the second part of the slide won't
10 come up, so we don't have to worry about that.
11 (Laughter.)
12 DR. CLAUW: I'm just going to present some
13 data very briefly. These studies were led by Chad
14 Brummett, where we've looked at the fibromyalgia
15 measure as a predictor of differential outcomes in
16 knee and hip arthroplasty, and we predicted that it
17 would predict nonresponsiveness to opioids and
18 nonresponsiveness to surgery.
19 We didn't just look at the fibromyalgia
20 measure in all of these studies. We had the
21 PainDETECT, catastrophizing, depression, and
22 anxiety, but this is really the only thing that was

Page 87

1 innovative about the studies, is on the day of
2 surgery, we gave people this measure to fill out,
3 and we looked at how the scores on this measure
4 influenced the opioid responsiveness on the first
5 24 to 48 hours after surgery.
6 This is acute opioid responsiveness, not
7 chronic opioid responsiveness, as well as how well
8 it influenced whether someone was going to get
9 better if we replaced their knee or replaced their
10 hip. This can be scored from 0 to 31 on this
11 scale.
12 So Fred Wolfe was totally right. It doesn't
13 matter where in the continuum someone is. Each
14 1-point increase in the fibromyalgia measure makes
15 people less opioid responsive and less surgery
16 responsive, and it doesn't matter if they're up by
17 13, which is the part of the scale that has said
18 you have fibromyalgia, or if they move from a
19 fibromyalgia score of 3 to 6. That 3-point
20 increase in the fibromyalgia measure leads to an
21 equal increase in opioid nonresponsiveness and
22 surgery nonresponsiveness regardless of where it is

Page 88

1 on the continuum.
2 These phenomena are largely independent and
3 certainly a lot stronger than classic psychological
4 factors like anxiety, depression, and
5 catastrophizing. In the final models in these
6 papers, none of the psychological factors were in
7 the final models. They didn't predict any of the
8 variance.
9 I like showing this data slide. These are
10 the 700 or so people in the knee and hip
11 arthroplasty studies. You see that the most common
12 fibromyalgia score was 5. The red line is 13.
13 People on the right side of that red line would be
14 said to have fibromyalgia based on the new
15 fibromyalgia criteria.
16 There were 55 people out of 700 people in
17 this study, that on the day of surgery when we gave
18 them that questionnaire, we saw they had
19 fibromyalgia. Guess how many of those 55 had
20 anything in their chart that indicated that they
21 had fibromyalgia or anything other than
22 osteoarthritis?

Page 89

1 MALE VOICE: Zero.
 2 DR. CLAUW: Zero. This is the problem here.
 3 Once people put a label like osteoarthritis on
 4 someone, they don't think of centralized pain.
 5 This is at the University of Michigan, which is
 6 arguably the epicenter for fibromyalgia research.
 7 I'm the one that gives the pain grand rounds for
 8 all of the departments. So if we're not seeing it,
 9 no one's seeing it.
 10 But again, the more stark findings
 11 here -- look at these two people, patient A and
 12 patient B, neither of whom has fibromyalgia, but
 13 look at how different their opioid requirements are
 14 in the first 24 to 48 hours and how different they
 15 are with respect to likelihood of responding to
 16 knee and hip arthroplasty with improvements.
 17 Patient B needs 90 milligrams more of in the first
 18 24 to 48 hours to control his pain and is 5 times
 19 less likely to get a benefit even though patient B
 20 doesn't have fibromyalgia, he has a higher
 21 fibromyalgia score.
 22 Suzie As-Sanie is over there. She's an

Page 90

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

Page 91

1 centralized pain.
 2 Now scoring high on the fibromyalgia
 3 measurement doesn't just tell you what isn't going
 4 to work; it tells you what is going to work. Lily
 5 started putting our body map in the duloxetine
 6 registration trials after duloxetine was already
 7 approved in the U.S. In fact, it was off patent in
 8 the U.S.
 9 This is a reason duloxetine studied low back
 10 pain, and it showed that duloxetine works a lot
 11 better in the low back pain patients with
 12 multifocal pain. The more sites of pain on the
 13 Michigan Body Map that the person had, the more
 14 likely duloxetine was going to work. And it worked
 15 60 percent better in people with low back pain plus
 16 5 other sites of pain compared to people with one
 17 single site of low back pain.
 18 I do consulting with a lot of different
 19 companies. This is a company, Samumed, that has a
 20 WNT inhibitor that's injecting into the knee. And
 21 I said to them early in their development program,
 22 "Put a body map in because this isn't going to work

Page 92

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

Page 93

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

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

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

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

Page 95

1 clearly see in these groups of people with
 2 interstitial cystitis, there's three different
 3 phenotypes. About 20 percent of them will have
 4 pain confined to the bladder, about another
 5 20 percent will have pain in the region of the
 6 pelvis and abdomen, and about 50 or 60 percent will
 7 have the more widespread pain phenotype.

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

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

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

Page 94

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

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

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

Page 96

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

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

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

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

Page 97

1 It may be that a drug for example, like a
 2 nerve growth factor antibody, that is able to
 3 entirely turn off that nociceptor would actually
 4 work better in a group of people with
 5 osteoarthritis that have central sensitization than
 6 it would in a group of people that don't.
 7 I think it's an open question, but I think
 8 until then, it would be a mistake to lump these two
 9 subsets of central sensitization together because
 10 from a treatment standpoint, there's going to be
 11 profound implications of whether that central
 12 process is being driven by an ongoing peripheral
 13 process or whether that central process is a
 14 fundamental brain central nervous system process
 15 that we're going to always have to treat with more
 16 centrally directed drugs.
 17 So when you look at the drugs that work for
 18 these centralized pain states, where you think
 19 primarily tricyclics, serotonin, norepinephrine
 20 reuptake inhibitors, and gabapentinoids, but you
 21 see that the drugs like opioids and NSAIDs don't
 22 seem to work in these pain conditions.

Page 98

1 If you look at the current treatment
 2 guidelines for the different product overlapping
 3 pain conditions, in virtually all of them, the
 4 people recommend strongly against the use of
 5 opioids. In some cases there are data supporting
 6 that, in some cases there are not. But it's almost
 7 unanimous, amongst the people treating these
 8 chronic overlapping pain conditions, that opioids
 9 are a bad idea.
 10 It may very well be that this is because of
 11 some of the findings that we've identified in
 12 people with fibromyalgia, that it looks like the
 13 endogenous opioid system in fibromyalgia is
 14 actually hyperactive. People are releasing high
 15 levels of endorphins and enkephalins. Those are
 16 probably binding to their mu opioid receptor, and
 17 when that endogenous ligand binds to that opioid
 18 receptor, if you give someone an exogenous ligand,
 19 i.e., an opioid drug, it's not going to work as
 20 well because there's not as many unoccupied mu
 21 opioid receptors.
 22 We clearly showed that in studies using PET

Page 99

1 with carfentanil and functional MRI at the same
 2 time, where it really looks as though the
 3 fibromyalgia patients have endogenous
 4 opioid-induced hyperalgesia, this is what we called
 5 it in this article. It really looked as though the
 6 endogenous opioid system might actually be
 7 participating in the pathogenesis of these
 8 conditions and why it might be a particularly bad
 9 idea to give these people on opioids.
 10 So even though we have a stable genius as a
 11 president, he didn't know that healthcare could be
 12 so complicated. In this editorial that I wrote a
 13 couple of years ago, I pointed out that one of the
 14 problems that I see with opioids is the opioid
 15 manufacturers have not been made to do trials in
 16 different pain states, so we don't really know what
 17 chronic pain conditions opioids might work in and
 18 might not work in because it's been a really narrow
 19 group of pain conditions.
 20 So I'd love to see the randomized controlled
 21 trials if anyone had the stomach to do that these
 22 days. Those probably are never going to happen in

Page 100

1 most of the chronic overlapping pain conditions,
 2 but I think there are a lot of data suggesting that
 3 not all pain conditions are the same, especially
 4 chronic pain conditions with respect to their
 5 opioid and responsiveness.
 6 So I do think we are moving towards the era
 7 where if we know the underlying mechanism of
 8 someone's pain, we can more logically pick a drug
 9 and non-drug therapies. Our group is starting to
 10 do a lot of work with cannabinoids now.
 11 We actually think that CBD might be a good
 12 cannabinoid for people with low grade inflammation
 13 in the periphery, i.e., something like
 14 osteoarthritis. But the recent studies that have
 15 been done, a couple that have been done suggesting
 16 a more centralized pain state, you're probably
 17 going to have to use a little bit of THC because
 18 that's a more centrally acting compound.
 19 Finally, I just want to talk about how
 20 important the non-pharmacologic therapies across
 21 pain conditions, but especially for these chronic
 22 overlapping and central pain conditions, because it

Page 101

1 seems as though a lot of things that have happened
 2 to people as they have chronic pain for long
 3 periods of time, they become deconditioned and they
 4 stop moving. They start sleeping more poorly.
 5 They become more stressed. They develop bad
 6 habits.
 7 These all then feed up to the brain, and I
 8 think that this is why, that in almost any chronic
 9 pain state, you can identify this subset of people,
 10 whether you want to call it central sensitization,
 11 chronification, whatever, but where these other
 12 factors, non-peripheral factors that are not coming
 13 exactly from the area of the body that the person's
 14 experiencing pain, play a prominent role.
 15 Again, this is why I think the non-drug
 16 therapies are more broadly being used and
 17 emphasized with respect to the treatments, is that
 18 these therapies in fact are in many cases more
 19 effective than some of the current drugs that we
 20 have available. So I will stop there and take
 21 questions if people have them.
 22 (Applause.)

Page 102

1 Q&A
 2 DR. SIMON: Lee Simon, Boston. Again,
 3 great. I was wondering, you mentioned
 4 Ehlers-Danlos syndrome, which is a genetic disease,
 5 for those who don't know, of connected tissue with
 6 the idea that you've got hyperelasticity,
 7 hypermobile function. You don't think that this is
 8 related to the genetic abnormalities of collagen
 9 and elastin. You think it may be due to the
 10 hypermobile state, and thus -- I'm not sure I could
 11 ask anybody else but you because you're a
 12 rheumatologist.
 13 So the hypermobile state, which then leads
 14 to premature OA and the symptoms associated with
 15 that, not because of the genetic abnormality
 16 directly.
 17 DR. CLAUW: Exactly.
 18 DR. SIMON: Okay.
 19 DR. CLAUW: And in fact, that has been shown
 20 as -- a benign hypermobility has very high rates of
 21 comorbid fibromyalgia, and those people don't have
 22 the underlying genetic. We think that in

Page 103

1 hypomobility, it would be the repeated trauma from
 2 the hypermobility as sort of a chronic, nociceptive
 3 state that then drives -- I'm actually giving the
 4 keynote next week at the Ehlers-Danlos meeting,
 5 because this is a huge problem for them.
 6 If you look at any of their literature, this
 7 is a tremendous problem for people with
 8 Ehlers-Danlos or hypermobility. They almost all
 9 look a lot more like fibromyalgia patients than
 10 they do like someone with just nociceptive pain in
 11 a single location.
 12 DR. MARKMAN: Roger?
 13 DR. FILLINGIM: Dan, you talked about these
 14 two different flavors of central sensitization. Do
 15 you think these are independent populations? Is
 16 this a progression? Do you go from bottom up to
 17 top down? Do people stay stable in their
 18 phenotype?
 19 Could you talk a little more about that?
 20 DR. CLAUW: Yes. I mean, I can tell you a
 21 lot more in two or three years. We're doing a
 22 series of studies now that's being funded by a

Page 104

1 center grant from NIAMS, where we take people with
 2 rheumatoid arthritis that are getting a new
 3 biologic, osteoarthritis that are getting hip
 4 arthroplasty, and carpal tunnel syndrome that are
 5 getting carpal tunnel repair. We fix the
 6 peripheral problem, and then we look at whether
 7 those people have resolution of their widespread
 8 pain of their central sensitization.
 9 So far, we do see two quite different
 10 patterns; that some people when you fix a
 11 peripheral problem, everything melts away, the pain
 12 in the knee and the more widespread pain. Then
 13 there's another group that it doesn't seem to make
 14 much of a difference; and, in fact, those are the
 15 people that don't respond very well to knee or hip
 16 arthroplasty. They have a transient improvement
 17 and for about a month or so it's more like a
 18 placebo effect, and then they almost go back to the
 19 way they were before.
 20 But we don't know of any other way to sort
 21 out right now the difference between those two.
 22 It's not until we study those people at baseline,

Page 105

1 and then we see how they do after the surgery, and
2 then we can put them in the category of top-down
3 and bottom-up based on how they respond to that
4 peripherally directed intervention.
5 But I don't know any other way to study this
6 phenomena. The only thing right now that we are
7 seeing, that we hypothesize and that we are seeing
8 that is different from those two groups is it
9 doesn't seem as though the bottom-up people have
10 sensitivity to other sensory stimuli, which would
11 sort of make sense. There wouldn't necessarily be
12 any reason you would -- that if this was being
13 driven by the kinds of mechanisms that Clifford
14 talked about, there isn't any reason that those
15 people would start to be more sensitive to auditory
16 stimuli or visual stimuli, which are cranial nerves
17 that are coming directly into the brain.
18 Yes, John?
19 DR. FARRAR: John Farrar, University of
20 Pennsylvania. Is there any evidence that using the
21 drugs that you suggest might reduce the
22 fibromyalgia, the central sensitization; that use

Page 106

1 of those in anticipation of an upcoming insult,
2 surgery or otherwise, might actually reduce the
3 likelihood of the chronic persistent pain? Let's
4 say in the arthritis, which honestly would be a
5 great model to look at.
6 DR. CLAUW: Yes. I think the data are
7 mixed. The two classes of drugs that have been
8 most widely used in this setting -- I guess three;
9 Clifford talked about ketamine, but it would be the
10 gabapentinoids or the SNRIs. And some of the data
11 suggest that those are helpful and some suggest
12 they aren't.
13 No one has done the study that I think needs
14 to be done, is only treat the subset of people that
15 score high on the fibromyalgia measure because I
16 think the problem with the studies that have been
17 done is you treat everyone, and not everyone needs
18 it. You can identify -- it's probably in most
19 cohorts about a third of the patients with
20 osteoarthritis that clearly have this superimposed
21 central sensitization. The trials would be better
22 if done looking just at that subset rather than

Page 107

1 giving the drug to a bunch of people that you don't
2 think really need it or are going to benefit from
3 it.
4 Ajay?
5 DR. WASAN: Ajay Wasan from University of
6 Pittsburgh. You dissed a lot of the psychological
7 factors --
8 DR. CLAUW: No, I --
9 DR. WASAN: -- and that's okay.
10 DR. CLAUW: I just want to deemphasize them
11 because they've been talked about forever as those
12 are the central factors. And I'm not saying
13 they're not important. I'm just saying that
14 they're not the same as this.
15 DR. WASAN: I get that, and that makes
16 sense. But would you agree that at least in the
17 patients that have, say, prominent psychological
18 factors, that at the very least you could say that
19 those factors are amplifying or worsening the same
20 mechanisms of sensitization or maybe creating their
21 own mechanisms of sensitization?
22 DR. CLAUW: Yes.

Page 108

1 DR. WASAN: Okay.
2 DR. CLAUW: So again, when someone has those
3 features in addition to chronic pain, they should
4 be treated. I'm just saying that if you look at
5 how this all evolves -- and we're starting to look
6 now in data sets of children, like 10-11 year olds
7 as they start to develop pain, and as soon as they
8 start to develop pain, you see the fatigue, memory
9 problems, and sleep disturbance, the more CNS
10 contributions.
11 The earlier that you do these studies, a lot
12 of times you see the psychological factors occur
13 because of the pain rather than are the root cause.
14 But of course, in a lot of clinical cohorts, these
15 psychological factors are front and center.
16 They're a big component of what we have to treat.
17 So I'm not trying to minimize the importance
18 of them clinically. I'm just saying that don't
19 think that they're the same thing as what I'm
20 talking about, because I think the biggest mistake
21 people have made is if you think of a fibromyalgia
22 patient, you think of prominent psychiatric

Page 109

1 comorbidities because most of them have it. If you
 2 then take that and infer that that means that the
 3 biology of fibromyalgia has prominent
 4 psychological/psychiatric underpinnings, I'm not
 5 necessarily agreeing at that point. I think you
 6 have to be a little bit careful about what caused
 7 what.
 8 DR. WASAN: Yes. I think it's the issue of
 9 teasing out the independent and shared variants --
 10 DR. CLAUW: Right.
 11 DR. WASAN: -- and that's the tricky part.
 12 DR. CLAUW: Yes.
 13 John?
 14 DR. MARKMAN: Dan, that was excellent. Can
 15 I just some questions as a clinician. As you said,
 16 the hallmark of these syndromes is the widespread
 17 distribution of symptoms. So in a patient who has
 18 widespread pain or widespread noxious, or however
 19 you want to characterize unpleasant symptoms, for
 20 whom you feel like you can exclude peripheral
 21 causes -- so they don't have OA, and they don't
 22 have some other inflammatory syndrome that Lee

Page 110

1 talked about.
 2 Can you just talk about what your
 3 differential diagnosis of widespread pain is in
 4 those patients? What are the other possibilities?
 5 DR. CLAUW: That's a really good question.
 6 I think a big part of it depends on how long
 7 they've had the symptoms. If you see someone in
 8 clinical practice that's starting out at age 13,
 9 had painful menstrual periods, and then they had
 10 irritable bowel, and functional abdominal pain a
 11 little bit later in their life, and then in their
 12 20s they had regional pain and interstitial
 13 cystitis, and then finally their pain becomes so
 14 widespread, I don't think there is a differential.
 15 If you have like a 15-20-year history of the
 16 classic chronic overlapping pain conditions
 17 occurring together in the same individual, I think
 18 in that individual, I'll do some regulars, some
 19 simple screening tests, thyroid function, those,
 20 but I'm not really looking that aggressively for
 21 anything else.
 22 I think that if someone presents subacutely

Page 111

1 with those same symptoms, I'm doing a really
 2 extensive diagnostic workup because early
 3 autoimmune diseases look a lot like fibromyalgia.
 4 So clinically, a lot of it depends on the history I
 5 get from that person, the workup that they'd have
 6 to date, and what already has been excluded versus
 7 what still in play.
 8 DR. MARKMAN: Just as a follow-up, as you
 9 pointed out with your initial OA slide and the
 10 certain catechism that was central to rheumatology
 11 training, in neurology training there's a catechism
 12 that everywhere is not a pattern.
 13 DR. CLAUW: Right.
 14 DR. MARKMAN: And again, we have things like
 15 epilepsy monitoring units where we monitor people
 16 for 7 days to see if they have electrographic
 17 correlates to their seizure activity and use that
 18 as a basis for deciding whether they get therapy or
 19 not.
 20 So again, I would just like you to react to
 21 that notion because I think that some of us
 22 are -- as you know, these are professional belief

Page 112

1 systems which are inculcated in people, and I'm
 2 happy to jettison it. But I want to hear how you
 3 respond to that idea that everywhere is not a
 4 pattern.
 5 Also, what would be your epilepsy monitoring
 6 unit analog? Is there any other way to tease out?
 7 I think maybe that's part of the question that
 8 Ajay's getting at, how do you -- again, other than
 9 this longitudinal historical view, which you just
 10 proposed, how else do you -- what is the diagnostic
 11 enterprise look like?
 12 DR. CLAUW: Just to be clear, is what you're
 13 questioning is when someone has widespread pain,
 14 how do I know whether that's real or not and
 15 whether it's credible? Because I'm not really
 16 following you.
 17 DR. MARKMAN: Well, it's always real. I
 18 don't think anybody's disputing whether it's real,
 19 but I do think that as a clinician, I'm sure we all
 20 have a sense of -- again, whether it's conscious or
 21 unconscious to the patient, there's a lot of
 22 volitional and self-report, which we are asked to

Page 113

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

Page 114

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

Page 115

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

Page 116

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

Page 117

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

Page 118

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

Page 119

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

Page 120

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

Page 121

1 have any way of dissecting them, nor do I know that
2 there would be a different -- again, except the
3 thing that's really important, I think, is that if
4 it's being peripherally driven, then peripherally
5 directed treatments might work really well. That's
6 where I hope people don't miss the central message
7 that the peripheral drive might be still incredibly
8 important for what's going on in the CNS.
9 DR. KATZ: There's some evidence that your
10 prediction is correct. I'll tell you about it in
11 the break.
12 DR. CLAUW: Yes.
13 DR. FARRAR: The one example I know of where
14 a local truly can reduce or eliminate a spreading
15 pain syndrome is certainly in some patients with
16 Morton's neuroma in their foot, they get a whole
17 foot, whole ankle, whole knee pain. And if you can
18 find the single point that hurts and inject it with
19 local anesthetics, sometimes the whole thing goes
20 away. Akin to what Mithcell Max used to do,
21 injecting capsaicin under the skin, getting
22 widespread pain. As soon as you numb the area

Page 122

1 where the capsaicin was injected, the whole
2 syndrome goes away.
3 The question I actually wanted to ask,
4 though, is that all of us have seen patients who
5 have undergone a surgery and end up with chronic
6 regional pain syndrome, a bunionectomy with a foot
7 that ends up being problematic, and it's an acute
8 event that occurs 6 weeks after.
9 Would you presume that there could be, as
10 opposed to the development of this slowly over a
11 period of years, from age 13 to whatever, an acute
12 onset of this central process that you're
13 describing?
14 DR. CLAUW: Oh, absolutely, and that's been
15 looked a lot at in fibromyalgia and irritable
16 bowel. Let me talk about something that you're not
17 used to hearing me talk about; irritable bowel. In
18 irritable bowel, there are 6 different infections
19 of the GI tract: salmonella, shigella,
20 campylobacter; that if someone has those
21 infections, 6 to 8 percent of those people, after
22 that infection clears, will be left with irritable

Page 123

1 bowel, just like 6 to 8 percent of people that are
2 in motor traffic accidents develop something like
3 fibromyalgia.
4 So it's very clear that different stress or
5 trauma -- and this was Gulf War. A lot of our
6 early working looking at his phenotype is people
7 that were deployed to war. After war, any war in
8 the U.S. goes to, there will be a group of people
9 that come back looking like this. After the first
10 Gulf War, it was just this; and after Iraq and
11 Afghanistan, it was this superimposed on PTSD and
12 the polytrauma triad right now. But I think this
13 can often be triggered by different types of
14 stressors, or events, or things like that, and then
15 come on much more subacute than this indolent onset
16 that I was talking about.
17 That's two questions. Am I done, John?
18 DR. MARKMAN: You're done.
19 (Applause.)
20 DR. MARKMAN: We'll take about an half-hour
21 break.
22 (Whereupon, at 10:08 a.m., a recess was

Page 124

1 taken.)
2 DR. MARKMAN: Our next speaker comes to us
3 from the Brigham and Women's Hospital. He is an
4 associate professor of anesthesiology and has
5 taught most of us about psychophysics and
6 psychosocial modulation of pain intensity, and
7 explaining variability with his work on
8 catastrophizing and other constructs.
9 Dr. Edwards, thanks for taking the time
10 Presentation - Robert Edwards
11 DR. EDWARDS: Good morning, everyone.
12 Thanks very much for having me, and thanks
13 especially for including me in the morning session.
14 I noted this is the only part of the session that
15 will be videotaped, from which I can only conclude
16 that the most physically attractive, intelligent
17 people were invited to speak in the morning --
18 (Laughter.)
19 DR. EDWARDS: -- so thank you. I'm
20 flattered. I'm happily married, but still
21 flattered nonetheless.
22 I'm going to spend the next 30 minutes or so

Page 125

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

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

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

Page 126

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

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

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

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

Page 127

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

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

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

Page 128

1 Is it even possible? Should we try?

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

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

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

Page 129

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

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

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

Page 130

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

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

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

22 As we're talking about symptom counts and

Page 131

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

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

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

Page 132

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

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

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

Page 133

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

7 We can get at some of this, at least to some
 8 degree, with noninvasive QST in the laboratory.

9 And as many of you know, some of the best validated
 10 and most commonly used methods for assessing
 11 endogenous pain modulation are CPM, or conditioned
 12 pain modulation, to measure pain inhibition, and
 13 temporal summation in order to measure pain
 14 facilitatory processes.

15 These are considered two distinct types of
 16 pain modulation and two distinct psychophysical
 17 procedures, although as we'll see later, these
 18 systems are probably interrelated to some degree.

19 And just like people vary in their pain
 20 sensitivity, there's wide variation, both in groups
 21 of chronic pain patients and in the pain-free
 22 population in general, in the amount of CPM or the

Page 134

1 amount of temporal summation that they evidence.

2 This is some nice data presented recently by
 3 Serge Marchand in fibromyalgia patients, as well as
 4 healthy controls. What you can probably see from
 5 those distributions is that no matter what group
 6 you're studying this in, some people have very good
 7 condition pain modulation, so potent pain
 8 inhibition, and some people show facilitation or
 9 hyperalgesia instead of pain inhibition with this
 10 2-stimulus CPM testing paradigm.

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

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

Page 135

1 pain conditions like fibromyalgia.

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

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

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

Page 136

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

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

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

Page 137

1 won't try.

2 But when you look in samples of patients, if

3 you look at that scatter plot on the bottom right,

4 there's a nice inverse -- it's modest. It doesn't

5 explain a ton of the variance, but there's a highly

6 significant inverse correlation between CPM and

7 temporal summation. The more effective your CPM

8 pain inhibitory mechanisms are, the less temporal

9 summation that you have, and this is in a group of

10 patients with chronic musculoskeletal pain.

11 All of these processes like temporal

12 summation and CPM are situated within the context

13 of the biopsychosocial model of pain, which I

14 suspect we all subscribe to, and which posits that

15 dozens, or hundreds, or maybe even thousands at

16 this point, of factors affect people's experience

17 of and report of their responses to pain.

18 I'm going to spend just a handful of slides

19 or so focusing on one small component of the

20 biopsychosocial model of pain, a commonly studied

21 risk factor for chronic pain. You heard in Dan

22 Clauw's talk some discussion of catastrophizing.

Page 138

1 This is one cognitive and emotional element of the

2 biopsychosocial model Thanks, Ajay, for letting me

3 borrow this slide.

4 I do need to emphasize that catastrophizing

5 is really strongly interrelated with all sorts of

6 other measures of negative affect like anxiety, and

7 depression, and neuroticism. So it's not as though

8 this is a perfectly unique labeled line style

9 factor that predicts all on its own. It occupies a

10 space in which it overlaps moderately or more with

11 all of these other factors that we measure

12 generally via questionnaire.

13 But that said, there are a number of

14 predictive studies that suggest that

15 catastrophizing uniquely can predict things like

16 the future onset of chronic back pain. This study

17 is almost 20 years old now, a prospective

18 epidemiologic study. If you take people who are

19 initially chronic pain free and split them

20 according to their baseline level of

21 catastrophizing, those who catastrophize most are

22 at 3 or 3 times greater risk for developing chronic

Page 139

1 or disabling low back pain over the next year

2 relative to those who are low in catastrophizing.

3 Within samples of patients who already have

4 chronic pain, catastrophizing is also an important

5 predictor. These are some data from a recent study

6 of neuropathic pain treatment. In this particular

7 study, the researchers look at pretreatment levels

8 of catastrophizing and their relationship with how

9 much analgesic benefit people get from medications

10 like amitriptyline, and nortriptyline, and

11 gabapentin, and pregabalin.

12 What you can hopefully see from that scatter

13 plot is the higher the catastrophizing score, the

14 less the reduction in neuropathic pain with these

15 treatments. In the figure on the right, the higher

16 the catastrophizing score, the more likely people

17 are to discontinue treatment, presumably because of

18 a greater experience of adverse side effects, which

19 I'll show some additional data on later.

20 So what I'm going to argue and hopefully

21 conclude is that catastrophizing as part of this

22 biopsychosocial model is really strongly linked

Page 140

1 with a variety of other elements of somatosensory

2 amplification and centralized chronic pain. Dan

3 Clauw's presentation was terrific and touched on a

4 number of aspects of centralized chronic pain.

5 What I hope to show you over the next

6 handful of slides or so is that catastrophizing

7 probably influences a lot of those centralized

8 chronic pain elements. I'm going to go through

9 these slides fairly quickly just to make sure that

10 I can finish on time and because they're fairly

11 straightforward in nature.

12 Our group, as well as a number of others,

13 has studied things like the relationship between

14 catastrophizing and pain sensitivity in the

15 laboratory in chronic pain conditions.

16 These are some data from a large recent

17 study of patients with chronic low back pain.

18 Those patients are more mechanically pain

19 sensitive, they're hyperalgesic relative to

20 controls, and they have higher levels of

21 catastrophizing, and those things are related.

22 When you run a mediational model, you see that,

Page 141

1 statistically, the higher catastrophizing in the
 2 patient group explains a substantial proportion of
 3 their increased pain sensitivity.
 4 Temporal summation, which I mentioned
 5 before, is also influenced by catastrophizing, or
 6 since a lot of this stuff is a cross-sectional, we
 7 could also suggest that catastrophizing is
 8 influenced by temporal summation. It is very
 9 likely that there are bidirectional reciprocal
 10 influences here, but in this case I'm going to talk
 11 about it as catastrophizing influencing temporal
 12 summation.
 13 What you can see from that graph is that the
 14 high catastrophizing musculoskeletal pain patients
 15 show elevated temporal summation relative to the
 16 low catastrophizers. This is a finding that has
 17 shown up in dozens of studies in all sorts of
 18 samples: chronic back pain, headache, healthy
 19 controls; it is very consistent.
 20 Catastrophizing is also related to reduced
 21 CPM in a number of chronic pain conditions. This
 22 is some data from a recent systematic review and

Page 142

1 meta-analysis of CPM in irritable bowel syndrome.
 2 The researchers find that CPM is reduced in IBS,
 3 and I'll just quote from the discussion section
 4 here.
 5 "In addition, reduced CPM responses were
 6 significantly correlated with higher anxiety,
 7 stress, and pain catastrophizing." The correlation
 8 coefficient R is around 0.4 or so, and it's
 9 noteworthy that the researcher showed that group
 10 differences in CPM responses were no longer
 11 significant when psychological factors were
 12 accounted for in the analysis.
 13 Catastrophizing, anxiety, stress, other
 14 sorts of indices of psychosocial distress seem to
 15 be strongly contributing to the reductions in pain
 16 inhibition in some of these chronic pain samples.
 17 We see a more subtle link between
 18 catastrophizing and impairment or reduction in CPM.
 19 These are some nice data collected by Ajay Wasan,
 20 oral opioid treatment of patients with chronic
 21 radicular low back pain. They're split into
 22 patients who have low and high levels of negative

Page 143

1 affect, so the high NA group has high
 2 catastrophizing, high anxiety, high depression.
 3 They don't differ from one another in CPM at
 4 baseline, but once you give them opioids, which
 5 we've shown in a previous slide can suppress CPM,
 6 only the high negative affect group, only the high
 7 catastrophizing group, only the high anxiety group
 8 shows a reduction in CPM with oral opioid
 9 administration.
 10 A number of groups have also shown that
 11 widespread pain, which is a hallmark of these
 12 centralized sorts of pain syndromes, is strongly
 13 influenced by catastrophizing. You can take
 14 patients with OA, or headache, or back pain, and
 15 the highest catastrophizing of those patients are
 16 more likely to report pain in pain sites other than
 17 the primary location of their initial pain.
 18 There are even some nicely done laboratory
 19 studies. This one is from Mick Sullivan's group up
 20 in Canada. He uses an exercise procedure in the
 21 lab, isometric or eccentric exercise that produces
 22 DOMS or are delayed onset muscle soreness. The

Page 144

1 exercises target the right pectoral muscle and the
 2 deltoid. Healthy subjects come in and do these
 3 exercises in the lab. They measure them 24 and 48
 4 hours later for the presence of post-exercise pain.
 5 What you might be able to see from that
 6 color plot there is that the high catastrophizers
 7 on the right report pain to a greater degree, or a
 8 higher percentage of them report pain in a variety
 9 of sites that weren't directly targeted by the
 10 exercise; so their other shoulder, their other arm,
 11 their forearm, their hand, et cetera. The high
 12 catastrophizers in response to this targeted
 13 exercise stimulus develop more widespread pain
 14 complaints.
 15 It is also true that high catastrophizers
 16 experience the most side effects from all sorts of
 17 treatments. I showed you the Corey Toth study
 18 earlier. This will just be some data from a recent
 19 study of ours at Brigham and Women's. Bob Jamison
 20 is one of the leaders in this area in terms of
 21 looking at opioid-related side effects in patients
 22 with chronic pain who are maintained on opioid

Page 145

1 therapy.

2 What you may be able to see highlighted

3 there is that the patients who report the highest

4 levels of side effects from oral opioid treatment

5 have much higher levels of catastrophizing than the

6 patients who report low side effects, which

7 presumably is one of the reasons that the highest

8 catastrophizers are most difficult to treat and

9 most often drop out of treatment.

10 I'm going to spend just a couple of slides

11 muddying the waters a little bit on whether

12 catastrophizing is consistently a unique predictor

13 of some of the most important pain-related outcomes

14 that were all focused on. In some studies, this

15 has turned out to be true. What I mean is when you

16 measure a handful or more of psychosocial factors

17 and look at all of their predictive influence,

18 sometimes catastrophizing comes out as the most

19 important predictor or even the sole significant

20 predictor.

21 In this study, trying to predict acute

22 postsurgical pain after hysterectomy, the

Page 146

1 researchers measure a number of psychosocial

2 factors, including catastrophizing and anxiety.

3 They're all significant at a univariate level, but

4 when you plug them all in, only catastrophizing

5 remains a unique predictor, and when you run

6 mediational models, catastrophizing mediates the

7 effect of anxiety on acute postoperative pain. So

8 catastrophizing emerges as the primary, or most

9 important, or sole unique predictor.

10 This is absolutely not the case in all

11 studies, and particularly when you measure a wider

12 variety of potential predictors, as we happen to do

13 in this study predicting acute outcomes after total

14 knee replacement, which you can hopefully see from

15 this table is that when you measure catastrophizing

16 in its univariate association with acute pain after

17 total joint replacement, the p-value for that is

18 0.002. It's a highly significant predictor.

19 So catastrophizing measured before surgery

20 predicts the severity of acute postoperative pain.

21 But when you include a number of other predictors

22 in the model, including psychophysical predictors

Page 147

1 like temporal summation, which you can maybe see at

2 the far right of that yellow or gold line, is that

3 catastrophizing is no longer a significant

4 predictor. That p-value is over 0.9, and temporal

5 summation of pain, again measured before surgery,

6 remains the single most important predictive factor

7 determining patient-reported severity of acute pain

8 after this surgery.

9 So sometimes catastrophizing emerges as a

10 sole predictor, particularly when it's in a mix

11 with just other psychosocial factors, but once you

12 include other overlapping elements, whether it's

13 temporal summation or other sorts of potential

14 predictive variables, catastrophizing can

15 absolutely lose some of its predictive ability, and

16 that is probably just the nature of the

17 interconnected biopsychosocial model of pain.

18 I'll come back to the OPPERA study briefly.

19 The pill, Pill, this symptom checklist, which is

20 the most important psychosocial predictor in terms

21 of the OPPERA study's models that predict the

22 development of temporomandibular joint disorder,

Page 148

1 The Pill remains a significant predictor in one of

2 the of the top 10 predictors overall, even when you

3 control for things like clinical history, and

4 comorbidities, and autonomic function, and pain

5 sensitivity measured by QST, and every other

6 psychosocial factor that you care to throw into the

7 mix.

8 Some of these things can remain unique

9 predictors, and it's very likely that different

10 elements of somatosensory amplification might

11 uniquely predict different outcomes. So perhaps

12 temporal summation is the best predictor of acute

13 outcomes after surgery. Perhaps a measure like The

14 Pill, or somatic focus, or somatization, whatever

15 we want to call it, is among the best predictors of

16 long-term outcomes, really long-term outcomes, like

17 the development of a chronic pain condition.

18 Not surprisingly, as you'd expect I hope,

19 based on the biopsychosocial model, there's a huge

20 amount of overlap between these different risk

21 factors or mechanisms. Probably all of them share

22 some neurobiological substrates, which is what I'm

Page 149

1 going to talk about over the next 3 or 4 minutes or
2 so before I wrap up.
3 I should emphasize now, and hopefully will
4 again, that the discussion of neurobiological
5 substrates is of course very appropriate, but in
6 some ways a little bit misleading because it
7 implies that the neurobiology comes first and then
8 drives all the other stuff. And I really
9 suspect -- and I bet many of us in this room do as
10 well -- that there are bidirectional relationships
11 here; that you can alter someone's cognitions and
12 emotions and change their neurobiology just like
13 you can alter their neurobiology and change their
14 cognitions and emotions.
15 So I'm not going to spend much time talking
16 about functional MRI studies of brain networks and
17 their potential maladaptive properties that
18 characterize patients with chronic pain, in part,
19 because Vitaly Napadow, my colleague and neighbor
20 in the back, is going to do a much better job of
21 that later this afternoon. But I do want to
22 emphasize just a couple of recent findings that

Page 150

1 have come out of some of our collaborative studies.
2 In general, what these studies do is use
3 functional MRI and connectivity analysis to look at
4 patterns of connectivity among different brain
5 networks that probably link to different aspects of
6 the pain experience. We'll look at networks like
7 the somatomotor network, the salience network, the
8 default mode network; and you heard Dan nicely
9 mention a few of these.
10 In general, what a lot of these studies
11 suggest is that these networks are maladaptively
12 interconnected or hyperconnected in patients with
13 chronic pain relative to demographically matched
14 pain-free controls. I want to just focus on two of
15 these networks, the somatomotor network and the
16 salience network, the somatomotor network as
17 exemplified by primary somatosensory cortex, and
18 the salience network as exemplified by anterior
19 insula.
20 One of our recent findings in this area
21 suggests that for patients with fibromyalgia, these
22 two networks are linked in a way that they're not

Page 151

1 in healthy controls. Furthermore, when we put
2 people in the scanner and apply a standardized
3 painful stimulus to them, mechanical stimulus
4 applied to the lower leg, the connectivity between
5 those networks increases to an unusual and probably
6 maladaptive degree in patients with fibromyalgia,
7 and this is compared to healthy controls.
8 So those networks are already
9 interconnected. In healthy controls, they're
10 unconnected. Put patients in the scanner, apply
11 experimental pain to them, and the connectivity
12 goes up quite a bit. There's variability in how
13 much that connectivity increases, and really what I
14 want to show you here is what that variability is
15 related to.
16 The amount of connectivity between the
17 anterior insula and primary somatosensory cortex,
18 when we apply pain to fibromyalgia patients in the
19 scanner, is correlated with how much clinical pain
20 severity they report in day-to-day life. It's
21 correlated with our pain catastrophizing scale
22 scores. It's correlated with how much attention

Page 152

1 they say they paid to the cuff pain when they're in
2 the scanner. This is the experimental stimulus we
3 apply; so think of this as a measure of
4 hypervigilance to pain. And it's correlated with
5 how much temporal summation we measure
6 psychophysically while they're in the scanner.
7 So all of these things, and probably all
8 elements of somatosensory amplification, probably
9 all moderately inner correlated with one another,
10 are also all moderately intercorrelated with what
11 we might think of as this neurobiological substrate
12 for pain measured as maladaptive degrees of
13 hyperconnectivity in these networks.
14 There are all sorts of other neurobiological
15 processes, way too many to get into, and I would be
16 way out of my depths with lots of them. But I want
17 to mention very briefly a bit of the recent
18 emerging story related to microglia and activated
19 microglia in the context of chronic pain.
20 Animal studies have suggested for a long
21 time that microglial activation plays a crucial
22 pathophysiologic role in all sorts of a chronic or

Page 153

1 long-lasting pain conditions; for example, after
 2 nerve injury in rats. It's only recently become
 3 possible to noninvasively measure microglial
 4 activation in humans using a fairly newly developed
 5 PET ligand as PBR-28.
 6 Vitaly and my colleague, Marco Loggia at
 7 Mass General, are leading many of these studies.
 8 And what you might be able to see from this cut-out
 9 on the lower right of the screen there is a
 10 comparison of fibromyalgia patients and healthy
 11 controls at two different sites. One's at Mass
 12 General and one's at Karolinska Institute in
 13 Sweden.
 14 At both sites, what they're looking at is
 15 the PET evaluated degree of microglial activation
 16 in pain-relevant brain regions. In a whole bunch
 17 of regions -- anterior cingulate cortex, sensory
 18 cortex -- these regions span -- all of those
 19 networks I was just talking about, the fibromyalgia
 20 patients have more microglial activation than the
 21 controls, which seems reasonable.
 22 We might conclude that there's a

Page 154

1 pathophysiologic role for microglial activation in
 2 fibromyalgia, and that seems all fine and good.
 3 But I just want to emphasize that in a number of
 4 studies, these micro activations are pretty
 5 strongly linked to psychosocial factors reflecting
 6 emotional distress or other elements of
 7 somatosensory amplification.
 8 In this study of healthy controls compared
 9 to patients with chronic back pain, what we see,
 10 and what you can see in those scatter plots, is
 11 there is a really tight relationship between
 12 patient's BDI score, so how distressed they are,
 13 and how much microglial activation they have in
 14 brain regions like the anterior and midcingulate
 15 cortex.
 16 If you split up patients, it is only the
 17 patients who have elevated psychological distress
 18 who show increases in microglial activation in
 19 those areas. The chronic back pain patients with
 20 low BDI scores look just like the controls when you
 21 look at their levels of microglial activation.
 22 This is cross-sectional. I don't know what

Page 155

1 drives what. Maybe microglial activation comes
 2 first, maybe depression comes first, or maybe, more
 3 likely, you can get to this final spot via either
 4 pathway, and depression, and distress, and
 5 catastrophizing, and anxiety create microglial
 6 activation. It's also the case that if you
 7 activate people's microglia and produce neuronal
 8 inflammation, you get a lot of those psychosocial
 9 factors as well. I suspect, but can't prove, that
 10 you can get there in either direction.
 11 To wrap up -- because I'm about a minute
 12 over here -- these various elements of
 13 somatosensory amplification that I've talked
 14 about -- somatization, sensitization, pain
 15 facilitation, catastrophizing -- all interrelate,
 16 at least moderately, with one another. They might
 17 all be both final, common pathways, as well as
 18 specific mechanisms getting to those final common
 19 pathways by which people can develop chronic pain
 20 conditions, as well as maintain those conditions.
 21 I just want to remind people that when we're
 22 talking about things like sensitization, there's a

Page 156

1 really broad array of manipulations that we could
 2 apply that have been shown to change people's
 3 sensitivity to pain; gender reassignment surgery.
 4 We can give people insomnia. We can inject LPS.
 5 We can make them catastrophize
 6 We can give them remifentanyl and
 7 opioid-induced hyperalgesia. We can give them the
 8 flu. We can make them depressed. We can give them
 9 surgery. We could socially isolate them. We could
 10 refuse to let them be physically active, and we
 11 could decondition them. And we could set up a
 12 nocebo paradigm that increases their pain
 13 sensitivity. I kind of ran out of room and
 14 breaths, but there are 200 other things we could
 15 put on that slide that influence, robustly,
 16 people's pain sensitivity and their measured levels
 17 of sensitization.
 18 Final slide, somatosensory amplification, a
 19 neat historical term that hasn't really been well
 20 defined. The term itself isn't widely used, but
 21 variations of that term are, and are clearly
 22 important. That construct or phenomenon shares a

Page 157

1 lot of space with other more commonly used terms
 2 that have proven to be important predictors of
 3 pain-related outcomes; all of these things strongly
 4 interrelated with one another.
 5 It seems likely to me, particularly based on
 6 data, that these things share neurobiological
 7 substrates, which Vitaly and other presenters will
 8 probably talk more about. It may be that different
 9 elements of somatosensory amplification
 10 differentially predict different outcomes, although
 11 we need quite a bit more work in that area.
 12 Really, the one question of interest for me
 13 is whether we should be trying to uniquely measure
 14 and analyze all of these elements separately. So
 15 for our clinical trials, should we be giving
 16 everyone a pill, and a PCS, and an anxiety measure,
 17 and doing a full QST battery, and doing fMRI, and
 18 doing PET, and doing everything else we can think
 19 of to measure these different elements, or does the
 20 overlap mean that we can just take a few of these
 21 and consider them as representative of the
 22 construct of somatosensory amplification?

Page 158

1 I don't know the answer to that myself, but
 2 I bet with the collective brain power in this room,
 3 we are smart enough to figure it out. So I will
 4 leave you with that, and thanks very much to my
 5 colleagues at Brigham, and Mass General, and to
 6 Ajay Wasan in Pittsburgh who really provided all of
 7 the data and work that went into collecting these
 8 findings. Thanks very much.
 9 (Applause.)
 10 Q&A
 11 DR. BRUEHL: This is Steve Bruehl; a quick
 12 question for you. In looking at the literature,
 13 have you ever encountered large sample studies that
 14 have used multiple of these options and applied
 15 something agnostic like cluster analysis to see if
 16 there's evidence for them all reflecting some
 17 underlying construct?
 18 DR. EDWARDS: The OPPERA study does probably
 19 as good or better a job of that relative to any
 20 other study I can think of. I'm not sure they did
 21 cluster analysis. Roger will know better. Yep,
 22 they may have done both cluster and factor

Page 159

1 analysis, and been able to derive sort of sets of
 2 these variables that tend to be most interrelated
 3 or hang together.
 4 Whether we can then take that data and
 5 select out specific elements of those clusters or
 6 factors, and just measure those things and consider
 7 them representative, I don't know for sure, but it
 8 might be beneficial for the field if we all went
 9 back and took a closer look at all those OPPERA
 10 papers because that's probably the best in the
 11 sense of that sort of thing being done.
 12 DR. FARRAR: John Farrar, University of
 13 Pennsylvania. I'm clearly pointing out something
 14 that you are aware of, but I think it may not be
 15 general, which is that you suggested that there
 16 were differences in terms of which was most
 17 important, catastrophizing or temporal summation,
 18 whereas in both studies, both of them had
 19 univariate effects.
 20 Now, which one stays in is going to be
 21 dependent on a host of factors that may have
 22 nothing to do with the relationship between them,

Page 160

1 and it may be the variability with which each is
 2 measured and the quirks about the population. And
 3 as many of us are familiar with, the Framingham
 4 study made a huge mistake when it put diastolic
 5 pressure into the model first, and then systolic
 6 pressure fell out. And all of a sudden somebody
 7 said, "Well, let's go look at the other way
 8 around," and it turned out that both are important.
 9 So I'm not sure that the data actually
 10 contradicts itself. The question, though, that I
 11 wanted to try and get to is what do you think
 12 catastrophizing is measuring in terms of brain
 13 function? Every psychosocial process is a
 14 transmitter, mediated, connection-involved,
 15 frequency and pattern process. I'm quite willing
 16 to accept that it's measuring something that is
 17 important and is part of this process, but I don't
 18 know that it argues that it is more or less
 19 important than some of the other things that we're
 20 measuring.
 21 So what do you think, from a brain
 22 perspective, we're actually measuring with

Page 161

1 catastrophizing?

2 DR. EDWARDS: That's a terrific question. I

3 agree with your premise that the predictive

4 capacity of any of these things is going to vary

5 quite a bit depending on the subtleties and nuances

6 and quirks of any individual study, and that's why

7 it's going to be really challenging -- although

8 hopefully we're up to the challenge -- to come up

9 with a list of definitive recommendations that

10 sound something like, "For all trials of X, we

11 should absolutely be measuring these 5 factors as

12 particularly important." So that's probably what

13 we'll spend some time working on tomorrow.

14 If you need me to put my nickel down right

15 now and identify the fMRI assessed neurobiological

16 substrates of catastrophizing, I would probably

17 ramble for a minute or two about alterations in

18 default mode network function and alterations in

19 default mode network connectivity with other

20 networks of interest like the salience network.

21 I'll put in a plug here for Vitaly, who may

22 touch on some of those issues in his talk. If he

Page 162

1 wasn't planning to, now he probably has to, so

2 sorry, Vitaly.

3 (Laughter.)

4 DR. EDWARDS: But some data that is emerging

5 from some of our studies. And I'd suggest that

6 some of the MAPP related data and some of Dan

7 Clauw's data as well I think seems to identify the

8 default mode network particularly as being

9 influential in some of these centralized chronic

10 pain syndromes, whether it's fibromyalgia patients

11 or whether it's pelvic pain patients with

12 widespread pain.

13 In general, those are the patients who

14 report the most catastrophizing, as well as the

15 most temporal summation, as well as the most other

16 physical symptoms, and all of those other things

17 together.

18 Clifford?

19 DR. WOOLF: How do you deal with the problem

20 of the difference between correlation, which is

21 strong in some cases, and causality? You're making

22 an assumption that these are driving the risk

Page 163

1 factor or driving the disease phenotype, whereas

2 they may just be correlated.

3 DR. EDWARDS: Very true. The one-word

4 answer to your good question about how I deal with

5 that problem is poorly. However, the longer term

6 answer is we're currently engaged in a number of

7 studies of non-pharmacologic treatments that

8 specifically target elements of patient's

9 presentation like catastrophizing, and we take all

10 sorts of measurements at various time points over

11 the course of those treatments, including our

12 admittedly crude measurements of pain neurobiology

13 using fMRI, PET, and other sorts of things.

14 Presumably, those longitudinal studies in

15 which we're systematically manipulating one of the

16 cognitive and emotional factors and measuring

17 changes in that, as well as changes in

18 neurobiological outcomes, will at least help us to

19 shed some light on the temporal dynamics of those

20 relationships.

21 There are no studies like this yet, but I

22 wouldn't be surprised if everything turns out to be

Page 164

1 bidirectional. And if you make people

2 catastrophize by, for example, giving them

3 information about their chronic pain syndrome and

4 how it can never be cured, it's going to ruin their

5 life, they better quit their job, probably their

6 marriage is going to fall apart, that sort of

7 thing, and you make them really anxious and

8 catastrophic about their pain, I'm quite confident

9 that that changes the dynamic interrelationships

10 between default mode network and some of these

11 other networks. I have no doubt that changes brain

12 function and probably eventually structure.

13 I suspect it's also true that if you had

14 really specific techniques, which we don't yet, and

15 you could do TDCS, or TMS, or a technique like

16 that, and selectively manipulate the default mode

17 network and its activity and its relationship with

18 other brain networks, you could produce a

19 catastrophizing state that way.

20 So I strongly suspect that either path can

21 influence the other, and how that happens most

22 often in patients, I don't know, and is to me a

Page 165

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

Page 166

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

Page 167

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

Page 168

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

Page 169

1 Presentation - Sharon Hertz
2 DR. HERTZ: Hi, everyone. I got here a
3 little late, so I haven't had a chance to say hello
4 to everyone. I'm just going to talk about
5 indications a little bit. It's a very different,
6 sort of a left turn, from this morning talk. When
7 we're thinking about these different processes,
8 hopefully eventually we're going to end up with
9 targeted treatments and how do we translate that
10 into an indication.
11 I'm going to talk a little bit about some of
12 the guidances that we've had, which try to define
13 how to study different aspects of pain. It's kind
14 of funny. I've been at the agency now, at the Food
15 and Drug Administration, for a little over 20
16 years, and we've been writing a pain guidance for a
17 little over 19.
18 (Laughter.)
19 DR. HERTZ: We've had a couple drafts. I
20 remember Bob Rappaport saying he was just insistent
21 that we get this thing done before he leaves, so
22 I'm not so hopeful.

Page 170

1 (Laughter.)
2 MALE VOICE: He's left.
3 (Laughter.)
4 DR. HERTZ: Yes.
5 The '92 guidance was in place for a long
6 time, and it was an interesting document. It
7 described a number of different things. This I
8 thought was interesting, the state of the art of
9 the controlled evaluation for effectiveness of
10 chronic analgesic administration, i.e., more than 2
11 to 3 days.
12 That's an interesting definition of chronic,
13 but I think, really, what it was distinguishing was
14 multiple dose versus single dose and how well the
15 models for single dose analgesic trials had been
16 established, and we were still trying to develop
17 additional models to study other, approaches to
18 drug administration, because clearly these pain
19 populations were not 2-to-3-day populations.
20 This was also very interesting. I focused
21 on the chronic part of this because acute pain has
22 always been a little bit easier to discuss. In the

Page 171

1 '92 guidance, it talked about how we should study
2 peripherally acting products for 6 months, but
3 centrally acting for at least a month because of
4 safety issues. I think it just reflects 1992 and
5 the time prior was just such a very, very different
6 time in this work.
7 Some of you may know that the history of
8 analgesic products at the agency has been
9 interesting. For a number of years, it was split
10 between two divisions. One division had the
11 Schedule 2's, and the other division had NSAIDs and
12 some Schedule 3 and 4's. The approach to
13 development kind of started separating, and they
14 were brought back together around 2005 or '06 when
15 we were reorganized, and we've been trying to clean
16 things up ever since. For those of you who
17 consult, I'm sure there's a variety of opinions on
18 how well we've done that.
19 One of the approaches that we used to try
20 and understand how to develop indications was to
21 have a scientific workshop. Bob was the first
22 author writing up the proceeds of that workshop.

Page 172

1 It talked about what we could do in terms of
2 extrapolating efficacy across different conditions
3 and some of the factors and what the considerations
4 were to do so.
5 I'm here five years later. That's super
6 quick by federal agency standards. We published
7 for comment a draft guidance, the 2014 draft
8 guidance, taking into consideration some of the
9 things we learned in the scientific workshop. And
10 the guidance, which by the way is also now off the
11 website, talked about what do we need to know about
12 an NME versus something that was not an NME, or
13 something that was new class versus not a new
14 class.
15 We were really focused on avoiding these
16 supraspecific or pseudospecific indications as a
17 way to get a product out in use but not have the
18 kind of information we need, particularly the
19 safety information, in the kind of populations in
20 which it would actually be used. So we to find
21 where we thought very, very narrow indications
22 would be appropriate, so if it only was going to

Page 173

1 work in a narrow population or if safety concerns
 2 would necessitate restricting it.
 3 We had a menu, effectively, of what it would
 4 look like to develop products for different
 5 conditions. We actually did have central
 6 neuropathic pain in there as opposed to peripheral
 7 neuropathic pain. Nobody has ever actually filled
 8 the menu items for general chronic pain indication,
 9 nor have we seen much in the visceral pain area for
 10 acute pain. We did talk about some subgroups of
 11 indications.
 12 So we're working on some more guidances now
 13 because I like working on guidances, to some
 14 extent, and we're going to be covering a number of
 15 things. You'll be seeing these hopefully -- well,
 16 you'll be seeing them depending on how long you
 17 stay active in the literature.
 18 (Laughter.)
 19 DR. HERTZ: What do we currently have in
 20 terms of indications? This is all fairly
 21 pragmatic. Indications are generally reflected,
 22 the underlying clinical studies, with some

Page 174

1 extrapolation. But our approach to study design
 2 has changed, therefore if you look at the range of
 3 indications out there in analgesic products across
 4 the span of the last couple of decades, it's pretty
 5 diverse.
 6 We've been working on harmonizing indication
 7 language to the extent that we have the information
 8 to do so. Another reason why indications may be
 9 changing is because of new information that becomes
 10 available, the opioids. Everything has to say the
 11 word "opioid" in it these days.
 12 The opioid indications are something that
 13 we've spent a lot of time working on. Labeling is
 14 the number one communication tool for FDA. This
 15 group is probably not a good group to survey in
 16 terms of who's actually read a label, but when I
 17 talk in front of a group of people who have MDs or
 18 other prescribing related degrees and I ask them
 19 who writes it, have you ever read one, it's pretty
 20 low numbers.
 21 So anyway, what we've done with the
 22 opioids -- this is the example of the current

Page 175

1 extended-release, long-acting indication -- is
 2 we've tried to combine both risk and benefit.
 3 Traditionally, indications tell you what something
 4 works in. Here, we seem to have a need to
 5 emphasize if you're going to use it to treat pain,
 6 don't forget the rest of the baggage that comes
 7 along with them. So we have the indication, which
 8 says if you use these products, other products that
 9 may have different or lesser risks aren't going to
 10 be suitable.
 11 We have a similar type of that for the IR
 12 products. Here's transmucosal immediate-release
 13 fentanyl label. In contrast to the ER/LA label,
 14 which is just pain severe enough to warrant the
 15 drug, this one is narrow, and this was narrowed
 16 based on safety concerns. The range of fentanyl
 17 doses in these products is pretty expansive, and
 18 the pharmacokinetics really made us concerned about
 19 what it would look like if these were widely used
 20 in a general way.
 21 The fact that the first one was a raspberry
 22 flavored lozenge, also referred to as "the

Page 176

1 lollipop," really made us worried about what would
 2 happen if these got into a very popular wide use
 3 without an understanding of the safety concerns, so
 4 this was very narrow.
 5 Here's a recent one, not controversial at
 6 all, the first sufentanil product that is not a
 7 parenteral or is not an ID formulation. Here, it's
 8 for pain, but again, heavy emphasis on the safety
 9 aspect of it being in a supervised setting, and we
 10 listed a whole lot of other things that people were
 11 worried about in the limitations of use.
 12 Going back to some of the non-opioids in
 13 older products, again, this was very much pragmatic
 14 what was studied, signs and symptoms of a variety
 15 of arthritides and pain. It's interesting that we
 16 have this signs and symptoms concept even though in
 17 some of these, there was no sign actually being
 18 measured; it was all symptoms for a number of them,
 19 but people seemed to understand how to use Naprosyn
 20 pretty well.
 21 Then we have another nonspecific,
 22 non-selective NSAID, which turned out it had a big

Page 177

1 problem with bleeding. So it got limited to a
2 shorter duration, and by some miracle people have
3 actually respected this one in contrast to anyone
4 here who's ever prescribed bromfenac, which had to
5 come off the market because the limitation on
6 duration wasn't being respected there were bad
7 outcomes.
8 Here's this centrally-acting drug, and the
9 indications that it currently has. Again, it's
10 indicated for the treatment of diabetic peripheral
11 neuropathy based on two studies of our standard
12 12-week duration, double-blind, placebo-controlled
13 fixed dose in this case in adults with diabetic
14 peripheral neuropathic pain.
15 For the fibromyalgia indication, again, two
16 studies using a CR criteria. I don't remember what
17 year these are from, but it's a few years old.
18 It's not the most current version. I'm glad that
19 we used a history of widespread pain in addition to
20 the tender points sites, which we know should be
21 more leery of, and of course chronic
22 musculoskeletal pain. This one was interesting

Page 178

1 because it actually was a combination of different
2 clinical trials that resulted in some measure of
3 extrapolation. We had studies in low back pain.
4 We had studies in OA. Boom. That's
5 musculoskeletal pain.
6 Another example would be Lyrica, which has a
7 number of interesting indications. The DPN,
8 diabetic peripheral neuropathy, is a common target.
9 Lots of people have it. It's easy to recruit, and
10 there's a big market.
11 Postherpetic neuralgia and fibro we also
12 have here, and also neuropathic pain associated
13 with spinal cord injury, which was interesting.
14 Does this constellation of indications suggest we
15 should be broadening this in some way? So far, the
16 company hasn't asked for it, so we don't go poking
17 bears if we don't need to, but that's how that
18 labeling stands.
19 So what would a truly novel indication be in
20 this current environment and referable to this
21 meeting? Could we indicate something for the
22 management of pain due to central sensitization? I

Page 179

1 think, Cliff, you might like that. You've long
2 supported the concept of mechanism-based drug
3 development. But what does that mean and how would
4 that be interpreted and used? Should it be somehow
5 narrower? Management of some aspect of what is
6 manifest in what could be coming from central
7 sensitization, or hyperalgesia or allodynia in the
8 setting of widespread pain, or specifically due to
9 that process?
10 Is the science ready to support that type of
11 clinical drug development? This is going to depend
12 on a number of factors to get to this type of an
13 indication, How do we define the population is
14 very much the topic here. What's the range of
15 manifestations? What's most important to the
16 patients? Can diagnostic criteria be translated
17 into a study population, and more importantly, can
18 it be translated into an indication or a way that
19 clinicians can apply a strategy with at least some
20 way of matching what was done in a clinical trial?
21 What about the measurements? For those of
22 you who've participated in our qualification

Page 180

1 process, first, I apologize --
2 (Laughter.)
3 DR. HERTZ: -- and second, we need to have
4 validated measures. I like the idea of putting
5 somebody through an fMRI, a PET scan, or a QST
6 battery, and the other things that were just
7 mentioned to define the population, but clearly
8 that's not going to translate into clinical
9 practice. So we need to have some way of defining
10 the population using reliable measures that can
11 then support a reasonable indication.
12 As we think about what the implications are
13 of what we know, once a lot of these questions get
14 better defined answers, I think we can start
15 looking at how to translate that into indications.
16 That's all I have.
17 (Applause.)
18 Q&A
19 DR. CLAUW: Thanks very much, Sharon. I'm
20 just wondering if we could use the drug duloxetine
21 as an example of, knowing what we know now rather
22 than what we knew 7 or 8 years ago when that drug

Page 181

1 was being developed, how one might be able to
2 approach, for example, an indication of chronic
3 musculoskeletal pain with a certain score on the
4 body map or the fibromyalgia measure.
5 In hindsight, that has almost
6 certainly -- we certainly know in low back
7 pain -- Lily did the study subsequently, and it was
8 the people with the higher score that were the ones
9 that duloxetine worked in. And that almost
10 certainly would be the case with the osteoarthritis
11 group as well. There's a lot of data that would
12 suggest that it would have been the people with OA
13 with either the more diffuse pain on body map or
14 the higher fibromyalgia score.
15 So I'm just wondering now if a company
16 approached you now and said we have a drug that we
17 think works across a number of different chronic
18 musculoskeletal pain indications in the subset of
19 people that have central sensitization, and we're
20 going to use this PRO that's been widely used and
21 shown in these different studies, and we even know
22 what this PRO relates to on fMRI and quantitative

Page 182

1 sensory testing.
2 What would be the reception that one would
3 get at the agency, and what types of things would
4 you be concerned about, worried about, so that we
5 could help move the field in that direction?
6 Because I think we all think that would be good for
7 the field if we could move in that direction.
8 DR. HERTZ: That's a great question, and
9 it's actually quite layered in terms of what
10 implications of that approach could be.
11 First of all, in the context of somebody
12 simply wanting to do that, conceptually if you
13 screen your patients and use that as a selection
14 criteria, you can improve your assay sensitivity.
15 You can see what the effect is in the population
16 that's going to respond. And presumably, a PRO
17 could even be useful for clinicians who are dealing
18 with pain patients in terms of drug selection.
19 Yes, as long as the PRO has adequate validation, I
20 think that it is certainly an approach that could
21 be considered.
22 What I wonder, though, is what percent of

Page 183

1 the population that would reflect, and then what
2 are the implications if we indicate the drug for
3 musculoskeletal pain in patients who are
4 characterized by this somehow? Because the reality
5 of the environment that we're in right now is what
6 about the other people who don't necessarily meet
7 those criteria but who might respond for other
8 reasons perhaps, and what about access to it? Is
9 being more focused going to create some type of
10 barriers?
11 I mean, aside from the practical aspects of
12 it, I think it would be great to have mechanisms to
13 evaluate patients that match them with the drugs
14 they're getting treated with as opposed to trial
15 and error. So instead of a number needed to treat
16 of 3, or 6, or whatever to find a person who
17 responds well, if you can get that down to 1 or 2,
18 well, that's terrific.
19 DR. RATHMELL: Jim Rathmell from Brigham and
20 Women's. I just want you to expand on that because
21 how does that differ from what's happening today
22 where we have these run-in periods where you enrich

Page 184

1 the population for responders before you do the
2 first treatment, and then you're analyzing the
3 data?
4 So just expand on how you approach the
5 current trial paradigm that increases the chances
6 of success, but then as you're evaluating the
7 compound, you know that the user, the end user, the
8 clinician, is going to completely ignore that the
9 trials that got it approved were enriched.
10 DR. HERTZ: Well, they're ignoring it
11 because they don't read our darn labels. We
12 describe that if a hundred people are run-in and 50
13 get to the next level because of meeting criteria,
14 then they already start to know that half the
15 population didn't respond. In fact, I think it's
16 higher.
17 Then surprisingly, in spite of enriching the
18 population, we still get a bunch of dropouts. I
19 mean, the whole point of the enrichment was to
20 avoid having so many dropouts. We're basing our
21 analysis on imputed data, which doesn't serve
22 anybody well, but then we still lose another 30

Page 185

1 percent.

2 So using a gross enrichment scheme just to

3 have enough people in the study, to keep them in

4 the study long enough to get outcomes, because they

5 either tolerate it or respond with some measure of

6 efficacy, how does that compare to this?

7 Well, I suspect that the -- because then

8 we've cut out the risk of a number of dropouts

9 early because we're removing some of the people who

10 can't tolerate the drug. We've potentially

11 excluded a number of people who might drop out for

12 lack of efficacy. We still have, at the end of the

13 day, only a portion of the population that

14 responds.

15 Enrichment, the way it's currently being

16 done -- which by the way is primarily being done in

17 opioid studies, not in some of the other drugs, and

18 I'll talk to that point in a minute -- it's a

19 sledgehammer. The potential PRO is much more of a

20 tweezer, picking people more appropriately as

21 opposed to just kind of whacking other people out

22 of the way.

Page 186

1 The reason why the approach was adopted for

2 opioids -- and this is a method that's been used in

3 other centrally-acting drugs for a variety of

4 different reasons. We actually borrowed this.

5 Just for the record, this was not created by

6 IMMPACT or ACTION. This was brought to IMMPACT or

7 ACTION by us because we saw this method being used

8 in other cases with somewhat low response rates as

9 a way to improve assay sensitivity; for instance,

10 depression.

11 So if you have a fixed-dose trial, and it

12 takes weeks and weeks for people to tolerate the

13 drug, and you don't have weeks and weeks to titrate

14 them and get them used to it -- plus, even with

15 enough time, there's a bunch of people who just

16 aren't going to like that particular drug for a

17 variety of reasons -- and then you force them to

18 get into the study to stay on a fixed dose for a

19 long period of time -- we were having dropout rates

20 of 50-60 percent. How do you analyze that?

21 Then you have to start powering your study

22 to be a responder, yes or no, and then you're

Page 187

1 increasing the size, and you're losing information.

2 That's a situation which a drug is not readily

3 tolerated in a method of use that doesn't

4 necessarily reflect clinical practice. With

5 duloxetine, that had a fixed-dose design. That was

6 more of a standard clinical trial design, and it

7 didn't run into the problem.

8 So I think you have to look at what the

9 enrichment is trying to achieve. In one case, it's

10 just trying to make the study feasible in the

11 context of you have data to analyze, and you don't

12 have a missing data problem. In the other hand,

13 and in this situation, it's actually trying to

14 select the right population. I still don't know in

15 the opioid study who is going to be a responder at

16 the end of a 12-week period. It's still not going

17 to be a 90 percent response rate. It's still going

18 to have a higher number needed to treat.

19 DR. DWORKIN: Sharon, I'm going to go back

20 to Dan's question. Let's say we have a PRO that we

21 predict identifies which patients treated with

22 duloxetine are going to respond robustly. Do you

Page 188

1 also want to see in the clinical trial that the

2 patients who score low on that PRO don't respond to

3 duloxetine? So are you really predicting that one

4 subgroup -- are you going to need to see data that

5 one subgroup responds robustly but another subgroup

6 doesn't, or is it sufficient to just show the

7 robust response and the high scores?

8 DR. HERTZ: That's the kind of question I

9 don't like to answer --

10 (Laughter.)

11 DR. HERTZ: because it kind of sounds like

12 advice about specific things. So I would say the

13 way in which you define the population should

14 reflect what you think will be acceptable labeling

15 and an acceptable way of defining your indication.

16 You don't have to prove drugs don't work. If you

17 enrich the population and a whole bunch of people

18 said it didn't work, you don't have to keep them in

19 the study; you can enrich them out, or let them

20 leave as part of the enrichment program. You don't

21 have to still prove it doesn't work in them because

22 that initial enrichment period, it's very blunt.

Page 189

1 So I would say to you, or to whomever, what
2 do you want to do? How do you want to define your
3 population and how do you want to define your
4 indication? Because there are going to be
5 implications to how you use any instrument or any
6 set of inclusion/exclusion criteria to define an
7 indication.
8 DR. WOOLF: Could I ask another theoretical
9 question? Assuming that Dan's correct, and we can
10 identify who's at risk and that potential
11 therapeutic, and prevent the evolution to
12 chronicity, how would you manage that as a
13 preventative rather than a symptom control?
14 DR. HERTZ: How would you manage that?
15 (Laughter.)
16 DR. HERTZ: I'm trying to think of specific
17 examples. There is some interest in the setting of
18 chemo-induced neuropathic pain to perhaps try to
19 prevent it as well as to try and manage it. The
20 questions I would ask are how well can you define
21 the at-risk population? What are the risks and
22 benefits of treating that population with whatever

Page 190

1 your product is, and what is the appropriate time
2 to decide whether or not it's actually
3 preventative? Do you have to stay on the drug or
4 not indefinitely? Does it prevent it and you're
5 good to go, or is it just an ongoing therapy?
6 Those are the kinds of questions that would
7 have to be considered. But yes, there's prevention
8 stuff all over the FDA, perhaps more in other
9 divisions. But yes, I think prevention is
10 something that can be considered.
11 Lesley?
12 DR. ARNOLD: Yes. Hi. Lesley Arnold,
13 Cincinnati. When we're talking about an indication
14 for central sensitization, we are talking symptoms
15 beyond pain because when someone has that
16 condition, as we've heard about, they have other
17 symptoms in addition to pain.
18 One of the challenges that we've faced over
19 the years is how to get a labeling for these other
20 important symptoms that these patients experience:
21 pain, fatigue, sleep disturbance. And we've worked
22 to develop different outcome measures that

Page 191

1 incorporate these symptoms, but they've never
2 really been used yet as a primary outcome in these
3 trials.
4 For example, Lyrica, pregabalin, works very
5 well on sleep disorders related to fibromyalgia,
6 but it never really reached a level of getting on a
7 label even though we know that it works. I think
8 it's just been very challenging for us to know how
9 to present this information to the prescribing
10 doctors so that they know about it and can take
11 advantage of the drug's capabilities, but also just
12 addressing all these multiple symptoms that these
13 patients experience so that they get a better
14 effect from their treatment.
15 DR. HERTZ: Well, it sounds like you're
16 talking about fibro. I'd have to go back and look
17 at the exact language for the products that have
18 fibro indications, but I think if your drug is
19 going to treat multiple aspects of a disease, then
20 we can think about a broad indication. We need to
21 know what's important, how you're going to define
22 it, and then you need good tools.

Page 192

1 If you ask a patient in the morning did they
2 sleep well at night, the answer is that's not an
3 adequate tool. That's what we get a lot of the
4 time, and that's a lot of why we don't see stuff in
5 labeling because we don't have a validated measure.
6 I think that you can think about what are validated
7 measures, and then you can design your study to
8 incorporate them with your statistical plan, taking
9 that into consideration.
10 DR. MARKMAN: Time for two more questions.
11 DR. CLAUW: This is a question I think you
12 can answer. I'm going to try and ask it.
13 (Laughter.)
14 DR. CLAUW: Is the process the same for
15 qualifying a PRO that we would, for example, try to
16 use for a label change, a PRO that matches sleep
17 with objective measures, and the same for the PROs
18 that we might use to enrich for a study? You
19 already apologized. I think many of us have found
20 that the process that is necessary to create the
21 former kind of PRO that would be used for a label
22 change is quite onerous.

Page 193

1 But I'm just sort of wondering if the PROs
2 we might use to segment -- something as simple as a
3 body map, if that would have to go through that
4 same process or if that could just be considered
5 this is what we're going to use, here's the data,
6 and we don't have to go through that.
7 DR. HERTZ: That's a nice technical
8 question, and I can --
9 (Laughter.)
10 DR. CLAUW: It's a yes/no. I've been trying
11 to ask you a question that you could answer.
12 DR. HERTZ: The qualification is intended
13 for outcome measures. So if a tool is being used
14 to help define the population, that's not an
15 outcome measure.
16 DR. CLAUW: Okay. Great. Thank you.
17 DR. MARKMAN: John?
18 DR. FARRAR: John Farrar, University of
19 Pennsylvania. Thank you for the talk. One of the
20 things that becomes clear in the opioid era is that
21 the extension of risk and benefit goes beyond the
22 population that may use the drug for therapeutic

Page 194

1 purposes to a larger issue. I'm not going to ask
2 you that question.
3 I think, though, what it suggests is that
4 there is a reason for people developing new agents
5 and things that they want to use to clearly
6 demonstrate safety, safety not only in the
7 population who might have a therapeutic benefit but
8 safety beyond.
9 It also suggests that trying to come up with
10 some mechanism for predicting which patients are
11 most likely to respond to that therapy, as you
12 suggest, not with MRIs and very expensive tests,
13 but with some patient-reported outcome or something
14 else, is going to be key issue trying to get
15 products to market.
16 It seems to me the question that I wanted to
17 ask is whether there has been thinking about the
18 concept of actually encouraging people who were
19 submitting analgesics in particular but drugs in
20 general, to add to studies measures that might help
21 in understanding later which population is most
22 likely to respond.

Page 195

1 In particular, I'm talking about Rob
2 Edwards' discussion of catastrophizing. It would
3 seem like if we had more clinical trials where we
4 had those measures included, it would benefit all
5 of us in terms of trying to think about it later.
6 I'm just wondering whether -- I know that
7 there are lots of issues involved in that, but what
8 I'm really asking is whether you think that's a
9 good idea and leave it at that.
10 DR. HERTZ: Scientifically, I think it's a
11 great idea. What it means in terms of an
12 application and all of that is a completely
13 different question. What goes in a label and what
14 goes in a study are going to overlap. You can't
15 put something in a label that wasn't in a study.
16 But you can have a boatload of stuff in the study
17 that doesn't go in a label, and publish it, and
18 that's informative and useful. We can't put a
19 complete study report in a label. We've got to
20 just kind of focus on stuff.
21 If I take your question a little
22 further -- well, I'm not going to take it further.

Page 196

1 (Laughter.)
2 DR. HERTZ: So, yes. I think that a lot of
3 that would be really helpful because I think, first
4 of all, the more you have, especially early in
5 development, the easier it is to figure out who to
6 put in a phase 3 study. The more you have early in
7 development really can give you a much clearer
8 sense of what at least the initial use of the drug
9 can be in a much more meaningful way than the sort
10 of shotgun approach we see more often than not.
11 Particularly -- I have to sort of anonymize
12 this -- I had an interaction under an IND for a
13 drug, and the phase 2 study, which was going to
14 enroll 400 patients, was based on a complete
15 experience of 65 patients previously, and we knew
16 nothing about the behavior. The results of the
17 65-patient study was highly encouraging enough to
18 go from that into a 400-patient study.
19 How many people have seen 65-patient studies
20 potentially mislead a program? So I think the key
21 is when and where you want to put that extra
22 information, those tools, in. If it's informative

Page 197

1 early on and helps you create a better targeted
2 phase 3, great. Then if you want to include it as
3 either inclusion criteria or as an outcome measure
4 that sounds like that's more of an inclusion
5 criterion, sure that can be reflected in describing
6 the patient population that benefits.
7 DR. MARKMAN: One last question, and then
8 we'll break for lunch.
9 MS. VEASLEY: Thanks. Chris Veasley,
10 Chronic Pain Research Alliance. Sharon, last
11 summer there was a first FDA-focused
12 patient -- what's it called? FDA patient-focused
13 drug development meeting.
14 DR. HERTZ: Patient-focused drug development
15 meeting.
16 MS. VEASLEY: Yes. So the conclusions of
17 that meeting are very similar to what we've just
18 been discussing, the impact that patients express,
19 the impact that pain has on their life, problems
20 with sleep, mood, so on and so forth, widespread
21 pain, and a lot of the things we've already
22 discussed today.

Page 198

1 So my question to you is what influence does
2 the findings of that report have, either on the
3 guidance -- so the question is, does that affect
4 the guidance that you provide to people doing
5 clinical trials and manufacturers, or do you simply
6 take that information into account when you're
7 reviewing applications or approvals, to say that it
8 lines up with.
9 Do you understand the question?
10 DR. HERTZ: I might need to sort of narrow
11 what I'm trying to answer with you a little bit.
12 Are you asking about how many of those endpoints,
13 or symptoms, or signs should be included in the
14 clinical trial, should be included in labeling, or
15 should be required by us?
16 MS. VEASLEY: As John just mentioned, the
17 difference that I'm asking is, are you simply
18 taking what the patients have said into account
19 when you're reviewing something that's already
20 being submitted to you, or are you saying or making
21 recommendations to the clinical research community
22 and manufacturers around what patients are saying

Page 199

1 to you, so on and so forth?
2 So it's not just the severity of pain, but
3 the fatigue and the sleep, so you're actually
4 giving guidance to the community on how they should
5 be looking at this when they're researching the
6 efficacy and outcome measurements for these trials.
7 DR. HERTZ: We are not going out and saying
8 we had this meeting and here's what was conveyed to
9 us to people in drug development. What we've done
10 is make that information available. It's on the
11 Web. We have summaries and we actually have a
12 transcript.
13 When somebody is coming in with a
14 symptomatic treatment, what's important to the
15 patient should be the first question. A lot of
16 times with analgesics, we just kind of skip to pain
17 intensity, and part of the reason for that is an
18 inability to convince people that these other
19 important domains -- going back to one of the
20 original papers produced by IMMPACT, the 6 domains
21 that are important in analgesic clinical trials I
22 think reflect very well what we've heard from

Page 200

1 patients recently, and this goes back many, many
2 years. It's good reinforcement.
3 If we go to sleep, for instance, though,
4 when we tell people you need to have a reliable
5 sleep instrument, not the did you sleep well last
6 night rated on a 0 to 10 scale, it often goes away.
7 Is that answering your question at all?
8 MS. VEASLEY: It does. It's kind of like
9 the cat and mouse here because when we talk to
10 companies who are doing trials for let's just say
11 low back pain, but they're not taking into count
12 multisite pain, they're not able to recruit enough
13 patients with just low back pain, so they're
14 recruiting a diverse set of patients into the
15 clinical trial.
16 We're saying, as Dan showed in the data that
17 he showed, multisite pain, widespread pain is an
18 important indication in terms of whether a patient
19 may or may not benefit from this.
20 They oftentimes will come back and say,
21 okay, that's interesting, but the guidance doesn't
22 reflect this or the FDA doesn't require it, so

Page 201

1 we're not going to do it. Do you see what I'm
2 saying? So if the communication comes from you
3 that this may be an important aspect to look at --
4 DR. HERTZ: It will have no -- I don't think
5 we can -- what can be required is negotiable and
6 difficult to state in an absolute way. We
7 certainly would entertain any useful way -- so what
8 these people are effectively doing is shooting
9 themselves in the foot by enrolling a diverse
10 population that has characteristics that may make
11 them particularly not just heterogeneous, but
12 really major subpopulations. Therefore, if it's
13 only going to work in one population and not the
14 other, you're going to lose your signal.
15 So it's expedience over logic, and you've
16 got to power it, that's great. But why you would
17 enroll that population without defining it better
18 and using inclusion/exclusion criteria likely to
19 define a successful population is a question I
20 can't -- I don't know why that's done, but it's
21 certainly not something we've said don't do.
22 (Applause.)

Page 202

1 DR. MARKMAN: We're going to break for
2 lunch. We'll be back here around 1 p.m.
3 (Whereupon, at 12:09 p.m., a lunch recess
4 was taken.)
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

Page 203

1 AFTERNOON SESSION
2 (1:20 p.m.)
3 Panel and Audience Discussion
4 DR. MARKMAN: We have a chance for the next
5 hour to have some live counterpoint between this
6 morning's speakers and also some additional
7 speakers here, Dr. Fields among them. So I'm just
8 going to start by opening up for questions from
9 people here, and then if not, I've got a few of my
10 own.
11 DR. COLLOCA: I have a question.
12 DR. MARKMAN: Dr. Colloca?
13 DR. COLLOCA: Yes. Luana Colloca from the
14 University of Maryland. This question is for the
15 panel. I don't know who I'd like to address. No
16 one mentioned, the nocebo effects, the power of
17 expectancy, how this patient looks like in terms of
18 what they expect, what they wish, and how much you
19 do to try to take into the neurobiology of
20 expectancy.
21 If you can comment on that, including the
22 FDA representative, how expectancy can be involved

Page 204

1 with in designing a clinical trial and
2 interpretation of the outcomes. Thank you.
3 DR. MARKMAN: Sharon, do you want to start?
4 DR. HERTZ: No.
5 (Laughter.)
6 DR. MARKMAN: Contestant number 2. Dan,
7 would you like to start?
8 DR. CLAUW: No.
9 (Laughter.)
10 DR. CLAUW: Let me just say, I agree. It's
11 a really good question. I don't think it's been
12 very well studied at all with any of the
13 techniques, like with functional MRI and things
14 like that.
15 DR. COLLOCA: Clinically.
16 DR. CLAUW: Right. That's what I'm saying,
17 is I think, experimentally, that's been well
18 studied, and we certainly know it to be the case,
19 but I likewise wouldn't know the answer to your
20 discrete question.
21 DR. FIELDS: Well, expectancy is an
22 inevitable part of every pain experience. It's a

Page 205

1 very clear variety of studies, and it's new, or
 2 it's not necessarily pathological.
 3 I thought this morning's talks were
 4 immensely informative. I certainly learned a lot.
 5 I was surprised that the word "expectancy" was not
 6 used.
 7 Some things that stood out to me from
 8 looking over the material that was sent before the
 9 talks, and then the talks, one of them is that
 10 central sensitization is normal. If you have a
 11 noxious stimulus, if you have a nociceptive input,
 12 by and large, you're going to get central
 13 sensitization. I'd like to know if there are
 14 examples of peripherally generated pain in which
 15 there is no central sensitization.
 16 Are there? Clifford, where are you?
 17 DR. WOOLF: Where am I?
 18 (Laughter.)
 19 DR. FIELDS: No more questions.
 20 DR. WOOLF: I think bringing up the notion
 21 of what is the protective function of pain is
 22 crucial here. In the setting of acute, transient,

Page 206

1 noxious stimuli that are non-tissue damaging, I
 2 think most of them do not generate central
 3 sensitization. There's not sufficient input to
 4 produce a detectable change.
 5 But the minute you cross that threshold and
 6 you actually get tissue injury, then that is the
 7 adaptive function of central sensitization because
 8 now it shifts from the need to protect the body
 9 against damage from now protecting the damaged part
 10 of the body again, and enabling healing to occur.
 11 That almost certainly has been the evolutionary
 12 drive for why we develop central sensitization.
 13 DR. FIELDS: So it's a good thing.
 14 DR. WOOLF: So that's a good thing. But the
 15 question there becomes pathologically, why in this
 16 setting of patients with fibromyalgia, or why in
 17 this setting of patients that have peripheral nerve
 18 injury does this adaptive pro-healing mechanism
 19 become pathologically present when there is no
 20 healing that occurs. And the same thing for
 21 [indiscernible - mic distortion] arthritis.
 22 It's one of those things where an adaptive

Page 207

1 response has been corrupted in a pathological
 2 setting. And I think the challenge for us is to
 3 try and tease out that -- and that again is, is
 4 that general or are there some individuals that
 5 have a very high risk of that for whatever reason.
 6 The question I've always struggled with is
 7 what is this massive gender imbalance? What is the
 8 driver? Is this completely genetic or are there
 9 some other factors that make women so much higher
 10 at risk? When you say that almost all the
 11 individuals with arthritis with no pain are male,
 12 if you could tease that out, would that provide us
 13 some claim to mechanism of pain and even
 14 potentially introduce a therapeutic means by which
 15 we can convert -- [indiscernible] at least as far
 16 as the central sensitization is concerned.
 17 DR. MARKMAN: Is any of that gender
 18 imbalance borne out in the central imaging data
 19 where you would expect to see some differential
 20 network activation in men versus women? Do you see
 21 that?
 22 DR. CLAUW: Yes, you do. And in fact,

Page 208

1 usually when you're doing functional imaging,
 2 you're analyzing the males and females separately
 3 if you have big enough data sets and cohorts
 4 because they really are quite different, and I
 5 think we're learning that in a lot of the studies
 6 that we and others are doing.
 7 This is a really interesting question. When
 8 you look at the sex and gender differences, I think
 9 there's a couple of things we know and a bunch that
 10 we don't know. It's clearly not estrogen and
 11 progesterone. It may be testosterone. It may be a
 12 lack of testosterone. There's a lot of emerging
 13 data in animals that testosterone is analgesic, and
 14 that may protect males.
 15 But if you go all the way back to just sort
 16 of basic sensory physiology, women are more
 17 sensitive to almost all of these sensory stimuli.
 18 And if they're unfortunate enough to be actively
 19 menstruating, they often get even more sensitive in
 20 the premenstrual phase of their cycle.
 21 So there's just something about being a
 22 female that makes them more pain sensitive and

Page 209

1 sensory sensitive. I think we understand that
2 fairly well now. I don't think we've yet figured
3 out how to tailor treatments differently to chronic
4 pain patients, based on their sex or gender.
5 DR. MARKMAN: Roger?
6 DR. FILLINGIM: If we're thinking that this
7 initial central sensitization is adaptive and that
8 it gets sort of hijacked and becomes pathological,
9 do we think that that's because the ongoing
10 pathological processes fail to stop or some more
11 adaptive resolution mechanism fails in certain
12 populations?
13 DR. WOOLF: I think at least there are hints
14 that has been [indiscernible]. I think part of the
15 issue also comes back to this mechanistic thing,
16 that the adaptive central sensitization is largely
17 this use-dependent transient [indiscernible]
18 reversible, whereas, at least in the neuropathic
19 pain setting, where the disinhibition is transient
20 [indiscernible], and there seems to be a loss of
21 inhibitory neurons, where irreversible changes in
22 the CNS participate.

Page 210

1 The big unknown is the fibromyalgia, in the
2 absence of any clear trigger, why in those
3 individuals is there this heightened amplification,
4 which is not restricted just to somatosensory
5 inputs, and is that mechanistically quite different
6 from either of those other two extremes.
7 DR. CLAUW: I think it is. I think some of
8 the animal models that purport to be animal models
9 of fibromyalgia, whether it's the swim stress
10 model, which I think is a pretty good model.
11 That's really more of a stress model of developing
12 central sensitization. In fact, there are a number
13 of models of central sensitization.
14 A lot of the work that -- at Kansas -- Julie
15 Christensen's done with visceral pain models, the
16 neonatal separation models, again, they're not
17 nociceptive input models. They're stress models
18 that lead to the development of these kinds of
19 conditions. So I think it's pretty clear that in
20 both animals and humans, people can develop pain
21 and other symptoms without clear, nociceptive
22 input.

Page 211

1 We did studies recently because we have been
2 arguing with people about what small fiber
3 neuropathy means, and that forced us to go into
4 preclinical models and do some -- and we showed
5 that by just increasing glutamatergic activity in
6 the brain, we could get all the pain behaviors that
7 you get in any of the animal models of pain.
8 So I think that -- and by the way, you also
9 get the exact same thing that looks like small
10 fiber neuropathy, which we think is just structural
11 reorganization of the peripheral nervous system in
12 any chronic pain state, not a specific finding that
13 tells you anything about the pain, but that's a
14 different conference for a different debate.
15 But literally in that preclinical model,
16 with Eva Feldman's group reading the biopsies,
17 which is a credible group that knows about small
18 fibers, we literally found that just by increasing
19 glutamatergic activity in the CNS, that we got,
20 quote/unquote "small fiber neuropathy."
21 But again, I think this is where we all have
22 to just -- it's all one nervous system. It's not

Page 212

1 peripheral or central. What happens in the central
2 nervous system profoundly impacts the tone or the
3 gain on what's going on in the periphery, and vice
4 versa. What's going on in the periphery, to a
5 great extent, can trigger central sensitization.
6 DR. MARKMAN: Dan, this is a follow-up to
7 that point, and you said in your talk that this
8 dichotomy between central and peripheral is a human
9 made or manmade distinction. So just for my own
10 clarification, why are we talking today about
11 central sensitization? Why aren't we just talking
12 about sensitization? Why are we trying to make
13 this split point between central sensitization?
14 DR. CLAUW: That's a good point. I probably
15 should do what I say people should do. But the
16 conference, to be fair, is on central
17 sensitization. And you can differentiate the
18 difference clinically between peripheral
19 sensitization and central sensitization.
20 Those papers that I alluded to that Yvonne
21 Lee did in rheumatoid arthritis, she found that the
22 amount of ongoing inflammation in a rheumatoid

Page 213

1 arthritis patient was very highly related to
2 peripheral sensitization: tenderness at the joints
3 or over the areas involved by the rheumatoid
4 arthritis. But she found that there was no
5 relationship at all between the amount of
6 inflammation and tenderness at a site like the mid
7 trapezius region or the sites that are tender in
8 people with more central sensitization.
9 So she could pretty clearly, in a series of
10 longitudinal studies, identify both peripheral
11 sensitization and central sensitization in
12 rheumatoid arthritis. To the extent that we can
13 experimentally do that, again, I am critical about
14 thinking of the nervous system as two different
15 nervous systems, but I think it's helpful from a
16 mechanistic standpoint to try to localize where the
17 sensitization is occurring. So there may be
18 differential treatment implications.
19 DR. MARKMAN: Just as a
20 clarification -- because tomorrow I think we're
21 going to be forced to think about inclusion/
22 exclusion criteria and considerations -- are you

Page 214

1 suggesting that perhaps as part of a way to define
2 a study population, we would need to look for a
3 range of peripheral inflammatory markers and
4 exclude them in a study population where we're
5 asking questions about central sensitization?
6 DR. CLAUW: I think it just depends on the
7 study question, but I wouldn't say as a blanket
8 statement that that would be necessary, especially
9 when you're looking at central sensitization
10 superimposed on an inflammatory state. The last
11 thing I'll say is the kind of inflammation, the
12 kind of low-grade inflammation that seems to track
13 with central sensitization is different than the
14 kind of inflammation we see in a classic autoimmune
15 disease. Andrew Schrepf has done a lot of this
16 work in the MAPP network.
17 But really, you don't see it unless you take
18 whole blood and stimulate with LPS or some other
19 way. It looks like the immune system is primed in
20 these individuals. The more widespread the pain is
21 in interstitial cystitis, the more of this
22 low-grade inflammation that you see.

Page 215

1 I want to contrast that as a rheumatologist
2 that treats inflammation clinically. That kind of
3 inflammation doesn't seem to go away with cortical
4 steroids or with the biologics that we use to treat
5 RA. It may be more neurologically driven
6 inflammation, and it may be that not all
7 inflammation is the same just like not all pain is
8 the same. It's a fundamentally different kind of
9 low-grade inflammation that's not going to respond
10 to our classic anti-inflammatory drugs we use to
11 treat autoimmune disease.
12 DR. FIELDS: I want clarification of what
13 Dan just said. When you say low-grade
14 inflammation, low-grade inflammation of what?
15 DR. CLAUW: All we know right now, in
16 several different studies, you can bring out this
17 difference between the people with central
18 sensitization versus those without by taking whole
19 blood and stimulating with LPS, and then seeing the
20 big increase in proinflammatory cytokines that
21 occur after 24 hours of stimulation.
22 The baseline measure --

Page 216

1 DR. FIELDS: In the central nervous
2 system --
3 DR. CLAUW: No, it is peripheral blood.
4 These are peripheral blood --
5 (Crosstalk.)
6 DR. FIELDS: So you're saying that there is
7 a peripheral inflammatory process in what you're
8 calling widespread pain.
9 DR. CLAUW: I'm saying that the immune
10 system is different, and it seems to be primed in
11 people with widespread pain. It does not look like
12 the same of inflammation we see like in an
13 autoimmune disease, where you could see a biopsy
14 and see inflammatory cells or anything like that.
15 It really seems to be a fundamentally different
16 type of inflammation.
17 DR. FIELDS: So it's inflammation, but it's
18 not autoimmune inflammation.
19 DR. CLAUW: Correct.
20 DR. FIELDS: Okay. I'm not a
21 rheumatologist. I'm having difficulty following
22 what you're saying.

Page 217

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

Page 218

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

Page 219

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

Page 220

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

Page 221

1 individual would not drive it, but in someone who
2 has a heightened responsiveness of CNS, some very
3 low level input may be sufficient to retain
4 the -- or whether in some conditions you truly can
5 have a fully centralized -- I think that has been
6 theoretical. I've never seen evidence that has
7 completely supported it.
8 DR. FIELDS: If anybody interpreted what I
9 said as a way of confusing central and peripheral
10 sensitization, I apologize. That was certainly not
11 my intention, and I'm fully aware of the
12 differences between the two. On the other hand,
13 there's some evidence in the literature that damage
14 primary afferents can become lower threshold and
15 fire spontaneously, and there's some evidence that
16 at least in some patients with fibromyalgia,
17 there's a process in the peripheral nervous system
18 that looks like damage.
19 DR. WOOLF: Right. One of the features that
20 has always suggested that is if someone has
21 particularly a neuropathic pain arising from a
22 neuroma, and you put a local anesthetic, the

Page 222

1 surprising features of that observation is that the
2 local anesthetic immediately blocks the pain. But
3 that very often has relief from pain that lasts for
4 6 weeks, whereas the local anesthetic only lasts
5 for an hour or so.
6 So again, that's showing that this
7 peripheral trigger is having very prolonged
8 effects --
9 DR. FIELDS: Absolutely.
10 DR. WOOLF: -- and that by regressing the
11 peripheral trigger, you can have very prolonged
12 relief as well.
13 DR. FIELDS: Sure. I don't have a problem
14 with that.
15 DR. MARKMAN: That's good. We have a couple
16 of questions. I'll start with Simon, who's been
17 waiting patiently, and then Mike.
18 DR. HAROUTOUNIAN: Hi. Simon Haroutounian,
19 Wash U. It was really interesting to hear the
20 morning sessions about different surrogate measures
21 of central sensitization in terms of constellations
22 of symptoms and signs, patient-reported outcome

Page 223

1 questionnaires, psychophysics, imaging, et cetera.
2 I was really wondering -- I want to hear the
3 panel's thoughts about should we sort of fight
4 which of the surrogate measures performs better and
5 stick to it, or we might want to think more broadly
6 in terms of combining several different modalities
7 in developing some sort of more sophisticated
8 overall measure that would represent central
9 sensitization, which could be, again, specific to
10 particular conditions.
11 DR. CLAUW: Let me take a crack at that.
12 One thing that I think everyone in the room would
13 agree, or most everyone, is that there should be a
14 body map in every clinical trial of a pain
15 condition because I think in its essence, the best
16 way to discriminate centralized from
17 non-centralized pain is by how widespread the pain
18 is, if you just look across all the studies.
19 If you then take some of the individual
20 questionnaires or PROs, whether our group says it's
21 the fibromyalgia measure or Charlie Cleeland says
22 it's his measure, or whatever, I don't know

Page 224

1 what -- we now have those in studies at the item
2 level. We're looking to see which other items
3 would best discriminate central sensitization from
4 not central sensitization. But I don't think the
5 studies have been done yet to say that one is
6 superior to another.
7 I think the fibromyalgia measure has been
8 used in more studies by our group to show that it
9 leads to differential treatment outcomes, whereas
10 the CSI that Charlie's developed has not been
11 validated or used in that same way.
12 So I like the measure we're using, but to be
13 more neutral, I would say that the starting point
14 should be to put a body map in the trial because
15 that will tell you a lot, and you can be a little
16 bit more agnostic to which of the specific measures
17 you then want to use above and beyond a body map.
18 DR. MARKMAN: So if I could just take the
19 liberty of putting someone on the spot, Nat, I know
20 you have some experience in terms of
21 operationalizing body map information, and if you
22 don't want to answer this, that's fine. But I just

Page 225

1 thought you could speak to this from a study
2 conduct issue. How simple do you think this would
3 be, how easy to interpret, could this be managed at
4 the site level? Again, do you think it separates
5 in terms of assay sensitivity in any studies that
6 you've seen conducted, and so forth?
7 DR. KATZ: I don't know about assay
8 sensitivity, but it's not hard to operationalize.
9 There are lots of studies that have used e-diaries
10 or whatever, and have used body maps, and it's easy
11 to collect the data and make it work at the clinic.
12 DR. MARKMAN: Is your a priori hypothesis
13 that in some conditions it would be useful in terms
14 of segregating or predicting responders from
15 non-responders?
16 DR. KATZ: Well, hearing all the
17 presentations this morning and seeing the data on
18 the relationship between widespread pain and this
19 concept of centralization and it's predictive
20 validity for the response to analgesics, at least
21 in some circumstances, it certainly seems worth
22 pursuing. It's easy enough to collect the data.

Page 226

1 I think, Dan, you and I were talking at
2 lunch that it may be worth collecting even some
3 additional information beyond that. We have a lot
4 of experience operationalizing a sensory testing
5 kit, if you will, by the bedside in a large
6 multicenter, U.S. based and global studies. If
7 there were value to that, even that is not hard to
8 do.
9 DR. MARKMAN: Great. Thank you.
10 DR. WOOLF: I was just going to say that I
11 think the accurate clinical phenotyping of
12 patients, as a non-clinician, is absolutely
13 crucial. It seems to me that one of the problems
14 has been the assumption that certain measures are
15 going to be important; in other words, a bias
16 selection of the phenotype.
17 With Jurgen some years back, we tried to do
18 an unbiased screen of all of the possible measures
19 that may predict the presence of different kinds of
20 pain, what we call the standardized evaluation of
21 pain step. It was an incomplete study; that the
22 thrust was we don't know which of those phenotypic

Page 227

1 measures are going to be important and relevant.
2 In fact, what turned out for us in that
3 initial trial to be the most sensitive measure was
4 that the presence of neuropathic pain wasn't a
5 single positive symptom, even though I think
6 90 percent of what we measured were positive
7 symptoms. But it was not too surprising, the loss
8 of sensation, the actual clinical evidence of some
9 nerve damage, and that was the most sensitive
10 measure.
11 So I would just say that to try and collect
12 as much information in an unbiased way because some
13 of our hypotheses may be rather imprecise, and we
14 don't always know what it is that's going to turn
15 out that's going to be able to identify the
16 patients or responders, or none.
17 DR. EDWARDS: One more quick follow-up.
18 Simon, it's a great question. By way of
19 deliberately putting words in your mouth, it sounds
20 like your question is implying that if we have all
21 of these various domains measured in different
22 ways -- QST, self-report, imaging, whatever it

Page 228

1 might be -- and they all interrelate and overlap,
2 but none of them anywhere near perfectly, which
3 means possibly they're all conveying important,
4 unique information, wouldn't it be an interesting
5 idea if we could develop a brief multimodal screen
6 for centralization or tendency toward
7 fibromyalgians, or whatever we might want to call
8 it, and maybe that screen would incorporate things
9 like a body map and some self-report questions on
10 emotional distress, and a brief measure of temporal
11 summation, and some assessment of sensitivity to
12 other physical symptoms or different sensory
13 modalities.
14 Maybe if we had a multimodal screen like
15 that, that you could do in 10 or 15 minutes, and
16 that captured, to at least some degree, all of
17 those various overlapping elements, and that got
18 validated and used in a number of trials, we'd wind
19 up with something that would be easy and convenient
20 to recommend for pretty much all future trials of
21 any kind of treatment in any pain condition.
22 I'd be delighted if we got to a spot like

Page 229

1 that, and maybe that's a project you'd be
2 interested in working on. And if so, sign me up as
3 a collaborator, but we'll probably have a little
4 ways before we get there.
5 DR. MARKMAN: Mike?
6 DR. ROWBOTHAM: Mike Rowbotham. I just
7 wanted to get some data out there and get some
8 comments from the panel. When I was studying
9 postherpetic patients back 2000-2010, publishing a
10 lot on the capsaicin response test, patients who
11 had long-standing postherpetic neuralgia of what we
12 were calling the allodynic type, very exquisitely
13 sensitive to touch, if you kept touching them -- so
14 temporal repeated stimulation -- the area of pain
15 would just get bigger and bigger and bigger, and
16 become more and more excruciating.
17 You put capsaicin, just over-the-counter
18 capsaicin, on a small square of skin, it would
19 greatly aggravate their pain. So then when we
20 looked at a cohort of acute zoster patients and
21 followed them, some up to 8 years, as they got
22 better, once their capsaicin response normalized,

Page 230

1 meaning it felt like it did in contralateral,
2 unaffected skin, they were basically out of the
3 woods. They no longer had pain, and their pain
4 ever came back again.
5 So the question is how would you take a very
6 crude but easy to administer test like that and use
7 it to distinguish between central and peripheral
8 sensitization? Could that even be done? How would
9 you modify it?
10 DR. FIELDS: That's a great idea. I think
11 one of the ways that occurred to me -- and I was
12 thinking about that last night -- that what you
13 could do is you could look at the time course of
14 the expansion of the allodynic area outside the
15 site where you injected the capsaicin.
16 DR. ROWBOTHAM: This is topical.
17 DR. FIELDS: Yes.
18 DR. ROWBOTHAM: It's over-the-counter cream.
19 DR. FIELDS: Or you could do a capsaicin
20 injection and look at the spread. Albeit the
21 intensity of the allodynia, there will be an extent
22 of the allodynia. That has to be central because

Page 231

1 it's outside the area where you injected the
2 capsaicin, so the fibers in that area won't be
3 directly affected.
4 Plus, since they're low-threshold
5 mechanoreceptors, they don't express the capsaicin,
6 the vanilloid receptor. So they're not going to be
7 activated; they don't get sensitized. So there, at
8 least in normal skin, you have a measure of central
9 sensitization, whatever the mechanism. That could
10 distinguish between patients with widespread pain
11 or not. It could distinguish between males and
12 females, so you have a lot of data, and you can use
13 that test as a way to evaluate drugs because they
14 could reduce the spread of the allodynia, the
15 extent of the allodynia.
16 So it seems like it might be a great way to
17 get preliminary data on drugs, the extent to which
18 they affect the capsaicin pain itself versus the
19 spreading pain.
20 DR. MARKMAN: We can even ask that question
21 now, potentially, because patients are
22 receiving --

Page 232

1 DR. WOOLF: Just to ask, as part of your
2 studies, you differentiated the irritable
3 nociceptor group from those -- so how did they fall
4 within the spectrum? Did those who were
5 non-irritable, did they respond with the --
6 DR. ROWBOTHAM: It didn't bother them. It
7 didn't provoke their pain. Some were so
8 deafferented, they barely even felt it, whereas the
9 other ones, what we call the irritableness receptor
10 subtype, it didn't take very long before -- because
11 it was just topical, so it wasn't a sudden all or
12 none phenomenon like when you do injection. It
13 would just build up, and it wouldn't take very many
14 minutes before they would start modest sensations,
15 and then the area of pain would start to expand.
16 So there's definitely a central component
17 because we could make the area of touch-evoked pain
18 expand into a very, very large extent with this
19 test, in many inches, actually, outside the area
20 where we'd applied it.
21 DR. MARKMAN: Do you think putting on an
22 8 percent high-dose capsaicin patch on a patient

Page 233

1 with postherpetic neuralgia -- where obviously in
 2 clinical practice, many of us do that. Some
 3 patients sit there and read the New Yorker calmly
 4 with no spike in their blood pressure, and other
 5 patients are weeping and need everything, including
 6 an epidural, potentially.
 7 DR. ROWBOTHAM: When those studies were
 8 done, they weren't doing that kind of profiling, I
 9 don't think.
 10 DR. MARKMAN: But in clinical practice now,
 11 we see -- I'm just wondering, we have an
 12 opportunity now to ask that question. We have
 13 patients every day, all around the country, who are
 14 getting high-dose capsaicin patches, who've had
 15 previous bouts of zoster. So perhaps there may be
 16 an opportunity to actually ask that question in a
 17 regular -- even in a clinical setting.
 18 DR. ROWBOTHAM: It's an easy test to do.
 19 It's a little scary in the sense that once it
 20 starts -- I mean, you can ice the area down, you
 21 can remove the capsaicin, and you can do those
 22 other things. You could even inject local

Page 234

1 anesthetic, but you don't really have a way of
 2 completely turning it off. I mean, it is a
 3 provocative test that can be quite painful and in
 4 some patients.
 5 DR. MARKMAN: Joachim?
 6 DR. SCHOLZ: Could the panel comment on
 7 assay validation? The measures that you discussed
 8 here, temporal summation, the capsaicin test, and
 9 all those phenotypical measures, how would you
 10 determine that they truly reflect central
 11 sensitization? Are you assuming that in a patient
 12 with chronic pain, if they correlate with the
 13 existence of this chronic pain, that's enough;
 14 that's demonstration of central sensitization?
 15 How do you separate from other mechanisms of
 16 pain? And within central sensitization, if you
 17 used a broad definition, how do you separate from
 18 the increase in the excitatory pathway from the
 19 lack of inhibition in a clinical context? What
 20 would be a path forward? Because otherwise, we have
 21 no way of assessing sensitivity and specificity of
 22 these assays. Then working at Biogen, it becomes

Page 235

1 useless in terms of proof of concept.
 2 DR. MARKMAN: Rob, is CPM the answer to
 3 that?
 4 DR. EDWARDS: Probably not, but it might be
 5 one component of a multimodal answer. That is also
 6 a terrific question, and I am doubtful I'll have
 7 any sort of definitive answer, and in fact I'll
 8 wind up deferring to my basic science colleagues on
 9 the panel who will know better.
 10 It seems pretty clear that we won't, for
 11 example, be recording from wide dynamic range
 12 neurons in the dorsal horn in humans anytime soon.
 13 But even if we did, would we really be able to
 14 distinguish between -- let's call it differences
 15 between bottom-up sensitization and top-down
 16 effects?
 17 So if we were trying to, in humans,
 18 determine whether temporal summation really is a
 19 perfect analog of wind-up in animal models, we
 20 would have to record from those WDR neurons, and I
 21 think we'd have to exclude the possibility of
 22 top-down influences, correct? And we're probably

Page 236

1 not spinalizing people either, I would guess for
 2 the purposes of doing that.
 3 I have trouble wrapping my head around how
 4 it would be possible to even come close to meeting
 5 the standard of perfectly precisely identifying
 6 those mechanisms, underpinning, things like CPM and
 7 temporal summation in humans. I think it can't be
 8 done. Even if fMRI gives us a little bit of
 9 insight into what the brain is doing, the spinal
 10 cord in humans is going to be a little bit of a
 11 black box in most of these questions.
 12 So I wonder if I might eventually be able to
 13 talk you into adopting a different and perhaps less
 14 stringent standard for considering some valid
 15 measure of an important phenotypic characteristic
 16 of patients.
 17 DR. FIELDS: Can I add to that?
 18 DR. MARKMAN: Yes.
 19 DR. FIELDS: I'll put on my basic science
 20 hat. One thing we might be able to do -- and I
 21 don't know the literature. Maybe Clifford knows
 22 some current stuff, but you could, say, a capsaicin

Page 237

1 application on one arm, and then look at pressure
2 pain thresholds or continuous thresholds on the
3 contralateral leg and see if you have a lowering of
4 threshold or if you have an enhancement of, let's
5 say, wind-up on the contralateral side. Then it
6 seems to me that it's peripheral -- I mean, it's a
7 central effect, and it reflects at least one form
8 of sensitization.
9 I kind of don't like the general term,
10 "sensitization." I like the specific term that
11 refers to a specific synapse of the dorsal or
12 ganglion cell on to the second order of cell in the
13 dorsal horn.
14 We know, for example, that if you block all
15 the myelinated fibers in your arm with a blood
16 pressure cuff, and even light touch produces
17 burning pain, and you get much greater spread of
18 sensation from the sight of stimulation, and that
19 happens immediately with no increase in glutamate
20 transmission, all it is a removal of some sort of
21 large cyber inhibitory effect, is that
22 sensitization?

Page 238

1 I don't know, but it would come under the
2 global sensitization. Loss of gabaergic neurons in
3 the dorsal horn, that would come under the general
4 term "sensitization." I kind of like the term
5 "amplification" a little bit better as a general
6 term than sensitization to do specifically with the
7 enhancement of transmission between the primary
8 afferent and the second-order neuron.
9 DR. BRUEHL: I'll kind of piggyback here on
10 this conversation here. Cutting across the talks
11 in the first part of today, one of the things that
12 I think about is Clifford's talk seems quite clear
13 that that true central sensitization happens after
14 something that causes nociceptive input. It's a
15 response to something. It's an adaptation to that.
16 But we look more broadly in the humans and
17 these supposed markers like temporal summation,
18 which are supposed to be tapping into the same
19 thing, are correlated with catastrophizing, and
20 depression, and these other things. And you look
21 at other literature, and it shows prospectively
22 that depression and catastrophizing predicts onset

Page 239

1 of new chronic pain, which to me suggests if it's a
2 sensitization of some kind, it's a preexisting
3 sensitization.
4 Maybe this is back to the top-down/bottom-up
5 idea, but it seems like you've got some people that
6 may be predisposed to a sensitizing response and
7 other people have that as a reaction to an insult.
8 I think if we're trying to assess that, it'd be
9 really important to make sure we have measures of
10 both of those aspects, although I'm not sure
11 exactly which those would be.
12 DR. MARKMAN: Is CRPS-1 a natural vehicle to
13 ask these questions in, given the lack of clarity
14 about a peripheral insult, or no?
15 DR. BRUEHL: I don't know the answer to
16 that. It's too complex. It's a messy condition.
17 I don't know if that would be ideal.
18 DR. MARKMAN: Does anyone have a response?
19 DR. FIELDS: CRPS-1 includes a condition
20 that used to be known as reflex sympathetic
21 dystrophy, which was easily diagnosed and had
22 objective changes in the periphery, including

Page 240

1 osteoporosis, swelling, and changes in sweating.
2 CRPS-1 includes that if it doesn't get better, plus
3 a whole lot of other things.
4 As a neurologist, I'm much more of a
5 splitter than I am a lumpner. I'd rather look for
6 subcategories and figure out what's the underlying
7 biology and group conditions together that might
8 have different causes and different underlying
9 mechanisms. I feel like if you do that, you're
10 kind of setting yourself up to fail in clinical
11 trials.
12 DR. BRUEHL: You're saying if you lump --
13 DR. FIELDS: If you're a lumpner, yes.
14 DR. BRUEHL: That is potentially what we're
15 doing with the broad terminology of somatic
16 amplification and central sensitization if it's two
17 entirely different processes that we're lumping
18 together.
19 DR. FIELDS: That's kind of what I'm saying,
20 yes.
21 DR. MARKMAN: If you could react to that,
22 that would be great.

Page 241

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

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

Page 242

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

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

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

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

Page 243

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

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

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

22 All the different ways someone can get to a

Page 244

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

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

17 DR. HERTZ: I'm not answering that.

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

22 DR. EDWARDS: Can I just follow up on that

Page 245

1 for one second? I'll make it quick, although
 2 perhaps I should take a page out of Sharon's and
 3 Bob Mueller's playbook --
 4 (Laughter.)
 5 DR. EDWARDS: -- and Todd and others
 6 playbook and have no comment more often. It's way
 7 too late.
 8 I want to follow up because I'm really
 9 enjoying mentally chewing over Joachim's good
 10 question about separating peripheral from central
 11 sensitization and Howard's very nice response,
 12 which involved a theoretical experiment where you
 13 apply capsaicin, topical or injected, intradermal
 14 capsaicin, to the left arm, and then you measure I
 15 think the right leg, temporal summation or some
 16 equivalent of that.
 17 I think if I were so inclined, I could cite
 18 some literature suggesting that any noxious
 19 stimulus you apply produces a physiological stress
 20 response that has manifestations in the periphery,
 21 and I could site some very specific literature that
 22 suggests that capsaicin application is associated

Page 246

1 with a quick and brief systemic inflammatory
 2 response.
 3 I don't actually know the time course of
 4 that, but I know it happens pretty quickly and goes
 5 away pretty quickly. But I could use that, I
 6 think, to argue -- I don't know if it would be
 7 perfectly persuasive, but I could use that to argue
 8 that any changes you see subsequent to that
 9 intradermal capsaicin on the left arm are all
 10 peripheral in nature and driven by a stress
 11 response or a circulating inflammatory response,
 12 and that's the reason you get the increase in
 13 temporal summation or wind-up.
 14 I wouldn't personally believe that, although
 15 I'm perfectly willing to argue things that I don't
 16 believe if it seems like fun.
 17 DR. FIELDS: You've done that repeatedly.
 18 DR. EDWARDS: I have. So that's part of why
 19 I say I wonder if it might be an unfair standard.
 20 And this is just going to sound like special
 21 pleading coming from a psychologist, but it might
 22 be possible that we can't ever a hundred percent

Page 247

1 precisely separate central from peripheral
 2 sensitization, and it might just be that we wind up
 3 having to live with some degree of that uncertainty
 4 and adopt measures that we can't characterize
 5 precisely but that we find are predictive on the
 6 basis of empirical data.
 7 DR. MARKMAN: John, and then Jim, and
 8 then --
 9 DR. FARRAR: Seeing that the time is getting
 10 a little bit later, I wanted to switch gears just a
 11 little bit, but not too far, which is that from my
 12 perspective, any place in the nervous system where
 13 there's a synapse, there's the potential for
 14 feedback loops and an effect on the threshold which
 15 the firing will take place. Most of those occur
 16 north of the peripheral nervous system. One could
 17 argue all of them do, but I'm having it open if
 18 people want to argue something else. The point I'm
 19 trying to make is that, clearly, this is a very
 20 complicated system.
 21 Rob, what you presented, you talked about
 22 catastrophizing, and I asked you the question about

Page 248

1 where is catastrophizing. It seems to me
 2 reasonable, in what we've heard today, to
 3 differentiate between a upregulation, an
 4 activation, a sensitization, whichever term you
 5 like, of the connections in the brain that monitor
 6 and do something about pain, which I think leads to
 7 the widespreadness and the other things that we're
 8 talking about, and, if you like, the super
 9 cortical, the cortical phenomenon that then impact
 10 that in terms of depression, catastrophizing, et
 11 cetera.
 12 To get at what Sharon was discussing before,
 13 that in order to get approval for or to think about
 14 even, in experimental settings, drugs that might
 15 affect this process, whatever it is, we need to
 16 have a measure that somehow gets at that, and that
 17 is not going to be overly responsive to some of the
 18 things that we're not interested in.
 19 So this question is for both you and Dan,
 20 which is, with the fibromyalgiansess, if you would
 21 treat a fibromyalgia patient who's severely
 22 depressed, my guess is that their overall pain and

Page 249

1 symptoms get better. Maybe they don't go away.
2 Maybe they still have widespreadness. But if I'm
3 doing a clinical trial, and
4 even if I'm measuring those things, it's going to
5 get very messy in terms of trying to differentiate
6 the effect of the change in mood, and depression,
7 and catastrophizing, and other pieces, to the
8 actual changes to that central pain processing
9 center or units, and I wonder what your thoughts
10 are.
11 DR. EDWARDS: I'm not at liberty to respond
12 to that question, and I defer to Dan.
13 DR. CLAUW: I'm going to use the Sharon-Bob
14 Mueller answer --
15 (Laughter.)
16 DR. CLAUW: -- the "I work in D.C." answer.
17 I guess I could try to answer it. No, I don't even
18 want to try to answer it.
19 DR. FARRAR: Let me ask you differently. If
20 patients get treated for depression, does their
21 score on the fibromyalginess questionnaire, that
22 you use widely, change?

Page 250

1 DR. CLAUW: In some cases when you treat
2 people's depression, their pain gets better, and I
3 think there's more evidence for the converse.
4 Because again, we have better interventions like
5 knee arthroplasty and biologics in RA that can make
6 pain better in a subset of people very rapidly. We
7 don't have drugs that make depression better so
8 rapidly, except ketamine or something like that.
9 I think there's a lot of evidence that
10 making people's pain better makes their depression
11 and their catastrophizing better, and there's some
12 evidence that making their depression or
13 catastrophizing better makes their pain better.
14 There's no question these are bidirectional, but I
15 actually think that if you look longitudinally in
16 the course of the life of a pain patient, I think
17 that, in many instances, the pain comes first, and
18 a lot of these other things sort of pile on
19 afterwards.
20 I think in those individuals, treating their
21 mood disorder, in my clinical experience, hasn't
22 been as likely to make their pain better because a

Page 251

1 lot of these other things have occurred as a
2 consequence of their pain, and I'm going to try to
3 target making their pain better.
4 DR. HERTZ: What's interesting, though, is
5 when you look at some of these patients, let's take
6 fibromyalgia with a fairly high frequency of
7 comorbid depression, what are you going to treat
8 them with? An antidepressant. So it gets even
9 more complicated because you may not be able to
10 establish what can you do first. You may not be
11 able to establish what's being treated. All you
12 know is at the end of the day, they're getting
13 better.
14 One of the things we did with one of the
15 drugs was we asked them to specifically look at
16 responses with and without depression to see if it
17 was really more a matter of treating the
18 depression. In that particular case, it wasn't,
19 but sometimes it's very hard to tease that out.
20 DR. CLAUW: But I think that is true. The
21 two classes of drugs we use most commonly that are
22 both antidepressants and analgesics, tricyclics and

Page 252

1 SNRIs, have in general not shown that the presence
2 of depression makes someone more likely to respond
3 to that drug as an analgesic.
4 That's why I made the statement that I made,
5 is that I don't think there's as much evidence for
6 treating depression and making pain better as there
7 is for the converse. Although again, of course
8 it's important. Of course if a chronic pain
9 patient is depressed, they're anxious, or
10 catastrophizing, I think that needs to be
11 addressed. But again, I think that the clinical
12 trial data are pretty clear with tricyclics and
13 SNRIs that it's not the case that you're treating
14 subclinical depression, and that somehow is
15 circling back to make the pain better. These are
16 directly analgesics.
17 (Crosstalk.)
18 DR. MARKMAN: I think maybe [indiscernible]
19 an attempt to design those trials, though, to show
20 their analgesic benefit. Just to make the point
21 the trials with the tricyclics, what I think the
22 attempt was in the design was to discern their

Page 253

1 analgesic benefit from their antidepressant
 2 benefit. Again, the fact it didn't show that may
 3 just be a function of how they were set up and
 4 designed.
 5 DR. WOOLF: Something I think we need to
 6 keep in mind -- we're talking here about depression
 7 and pain, but comorbidity has been a big feature of
 8 the discussion, but sometimes they may be
 9 mechanistically linked. We recently had a study on
 10 sleep deprivation, which was discussed, and we
 11 found that if you start off with a healthy mouse
 12 and you deprive it of sleep by just letting it play
 13 with toys over the night every time the EEG
 14 indicates it's about to fall asleep, after 5 days,
 15 the animal has heightened pain sensitivity and a
 16 reduced response to standard analgesics.
 17 So that is part of the link between the two,
 18 as you've kept on saying, and we perhaps should not
 19 artificially separate them because they are part of
 20 the same package.
 21 DR. MARKMAN: We're in the final 5 minutes,
 22 so I just want to let Jim and Ian ask their

Page 254

1 question.
 2 DR. RATHMELL: Jim Rathmell. Not to beat it
 3 too death, but as a clinician, the idea that you're
 4 going to be able to clinically, even in the context
 5 of a very carefully constructed trial,
 6 differentiate peripheral from central
 7 sensitization, it doesn't seem, to me, to matter
 8 that much.
 9 What I want to know is -- mechanistically,
 10 it matters a lot, but at the bedside, if you've got
 11 a patient with either chronic widespread pain or
 12 heightened pain sensitivity on testing, those are
 13 the things that probably allow you to lump them
 14 easily at the bedside, and it's hard to get that
 15 underlying mechanism. So be pragmatic as we come
 16 up with what is the paradigm that we're going to
 17 test.
 18 DR. GILRON: I've been following the
 19 peripheral/central discussion, and I'm just
 20 wondering if there's a need to distinguish between
 21 sensitization as a facilitative state or condition
 22 and the presence and location of the pain

Page 255

1 generator.
 2 Is there actually a source of ongoing
 3 nociception versus -- well, I don't know, someone
 4 who's purely fibromyalgia 100 percent and
 5 apparently has no source of nociception, or
 6 osteoarthritis, or anything, as sort of a separate
 7 beast to someone who had shingles or has diabetic
 8 neuropathy and happens to have pain or the OA
 9 situation?
 10 DR. MARKMAN:
 11 I'm not sure what the
 12 question was, Ian.
 13 DR. GILRON: Okay. If we were going to
 14 define an inclusion criterion, do we want to
 15 exclude people who have -- I mean, you can have OA
 16 of your shoulder, and gout in your toe, and low
 17 back pain, so you've got chronic widespread pain,
 18 but you've got a pain generator in those
 19 situations. Would that person fit into a clinical
 20 trial of central sensitization?
 21 DR. CLAUW: Well, I think they were put in
 22 all the trials of fibromyalgia patients because if
 you look at the average age of the fibromyalgia

Page 256

1 patients in the registration trials, they were
 2 50-ish. Almost certainly, a lot of those people
 3 had some incident OA, and myofascial pain, and
 4 things like that; it's hard to imagine they
 5 wouldn't have.
 6 So I think that the registration trials that
 7 were done in fibromyalgia were probably not done in
 8 pure -- because although all those trials did
 9 exclude like rheumatoid arthritis, and lupus, and
 10 things like that -- and they may have said we
 11 exclude OA -- they were never screening for away
 12 and really excluding OA because there probably
 13 would be no one in the trial.
 14 So I think that those trials did end up
 15 including a bit of a mix. I think the people had
 16 to have widespread pain, but many of them probably
 17 had something above and beyond that. But maybe
 18 that would account for that the average effect
 19 would be better if we could look at the people who
 20 don't have those peripheral drivers, and thus,
 21 don't respond to a pure peripheral therapy.
 22 DR. FIELDS: I just wanted to say there's

Page 257

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

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

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

Page 258

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

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

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

Page 259

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

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

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

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

Page 260

1 several cases; that they just forgot.

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

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

Page 261

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

Page 262

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

Page 263

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

Page 264

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

Page 265

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

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

Page 266

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

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

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

Page 267

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

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

18 I cite this study here. I unfortunately
 19 don't know how to pronounce the last name, but they
 20 did a really interesting analysis where they pulled
 21 apart depression in fibromyalgia patients and
 22 looked at rates of depression when it was

Page 268

1 self-reported versus when it was expert diagnosed.
 2 As you might imagine, self-reported rates of
 3 depression were much higher in fibromyalgia
 4 patients compared to expert guided.

5 What that means, it could of course be a
 6 reporting bias. The point from that paper was to
 7 lean more towards more structured ways to diagnose
 8 these psychiatric outcomes in studies looking at
 9 comorbidities, so that's what we did.

10 Our initial search -- sorry this is so
 11 small -- 806 articles were retrieved from that. I
 12 found another 49 looking at reference lists. So we
 13 had 683 after duplicates were removed, just meaning
 14 same article pulled from separate databases. We
 15 did a title and abstract review and excluded a
 16 bunch more, and we arrived at 169. We did a
 17 full-text review. You'll see here 125 were
 18 excluded at that stage, which is a pretty high
 19 number, and I'll go on the next slide into details
 20 on that.

21 Our final count, if I pull you down to the
 22 very bottom, are 41 studies. We did have 6 studies

Page 269

1 that overlapped, so they had been published in
 2 separate journals but reported on the exact same
 3 data and patient sample, so I combined all those.
 4 I didn't want redundancy there.
 5 We did have two studies that looked at
 6 fibromyalgia and temporomandibular disorder
 7 patients in the same study and did head to head
 8 comparisons, so they counted as two studies even
 9 though they were only one citation. The main point
 10 there is if you try to sum across a lot of my
 11 slides with the counts, you can drive yourself mad
 12 because the counts don't always add up because
 13 there's a lot of multiple findings in each study.
 14 Like I said, we had a lot of excluded
 15 studies. The main reason I would say, 75 percent
 16 of studies, were that the diagnostic criteria for
 17 our psychiatric disorders and for our index
 18 disorders, they didn't meet what we required. I do
 19 want to point out for chronic pain comorbidities,
 20 we had no restrictions on that except that they had
 21 to be chronic pain, but we didn't require that they
 22 had to be assessed a certain way. We tried to keep

Page 270

1 those requirements liberal.
 2 Most 47 of these were excluded due to
 3 self-report psychiatric disorders or survey
 4 instruments that weren't standardized or
 5 administered by a trained professional; 33,
 6 fibromyalgia wasn't diagnosed using criteria as
 7 specified, and then 15 for TMD. If you go on down,
 8 these next two bullets mainly just didn't meet our
 9 really broad criteria, so they didn't present data
 10 on prevalence or incidence, and it wasn't a
 11 research study, and so on.
 12 There was one study we identified I cited
 13 here that specifically noted that the TMD patients
 14 they are looking at, it was the acute phase. I
 15 wanted to flag that because it was very helpful and
 16 important. I am learning about this shift from
 17 acute to chronic pain, but that definitely, if that
 18 hadn't been specified, is a way that our results
 19 when reporting them in a systematic review can get
 20 a little messy because then the patients aren't
 21 exactly consistent if they are in an acute phase,
 22 so we excluded that.

Page 271

1 We had 41 studies like I said. Although we
 2 were looking for cohort studies that were trying to
 3 specify incidence, we didn't locate any published
 4 studies that reported on incidence of these
 5 comorbidities in the index disorders, so all
 6 studies' report on prevalence were cross-sectional.
 7 Publication years, I mentioned the '90s to the
 8 present, so '92 to 2018. Most studies were in the
 9 U.S. and Italy, and scattered throughout some other
 10 countries.
 11 Consistently, patients or participants were
 12 recruited from outpatient clinic settings using
 13 convenience sampling, and a subset, so I'm
 14 categorizing consecutive sampling as a type of
 15 convenience sampling here. So they were a subset
 16 that just as patients came in, they recruited.
 17 We'll talk a little bit about that once I show the
 18 figures how that can isolate the findings to
 19 various specific patient populations and possibly
 20 contribute to bias in estimating prevalence.
 21 Sample sizes, a really wide range, a very
 22 small sample, 22 up 70 some thousand. However, the

Page 272

1 median was 100, so rather small. Mean participant
 2 age, as you might imagine, middle age, this didn't
 3 differ between the temporomandibular disorder
 4 studies and fibromyalgia, which I'll break down
 5 further on the next slide.
 6 Most studies were majority women, so over 50
 7 percent I'd say it was rare -- there was only one
 8 study that had more men, and nearly half of the
 9 studies included only women. So this was
 10 definitely a female dominated population of
 11 studies. Disease duration was most often reported
 12 for fibromyalgia, not for temporomandibular
 13 disorders. However, when reported, they were about
 14 the same with a median of a little over 7 years.
 15 Because there are so many buckets of data,
 16 I've tried to use some parallel construction on
 17 this slide and our figures so I don't lose you as I
 18 present. What we've got here is 4 main categories
 19 of the data. This sort of maps on to, you've got
 20 fibromyalgia and temporomandibular disorders on the
 21 left, so we ended up including 37 studies that
 22 focused on fibromyalgia and only 10 with TMD, and

Page 273

1 then our comorbid disorders, and we had about an
 2 equal split there.
 3 So what I'm going to do is show you findings
 4 starting in the upper left with the chronic pain
 5 fibromyalgia studies and move through there. I'll
 6 try to do this each time so I don't lose you. I
 7 found myself getting confused just giving this
 8 presentation, so slow me down if talk to fast here,
 9 please.
 10 Lifetime and current prevalence were
 11 reported in different studies, so I'll always start
 12 with lifetime prevalence. For fibromyalgia and
 13 chronic pain, there were 4 studies. So what you
 14 see on the Y-axis are the different types of
 15 chronic pain comorbidities that we identified.
 16 These were dictated by the literature, so we
 17 weren't specifically looking for, say, interstitial
 18 cystitis. We would just let the research dictate
 19 that.
 20 Then you have the bars representing
 21 percentage, so prevalence there. And you'll notice
 22 these, if you can see them, the black bolded

Page 274

1 numbers at the end of each bar. Those are cases or
 2 counts that correspond to that percentage. I
 3 wanted to give you a sense of the sample size of
 4 some of these studies. For example, for this lower
 5 back comorbidity, the purple bar, it's getting up
 6 close to 70 percent of that population, but there
 7 were only 14 of those people in that study.
 8 What you see here, I'll give you a brief
 9 idea, and I'll try to summarize it. But we haven't
 10 used any quantitative statistics to combine these.
 11 In fact, everything I'll do is narrative or
 12 descriptive today. But the idea is to show you
 13 it's very difficult to combine these findings,
 14 especially when you only have four studies
 15 represented across all these bars. So what that
 16 means is it was often the case that one study would
 17 look at migraine, irritable bowel syndrome, lower
 18 back pain, and TMD.
 19 So only four studies are represented across
 20 here. You get some outliers. Irritable bowel
 21 syndrome was often measured in these studies, and
 22 you see those are hovering around lifetime 50.

Page 275

1 Here's current prevalence. More studies
 2 measured current prevalence, and this is, again,
 3 fibromyalgia and chronic pain. What I noted here
 4 was TMD, or temporomandibular disorders, were
 5 rather high in two of the studies. You have
 6 multiple studies looking at an irritable bowel but
 7 not necessarily consistently finding things and
 8 also quite variable in the number of participants.
 9 I've tried to group at the top the head
 10 related pain, analgesic overuse, trauma related, or
 11 all headache type pains. U There was one study that
 12 measured multiple types of headaches in the same
 13 sample of participants, so you also get that type
 14 of bias.
 15 To walk you down to the next one, here we
 16 have 9 studies that looked at chronic pain in TMD.
 17 Again, if you try to sum across, as I present each
 18 slide, it doesn't necessarily equal the 13 or 9
 19 because some studies reported current and lifetime
 20 prevalence; just so you don't drive yourself mad in
 21 that regard. Only two studies looked at lifetime
 22 prevalence of chronic pain comorbidities in TMD.

Page 276

1 I think the most obvious thing was that the
 2 percentages were much lower. The prevalence was
 3 considerably lower than fibromyalgia, but, again,
 4 there could be multiple reasons for that, not
 5 necessarily the true existence of those
 6 comorbidities. For example, is it true that
 7 fibromyalgia patients tend to over-report certain
 8 health conditions, or maybe they're seeking out
 9 health care more than this population. Here, we
 10 have current prevalence for TMD and chronic pain, a
 11 few more studies.
 12 I was surprised I didn't see more headache
 13 related assessments there. I guess the main
 14 finding I saw on here is, if you remember, current
 15 prevalence in fibromyalgia and chronic pain, these
 16 blue bars at the bottom represented TMD, and they
 17 were up near 80. You're just not seeing that
 18 same -- but only in two studies -- increased
 19 prevalence of fibromyalgia in TMD patients.
 20 Next, is the most common comorbid morbid
 21 disorder assessed, and that's in fibromyalgia
 22 studies. This one gets even more complicated.

Page 277

1 Because there were so many, I've split anxiety
 2 disorders separate from mood disorders. There was
 3 one personality finding, and I just realized I
 4 didn't include it on the slides, but, actually,
 5 there was only one study that looked at personality
 6 disorders, so I've only focused on anxiety and mood
 7 disorders.
 8 Here we've got fibromyalgia and anxiety and
 9 lifetime prevalence, 10 studies. At the top, we
 10 start with different types of phobias in the
 11 purple, going down to lighter. Then you've got
 12 obsessive compulsive disorder, panic disorder, all
 13 the way down to generalized anxiety disorder.
 14 Sometimes titles change depending on the studies.
 15 On the next slide, you'll see a whole
 16 category of studies that just labeled it anxiety.
 17 It's not even clear if this was generalized anxiety
 18 disorder. One other thing I'd like to point out
 19 making this challenging is PTSD in the most recent
 20 revision to the DSM got moved out of anxiety
 21 disorders into a separate category. I still
 22 included it because there was a lot of talk, at

Page 279

1 disorder and general depression as labeled by the
 2 studies, and those are rather high compared to the
 3 other figures we've seen.
 4 Now, whether or not, again -- and we've been
 5 talking about depression -- what's fueling this,
 6 including whether researchers -- maybe more studies
 7 are focusing on depression than other psychiatric
 8 disorders, we can't really say, but we can describe
 9 what's out there. So similarly, for current
 10 prevalence of mood disorders, you're getting higher
 11 levels or higher prevalence compared to anxiety.
 12 There is a systematic review out looking at
 13 major depressive disorder. It's the one I cited
 14 earlier that was talking about self-report versus
 15 expert diagnosed depression. They do a
 16 meta-analysis and actually do suggest that there is
 17 an increased prevalence. We can talk about that,
 18 too.
 19 One other surprised finding was that there
 20 were so few studies that were included that look at
 21 psychiatric outcomes in temporomandibular
 22 disorders, so I just broke this one down on one

Page 278

1 least in the background of these papers, the role
 2 of PTSD in fibromyalgia.
 3 Many studies looking at panic disorder here.
 4 I don't feel confident making any conclusions from
 5 this. This is lifetime prevalence. It looks like
 6 panic disorder appears higher than others, but
 7 again, you're getting really small sample sizes of
 8 12-20 in some of these studies. I was surprised to
 9 not see more studies looking at generalized
 10 anxiety.
 11 This is what I'm mentioning, the red bars at
 12 the bottom, different types of anxiety, panic
 13 disorder. This is current prevalence. More
 14 studies looking at PTSD, that was one that stood
 15 out at me as a signal. But again, I didn't have a
 16 lot of confidence giving sample sizes of some of
 17 them.
 18 I would say that -- I'll be showing you the
 19 mood disorders on the next slide, and I do those
 20 bars in blue. It was interesting how higher the
 21 prevalence was of these. Here you have lifetime
 22 prevalence of mood disorders, so major depressive

Page 280

1 slide. This was published in 2007. The sample
 2 size was 63 and looked at current psychiatric
 3 comorbidities, from 17.5 percent for depression and
 4 a little lower for the others.
 5 Basically, a quick snapshot of what I found
 6 before I dig into some lessons learned. All
 7 studies were cross-sectional. We only retrieved 41
 8 that met criteria. They all included adult
 9 patients from outpatient clinics. Most included
 10 middle-aged women and most focused on fibromyalgia.
 11 Perhaps I'm not familiar with the funding
 12 situation, maybe that's a reason, or maybe it's
 13 just a fact that there's more people diagnosed with
 14 fibromyalgia. I'm not sure if that's true either,
 15 but it certainly is taking up more space in the
 16 published literature.
 17 If forced, I felt bad coming here not
 18 telling you all some sort of prevalence summary. I
 19 looked and used my own criteria, so if there were
 20 at least two studies that we included for review
 21 with a prevalence estimate of over 30 -- I was
 22 being very generous here -- what could I give you

Page 281

1 as a take home? What we were seeing is IBS and TMD
2 were most likely in fibromyalgia as chronic pain
3 comorbidities, and depression and PTSD, but PTSD, a
4 very limited number of studies. I would say double
5 that for depression.
6 TMD, the best I could do is headache
7 disorders, but there really weren't a lot of
8 studies, and it makes sense given where TMD pain
9 takes place, and of course there was only one study
10 for psychiatric outcomes for TMD.
11 Where would we go from this? Obviously, I
12 wouldn't feel confident giving someone these sides
13 so they could cite in a paper the prevalence of
14 this or make the argument confidently that there's
15 a particular comorbidity more common in one index
16 disorder or the other. But we know that it's very
17 difficult to measure incidence in these chronic
18 type conditions, so that isn't in the literature as
19 we reviewed it.
20 Potential for selection bias, we've got
21 small sample sizes. Patients were recruited
22 through convenience sampling. They were already

Page 282

1 in, say, rheumatology clinics or pain clinics, so
2 that self-selects them. This was a methodological
3 trade-off, large sample population-based studies.
4 I'll just say database studies that didn't specify
5 diagnostic criteria were not included, but that
6 could be a nice comparison in a review like this to
7 see what type of information that gives us.
8 Like I said, all or majority of studies
9 focused on women in fibromyalgia. I've noted the
10 Wolfe paper, which is suggesting maybe we need to
11 rethink this idea that women are the focus of
12 fibromyalgia, and it may be arising from our bias
13 and sampling and the way we determine prevalence.
14 Also, you can't deny that as we have gained
15 understanding and as we're here today to try to
16 understand these disorders so has diagnostic
17 criteria evolved. I know ACTION has a couple of
18 working groups that have published specifically on
19 fibromyalgia and TMD diagnostic criteria and really
20 refining this process. Our literature span this
21 whole time, so as those criteria were changing,
22 it's certainly added error to how we estimate

Page 283

1 prevalence.
2 Another topic -- and we haven't talked a lot
3 about it here. I am not that familiar with it, but
4 we didn't include juvenile fibromyalgia, but I see
5 in the literature that's a topic that's come up a
6 lot, and almost a different beast, in a way, if we
7 were to include them in the review.
8 Temporal order of co-occurring index in
9 comorbid conditions is an obvious problem with
10 cross-sectional studies, and it's coming up. We
11 just talked about depression and fibromyalgia, and
12 the idea of what contributes to what. Known
13 relationships between comorbidity, so we know that
14 anxiety and depression are more likely to be
15 diagnosed in the same person, and that also
16 influences their relationship with index disorders,
17 so we can't ignore that.
18 I wanted to mention sleep. I heard it come
19 up a couple times. This was another outcome or a
20 comorbid issue that we were thinking about
21 including. Our review is getting so large, we
22 decided to leave it out, but a recent paper from a

Page 284

1 working group through ACTION noted sleep issues
2 are a key symptom of fibromyalgia.
3 I did try to see what's been done. There
4 are two systematic reviews looking at sleep quality
5 in populations like FM or TMD, but I have to say I
6 didn't see sleep being measured very often. Of
7 course, we weren't looking for it. It's not
8 something I commonly saw. I guess it's a variable
9 that's very important for all of these outcomes.
10 Well, special thanks to my co-reviewers,
11 McKenzie and Ewan, thank you. Any questions?
12 (Applause.)
13 DR. WASAN: Thanks.
14 DR. KLEYKAMP: Are we waiting?
15 DR. WASAN: I think maybe in the interest of
16 time, we'll do all the questions at the Q&A. Maybe
17 that will help us make up a little bit of time.
18 Next, we have one more speaker, and then we'll have
19 a break, and then we'll have another speaker, and
20 then a Q&A.
21 Our next speaker is Dr. Roger Fillingim,
22 which almost all of us know here. He's done so

Page 285

1 much important work in actually most of everything
2 we're talking about today, so he's going to be a
3 great contributor here. As I said, we all know him
4 well. He's a distinguished university professor at
5 the University of Florida in the College of
6 Dentistry. He's a pain psychologist by training,
7 and he also is director of the Center for Pain
8 Research and Intervention, Center of Excellence at
9 the University of Florida within the College of
10 Dentistry.
11 Roger, please go ahead.
12 Presentation - Roger Fillingim
13 DR. FILLINGIM: Great. Well, thanks, Ajay.
14 I meant to talk about central sensitization and
15 overlapping pain conditions, which is a bit
16 daunting since I now realize we don't know what
17 central sensitization is.
18 (Laughter.)
19 DR. FILLINGIM: I felt somehow like
20 consensus would be more clarifying, but first let
21 me just talk about the fact -- and we just heard
22 about this nicely from Annie -- that pain

Page 286

1 conditions certainly overlap. Chris Veasley and
2 the Chronic Pain Research Alliance has really moved
3 this forward quite a bit. One thing I might bring
4 up is osteoarthritis. We heard Dan talk about
5 osteoarthritis a bit; I'll talk about it, and where
6 that fits in with these other commonly overlapping
7 pain conditions is not clear.
8 I'll show you some data from the OPPERA
9 study. And that looks like I have 4 minutes left,
10 so that's a little daunting as well.
11 (Laughter.)
12 DR. FILLINGIM: Here are some early data
13 from the OPPERA study. We have a bunch of controls
14 and a smaller number of TMD cases. What you see is
15 the prevalence of 0 to 4 other idiopathic pain
16 conditions in these two groups. If you have zero
17 other pain conditions, your odds of TMD are 1 here,
18 so that's a reference group. If you happen to have
19 all four of the other overlapping pain conditions,
20 you're 170 times more likely to also have TMD than
21 if you have no overlapping pain conditions. So the
22 presence of other pain conditions in this

Page 287

1 particular analysis increases the risks that you're
2 also a TMD case.
3 Some more recent data that you may not be
4 able to read, but this is from our OPPERA-2 study,
5 and what you see are the index conditions in the
6 bolded letters here. If we take fibromyalgia, for
7 example, fibromyalgia right here on the upper, your
8 left, the little cutout is the proportion of
9 fibromyalgia cases who didn't have any other of the
10 pain conditions, and the other pain conditions are
11 headache, irritable bowel syndrome, low back pain,
12 and TMD.
13 So 10 percent of fibromyalgia cases had
14 fibromyalgia alone. The rest of them had some
15 combination of these other conditions; whereas if
16 you move over here to the right to headache, you
17 see fully half essentially of the headache cases
18 had headache alone and none of the other
19 conditions. So that's an interesting way to look
20 at this.
21 Then when you get the slides and can look at
22 them in your own time, we have the different

Page 288

1 combinations that are available here. For
2 fibromyalgia there, you see T, H, I, B, and F, that
3 is a quarter of the fibromyalgia cases had all of
4 the pain conditions, and then you can see the other
5 combinations there. So this is a fairly detailed
6 look at the overlap that occurs across these
7 different pain conditions, and you can see it's
8 quite substantial.
9 What does this have to do with central
10 sensitization? Of course, we've heard very nicely
11 from Clifford about what central sensitization is
12 and where it came from. This quote from his 2011
13 paper, in which he summarized a lot of this work,
14 says, "central sensitization is amplification of
15 neural signaling within the CNS that elicits pain
16 hypersensitivity." He identifies several clinical
17 signs that we might see in patients that might
18 reflect central sensitization.
19 We can also think about risk factors that
20 are common to these sort of prototypical
21 overlapping pain conditions, which include female
22 sex. We've heard a lot about today widespread pain

Page 289

1 sensitivity, which is what I'm primarily talking
2 about; psychological factors, somatic symptom
3 burden, and familial and genetic factors. I note
4 that one of these is pain sensitivity, and the
5 others have been associated with pain sensitivity.
6 So all of these risk factors might have a common
7 link to central sensitization.
8 If we talk about sex for a moment, not only
9 are females at greater risk for each of these
10 conditions individually -- again, some more OPPERA
11 data -- the female predominance increases as the
12 number of overlapping pain conditions increases
13 here. So you see that it's getting close to almost
14 exclusively females who have essentially all of the
15 overlapping pain conditions that we studied in
16 OPPERA.
17 Family history, here we have the TMD bars.
18 In purple, you see cases of TMD. The height of the
19 bar reflects the proportion of those TMD cases who
20 also report that they have a family history of TMD,
21 and the same for headache, family history of
22 headache. And in yellow, you see the proportion of

Page 290

1 cases who report no family history of that
2 particular index condition, and you can see that
3 for everything, except for, surprisingly, low back
4 pain here. There's a strong, at least
5 self-reported, familial history of that particular
6 condition.
7 What about psychological factors? We've
8 heard quite a bit about this. These again are
9 OPPERA data, and the text is intentionally small
10 enough to where you can't make anything out of it.
11 But the heat map here, the darker the shade of
12 orange would be a stronger association of, for
13 example, TMD in the first column with that
14 particular psychological measure.
15 The first two psychological measures are
16 measures of somatic symptoms, and you see that they
17 seem to be more strongly associated with each of
18 the index pain conditions, particularly for
19 fibromyalgia, low back pain, and TMD.
20 Then as you go down, you see there are some
21 weaker associations. There are coping strategies
22 at the bottom. Catastrophizing is in the middle

Page 291

1 and so on and so forth. But you don't see so much
2 a smoking gun; that is this psychological factor is
3 associated with this pain condition, whereas this
4 other psychological factor is associated with this
5 other pain condition.
6 The psychological factors maybe to some
7 degree are agnostic to the pain condition, and you
8 see that the strongest associations between
9 psychological factors and any of the pain
10 conditions seem to occur around somatic symptoms,
11 at least of the psychological factors we've studied
12 in OPPERA.
13 Maybe a little more impressive is this heat
14 map, which shows the association of the same
15 psychological factors with the number of pain
16 conditions somebody is reporting, and the
17 comparison here is always to people who don't have
18 any of the pain conditions. So the further right
19 you go, the darker colors indicate a stronger
20 association of that psychological factor with more
21 idiopathic pain conditions.
22 The message here is very straightforward;

Page 292

1 that is the more idiopathic pain conditions you
2 have, the stronger the psychological burden or the
3 association with psychological symptoms, maybe not
4 terribly surprising.
5 So for another ACTION initiative, we put
6 together some ideas about mechanism-based pain
7 assessment, if you will. On the left you see pain
8 related factors that might tell us a little
9 something about mechanisms, although not
10 specifically, and then on the right some other
11 techniques that are primarily research-based that
12 can also give us mechanism-based information.
13 I'll give a few examples of at least some of
14 these: pain distribution and qualities, QST
15 findings, and I'll hint at neuroimaging, but I'll
16 let somebody who actually knows about this, Vitaly,
17 talk about this after the break.
18 One thing in terms of the widespreadness of
19 pain -- this is some data from Chung Jung Mun, who
20 is now working with Claudia at Hopkins, I believe.
21 They recently published this paper where they had a
22 large cohort of people who were known, who were

Page 293

1 recruited to have chronic pain, and they looked at
 2 the different conditions that people reported and
 3 the number of body sites at which people reported
 4 pain.
 5 You can see, for example, people with
 6 cluster headache, the blue bar indicates that they
 7 reported having 4 and a half on average pain
 8 conditions. I'm not sure what half of a pain
 9 condition feels like to somebody. So you see
 10 there's a lot of comorbid pain conditions, which we
 11 already know, and there are even more pain sites at
 12 which people are experiencing non-transient pain.
 13 Again, here's some data from OPPERA here,
 14 and these are heat maps based on an OPPERA version
 15 of a body map. On the far left there you see what
 16 controls were reporting; that is these are people
 17 who had no idiopathic pain conditions, and the
 18 other heat maps show you where people are reporting
 19 pain on the front and the back, and not
 20 surprisingly, the heat map is much stronger for
 21 people with fibromyalgia. People with low back
 22 pain are reporting pain in the low back, but a lot

Page 294

1 of people are reporting a large amount of pain in
 2 the head, especially posteriorly.
 3 It looks like overlapping pain conditions
 4 are not agnostic to the location of pain. These
 5 are some data from OPPERA that Gary Slade published
 6 recently. This is the odds of TMD based on where
 7 other comorbid pain conditions were, and people
 8 with headache had a much higher prevalence or odds
 9 of TMD. Next was neck pain, and next was pain
 10 below the neck.
 11 These are the figures for OPPERA data. Gary
 12 also looked at two large data sets, national data
 13 sets, and really showed the same pattern, so there
 14 may be some segmentality to this, although your
 15 odds of TMD are still significantly higher than the
 16 general population, even if your other pain
 17 conditions are below the neck.
 18 So if we turn to quantitative sensory
 19 testing as maybe the most common method for
 20 assessing something like central sensitization,
 21 there are any number of papers out there now that
 22 have used quantitative sensory testing to show that

Page 295

1 people with a variety of chronic pain conditions
 2 respond differently on QST than people without
 3 those conditions, whether you want to call this
 4 pain sensitivity or altered pain modulatory
 5 balance.
 6 An example is the OPPERA study here where we
 7 were looking at pressure pain thresholds at sites
 8 across the body. In the blue bars, you see the
 9 threshold for controls; the red bars for TMD cases.
 10 What we see is that no matter where we're poking
 11 TMD cases, they're more sensitive than controls,
 12 and this has been a common finding for TMD but also
 13 for many of the other conditions that we're talking
 14 about here.
 15 We've done some of this work in
 16 osteoarthritis, which, as Dan talked about, has
 17 historically been viewed as the classic
 18 peripherally-based regional pain condition. Chris
 19 King looked at our data, and we broke it
 20 down -- our OA group, we broke into those who had a
 21 high degree of knee pain versus a low degree of
 22 knee pain. This was a community based sample based

Page 296

1 on the characteristic pain intensity score. When
 2 we start looking at quantitative sensory testing
 3 measures, essentially the high pain OA group was
 4 always more sensitive than the other two groups,
 5 and the low pain OA group was somewhat intermediate
 6 between controls in the high OA pain group.
 7 These are pressure pain thresholds. Medial
 8 and lateral are on the joint line of the affected
 9 knee, the quadriceps of the ipsilateral leg, and
 10 then the trapezius and the arm on the ipsilateral
 11 side. So whether we're, again, poking people where
 12 their clinical pain is or we're poking them in
 13 non-painful sites, our high OA pain group is more
 14 sensitive.
 15 If we look at temporal summation of
 16 mechanical pain using a von Frey hair, after one
 17 trial, the high OA pain group reports higher pain,
 18 but then that slope is much deeper after we've
 19 poked them 10 times once a second. That slope is
 20 representing what we think is some kind of
 21 mechanical temporal summation, and that slope is
 22 steeper in our high pain OA group than in controls;

Page 297

1 again, whether we're poking them on the knee or an
 2 unaffected area, which is the hand.
 3 Similar findings with temporal summation of
 4 heat pain, both more pain and a steeper slope to
 5 that summation of pain across trials in the high
 6 pain group with OA. I mentioned earlier, in terms
 7 of mechanism-based pain assessment, that features
 8 of the pain, qualities of the pain might matter, so
 9 we had the pain detect to examine neuropathic like
 10 symptoms in our knee osteoarthritis group.
 11 Roughly, 17 percent of our osteoarthritis group
 12 reported or exceeded the standard cutoff on the
 13 pain detect for classifying neuropathic pain.
 14 These were more likely to be non-white,
 15 obese, and were slightly younger actually. So we
 16 controlled for these factors when we were making
 17 the other comparisons. First of all, they just
 18 report more pain in general. Their knee pain is
 19 more severe, the people who reported neuropathic
 20 features. This is on the McGill Pain Questionnaire
 21 short form. All of the subscales are higher for
 22 the neuropathic like group than the

Page 298

1 non-neuropathic.
 2 When we looked at movement evoke pain, this
 3 is a short physical performance battery where we
 4 have them do a balance task, a chair standing task,
 5 and a walking task. When we ask how much each of
 6 those things hurt, that pain was higher in the
 7 people who reported neuropathic features.
 8 Then when we look at our quantitative
 9 sensory testing results, we see that it's really
 10 only temporal summation. Of the many quantitative
 11 sensory tests that we did, only temporal summation
 12 distinguished the neuropathic pain like group from
 13 their non-neuropathic counterparts.
 14 This is mechanical temporal summation, and
 15 we see the same effect with -- I'm sorry. That was
 16 heat pain, temporal summation, and we see the same
 17 effect with mechanical temporal summation. So this
 18 sort of heightened pain facilitation but not
 19 conditioned pain modulation distinguished these two
 20 groups. So some of the features of neuropathic pain
 21 might be mechanistically relevant in this sample.
 22 If we look at quantitative sensory testing

Page 299

1 measures back to the OPPERA study using these same
 2 heat maps, the top QST measure there is pressure
 3 pain threshold measured on the temporalis muscle.
 4 Maybe not surprisingly, that's strongly associated
 5 with TMD because those muscles hurt in TMD cases.
 6 Moderately associated with fibromyalgia, we see a
 7 little more darkness in the fibromyalgia and TMD
 8 compared to the other groups, but not terribly
 9 strong associations between QST and individual
 10 index pain conditions.
 11 However, again, when we look at the number
 12 of idiopathic pain conditions, the heat map gets
 13 more darker shading as we go to the right here. If
 14 you have all of the idiopathic pain conditions,
 15 you're fairly sensitive to however we choose to
 16 hurt you here.
 17 (Laughter.)
 18 DR. FILLINGIM: So this is, again, an
 19 example of QST connected to different idiopathic
 20 pain conditions. Here are some of the same data
 21 shown in graphical form. You see on the X-axis the
 22 number of idiopathic pain conditions; on the

Page 300

1 Y-axis, the Z score for that particular pain
 2 measure. If we look at the top- left there,
 3 pressure pain on the temporalis, there's a pretty
 4 linear relationship between the number of
 5 idiopathic pain conditions and one's pressure pain
 6 threshold on the temporalis.
 7 But if you look at a couple of these after
 8 sensation measures on the bottom panels, it looks
 9 like there's sort of a break point where once you
 10 hit three or maybe for idiopathic pain conditions,
 11 that's where you're more likely to have after
 12 sensations; that is we've applied mechanical pain
 13 stimuli, or heat pain stimuli. We stopped, and 15
 14 seconds later it still hurts you.
 15 So there's again some links, but the
 16 associations between QST measures and the number of
 17 idiopathic pain conditions seem to vary somewhat,
 18 depending on which QST measure we're looking at.
 19 These are all cross-sectional data that I've
 20 been showing you, so an obvious question is, is
 21 central sensitization a predictor, or consequence,
 22 or epi phenomenon of chronic overlapping pain

Page 301

1 conditions? This was the original OPPERA incidence
 2 study that Joel Greenspan published, and what you
 3 see here are the hazard ratios; that is what is the
 4 risk of developing TMD in the future based on what
 5 your QST responses were before you had TMD.
 6 We see a few -- they're all weak, but a few
 7 significant findings in the heat pain area here. A
 8 couple of the pressure pain sensitivity measures,
 9 particularly those on the head, predicted future
 10 development of TMD. But these are quite modest
 11 associations compared to some of the psychological
 12 factors and clinical factors we've looked at.
 13 More impressive from the OPPERA study are
 14 findings that as people are developing TMD pain,
 15 their pressure pain sensitivity is changing. This
 16 is the baseline value. At that point, nobody in
 17 the study has TMD. At some point, some people are
 18 developing symptoms of TMD, and we bring them back
 19 to the clinic to determine whether they actually
 20 have TMD with a standardized exam.
 21 There are two groups of people who developed
 22 TMD. One group we later classified as persistent

Page 302

1 TMD because when we re-examined them 6 months
 2 later, they still met criteria for TMD. Another
 3 group 6 months later no longer met criteria for
 4 TMD, so we called them transient TMD, and then here
 5 we have controls who never developed TMD.
 6 What you see is that from the time that we
 7 first met them to the visit at which we classified
 8 them as having TMD, their pressure pain thresholds
 9 decreased significantly. You see that in the
 10 transient cases, there's a trend toward their
 11 pressure pain thresholds renormalizing, whereas in
 12 those whose TMD persisted, their pressure pain
 13 thresholds stayed low, suggesting that pressure
 14 pain threshold is more of a consequence or a
 15 co-occurrence with the development of TMD than a
 16 predictor of future development of TMD.
 17 On the other hand, Tuhina Neogi's group at
 18 Boston recently published this study, so they had a
 19 large group of individuals who didn't have knee OA
 20 but were at risk for developing knee OA in the MOST
 21 study. They identified 4 clusters of people in
 22 their sample based on quantitative sensory testing

Page 303

1 profiles. One cluster had high pressure pain
 2 sensitivity and moderate facilitated temporal
 3 summation.
 4 So this was the most pathological pain
 5 sensitivity profile, and they had about double the
 6 risk of developing a way over the follow-up period
 7 compared to the low to moderate proportion of pain
 8 sensitivity; essentially the low pain sensitivity
 9 group. In this study, baseline measures of
 10 quantitative sensory testing were predictors of
 11 future risk for developing, in this case,
 12 osteoarthritis and a fairly strong effect here.
 13 I'm not going to get too much into
 14 neuroimaging. There is some work looking at
 15 whether brain structure is associated with one's
 16 pain sensitivity, and that's inconsistent. Some
 17 findings show a relationship between reduced either
 18 cortical thickness or gray matter volume and pain
 19 sensitivity measures. Other studies find no such
 20 associations.
 21 But I did want to at least mention this
 22 study of structural brain alterations before and

Page 304

1 after knee arthroplasty. What they showed is that
 2 after knee arthroplasty, patients show significant
 3 increases in gray matter in several brain regions,
 4 and actually decreases in gray matter volume and
 5 bilateral somatosensory cortex.
 6 This was also accompanied by QST changes;
 7 that is, their temporal summation profile decreased
 8 significantly, and their pain inhibitory response
 9 improved significantly, suggesting that this
 10 corrective treatment or pain-reducing treatment
 11 normalized both quantitative sensory testing
 12 responses, as well as brain volumetric measures.
 13 So we come to this. This is the original
 14 OPPERA model that's been modified over the years,
 15 which is based on the notion that a variety of
 16 genetic factors combined with environmental
 17 contributions would drive changes in two
 18 intermediate phenotypes, high psychological
 19 distress and a high state of pain amplification,
 20 and those intermediate phenotypes are associated
 21 with increased risk of painful, chronic overlapping
 22 pain conditions.

Page 305

1 One thing we need to think about, we've
2 heard a lot about somatic symptoms, somatosensory
3 amplification, and central sensitization. In the
4 original OPPERA model, we classified this as
5 psychological distress, although one could easily
6 put it in the pain amplification bucket. So we
7 need to think about how some of these constructs
8 are related and what the mechanisms are.

9 In conclusion, chronic overlapping pain
10 conditions seem to exhibit multiple signs of
11 central sensitization. As we increased the number
12 of pain conditions, that is associated with
13 significantly increased pain sensitization, if you
14 will. Sensitization could be a risk factor or
15 could be a consequence. There's evidence for both
16 depending on the study.

17 These various domains that we measure with
18 different methods, that may all reflect to some
19 degree mechanisms associated with central
20 sensitization, we need to somehow reconcile these
21 and develop models as to how to put them together,
22 as we've talked about already. I'll certainly

Page 306

1 acknowledge my many colleagues and funding
2 agencies, and that's all I have.

3 (Applause.)

4 DR. WASAN: That's great. Actually, both
5 speakers helped us make up some time.

6 Dennis, do you want to go to break now or
7 should we actually -- we made up a little time.
8 Should we go to break instead of questions. Okay.
9 Do you want to do the full 30 minutes or 20-minute
10 break? What would you like?

11 DR. TURK: Use your discretion. Surprise
12 us.

13 DR. WASAN: Okay. Surprise, surprise.
14 We'll do a 20-minute break. That will pick us up
15 and get us closer to be on track.

16 (Whereupon, at 3:18 p.m., a recess was
17 taken.)

18 DR. WASAN: Thanks, folks. This will be our
19 last talk, and then we'll have the Q&A. I think
20 Vitaly probably feels under a lot of pressure
21 because he's had a lot of buildup. People keep
22 referring to the talk of Vitaly, the talk of

Page 307

1 Vitaly; what's going to happen?

2 Dr. Napadow is one of my closest colleagues
3 for many years. He's a biochemical engineer and an
4 acupuncturist. He's an associate professor of
5 radiology at the Harvard Medical School and
6 Massachusetts General Hospital, and he's director
7 of the Center for Integrative Pain Neuroimaging
8 there at the Martinos Center, which is a large
9 neuroimaging center that is part of MGH. So he's
10 going to speak to us today about a lot of the pain
11 imaging findings in the brain, and then we'll have
12 a Q&A after that.

13 Presentation - Vitaly Napadow

14 DR. NAPADOW: Thank you very much. It's a
15 real pleasure to be here and get the chance to
16 present to you. For my talk today, I've been
17 tasked with an overview of central sensitization
18 and neuroimaging, and neuroimaging applications to
19 try to better understand central sensitization and
20 some of the markers and some of the metrics that
21 we've been talking about in the last few talks.
22 I'm not really going to go too much into

Page 308

1 this, we've already had a lot of discussions, but
2 just the general idea that there is this ontology
3 that I think still needs to be develop around the
4 term "central sensitization," and I think is an
5 evolving discussion that I guess we're all having.
6 But strictly defined, central sensitization refers
7 to a controlled stimulus that is imparted, and then
8 measuring some sort of neuronal event that is
9 happening in response to that controlled stimulus.

10 Clinically, obviously, there are certain
11 limitations in what we can do in humans versus
12 animal models, but clinically, sensitization can
13 be inferred indirectly from phenomenon such as
14 hyperalgesia and allodynia, but there's also other
15 phenomenon that are associated with this central
16 sensitization such as temporal summation of pain,
17 reduced conditioned pain modulation, reduced
18 habituation, cortical amplification, increased
19 receptive field size, and sort of plasticity and
20 cortical representations.

21 So all of these concepts I'm going to try to
22 overview in my talk.

Page 309

1 The question is how do we assess this with
 2 neuroimaging? I know we're a multidisciplinary
 3 crowd here, so I wanted to take just a very brief
 4 step back and talk about just the general idea that
 5 functional neuroimaging actually involves multiple
 6 different modalities that can get at different
 7 aspects of brain structure and function.
 8 If we think of a neuronal event that's
 9 happening somewhere in the brain, there's an
 10 electromagnetic response that's imparted in
 11 response to these neuronal events. This type of
 12 activity can be picked up with technologies such as
 13 EEG and MEG. There's a neurotransmitter response.
 14 Glutamate and GABA concentrations, for example, can
 15 be assessed with magnetic resonance spectroscopy,
 16 whereas endorphins and receptor binding can be
 17 assessed with positron emission tomography, PET.
 18 Then there's a hemodynamic response. When
 19 you have an neuronal event, you have this
 20 concomitant increase in blood flow, and that can be
 21 picked up with optical techniques, imaging
 22 techniques, as well as a variant of MRI called

Page 310

1 functional MRI or fMRI, and that's principally what
 2 we're going to be focusing on in this talk.
 3 With fMRI, there's a contrast called BOLD,
 4 or blood oxygenation level dependent. With this
 5 contrast, basically you can think of a basal state
 6 of brain activity where there's a basal amount of
 7 activity, there's a basal amount of blood flow to
 8 these capillary beds, and a basal relative
 9 concentration of oxygenated and deoxygenated
 10 hemoglobin, and then a basal MRI signal.
 11 When that area of the brain becomes
 12 activated, and there's an activated state, you now
 13 have an increase in blood flow, an increase in
 14 oxygenated hemoglobin because basically what
 15 happens is there's a decrease in oxygenation very
 16 locally, but then there's an in-rush of new blood,
 17 which then brings more oxygenated hemoglobin and a
 18 decrease in deoxygenated hemoglobin. And it's
 19 actually this decrease in concentration of
 20 deoxygenated hemoglobin that leads to lower field
 21 gradients around the vessels that it's feeding,
 22 which then leads to an increase of the MRI signal

Page 311

1 because there's lower field gradients.
 2 So in review, an activation somewhere in the
 3 brain leads to an increase in the ratio of
 4 oxygenated to deoxygenated hemoglobin, leading to
 5 an increase of this MRI parameter called T2-star,
 6 which then leads to an increase in the MRI signal,
 7 and that's ultimately what we're tracking with this
 8 technology.
 9 What does fMRI data look like? Well, it
 10 kind of looks like MRI data. You take an image of
 11 the entire brain every, say, 1 to 2 to 3 seconds,
 12 and then you can get a time course by just looking
 13 at the brightness of any voxel or volume element
 14 anywhere in the brain over time. If you have a
 15 typical experimental design where you have -- this
 16 is called a block design where you're not doing
 17 something and you're doing something. Let's say
 18 you're stimulating with a painful stimulus over
 19 here and then stop stimulating.
 20 You are then calculating a statistical test
 21 to see how the MRI signal time series everywhere in
 22 the brain relates to what it is that you are doing,

Page 312

1 and the result of that test can then be appreciated
 2 by these color-coded maps over the brain. So when
 3 you see these pretty pictures, all they really are
 4 is the results of a statistical test, or a series
 5 of statistical tests, corrected from multiple
 6 comparisons of course, where you see this signal
 7 either increasing, such as red and yellow over
 8 here, in response to some sort of stimulus, or
 9 decreasing such as blue and cyan over here in
 10 response to that stimulus.
 11 So hopefully we're generally on the same
 12 area now in terms of understanding some of these
 13 imaging modalities. One good place to start I
 14 think, because they're actually has been quite a
 15 lot of work that's done in the pain imaging field,
 16 is to look at a meta-analysis. So you're probably
 17 familiar with clinical trials meta-analyses.
 18 You can do something similar with functional
 19 imaging, where basically a lot of these papers have
 20 tables published where you have locations of
 21 activations and deactivations in response to pain
 22 stimulation, and you can take those

Page 313

1 locations -- these are kind of like the little red
 2 dots over here -- and you can feed those into
 3 meta-analytic algorithm called ALE for activity
 4 likelihood estimation; they called it in ginger ale
 5 as the software
 6 Basically, there's a series of these, but I
 7 happen to choose this one because they talked about
 8 sensitization. In this study, you can see there's
 9 more than 200 studies that went into this
 10 meta-analysis. Over 150 papers were with healthy
 11 controls; 32 papers in chronic pain patients, and
 12 about 9 studies that were there looking at
 13 hyperalgesia. I'll talk about this in a little bit
 14 of detail.
 15 First of all, looking at the response in
 16 healthy controls, this is basically just response
 17 to -- in this case it was cutaneous. This
 18 particular meta-analysis focused on cutaneous pain
 19 stimulation, principally heat pain. What you see
 20 here is activation in a lot of the brain areas that
 21 are modeled and from review papers we know to be
 22 important for nociceptive processing.

Page 314

1 You have the thalamus over here; we have the
 2 thalamus over here. We have both anterior insula,
 3 posterior insula. We have S2, or secondary
 4 somatosensory cortex; ACC or anterior cingulate
 5 cortex that are activated in response to these pain
 6 stimulations in healthy subjects, and also some
 7 pain modulatory areas, importantly to note, such as
 8 ventrolateral prefrontal cortex and VTA, ventral
 9 tegmental area.
 10 How about in induced sensitization, induced
 11 hyperalgesia, with these studies, it's a smaller
 12 number of studies, but typically in these studies,
 13 it's a model in healthy subjects where you inject
 14 or use some sort of capsaicin intervention to
 15 induce a secondary hyperalgesia, which is thought
 16 to be reflective of central sensitization.
 17 While the localization between the
 18 normalgesia and the hyperalgesia in healthy
 19 controls actually did not differ, and the regions
 20 that were activated in this state did not differ
 21 between injecting capsaicin versus not injecting
 22 capsaicin, the strength of the activation did

Page 315

1 differ. They show greater activation in regions
 2 such as the anterior insula, posterior insula,
 3 secondary somatosensory cortex, and the anterior
 4 cingulate.
 5 Basically, this can be inferred only from
 6 studies that actually did a direct contrast of
 7 hyperalgesia versus normalgesia, so then those
 8 coordinates can be passed up to this meta-analytic
 9 level. That's something important to understand.
 10 Basically, there's a generalized
 11 upregulation of pain and salience processing area
 12 such as the insula, secondary somatosensory cortex,
 13 and the cingulate in this capsaicin-induced
 14 hyperalgesic state. This is very much consistent
 15 with EEG.
 16 I'm not going to talk a lot about EEG, but
 17 it's very much consistent with EEG studies that
 18 have used this kind of model with this
 19 capsaicin-induced central sensitization, where you
 20 basically generally get this elevation of what's
 21 called the N2 peak over here, around 180 to
 22 200 milliseconds after the stimulus. They induce

Page 316

1 capsaicin injection in the hand, only in one hand,
 2 not the other, and then do a punctate probe and
 3 look at EEG response. So you see this elevation of
 4 the N2 peak as kind of a marker of central
 5 sensitization.
 6 What about chronic pain patients? This is
 7 where it gets interesting, and this is a quote from
 8 the review. Remarkably, similar activation
 9 patterns in healthy controls in chronic pain
 10 patients, there was no significant differences in
 11 the spatial localization of nociceptive processing
 12 between healthy subjects and chronic pain patients;
 13 no significant differences in the intensity of
 14 activation.
 15 Those studies that directly calculated the
 16 chronic pain versus healthy control contrast also
 17 did not find any differences. No significant
 18 differences for subgroup of fibromyalgia versus
 19 healthy. This is all chronic pain patients. If we
 20 just look at subgroups, let's say just widespread
 21 pain, just fibromyalgia, there was also no
 22 differences found there. And this is in cutaneous

Page 317

1 pain, so what's going on here.
2 So maybe it's just continuous pain. We did
3 a study where we used deep-tissue evoked pain where
4 we have this a cuff that's inflated over the lower
5 leg from outside of the scan room, and we looked at
6 response to this deep-tissue evoked pain; nice
7 activation pattern in healthy controls; nice
8 activation pattern in fibromyalgia patients.
9 Contrasting the two, no significant differences
10 whatsoever.
11 There's definitely hyperalgesia. This is
12 the pressure. This was a percept-matched study.
13 This is the pressure that was used to evoke an
14 equal amount of pain in the fibromyalgia patients
15 and in the healthy controls, a very significant
16 difference there, but yet no differences in brain
17 response.
18 Why no difference? I don't know, but one
19 potential reason is that most of the studies in
20 that meta-analysis, and our study in particular,
21 used percept-matched stimulation. If you look at a
22 stimulus-matched condition -- this was a nice study

Page 318

1 out of a Tor Wager's lab -- they used both a
2 percept-matched and a stimulus-matched condition,
3 and what they found is that when both fibromyalgia
4 patients and healthy controls receive an -- this is
5 a thumb-squished pain -- equal amount of pressure
6 on the thumb, the fibromyalgia patients report that
7 as a significantly greater pain stimulus than do
8 the healthy control subjects; whereas they also
9 induced a higher input, higher pressure, in the
10 healthy controls that readily matched the amount of
11 pain that was reported between the fibromyalgia
12 patients' healthy controls.
13 If you look at the brain response in these
14 two different conditions, what you see is that it's
15 completely following the perception of pain in
16 these subjects, be they chronic pain patients or
17 healthy controls. The amount of activation in the
18 match, in the stimulus-matched condition with 4.5
19 kilograms, was significantly larger in the chronic
20 pain patients, and that was the case for all of
21 these regions. Be it the anterior insula, the
22 cingulate cortex, posterior insula, they all showed

Page 319

1 the same general pattern, whereas if you matched
2 the amount of pain that the healthy controls are
3 feeling by having a larger input, now you don't
4 have a significant difference between the brain
5 response. So that's, I think, pretty interesting.
6 We also know that this is not just a case
7 for pain stimulation. This is a pain-sensory
8 effect, and Dan very nicely talked about this
9 earlier. This was from the Clauw group where they
10 had a visual stimulation and they looked at
11 different lux or different intensities of this
12 alternating checkerboard. These things were rated
13 as more and more unpleasant as the lux increases,
14 and fibromyalgia patients were hypersensitive to
15 this. At any given lux, they were rating the
16 unpleasantness of the stimulus as more.
17 Basically, if you then compare this very
18 intense condition, which is what they did here with
19 the brain imaging, you find an elevation of
20 response specifically in the anterior insula
21 cortex, and I'll come back to this region in a
22 little bit. I think what was actually really

Page 320

1 interesting is that the amount of response in the
2 anterior insula cortex was correlated with the
3 amount of clinical pain that the patients happened
4 to be in at the time of the scan.
5 How about some other fMRI metrics of central
6 sensitization? Actually, this has not been talked
7 about very much. There was some talk about this I
8 think in Clifford Woolf's talk, the idea of
9 receptive field size, and the correlate from a
10 neuroimaging standpoint of that might be considered
11 cortical representations in the primary
12 somatosensory cortex.
13 We've known for a long time that S1, or
14 primary somatosensory cortex, is organized in a
15 somatotopic fashion over here. This is from the
16 early studies with Penfield. We can use
17 neuroimaging and functional MRI noninvasively. We
18 don't have to open up the skull in these epileptic
19 patients and map out their homunculus. We can
20 actually do this noninvasively with functional MRI.
21 For example, this is the response masked for
22 the primary somatosensory cortex, which is over

Page 321

1 here in the postcentral gyrus. This is the
 2 response to the stimulation of the second finger,
 3 the third finger, and the fifth finger. And I
 4 think if you can imagine the center of mass of
 5 these little activation clusters, you go up the
 6 gyrus as you go from 2 to 3 to 5, and that's
 7 exactly what Penfield found back in the 1930s, that
 8 as you go up the gyrus, you can track out these
 9 different fingers.

10 So what we did is we mapped out these finger
 11 representations in neuropathic pain patients,
 12 specifically carpal tunnel syndrome patients, where
 13 we also looked at the nerve conduction velocities
 14 at the wrists, so electrophysiological findings at
 15 the local peripheral median nerve. What we found
 16 is that patients suffering from carpal tunnel
 17 syndrome have wider cortical representations and
 18 board cortical representations.

19 This is the normal separation in healthy
 20 subjects from digits 2 to 3 to 5, and only those
 21 digits that are innervated by the median nerve in
 22 these patients show contracted representations.

Page 322

1 The representations are closer to one another in
 2 the postcentral gyrus, whereas digit 5, which is
 3 ulnar nerve innervated, the pinky, is nicely
 4 separated from those other digits in both healthy
 5 subjects and in CTS patients.

6 This was a finding back in I think 2006, and
 7 then we were able to replicate that with a much
 8 larger study in 2014. The interesting thing that
 9 we found, at least in an earlier study, was that
 10 the separation distance, the more contracted the
 11 D2/D3 separation distance here on the Y-axis, the
 12 greater the median nerve latency.

13 This is a measure of median nerve pathology,
 14 or pathology at the peripheral nerve at the wrist
 15 is correlated with this cortical representation
 16 remapping or this maladaptive neuroplasticity that
 17 we see in the brain. That's a nice way to get from
 18 the peripheral effect to the central effect,
 19 because I think that's actually been talked about
 20 lot here, is what are the limitations of functional
 21 neuroimaging in looking at the brain responses
 22 versus some of the cord responses that has been the

Page 323

1 focus of a lot of animal research.

2 What about other fMRI metrics of central
 3 sensitization such as temporal summation and
 4 conditioned pain modulation? This has also been
 5 brought up a few times here. There are issues. It
 6 is not so straightforward to assess these
 7 phenomenon in a neuroimaging setting. For example,
 8 with temporal summation, which is assaying a pain
 9 facilitation, the stimulus frequency is such that
 10 it makes it difficult to really track this nicely
 11 with functional MRI.

12 So it's less amenable to these fMRI event
 13 related designs because of the slow hemodynamic
 14 response to any neuronal event, which is peaking
 15 roughly 5 to 6 seconds after a neuronal event. So
 16 it makes it difficult to assess this with a
 17 repeated series of stimuli as you would like to do.

18 One thing that we've been working with to
 19 try to get over some of these barriers is to look
 20 at not just evoked response with these kind of
 21 block designs or event related designs, but to look
 22 at other metrics such as a brain connectivity.

Page 324

1 Functional brain connectivity has actually
 2 kind of started to dominate the functional imaging
 3 field I would say in the last 10 years. Just a
 4 little bit about this, this is the idea that even
 5 in a resting state, if you just collect data, not
 6 have any sort of block design, but you just have
 7 the subject lying there in a scanner and you're
 8 collecting functional MRI data, you see these
 9 fluctuations.

10 Here, this is kind of a video of the MRI
 11 signal over time, and red and yellow is when, on
 12 average, the signal rises, and blue and cyan is on
 13 average when the signal drops below some mean
 14 level. What you can see here is that these
 15 fluctuations are not chaotic, they're not random.
 16 They actually follow in these kind of distinct
 17 networks. When this particular part of the brain
 18 activates, this other particular part of the brain
 19 also activates.

20 So the idea here is that if you do, say, an
 21 independent component analysis or some other time
 22 frequency analyses, you can actually pick out these

Page 325

1 distinct networks, and these networks are kind of
2 like assemblies that rise and fall over time. So
3 when one network is activated, another network is
4 deactivated.

5 Our brain is constantly cycling through
6 this. We're never completely at rest. The brain
7 is always doing something if we're alive. These
8 networks have been described, and some of the
9 canonical networks include networks that are very
10 important for pain and nociception processing.
11 These include the somatomotor network where S1 and
12 primary somatosensory cortex is located for
13 intensity and location and discrimination of pain.

14 Also, the salience network, which has
15 previously been partially dubbed the pain
16 neuromatrix, which is a term that which fallen
17 significantly out of favor in the pain neuroimaging
18 community. The salience network is looking at
19 nodes such as the anterior cingulate cortex, the
20 anterior insula, temporoparietal junction.

21 These are brain areas that respond to
22 salient stimuli, be there painful or non-painful.

Page 326

1 These are stimuli that are defined as something
2 that stands out from the background and stands out
3 from other stimuli. That's why it's called the
4 salience network, so you can see that a lot of
5 these brain areas are also involved here in reviews
6 of nociception processing in the brain.

7 They're highly relevant. One set of
8 experiments that we've done is to take our cuff
9 pain provocation, or cuff pain device, and one nice
10 thing about this is that we can actually -- it's
11 not like a heat pain device where you don't want to
12 burn somebody, so there's a limitation of how much
13 time you can keep this on. With the cuff pain, you
14 can inflate this cuff, and you can keep it on there
15 for four minutes, sometimes even tens of minutes in
16 some labs.

17 So we were able to then keep it on for, say,
18 6 minutes, a period of time of 6 minutes, and this
19 is kind of a sustained deep tissue pain. We can
20 contrast that with a resting state, where it's a
21 more usual way of running these kinds of
22 connectivity analyses, where you just have the

Page 327

1 subjects lying there at rest.

2 What we found, at least in healthy subjects
3 over here, is that these networks shift their
4 connectivity in a sustained pain state versus a
5 resting state. In a sustained pain state, the
6 areas that are activated, primary somatosensory
7 cortical areas that were known to be activated by
8 the stimulus, because they're in the representation
9 of the leg over here in S1, are shifting from their
10 quote/unquote, "home network," which is this
11 sensory motor network, to the salience network.

12 So we have a decrease over here for pain
13 versus rest in this area to the sensory motor
14 network, and the same exact area is also increasing
15 its connectivity to the salience network. Now this
16 location mapping, this area in your body, has
17 become more salient to you because you're feeling
18 the stimulus in that area. It kind of makes sense
19 but hadn't been shown before.

20 If we then look at this in chronic pain
21 patients, in fibromyalgia patients, we see
22 something very, very similar, that if we take a

Page 328

1 seed in the S1 leg area and we see what that's
2 connected to, and we contrast that for a sustained
3 pain state versus a resting state, we see that
4 there's an increase between S1 leg connectivity and
5 other key nodes of this salience network such as
6 the anterior insula over here. That's the case for
7 both the right and the left anterior insula.

8 But interestingly enough, you can also
9 measure temporal summation during this period.
10 This is a little bit different than temporal
11 summation as it's measured with, say, pinprick
12 probes or something like that at once a second.
13 But if you ask subjects how much pain were you in
14 the last 2 minutes of that 6-minute period versus
15 the first 2 minutes of that 6-minute period, you
16 can get this assessment of a temporal summation,
17 sort of an increase or habituation, or a decrease
18 in the amount of pain that they're in towards the
19 end of the scan versus the beginning of the scan.

20 We look at this as a temporal summation
21 index, and we see that fibromyalgia patients report
22 a larger sort of summation of pain during the last

Page 329

1 2 minutes versus the first 2 minutes. If we then
 2 look at that summation index and we see how that
 3 relates to S1 leg connectivity, we find that the
 4 greater the S1 leg connectivity specifically to the
 5 anterior insula, the greater the temporal summation
 6 that was reported by the patients.
 7 This is kind of looking at the circuitry
 8 underlying temporal summation. It clearly involves
 9 not just salience and anterior insula processing
 10 areas, but also primary somatosensory processing
 11 areas. I think that's one interesting thing that
 12 we found in these studies.
 13 What about conditioned pain modulation?
 14 Here, we also have a lot of problems. There have
 15 been very few studies that have been published
 16 trying to assess conditioned pain modulation in the
 17 scanner, and this is problematic for, a host of
 18 reasons. But in looking through this literature,
 19 one study that did I thought kind of a nice job of
 20 this was out of -- I think this is a group out of
 21 Hamburg.
 22 First of all, what was nice is that they

Page 330

1 actually found the group effect for conditioned
 2 pain modulation. Many of the studies that have
 3 been published look at just individual subject
 4 variability and don't actually find a main effect
 5 of group, so a main effect with the conditioning
 6 stimulus versus without the conditioning stimulus.
 7 This study actually did do that and had a
 8 pretty straightforward design. I'm not going to
 9 talk much about this naloxone part of this, but
 10 they also included an opioid blocker here as well
 11 to try to better understand the mechanisms.
 12 In this study, what was interesting is that
 13 they actually tried to replicate some of the cold
 14 CPM studies for conditioning stimulus, where they
 15 put one of the subjects legs into this wooden kind
 16 of crate, and then took ice bags and put a bunch of
 17 ice bags around the leg in order to induce the
 18 condition stimulus, a continuous stimulus of the
 19 cold pain. And they counteracted that with saline
 20 at room temperature as a control.
 21 What they found, first of all, was a very
 22 nice effect of CPM. With the cold over here, you

Page 331

1 get a very nice and significant reduction in the
 2 pain rating reported by the sub [indiscernible].
 3 These are healthy controls by the way. Also, if
 4 you look at the brain response with the cold pain
 5 versus without the cold pain, you see a very nice
 6 reduction -- this is actually coding for reduction;
 7 it's red -- a reduction in areas such as the
 8 thalamus, the insula, S2, midcingulate cortex.
 9 These are all kind of nociceptive processing areas.
 10 This was I think a really nice result for CPM is
 11 also affecting this kind of common pathway of
 12 nociceptive processing areas in the brain.
 13 One question is, let's talk about where is
 14 the central sensitization happening? If it's from
 15 peripheral to central, is it something that's
 16 specific in the cord, or is it something that also
 17 could be in the brain, or is it potentially both?
 18 Do chronic pain patients, for example, show
 19 amplification at the primary synapse, such as the
 20 dorsal horn over here, or is it higher up in the
 21 brain, or both?
 22 One way to get at this, as we were thinking

Page 332

1 of how to do this, is to look at facial pain and
 2 facial stimulation, because with facial
 3 stimulation, this is an example of just raw fMRI
 4 data that we're able to collect. You can see here
 5 that not only can you acquire data from the cortex
 6 and subcortical supraspinal regions, but you can
 7 also collect data from the brainstem. If you
 8 impart stimuli over the trigeminal pathways on the
 9 face, you can also assess activity in the spinal
 10 nucleus of the trigeminal nerve, over here, Sp5, in
 11 the medulla and the pontomedullary junction.
 12 What we did is that we used a stimulation
 13 design where we had a facial stimulus. In this
 14 case, it was kind of an aversive air puff
 15 stimulation, and we looked at migraine patients and
 16 healthy controls. These were interictal episodic
 17 migraine patients.
 18 The air puff stimulation was at a frequency
 19 that we thought was high enough to induce some sort
 20 of summation effect as well to be more aversive in
 21 the patients. What we did is that we had a series
 22 of 14-second long stimulation periods interspersed

Page 333

1 with 20-second duration resting periods. We had 11
2 of these stimuli, and I'll come back to why that's
3 important.
4 If we combine the brain response across
5 patients in healthy controls in terms of both
6 brainstem and brain response, we see that there was
7 nice activation in Sp5, or spinal trigeminal
8 nucleus, in the brainstem, which is right around
9 the pontomedullary junction over here. There was
10 also nice activation in S2 and posterior insula
11 regions, as well as the hypothalamus over here,
12 which is kind of interesting. You don't always see
13 hypothalamic response, but perhaps this was due to
14 the fact that we were studying migraine patients.
15 One interesting thing that we found is that
16 there was actually no difference between migraine
17 patients and healthy controls in response at the
18 primary synapse. This is kind of the analog of the
19 dorsal horn. In this case, these were episodic
20 migraine patients. There was an equal amount of
21 response activation in Sp5 across different groups.
22 However, when we then calculated an

Page 334

1 amplification ratio, which is the amount of
2 activation in these other regions such as posterior
3 insula and S2 and hypothalamus relative to the
4 amount of Sp5 activation, sort of this analog of
5 the dorsal horn, that's where we saw this very nice
6 difference between migraine patients and healthy
7 controls. We see this elevation or this ratio that
8 we refer to as kind of a cortical amplification
9 ratio, which is relative to the gain that you have.
10 It's the gain from the primary synapse in the
11 brainstem up to the cortex.
12 Another interesting thing that we did is
13 that we looked at habituation. Instead of
14 analyzing all of the stimulation blocks equally, as
15 is typically done in fMRI experiments, one nice
16 thing about pain and evoked pain, actually, is that
17 it's a very strong -- it's a very high SNR stimulus
18 in terms of fMRI response.
19 You can actually look at individual blocks
20 of stimulation and assess brain response to
21 individual blocks of stimulations. It's very hard
22 to do this for cognitive tasks for example, by the

Page 335

1 way, which is typically why you have multiple
2 repetitions, and you're averaging, averaging,
3 averaging. But you can do this for pain stimuli
4 because the SNR is nice.
5 What we did is that we calculated brain
6 response to each of these individual stimuli
7 independently, and we looked to see what happened
8 over time, and we could fit, basically, regression
9 lines to each individual subject's response to
10 seeing these tracks over time.
11 What we found is that whereas in healthy
12 controls, these are the open circles, you see this
13 nice kind of habituation as you go from the first
14 stimulus down to the 11th stimulus, and that was
15 less so the case for migraine patients. Migraine
16 patients tended to have a flattened response and a
17 lower slope of this habituation from time to time.
18 One potential marker of central
19 sensitization might also be this reduction in
20 habituation in repeated stimuli as you see over
21 time. In fact, there was a correlation between the
22 amplification ratio that I showed you previously

Page 336

1 and the habituation slope such that the more they
2 amplify, the more the subjects amplify in regions
3 such as posterior insula cortex, the more they also
4 have sometimes even a positive habituation slope.
5 This means that there's a facilitation, an
6 increase, in response as they go from the 1st to
7 the 11th stimulus.
8 Now, a little of summary. Differentiating
9 central sensitization metrics in the brain with
10 functional MRI, we showed you elevated or altered
11 fMRI response in chronic pain patients specifically
12 when the stimulus was stimulus matched between
13 groups, between patients and healthy controls in
14 areas such as the thalamus, S1, S2, anterior
15 insula, which was also there for visual stimulation
16 sensory stimuli, by the way, posterior insula, and
17 ACC.
18 Temporal summation was encoded not just by
19 insula response but also connectivity between the
20 insula and primary somatosensory cortex. Also,
21 brain amplification and reduced habituation were
22 noted in specifically the posterior insula in

Page 337

1 migraine patients. So this is another potential
 2 nice approach to look at more specific brain-based
 3 central sensitization metrics in patients.
 4 I don't mean to say that these are the only
 5 areas where centralization is to occur and these
 6 are the only circuitry for central sensitization,
 7 because these responses might actually be mediated
 8 by other brain regions. If you look at the
 9 original description of pain processing,
 10 nociception processing, and chronic pain, there are
 11 other areas here such as the prefrontal cortex,
 12 which I haven't talked about at all, and posterior
 13 cingulate cortex.
 14 So how do these regions come into play?
 15 Well, a recent study that we completed is we
 16 actually had fibromyalgia patients induced to
 17 catastrophize. So we had them in the scanner, and
 18 during specific periods of time, we told them to
 19 reflect on some of the pain catastrophizing
 20 statements that are in the PCS scale.
 21 So the degree to which different patients
 22 identified with these catastrophizing statements

Page 338

1 were correlated with the amount of activation
 2 response in areas such as the ventral PCC. You
 3 see, basically, the posterior cingulate cortex and
 4 medial prefrontal cortex over here as kind of
 5 encoding the catastrophizing portion of what the
 6 subjects were doing, and the degree to which they
 7 were internal -- because not all fibromyalgia
 8 patients catastrophize; but the degree to which
 9 they reported that they were able to encapsulate
 10 these catastrophizing statements was nicely
 11 correlated with the activation in specifically
 12 ventral PCC.
 13 In conclusion, central sensitization, once
 14 considered purely a spinal cord phenomenon, is
 15 clearly noted in multiple brain responses,
 16 including primary somatosensory cortex. Different
 17 aspects of central sensitization, such as CPM,
 18 temporal summation, gain habituation, all these
 19 receptive fields sizes, can be assessed by
 20 different fMRI methods and support different brain
 21 circuitries. I think in the future, we need to
 22 spend more time in developing novel experimental

Page 339

1 designs to better assess these different aspects of
 2 central sensitization.
 3 I thank you for your attention, and I thank
 4 the funders for a lot of this research and my
 5 colleagues, specifically Jeungchan Lee, and Jieun
 6 Kim, who did a lot of the imaging analyses in these
 7 studies, and Rob Edwards, my close collaborator at
 8 Brigham.
 9 (Applause.)
 10 Q&A and Panel Discussion
 11 DR. WASAN: Why don't we have the rest of
 12 the panel come up, and then we'll have the Q&A.
 13 We're also going to be joined by Christin Veasley,
 14 who is the director of the Chronic Pain Research
 15 Alliance in Rhode Island, and also a Shannon Smith,
 16 who's assistant professor in the Department of
 17 Anesthesiology at the University of Rochester and
 18 part of the IMMPACT-ACTION group as well, who does
 19 a lot of systematic reviews and does a lot of
 20 foundational work that I mentioned.
 21 I thought maybe I would just start out with
 22 one question, and then we'll get the ball rolling.

Page 340

1 I don't need to intentionally start this off with a
 2 hard question, but it got me thinking from this
 3 morning, this issue of association versus
 4 causality. We know that applies to any of the
 5 things we're looking at, whether it's QST, or fMRI,
 6 et cetera.
 7 This is really a question for all of us
 8 here, but also, I'd like to hear what the
 9 biostatisticians in the room think, which it seems
 10 to me that in a lot of our literature, there's very
 11 little use of causal inference statistics, so
 12 things like Bayesian network analysis, CART, things
 13 like that, which might get at some of this
 14 association versus causality kind of questions.
 15 I just want to get some reactions from the
 16 panel what you all think about that; have you
 17 thought about it in your work; is there a next step
 18 forward using those other type of statistical
 19 approaches? Would they have any advantages? So
 20 come up with all the stuff you've done.
 21 DR. NAPADOW: From a statistical modeling
 22 approach to get at issues of causality, it depends

Page 341

1 if you consider mediation modeling to be causal in
2 nature. With some of the other methodologies,
3 Bayesian modeling, and predictive coding, and stuff
4 like that, the problem is that you need a lot of
5 stimuli, and you need a lot of repetitions to
6 really adequately use some of these models, and
7 that can be difficult with pain stimuli, especially
8 with chronic pain patients. For getting at issues
9 of central sensitization in chronic pain patients,
10 those are some of the limitations of those kinds of
11 approaches.

12 DR. FILLINGIM: I don't understand any of
13 those statistics, so I probably shouldn't comment
14 on those. Some of the folks in OPPERA have used
15 some causal modeling, in particular looking at
16 sleep and stress over time and how that predicted
17 first onset TMD. But I think we also need to think
18 about our experimental designs and collecting
19 prospective data, really, and ultimately doing
20 experimental manipulations, whether those are
21 clinical trials or other types of manipulations, in
22 order to make true causal inferences, with all due

Page 342

1 respect to all the statisticians in the audience.

2 DR. WASAN: If there are any statisticians
3 who want to chime in on this, we have a couple of
4 here. Is anyone here? Is Scott here, or someone
5 in the back as well? Go ahead, John.

6 DR. FARRAR: I wanted to ask another
7 question, but I'll chime in on the comment. I
8 think the comment made is the key one, which is
9 that there isn't anywhere near enough data to do
10 it. These studies are all less than a hundred
11 people, probably less than 20, and many of them are
12 30, which is wonderful because you get
13 statistically significant changes. But it's only
14 one 30 people, so all you can comment on is the 30
15 people. Whether that 30 people are representative
16 of the population is a completely different issue.
17 So I think we're not there yet, and maybe we'll get
18 there at some point.

19 What I wanted to ask, actually, was just a
20 specific question about the imaging data. All the
21 data you presented was BOLD. ASL obviously has a
22 whole different set of features. One of the things

Page 343

1 that has intrigued me about the differences between
2 the two is that you might be able to superimpose
3 the BOLD and the ASL.

4 For instance, ASL is very good at looking
5 at -- as in any mechanism, you really have to look
6 at chronic pain, and there is some disagreement
7 about that. But in general that's, I think, an
8 acceptable statement. One of the thoughts would be
9 if you initially imaged with ASL to get a sense as
10 to how much pain the patient seemed to be
11 experiencing that day, and then tried some of the
12 stimuli on top of that, where then you might gain
13 additional information about the state of the brain
14 and then its response to stimulation. I wonder
15 what your thoughts were.

16 DR. NAPADOW: I won't take the bait in
17 arguing with you about chronic pain in ASL --
18 (Laughter.)

19 DR. NAPADOW: -- or maybe I will. I've
20 published with ASL. I mean, ASL certainly has some
21 advantages. It's not as sensitive to large
22 draining veins as BOLD is. One problem with ASL is

Page 344

1 that the SNR is much lower than with BOLD. There's
2 also controversy about what type of ASL we should
3 be using, peak ASL versus ASL.

4 I think ASL kind of has its uses, but it's
5 not going to be a panacea. I guess my quibble with
6 your statement is that that's part of what
7 connectivity analyses can be used with BOLD data,
8 and BOLD is much better for connectivity analyses
9 because you get much better temporal resolution
10 with BOLD than you do with ASL. The temporal
11 resolution with ASL is like 9 seconds. The
12 temporal resolution with BOLD can be as low as a
13 second and a half, 2 seconds, or something like
14 this.

15 DR. FARRAR: To push back a little bit, I
16 completely agree with in terms of your assessment
17 of ASL, in terms of its sensitivity, but it does
18 give an absolute value for blood flow. And it
19 would be, I think, useful in interpreting the
20 stimuli data, to know that a particular part of the
21 brain has already got a higher level of blood flow
22 to start, and to see whether that might in some way

Page 345

1 influence its ability to respond.
2 The other piece of it that is very
3 interesting to me is that there have been a couple
4 of studies where they've applied chronic pain using
5 a blow-up cuff on an arm. Actually, the study I'm
6 thinking about was an injection of hypertonic
7 saline into the muscle, which hurts. They
8 maintained the level of and reported the patient
9 the same, but over time, the blood flow to the
10 brain in the areas involved actually returned to
11 normal.
12 One of the arguments there is that what
13 we're measuring here is blood flow. Blood flow is
14 2 or 3 steps removed from the actual thing we're
15 interested. And it may be that blood flow
16 basically exceeds what is needed, and then slowly
17 returns to a more normal. And it raised the
18 question of what happens when you do those kinds of
19 studies, the BOLD studies, over a period of 4, 5,
20 or 10 minutes because maybe the brain has a
21 differential response over time.
22 All of that to say that this is still very

Page 346

1 interesting stuff. I'm worried that we need to
2 take some of that with a grain of salt before we
3 go --
4 DR. WASAN: Just to clarify, folks, ASL
5 refers to arterial spin labeling.
6 DR. FARRAR: I'm sorry, yes.
7 DR. WASAN: It captures the magnetic moments
8 related to the arterial flow versus the magnetic
9 moments related to the BOLD signal, which is the
10 draining venous flow. Vitaly is underplaying his
11 hand a little bit. He has a whole bunch of ASL
12 studies that have been done, and looked at that
13 carefully, and looked at the overlap, and, clearly,
14 there's a role.
15 Does anybody else have any other comments on
16 John's question, Dr. Farrar's question? Yes?
17 DR. WOOLF: Related to that, I find it
18 difficult to deal with a technology that operates
19 at seconds, whereas ACTION's potential lasts
20 milliseconds, and that measures your voxel at
21 100,000 neurons -- something like that; maybe
22 that's an underestimate -- but a mixture of

Page 347

1 excitatory, inhibitory projection locally, et
2 cetera.
3 So in the end, what is it that you're
4 measuring? Yes, you're measuring changes in blood
5 flow that perfect activity, but in a very crude
6 way, especially n temporally, when you say these
7 are measures of the function of the nervous system,
8 I would say, no they aren't. They are an
9 integrated set or changes at a very gross and crude
10 level, and we've got to be extremely careful about
11 what they mean, and what the connectivity map
12 actually means in terms of the actual function of
13 the node [indiscernible] system.
14 DR. NAPADOW: I can't argue with that. The
15 types of tools that we have for looking at rats,
16 and mice, and other animal models are orders of
17 magnitude better, but we have certain tools that we
18 are able to use in humans. What I'm trying to
19 argue is not that I'm able to pick out inhibitory,
20 versus excitatory, versus specific neurons, or
21 types of neurons, but that there is some rationale
22 in what we're looking at.

Page 348

1 By looking at the strength of the response,
2 by looking at relative strengths of responses
3 between different brain areas, and looking at
4 things like amplification ratios, I think it's
5 highly relevant, and we're seeing these things in
6 somatotopically toxic defined areas. So it's not
7 just like a big wash over the entire brain.
8 DR. FIELDS: Actually, Bob [indiscernible -
9 too close to mic] that particular point, the last
10 point that you made is crucial, novel, and
11 important. It is this idea of the amplification
12 [indiscernible] -- draining starts with a known
13 stimulus. You can actually show that the BOLD
14 signal correlates with the intensity of the
15 stimulus, or with the intensity of the reported
16 pain, or both.
17 Then there's reason to believe that the
18 information that gets to the cortex has to go
19 through the trigeminal nucleus caudalis, where you
20 have sufficient spatial resolution; if not good
21 enough temporal resolution. But the idea that for
22 a given signal in the trigeminal nucleus to show an

Page 349

1 enhanced response in the cortex in a subset of
2 patients is, in my mind, direct evidence that there
3 is a specific central component of amplification.
4 It's in the cortex.
5 Well, actually I don't know that because
6 there's no direct projection from TNC to insula.
7 So there, the question is, is it there in the
8 thalamus; is it via the parabrachial nucleus; is it
9 via the amygdala? In theory, you could determine
10 that.
11 So the question I have -- now that I'm
12 getting to a question -- is could you vary the
13 analysis with respect to the stimulus in such a way
14 that you could see whether there's a delay in the
15 onset of activity between the TNC and the insula?
16 Then, you should be able to do that.
17 DR. NAPADOW: In theory, yes. In reality,
18 there are certain assumptions that are made with
19 fMRI data analysis about the hemodynamic response
20 function that I mentioned before, about 5 or
21 6 seconds peaking after a neuronal event. That's
22 an assumption, and actually there is variability

Page 350

1 across the brain and probably what the hemodynamic
2 response function actually is.
3 So I personally have always been very
4 skeptical with causality types of analyses with
5 fMRI data because if you see that, say, the insula
6 is peaking before the secondary somatosensory
7 cortex, you don't know if that's really because of
8 an actual neuronal event that happened preceding
9 the somatosensory cortex or whether the hemodynamic
10 response function in the insula happens to be a
11 little bit faster because the arteries that are
12 feeding that area are maybe a little bit larger for
13 any number of reasons.
14 So that's why I've always been -- signal
15 processors will go in, and they'll run their
16 algorithms on anything, but the neurophysiology
17 behind all this is such that I kind of am a little
18 bit hesitant about causality types of analyses, and
19 the question that you just asked about what's
20 peaking first.
21 DR. SRINIVASA: It's a question for both
22 Roger and Vitaly. Both of you have demonstrated,

Page 351

1 with both quantitative sensory testing measures or
2 imaging, that there are measures that clearly
3 differentiate normal subjects with central
4 sensitization disorders suggestive of amplification
5 or central sensitization, but clinicians are often
6 dealing with single individuals.
7 Do any of these measures diagnose
8 abnormality of central sensation in a given
9 patient? If so, what would be the sensitivity and
10 specificity of these measures?
11 DR. FILLINGIM: I think for QST, we don't
12 know. There is probably a QST profile that
13 everybody would say is abnormal. How far down the
14 continuum you have to go in order to have a QST
15 profile, I don't know. They haven't been really
16 applied diagnostically. They've been much more
17 used as research tools based on their continuous
18 values, and so on and so forth.
19 I think if we ever want to move this into
20 more practical use, there's a lot of work to be
21 done in terms of the psychometrics and validation
22 of at least QST types of tools for the clinical

Page 352

1 setting.
2 DR. BRUEHL: I've got another assessment
3 type question. Vitaly, your data nicely showed
4 that there is some central amplification above the
5 spinal cord, and it got me thinking about the
6 measures. So what we were looking at in the
7 overlapping conditions was qualitative; yes or no,
8 do you have a diagnosis there? A lot of times,
9 like in Dan's work, we're talking about multiple
10 pain locations but, again, it's yes or no; do you
11 have them?
12 I'm wondering if we're talking about
13 amplification, wouldn't the intensity of the
14 stimulus at each of those locations make a
15 difference as well? I don't know if people who use
16 pain drawings or variants of the Michigan Body Map
17 actually get stimulus or pain intensity in each of
18 those areas, but I wonder what the value of that
19 would be if indeed what's going on is an
20 amplification, because it would imply you get
21 bigger effects for people. Like for someone who
22 had 8 out of 10 pain in 5 locations is very

Page 353

1 different than someone who has 8 out of 10 in one
 2 location and then a 1 in all the other locations.
 3 DR. NAPADOW: I'll let Dan answer, but I
 4 think that's exactly why Dan advocates not just
 5 using the map but using intensity values at all
 6 those different locations that they're reporting.
 7 DR. CLAUW: I wouldn't say, and John can
 8 acknowledge the fact, that it will make your head
 9 explode if you collect intensity at every single
 10 point. So that's what we decided to do in the map,
 11 and I think that's a really bad idea.
 12 What we do in our studies is the digital
 13 body map, if you check the region of the head, you
 14 get a drop-down thing that you have to rate the
 15 pain in that region, but we only make people rate
 16 in each of 7 regions, the 2 arms, the 2 legs, the
 17 front of the trunk, the back of the trunk, and the
 18 head. We found that when you start asking people
 19 to rate at up to 35 sites, which is what the body
 20 map has, then big question that we grapple with in
 21 the map is what would be a checkbox? Because we
 22 used to just say yes/no, but what do you count like

Page 354

1 a pain level of 1 in a site? Do you say that's,
 2 yes, pain?
 3 So anyway, the way we tried to do it really
 4 granularly in the map I think is overkill.
 5 DR. FARRAR: Actually, if I could just add
 6 to that. In the current map, we used the CHOIR
 7 map, which is 64 spaces. Each space gets a rating.
 8 (Laughter.)
 9 DR. FARRAR: To put it mildly, the patients
 10 get tired of it after awhile. And in analysis of
 11 that data, the best cutpoint is between 0 and 1,
 12 maybe between 1 and 2; so pain, yes or no on a
 13 site. And whether you reduce it to 7 or to 14, one
 14 can argue about, but certainly not 64, so I think a
 15 much simpler map.
 16 Then a question this morning to Nat about
 17 the usability of a body map, we've actually spent
 18 some time developing an app that allows a patient
 19 to click on 7 sites and actually rate those
 20 7 sites. It can be completed in 30 seconds. So it
 21 can be used and used regularly over time if you
 22 wanted to use it in a measured study.

Page 355

1 DR. FILLINGIM: If I can just jump on that,
 2 in order to make this just completely ridiculous,
 3 intensity is not the only and maybe not the most
 4 important thing we should measure. What about the
 5 duration of pain? What about the temporal
 6 features? Do they have pain 24 hours a day or does
 7 it fluctuate? What about the sensory qualities,
 8 and so on and so forth.?
 9 So depending on what our question is, I
 10 think it's a fair message we need to do better with
 11 pain assessment. Epidemiological studies are
 12 still, do you have chronic pain; yes or no? That's
 13 almost completely uninformative. So we can do
 14 better, but we can also go to the point of no
 15 return and impossibility in terms of assessment.
 16 DR. WASAN: To follow up on that, one thing
 17 we were talking about a little bit at the break is
 18 that so far we've talked a lot about how
 19 somatosensory amplification, one of the best
 20 clinical indicators is the extent of widespread
 21 pain. But then there also of course many other
 22 pain conditions, which have some somatosensory

Page 356

1 amplification components but are focal pain
 2 conditions; the data on abnormal QST responses in
 3 patients with back pain who do not have fibro, who
 4 have more isolated pain.
 5 So maybe some question to follow up on this,
 6 which is what the panel thinks about are there
 7 other of indicators of somatosensory amplification
 8 clinically besides just the pain and number of body
 9 regions, or other things people would chime in
 10 with.
 11 DR. FILLINGIM: Do you want to respond to
 12 that, Penney?
 13 MS. COWAN: No, I don't, but I want to
 14 respond to something you just said about measuring
 15 the pain. For people living with pain, it's more
 16 than just the intensity of the pain; it's the
 17 impact it has on their life. I know that's not
 18 part of that, but it's huge for that person living
 19 with pain.
 20 I don't want to you to forget that it's not
 21 just about the measure of pain. There are so many
 22 other factors that are involved in that when you're

Page 357

1 actually looking at a person living with pain and
 2 their ability to function and actually live a full
 3 life in spite of the pain.
 4 DR. WASAN: I think that's a good point,
 5 too, that one of those bidirectional relationships
 6 perhaps related to somatosensory amplification is
 7 the impacts on life. That's a big broad term for a
 8 lot of things. But as well, that may impact the
 9 degree of amplification, and the amplification may
 10 impact the degree of impacts on life. So it's
 11 another one of those bidirectional things.
 12 I think that's another issue maybe for us to
 13 address tomorrow when we talk about a manuscript,
 14 which is what are all the different possible
 15 clinical indicators of somatosensory amplification,
 16 suggestive of such a process going on?
 17 DR. FILLINGIM: I think, certainly, as Dan
 18 talked about that there are not a lot of non-pain
 19 sensory experiences, they don't have to be
 20 somatosensory. They can be other senses but within
 21 the somatosensory system. Things like The Pill,
 22 which we've used a lot, and OPPERA, assess a wide

Page 358

1 range of bodily symptoms from itchy throat, to
 2 runny nose, to breathing problems, to whatever.
 3 And those are some of our best predictors of who's
 4 at risk for developing TMD in the future.
 5 So it certainly goes beyond the pain space.
 6 I think if at this meeting we can come to some
 7 consensus about what's central sensitization, and
 8 what's other stuff, and where do they overlap, and
 9 if they're separate constructs, how and what should
 10 we measure, I think it would be a huge contribution
 11 to the field.
 12 DR. WASAN: Yes, Simon?
 13 DR. HAROUTOUNIAN: I have a question. Do we
 14 know which among those different sensitization
 15 symptoms that we discussed are more bothersome for
 16 patients, or which are considered more key ones
 17 from a patient's perspective rather than ours, or a
 18 researcher, or a clinician perspective if we're
 19 thinking about sensitivity to noises, to light, to
 20 touch? Or are there particular conditions in which
 21 patients tend to express more concern with specific
 22 sets of symptoms or signs?

Page 359

1 DR. WASAN: There's actually good data on
 2 lumbar radicular pain, that the radicular component
 3 of pain is one of the most bothersome aspects of
 4 chronic low back pain. And the same would apply to
 5 neck and arm radicular pain in terms of how you
 6 measure it and comparing it to all the other
 7 impacts related to pain. There are a lot of
 8 studies on that, so definitely with bothersomeness,
 9 really, the radicular pain seems to be one of the
 10 most distressing that people have.
 11 Other questions or comments? Nat?
 12 DR. KATZ: Has functional neuroimaging shed
 13 any light on the relationship between mood
 14 disturbances and chronic pain, whether there is any
 15 common circuitry?
 16 DR. NAPADOW: Yes, I think there is a lot of
 17 common circuitry there. A lot of depression
 18 research is also pointing to some of these kind of
 19 salience processing brain areas.
 20 Also, this whole idea -- I was recently
 21 going through the literature on some of our
 22 findings linking cross kind of connectivity between

Page 360

1 default mode network and salience processing areas
 2 as underlying chronic pain severity. Looking
 3 through the depression literature, there's a lot of
 4 evidence for cross-correlation between default mode
 5 network and insula salience processing areas in the
 6 depression space.
 7 So yeah. I think there's a lot of overlap
 8 there. In fact, our most recent publication was
 9 actually very interesting. I didn't talk about
 10 this at all, but we have this marker of DMN and
 11 insula connectivity as a potential marker for pain,
 12 for chronic clinical pain. We identified this in
 13 different cohorts. I think Dan talked about it a
 14 bit in fibromyalgia, as well as low back pain
 15 populations.
 16 In the most recent low back pain study that
 17 we ran, which was fairly large, almost over a
 18 hundred patients, we did not find it, and I was
 19 very surprised about that. Originally, we wrote up
 20 the paper and we sent it in. The paper was
 21 rejected, and the reviewer said, "How come you're
 22 not talking about DMN and insula connectivity?"

Page 361

1 I've seen all your papers about it." So I said,
 2 "It's very strange."
 3 So we went back, and we actually looked at
 4 catastrophizing. One thing we noticed is that
 5 compared to our previous studies, the
 6 catastrophizing intensity, or the catastrophizing
 7 load [ph] on the PCS scale was significantly lower
 8 in our newer, larger study. These were healthy,
 9 fairly active low back pain patients.
 10 When we then stratified by
 11 catastrophizing -- we divided it into thirds. When
 12 we looked at the just high pain catastrophizing, we
 13 saw exactly the same result, where a DMN and insula
 14 connectivity was related to pain intensity in these
 15 subjects, but only for the high catastrophizing
 16 group.
 17 So there's this very interesting influence
 18 of negative affect and catastrophizing in these
 19 markers that are associated with pain intensity.
 20 DR. FILLINGIM: I think this brings up a
 21 broader point, and I think Annie spoke about this
 22 in her talk, our recruitment biases. Whether we're

Page 362

1 doing a neuroimaging study, or whether we're doing
 2 a clinical trial, the OPPERA study, or we're
 3 recruiting from the clinic, well, that's going to
 4 bias us towards certain conclusions about
 5 depression and maybe bias us toward certain
 6 neuroimaging findings versus community-based
 7 samples, and so on and so forth. And how we
 8 generate a representative sample we can still make
 9 sense of, I just think that's a critical issue.
 10 DR. WASAN: There were some other -- Rob?
 11 Go ahead, Dr. Dworkin.
 12 DR. DWORKIN: Vitaly, if I gave you -- and
 13 you'd be blinded -- 10 fMRIs, you could tell me how
 14 to capture them, of patients with kind of classic
 15 fibromyalgia, and 10 MRIs of patients with classic
 16 postherpetic neuralgia matched for age and sex,
 17 would you be able to sort them accurately into two
 18 piles?
 19 DR. NAPADOW: Maybe if I got really lucky.
 20 (Laughter.)
 21 DR. DWORKIN: I think that's a no.
 22 DR. NAPADOW: I think that's a no.

Page 363

1 DR. DWORKIN: So does that mean that we are
 2 nowhere near being able to use fMRI for diagnostic
 3 phenotyping purposes?
 4 DR. NAPADOW: Yes, clinical applications, we
 5 are nowhere near that. We do not have a
 6 painometer. I do not think we will ever have a
 7 painometer. Applying these kinds of technologies,
 8 I'm very much -- I'm not against sensitivity and
 9 specificity analyses, and these kinds of things,
 10 and trying to find biomarkers and all this kind of
 11 thing. But in terms of actually applying these in
 12 the clinic, I don't see us getting there.
 13 DR. WASAN: Yes, Clifford?
 14 DR. WOOLF: A couple of points for you.
 15 Sorry to be picking at -- you haven't mentioned AI
 16 machine learning analyses. I'm a bit surprised
 17 about it. It seems like that at least is one way
 18 to remove the bias from the analysis.
 19 The other one is when you're talking about
 20 amplification with the trigeminal system, how much
 21 of that is due to true increased activity or
 22 progressive [inaudible - coughing] more and more

Page 364

1 neurons as you go up the pathway towards the cortex
 2 from the trigeminal nucleus of the -- the spinal
 3 nucleus of the trigeminal?
 4 DR. NAPADOW: I'll hit the second point
 5 later. But that's why we're comparing of patients
 6 to healthy controls, unless you think that there's
 7 a vast difference in the number of neurons in
 8 healthy controls versus migraine patients or vice
 9 versa, and that's why we're seeing it.
 10 So, yes. I'm sure there is a difference in
 11 the number of neurons that we're capturing in Sp5
 12 versus in the cortex, but that would be the case
 13 for healthy controls and for patients. So the
 14 amplification ratio we're looking at is
 15 cross-comparing these two groups, so in theory we
 16 should be able to equate for that.
 17 DR. WOOLF: Machine learning.
 18 DR. NAPADOW: Machine learning.
 19 So yes, there has been AI types of analysis
 20 that have been applied and multivariate pattern
 21 analyses in these kinds of things because it's such
 22 a large -- we're talking about 40 to 80, depending

Page 365

1 on the spatial resolution, thousands of voxels that
2 we're assessing.
3 We've done some of this to try to take these
4 markers that we're finding, either with
5 connectivity or in that case actually with ASL, and
6 other markers to see if we can predict clinical
7 pain intensity. So these things have been done
8 with evoked pain. There was a Tor Wager's paper in
9 New England Journal of Medicine. That was for heat
10 pain. We just published something in Pain with
11 clinical pain, where we exacerbated patient's pain
12 similar to Ajay's model of pain exacerbation of low
13 back pain.
14 So we've applied machine learning in those
15 types of cases to try to better predict clinical
16 pain intensity. But in terms of -- so yes, there's
17 been a lot of this kind of work done; less so I
18 think in the pain field. I think pain lags
19 sometimes some of the other larger analyses, larger
20 applications in terms of like mental health and
21 other applications of fMRI. But I think it's
22 coming, and there are definitely a lot of groups

Page 366

1 that are applying these tools.
2 DR. WOOLF: We don't have a painometer, so
3 you don't think this represents a potential pain
4 biomarker then, a way of measuring presence of pain
5 or its response to analgesic interventions?
6 DR. NAPADOW: I mean, it could. I'm not
7 saying that we shouldn't try to apply these
8 methods. I'm giving you, I guess, my prediction.
9 My educated prediction is that our area under
10 curve, our sensitivity, specificities, and
11 accuracies that we're going to be able to get at
12 are probably not going to be to the case that a
13 random clinician or a family practice doc somewhere
14 is going to be able to send somebody to do an fMRI
15 and tell them -- when I'm in a cab or in an
16 elevator with an MD, and they ask me what I do, and
17 I tell them, they said, "Oh, I would love to have
18 this objective test. You've got to figure
19 something out," because, ultimately, a lot of them
20 don't trust their patients, so they want this
21 objective clinical test because there's no way that
22 Mrs. Smith is really a 10 out of 10 pain. I don't

Page 367

1 think she's showing that.
2 So that's why they want it, and I don't
3 think that's the best rationale for why we should
4 be doing this.
5 DR. COLLOCA: I would like to comment on
6 this last thing because today we saw from Daniel
7 that some patients with osteoarthritis come with
8 radiographic changes, and some not radiographic
9 changes.
10 First, we don't have, with fMRI, the
11 specificity for the single participant yet. We do
12 that analysis of a big number of participants, and
13 the larger the number, the better ability to be
14 precise with our estimation of the pain.
15 But also once we will have this sense of
16 greater, more activation, still the patient's going
17 to say, this painful stimulation doesn't bother me.
18 And that is what we observe, at least in my
19 experience, people with wonderful activation in the
20 brain, in the area that we expect, and they don't
21 feel that intensity as something that is high or
22 unpleasant to them.

Page 368

1 So we don't have to forget that pain can't
2 be reduce to a number, a numerical rating scale,
3 that drove [indiscernible], neither to a bold
4 activation, even if we will end up being able to
5 study bold responses in each single participant.
6 DR. WASAN: Yes? Go ahead, Mike.
7 DR. ROWBOTHAM: I have two questions. One
8 is about the migraine diagnoses. Are you including
9 the classic migraine with aura [indiscernible - off
10 mic]? The other is, can somebody comment about
11 primary pain, what's going into ICD-11? Because
12 it's hard to distinguish how that difference
13 [indiscernible - mic fades] -- overlapping pain
14 syndrome --
15 DR. FILLINGIM: Just really quickly, it's a
16 relatively small sample. Some of the subjects had
17 aura, some did not, but they were all interictal.
18 DR. ROWBOTHAM: Okay. I'm thinking about
19 all of the studies that were presented today
20 because [indiscernible - mic fades] a lot of them
21 included migraine along with -- sort of what they
22 call common migraine or tension migraine

Page 369

1 [indiscernible].
2 DR. FILLINGIM: In OPPERA, it would have
3 been anything that met ICHD criteria for any kind
4 of migraine.
5 DR. KLEYKAMP: And for the epi studies, most
6 often -- I don't remember exactly, but I don't
7 remember logging anything related to aura. It was
8 very general, and they didn't break down the
9 different migraine types. They did sometimes have
10 chronic tension type separate from migraine, but
11 they were generally grouped, so you couldn't be
12 very precise.
13 DR. WASAN: And the ICD-11 issue, I don't if
14 anybody --
15 DR. ROWBOTHAM: [Indiscernible - off mic].
16 (Crosstalk.)
17 DR. ROWBOTHAM: [Indiscernible - off mic].
18 There's an elephant in the room.
19 DR. DWORKIN: I was going to start off
20 tomorrow afternoon by talking about this. After
21 our lunch break, I looked at the criteria for
22 chronic primary pain, and it's interesting.

Page 370

1 There's three criteria longer than 3 months. And
2 second is associated with significant emotional
3 distress or functional disability. And the three
4 criterion is not better accounted for by another
5 condition.
6 So I don't think what we've really been
7 talking about for the last hours is this. This is
8 a waste basket category. There's nothing about
9 central sensitization, centralized pain. It's just
10 longer than 3 months, kind of functional and
11 emotional disability, and no other explanation.
12 But we can revisit this tomorrow at 1:00, but I'm
13 not sure it's a problem for us.
14 DR. WASAN: I don't know if anybody here was
15 actually on the IASP task force that advises --
16 MALE VOICE: No [indiscernible - off mic].
17 DR. WASAN: So that's why I was going to ask
18 about that.
19 On the artificial intelligence question, we
20 talk about that a lot, and it's emerging. I think
21 it's important, too, that we keep in mind that even
22 that has its own biases, too, because you can

Page 371

1 adjust all sorts of parameters and creating these
2 algorithms for how you're going to identify
3 patterns, and then the unbiased part is applying
4 and seeing if that pattern fits a new chunk of data
5 that you have. But there are all sorts of
6 processes involved in adjusting the parameters to
7 actually come up with the AI algorithm you're going
8 to apply; so just something to keep in mind, too.
9 Dan, yes?
10 DR. CLAUW: I just want to talk a little bit
11 about how functional imaging may creep into
12 clinical care in a meaningful way. I completely
13 agree with Vitaly it's not on the horizon that
14 we're going to have a painometer, that we're going
15 to be able to look in someone's brain and say
16 that's a 3, that's a 5, that's a 7. But I actually
17 think there are things, that in the not too distant
18 future we will be able to use functional imaging.
19 Regular 3T scanners can do kind connectivity
20 fairly well and do proton spectroscopy fairly well.
21 I think proton spectroscopy, we are doing a study
22 with a company now that we thought their drug would

Page 372

1 work a lot like pregabalin, and we had a whole
2 number of a priori hypotheses about the high
3 glutamate, and the insula was going to predict the
4 people who responded to the drug, and it would
5 change connectivity, and everything that we
6 hypothesized happened.
7 That was really helpful during drug
8 development for that company because they would
9 have otherwise closed down this program if not for
10 the incredibly strong, functional imaging signal
11 that we had. Those early trials were only 4-week
12 trials, and we said to them, "Please don't close
13 this down." And Irene said the same thing when she
14 was consulting, is that it really looks like the
15 drug is working, but you probably haven't given it
16 enough time to work.
17 So I think that looking in individuals,
18 looking for patterns that predict responsiveness to
19 different types of drugs, I think that will occur
20 well before we have a painometer, but I don't want
21 to in any way say that functional neuroimaging
22 won't creep into clinical practice in a meaningful

1 way because I actually think that it can, and it
2 will the next 5 to 10 years.
3 DR. WASAN: Emerging technologies, too, so
4 functional near-infrared spectroscopy, which is a
5 portable unit. You can get a little bit of the
6 cortical activation, some more on the surface
7 areas. But you can take it from room to room when
8 you're doing a clinical trial, and you can apply
9 it. And that's being developed, too, and looked
10 at.

11 DR. CLAUW: And all these technologies are
12 better at looking at an individual longitudinally
13 and looking at change in individual, but
14 cross-sectionally, they're all abysmal as far as
15 just looking at someone at a single point in and
16 say they have this diagnosis or they don't. But
17 longitudinally, I think they tell us a lot more.

18 DR. WASAN: Any other comments?

19 (No response.)

20 DR. WASAN: Okay. Any other comments or
21 questions people have? We can actually finish five
22 minutes early.

1 (No response.)

2 Adjournment

3 DR. WASAN: Okay. Great. See you all at
4 dinner. Thank you.

5 (Applause.)

6 (Whereupon, at 4:50 p.m., the meeting was
7 adjourned.)

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

[63:15;122:14;146:10; 147:15;161:11;222:9; 226:12	54:12;243:4	100:11;103:3;106:2; 116:8;122:3;127:6; 160:9,22;172:20; 173:5,7;174:16; 176:17;177:3;178:1; 182:9;186:4;187:13; 190:2;194:18;199:3, 11;206:6;220:13; 232:19;233:16; 242:14;246:3;250:15; 255:2;262:1;263:22; 265:13;277:4;279:16; 285:1;292:16;297:15; 301:19;304:4;306:4,7; 309:5;310:19;312:14; 314:19;315:6;319:22; 320:6,20;322:19; 324:1,16,22;326:10; 330:1,4,7,13;331:6; 333:16;334:16,19; 337:7,16;342:19; 345:5,10;347:12; 348:8,13;349:5,22; 350:2;352:17;354:5, 17,19;357:1,2;359:1; 360:9;361:3;363:11; 365:5;370:15;371:7, 16;373:1,21	252:11 addressing (1) 191:12 adds (1) 265:15 adequate (2) 182:19;192:3 adequately (1) 341:6 adjoined (1) 374:7 Adjournment (1) 374:2 adjust (1) 371:1 adjusting (1) 371:6 administer (1) 230:6 administered (1) 270:5 administration (5) 69:21;143:9; 169:15;170:10,18 admit (2) 26:3;44:21 admittedly (1) 163:12 adopt (1) 247:4 adopted (1) 186:1 adopting (1) 236:13 adult (1) 280:8 adulthood (1) 258:4 adults (1) 177:13 advantage (1) 191:11 advantages (2) 340:19;343:21 adverse (2) 43:11;139:18 advice (1) 188:12 advises (1) 370:15 advocates (2) 78:10;353:4 affect (9) 136:19;137:16; 138:6;143:1,6;198:3; 231:18;248:15;361:18 affected (2) 231:3;296:8 affecting (1) 331:11 afferent (2) 27:14;238:8 afferents (11)
[inaudible (1) 363:22 [indiscernible (9) 67:1;206:21;348:8; 368:9,13,20;369:15, 17;370:16 [indiscernible] (16) 43:3;60:9;83:16; 207:15;209:14,17,20; 219:19;220:2;241:3; 252:18;331:2;347:13; 348:12;368:3;369:1 [ph] (2) 60:19;361:7	abstract (1) 268:15 abysmal (2) 259:13;373:14 ACC (2) 314:4;336:17 accept (2) 62:9;160:16 acceptable (3) 188:14,15;343:8 access (3) 7:7;15:21;183:8 accidents (1) 123:2 accompanied (1) 304:6 according (1) 138:20 account (3) 198:6,18;256:18 accounted (4) 74:22;81:4;142:12; 370:4 accumulated (1) 32:16 accuracies (1) 366:11 accurate (1) 226:11 accurately (2) 74:6;362:17 achieve (2) 62:20;187:9 acknowledge (5) 15:14;78:13;82:21; 306:1;353:8 acknowledgement (1) 15:16 acquire (1) 332:5 acquired (1) 127:11 ACR (1) 267:7 acronyms (1) 267:8 across (18) 90:16;92:18; 100:20;172:2;174:3; 181:17;223:18; 238:10;269:10; 274:15,19;275:17; 288:6;295:8;297:5; 333:4,21;350:1 act (2) 73:3;220:16 acting (3) 100:18;171:2,3 action (5) 51:13,17;53:19;	activate (6) 33:16;51:7,11,13; 52:5;155:7 activated (17) 6:7;23:14;31:7; 38:14;40:9,11;41:13; 55:21;152:18;231:7; 310:12,12;314:5,20; 325:3;327:6,7 activates (2) 324:18,19 activating (1) 42:5 activation (41) 24:2;32:8;41:18; 42:4,17;66:8;152:21; 153:4,15,20;154:1,13, 18,21;155:1,6;207:20; 219:21;241:18;248:4; 311:2;313:20;314:22; 315:1;316:8,14;317:7, 8;318:17;321:5;333:7, 10,21;334:2,4;338:1, 11;367:16,19;368:4; 373:6 activations (2) 154:4;312:21 active (6) 23:21;94:14,16; 156:10;173:17;361:9 actively (2) 208:18;241:10 activity (26) 30:1;32:3,7;55:16; 67:19,22;68:7,10,16; 69:17;70:1,6;96:12; 111:17;164:17;211:5, 19;220:22;309:12; 310:6,7;313:3;332:9; 347:5;349:15;363:21 activity-dependent (2) 43:1;96:6 ACTION (14) 4:9;7:7;8:5;15:17; 16:18;186:6,7;262:11, 20;264:2,5;282:17; 284:1;292:5 A-C-T-T-I-O-N (1) 7:7 A-C-T-T-I-O-Norg (1) 15:18 ACTION's (1) 346:19 actual (7) 31:17;47:6;227:8; 249:8;345:14;347:12; 350:8 actually (103) 6:17;19:2;28:17; 30:12;46:11;51:3; 66:19;68:15;70:3; 73:5;97:3;98:14;99:6;	100:11;103:3;106:2; 116:8;122:3;127:6; 160:9,22;172:20; 173:5,7;174:16; 176:17;177:3;178:1; 182:9;186:4;187:13; 190:2;194:18;199:3, 11;206:6;220:13; 232:19;233:16; 242:14;246:3;250:15; 255:2;262:1;263:22; 265:13;277:4;279:16; 285:1;292:16;297:15; 301:19;304:4;306:4,7; 309:5;310:19;312:14; 314:19;315:6;319:22; 320:6,20;322:19; 324:1,16,22;326:10; 330:1,4,7,13;331:6; 333:16;334:16,19; 337:7,16;342:19; 345:5,10;347:12; 348:8,13;349:5,22; 350:2;352:17;354:5, 17,19;357:1,2;359:1; 360:9;361:3;363:11; 365:5;370:15;371:7, 16;373:1,21 acupuncturist (1) 307:4 acute (23) 43:1;54:20;64:10; 69:14,16;87:6;122:7, 11;145:21;146:7,13, 16,20;147:7;148:12; 170:21;173:10; 205:22;229:20;260:6; 270:14,17,21 adaptation (1) 238:15 adaptive (6) 206:7,18,22;209:7, 11,16 ADC (1) 27:19 add (6) 25:9;80:11;194:20; 236:17;269:12;354:5 added (1) 282:22 Addiction (2) 168:20;263:3 addition (8) 47:1;53:18;56:19; 108:3;132:21;142:5; 177:19;190:17 additional (6) 13:6;139:19; 170:17;203:6;226:3; 343:13 address (2) 203:15;357:13 addressed (1)	
A abdomen (1) 95:6 abdominal (1) 110:10 abhor (1) 56:15 ability (6) 11:14;147:15; 259:12;345:1;357:2; 367:13 able (43) 6:19;10:13;11:7; 12:8;22:12;51:7;57:2, 14;59:12;97:2;132:2; 136:21;144:5;145:2; 153:8;159:1;181:1; 200:12;227:15; 235:13;236:12,20; 243:19;251:9,11; 254:4;287:4;322:7; 326:17;332:4;338:9; 343:2;347:18,19; 349:16;362:17;363:2; 364:16;366:11,14; 368:4;371:15,18 abnormal (3) 66:16;351:13;356:2 abnormalities (1) 102:8 abnormality (3) 102:15;217:18; 351:8 above (4) 224:17;256:17; 265:3;352:4 absence (2) 65:19;210:2 absent (1) 134:20 absolute (2) 201:6;344:18 absolutely (11) 28:10;38:1;57:9,11;				

37:19;38:2,14,14; 40:10;50:16;51:14,18; 52:11,12;221:14 affirmatively (1) 16:10 Afghanistan (1) 123:11 afloat (1) 92:4 afternoon (5) 10:5;13:5;24:19; 149:21;369:20 afterwards (1) 250:19 again (72) 16:1;28:19;29:18; 38:2;46:10;49:6; 50:13,20;52:18;61:9; 65:22;66:3;68:13; 77:18;79:19;89:10; 92:17;101:15;102:2; 108:2;111:14,20; 112:8,20;114:19; 115:19;117:18;118:2; 119:16;120:18,21; 121:2;147:5;149:4; 176:8,13;177:9,15; 206:10;207:3;210:16; 211:21;213:13;219:5, 11;222:6;223:9; 225:4;230:4;250:4; 252:7,11;253:2;258:1, 9;264:13,14;275:2,17; 276:3;278:7,15;279:4; 289:10;290:8;293:13; 296:11;297:1;299:11, 18;300:15;352:10 against (3) 98:4;206:9;363:8 age (6) 110:8;122:11; 255:22;272:2,2; 362:16 agencies (1) 306:2 agency (4) 169:14;171:8; 172:6;182:3 agenda (1) 10:1 agents (1) 194:4 aggravate (1) 229:19 aggressively (1) 110:20 agnostic (4) 158:15;224:16; 291:7;294:4 ago (5) 78:9;79:15;80:6; 99:13;180:22 agree (13)	21:1;83:5;96:20; 107:16;161:3;167:6; 168:9,14;204:10; 220:11;223:13; 344:16;371:13 agreed (1) 79:16 agreeing (2) 14:16;109:5 agreement (5) 12:19,21,22;14:19; 20:21 ahead (5) 8:13;285:11;342:5; 362:11;368:6 AI (3) 363:15;364:19; 371:7 aimed (1) 95:11 air (2) 332:14,18 Ajay (9) 107:4,5;138:2; 142:19;158:6;261:11, 12,15;285:13 Ajay's (2) 112:8;365:12 akin (2) 80:9;121:20 al (1) 71:11 Albeit (1) 230:20 ALE (2) 313:3,4 algorithm (2) 313:3;371:7 algorithms (2) 350:16;371:2 aligned (1) 37:9 alive (1) 325:7 Alliance (3) 197:10;286:2; 339:15 Allison (1) 26:13 allodynia (16) 49:13;50:12;53:1; 61:16;66:10;76:17; 77:17;118:6;179:7; 230:21,22;231:14,15; 241:20;257:6;308:14 allodynic (2) 229:12;230:14 allow (4) 9:12;243:6;254:13; 266:16 allows (1) 354:18 alluded (2)	78:8;212:20 alluding (1) 75:18 almost (31) 30:5,17;72:4;73:1; 77:22;83:1;85:1;90:2, 4;93:8;98:6;101:8; 103:8;104:18;120:22; 132:13;138:17;167:2, 6;181:5,9;206:11; 207:10;208:17; 241:17;256:2;283:6; 284:22;289:13; 355:13;360:17 alone (2) 287:14,18 along (4) 84:13;175:7; 262:12;368:21 alter (2) 149:11,13 alterations (4) 50:22;161:17,18; 303:22 altered (3) 48:21;295:4;336:10 alternating (1) 319:12 alternative (1) 28:15 although (18) 12:8;28:6;32:20; 43:13;49:21;133:17; 157:10;161:7;239:10; 245:1;246:14;252:7; 256:8;265:8;271:1; 292:9;294:14;305:5 always (29) 7:2;8:10;9:17; 11:18;12:4;33:17; 52:9;73:15;74:8; 77:22;97:15;112:17; 113:13;114:12; 127:11;166:16; 170:22;207:6;220:21; 221:20;227:14; 269:12;273:11; 291:17;296:4;325:7; 333:12;350:3,14 ambitious (1) 267:3 amenable (1) 323:12 amitriptyline (1) 139:10 among (5) 148:15;150:4; 203:7;265:20;358:14 amongst (2) 48:8;98:7 amount (24) 46:3;80:8;133:22; 134:1;148:20;151:16;	167:12;212:22;213:5; 294:1;310:6,7;317:14; 318:5,10,17;319:2; 320:1,3;328:18; 333:20;334:1,4;338:1 amounts (1) 90:4 amplification (61) 48:15,22;49:8; 52:21;59:7,9,17,20; 61:11,17;65:7;66:13; 82:10;85:15;125:1,16, 20,22;126:6,22;127:9, 20;129:1;131:1; 140:2;148:10;152:8; 154:7;155:13;156:18; 157:9,22;210:3;238:5; 240:16;288:14; 304:19;305:3,6; 308:18;331:19;334:1, 8;335:22;336:21; 348:4,11;349:3;351:4; 352:4,13,20;355:19; 356:1,7;357:6,9,9,15; 363:20;364:14 amplified (2) 37:6;68:22 amplify (2) 336:2,2 amplifying (3) 62:6;72:17;107:19 amygdala (1) 349:9 analgesia (2) 45:10;135:8 analgesic (16) 46:4,14;54:10; 135:7;139:9;170:10, 15;171:8;174:3; 199:21;208:13;252:3, 20;253:1;275:10; 366:5 analgesics (10) 53:17;54:2;168:20; 194:19;199:16; 225:20;243:10; 251:22;252:16;253:16 analog (4) 112:6;235:19; 333:18;334:4 analogy (2) 80:5,7 analyses (14) 56:7;129:9,12; 324:22;326:22;339:6; 344:7,8;350:4,18; 363:9,16;364:21; 365:19 analysis (17) 34:9;142:12;150:3; 158:15,21;159:1; 184:21;267:20;287:1; 324:21;340:12;	349:13,19;354:10; 363:18;364:19;367:12 analytic (1) 9:7 analyze (3) 157:14;186:20; 187:11 analyzing (3) 184:2;208:2;334:14 anatomy (1) 20:3 and/or (1) 75:10 Andrew (1) 214:15 anecdotal (1) 263:9 anecdotes (1) 25:6 Anesthesia (1) 168:20 anesthesiologist (1) 45:4 anesthesiology (3) 71:4;124:4;339:17 anesthetic (7) 30:16;31:3;35:20; 221:22;222:2,4;234:1 anesthetics (1) 121:19 anesthetized (3) 30:18,19;45:16 animal (15) 51:20,20;72:14; 152:20;210:8,8;211:7; 235:19;253:15;257:1, 6,8;308:12;323:1; 347:16 animals (6) 31:2;36:22;60:17; 67:4;208:13;210:20 ankle (1) 121:17 ankylosing (1) 75:19 Anne (2) 26:13;41:3 Annie (4) 262:16,18;285:22; 361:21 anonymize (1) 196:11 antagonists (3) 43:5,8;53:18 Antareesey (1) 60:19 anterior (19) 150:18;151:17; 153:17;154:14;165:5; 314:2,4;315:2,3; 318:21;319:20;320:2; 325:19,20;328:6,7; 329:5,9;336:14
--	--	---	---	--

<p>antibody (1) 97:2</p> <p>anti-CGRP (1) 54:11</p> <p>anticipated (1) 69:5</p> <p>anticipating (1) 45:22</p> <p>anticipation (1) 106:1</p> <p>antidepressant (2) 251:8;253:1</p> <p>antidepressants (1) 251:22</p> <p>anti-inflammatory (1) 215:10</p> <p>anti-NGF (1) 54:10</p> <p>antinociceptive (1) 135:17</p> <p>anxiety (28) 72:11,16;74:18; 75:1;86:22;88:4; 128:7;138:6;142:6,13; 143:2,7;146:2,7; 155:5;157:16;267:11; 277:1,6,8,13,16,17,20; 278:10,12;279:11; 283:14</p> <p>anxious (2) 164:7;252:9</p> <p>anymore (1) 73:4</p> <p>apart (5) 58:13,17;164:6; 266:17;267:21</p> <p>aplysia (3) 43:22;44:3,22</p> <p>apologize (2) 180:1;221:10</p> <p>apologized (1) 192:19</p> <p>app (1) 354:18</p> <p>apparently (1) 255:5</p> <p>appearance (1) 28:9</p> <p>appears (2) 125:3;278:6</p> <p>Applause (12) 58:3;101:22; 123:19;158:9;168:17; 180:17;201:22;261:5; 284:12;306:3;339:9; 374:5</p> <p>application (3) 195:12;237:1; 245:22</p> <p>applications (5) 198:7;307:18; 363:4;365:20,21</p> <p>applied (9)</p>	<p>125:13;151:4; 158:14;232:20; 300:12;345:4;351:16; 364:20;365:14</p> <p>applies (1) 340:4</p> <p>apply (13) 151:2,10,18;152:3; 156:2;166:13;179:19; 245:13,19;359:4; 366:7;371:8;373:8</p> <p>applying (5) 94:20;363:7,11; 366:1;371:3</p> <p>appreciate (3) 43:18;58:1,5</p> <p>appreciated (3) 27:18;42:4;312:1</p> <p>appreciation (1) 37:10</p> <p>approach (14) 28:15,16,17;69:11; 171:12;174:1;181:2; 182:10,20;184:4; 186:1;196:10;337:2; 340:22</p> <p>approached (1) 181:16</p> <p>approaches (5) 9:7;170:17;171:19; 340:19;341:11</p> <p>approaching (1) 25:18</p> <p>appropriate (4) 19:21;149:5; 172:22;190:1</p> <p>appropriately (1) 185:20</p> <p>approval (1) 248:13</p> <p>approvals (1) 198:7</p> <p>approved (3) 91:7;94:7;184:9</p> <p>April (1) 267:4</p> <p>area (30) 13:13;42:11; 101:13;121:22; 144:20;150:20; 157:11;173:9;229:14; 230:14;231:1,2; 232:15,17,19;233:20; 297:2;301:7;310:11; 312:12;314:9;315:11; 327:13,14,16,18; 328:1;350:12;366:9; 367:20</p> <p>areas (29) 41:19;47:15;49:10; 50:3;154:19;213:3; 313:20;314:7;325:21; 326:5;327:6,7;329:10,</p>	<p>11;331:7,9,12;336:14; 337:5,11;338:2; 345:10;348:3,6; 352:18;359:19;360:1, 5;373:7</p> <p>arguably (1) 89:6</p> <p>argue (9) 139:20;246:6,7,15; 247:17,18;347:14,19; 354:14</p> <p>argued (1) 40:2</p> <p>argues (1) 160:18</p> <p>arguing (2) 211:2;343:17</p> <p>argument (2) 66:4;281:14</p> <p>arguments (1) 345:12</p> <p>arising (1) 282:12</p> <p>arm (8) 144:10;237:1,15; 245:14;246:9;296:10; 345:5;359:5</p> <p>arms (1) 353:16</p> <p>Arnold (5) 117:2,2;118:9; 190:12,12</p> <p>around (17) 5:21;14:5;21:7; 142:8;160:8;171:14; 198:22;202:2;233:13; 236:3;274:22;291:10; 308:3;310:21;315:21; 330:17;333:8</p> <p>arranged (1) 13:5</p> <p>array (1) 156:1</p> <p>arrived (1) 268:16</p> <p>art (1) 170:8</p> <p>arterial (2) 346:5,8</p> <p>arteries (1) 350:11</p> <p>arthritic (1) 257:18</p> <p>arthritides (1) 176:15</p> <p>arthritis (24) 73:7;75:16;80:2; 83:12,15;93:9;94:13; 96:9;104:2;106:4; 116:2,6;120:6,13; 206:21;207:11; 212:21;213:1,4,12; 217:6,22;256:9;</p>	<p>265:11</p> <p>arthroplasty (16) 54:19;64:19;75:8, 14;84:19;85:4;86:16; 88:11;89:16;104:4,16; 167:10;168:8;250:5; 304:1,2</p> <p>Arthur (1) 125:18</p> <p>article (4) 44:4;99:5;127:9; 268:14</p> <p>articles (2) 125:6;268:11</p> <p>articulate (1) 16:20</p> <p>artificial (2) 56:6;370:19</p> <p>artificially (3) 117:16;220:12; 253:19</p> <p>aside (1) 183:11</p> <p>asker (1) 168:14</p> <p>ASL (18) 342:21;343:3,4,9, 17,20,20,22;344:2,3,3, 4,10,11,17;346:4,11; 365:5</p> <p>asleep (1) 253:14</p> <p>aspect (4) 46:16;176:9;179:5; 201:3</p> <p>aspects (12) 41:17;127:19; 140:4;150:5;169:13; 183:11;191:19; 239:10;309:7;338:17; 339:1;359:3</p> <p>As-Sanie (1) 89:22</p> <p>assay (5) 182:14;186:9; 225:5,7;234:7</p> <p>assaying (1) 323:8</p> <p>assays (2) 234:22;241:3</p> <p>assemblies (1) 325:2</p> <p>assess (9) 239:8;309:1;323:6, 16;329:16;332:9; 334:20;339:1;357:22</p> <p>assessed (6) 161:15;269:22; 276:21;309:15,17; 338:19</p> <p>assessing (4) 133:10;234:21; 294:20;365:2</p>	<p>Assessment (11) 17:14;166:11; 228:11;267:17;292:7; 297:7;328:16;344:16; 352:2;355:11,15</p> <p>assessments (1) 276:13</p> <p>assign (1) 135:14</p> <p>assistant (2) 26:15;339:16</p> <p>associate (3) 124:4;262:10;307:4</p> <p>associated (21) 47:5;63:5;64:19; 102:14;178:12; 217:14;245:22; 258:17;289:5;290:17; 291:3,4;299:4,6; 303:15;304:20; 305:12,19;308:15; 361:19;370:2</p> <p>association (7) 146:16;290:12; 291:14,20;292:3; 340:3,14</p> <p>associations (6) 290:21;291:8; 299:9;300:16;301:11; 303:20</p> <p>assume (1) 6:9</p> <p>assuming (3) 165:14;189:9; 234:11</p> <p>assumption (3) 162:22;226:14; 349:22</p> <p>assumptions (1) 349:18</p> <p>at-risk (1) 189:21</p> <p>attempt (2) 252:19,22</p> <p>attended (1) 15:14</p> <p>attending (1) 96:1</p> <p>attention (6) 15:7;24:1;50:21; 151:22;167:19;339:3</p> <p>attorneys (2) 22:19;23:2</p> <p>attractive (2) 4:11;124:16</p> <p>audience (3) 46:20;203:3;342:1</p> <p>audio (1) 5:19</p> <p>audioed (1) 21:22</p> <p>audiotape (1) 22:15</p>
--	--	---	--	--

audiotaped (2) 5:18;23:8	64:8;65:22;78:4,15; 83:13;90:10;91:9,11, 15,17;104:18;114:3,8; 117:3,18;123:9;	57:15;58:21;88:14; 105:3;148:19;157:5; 175:16;177:11; 196:14;209:4;226:6; 258:13;293:14;294:6; 295:22,22;301:4; 302:22;304:15;351:17	bedside (3) 226:5;254:10,14	6,7,10,11,13,13,22; 251:3,13;252:6,15; 256:19;262:5;266:17; 307:19;330:11;339:1; 344:8,9;347:17; 355:10,14;365:15; 367:13;370:4;373:12
auditory (1) 105:15	126:16;138:16;139:1; 140:17;141:18; 142:21;143:14; 147:18;149:20;154:9, 19;159:9;171:14; 176:12;178:3;181:6; 187:19;191:16; 199:19;200:1,11,13, 20;202:2;208:15; 209:15;218:12; 226:17;229:9;230:4; 239:4;241:5;242:22; 252:15;255:16; 259:20;265:18;274:5, 18;287:11;290:3,19; 293:19,21,22;299:1; 301:18;309:4;319:21; 321:7;322:6;333:2; 342:5;344:15;353:17; 356:3;359:4;360:14, 16;361:3,9;365:13	218:20,21;301:16; 303:9	began (7) 26:9;37:11,13; 43:18;45:3;46:21; 72:8	251:3,13;252:6,15; 256:19;262:5;266:17; 307:19;330:11;339:1; 344:8,9;347:17; 355:10,14;365:15; 367:13;370:4;373:12
augmenting (2) 72:17;81:6	259:20;265:18;274:5, 18;287:11;290:3,19; 293:19,21,22;299:1; 301:18;309:4;319:21; 321:7;322:6;333:2; 342:5;344:15;353:17; 356:3;359:4;360:14, 16;361:3,9;365:13	baseline (9) 104:22;130:10; 138:20;143:4;215:22; 218:20,21;301:16; 303:9	begin (11) 27:10;31:16;40:18; 41:13;50:6;56:18; 57:3;58:1;66:12; 115:10;125:19	beyond (10) 35:10;47:9;67:14; 190:15;193:21;194:8; 224:17;226:3;256:17; 358:5
aura (3) 368:9,17;369:7	277:1;326:2	basic (4) 80:6;208:16;235:8; 236:19	beginning (4) 10:5;33:13;54:6; 328:19	bias (9) 226:15;268:6; 271:20;275:14; 281:20;282:12;362:4, 5;363:18
author (4) 14:2;15:16;34:13; 171:22	background (5) 8:17,19;263:2; 278:1;326:2	basically (19) 14:17;60:20;78:18; 230:2;243:1;261:13; 280:5;310:5,14; 312:19;313:6,16; 315:5,10,20;319:17; 335:8;338:3;345:16	behaves (2) 63:10;81:16	biases (2) 361:22;370:22
authors (1) 11:21	backpack (1) 242:21	basing (1) 184:20	behavior (4) 51:19;52:13;56:9; 196:16	bidirectional (7) 81:12;141:9; 149:10;164:1;250:14; 357:5,11
autoimmune (5) 111:3;214:14; 215:11;216:13,18	bad (8) 84:18;98:9;99:8; 101:5;177:6;257:13; 280:17;353:11	basis (9) 76:13;77:20;82:20; 111:18;113:19;127:5, 5,10;247:6	behavioral (1) 56:10	big (16) 21:9;41:1;65:2; 108:16;110:6;176:22; 178:10;208:3;210:1; 215:20;253:7;260:5; 348:7;353:20;357:7; 367:12
autoimmunity (1) 217:16	baggage (1) 175:6	basket (1) 370:8	behaviors (1) 211:6	bigger (9) 35:19;38:9;59:16, 16;115:3;229:15,15, 15;352:21
autonomic (2) 18:4;148:4	bags (2) 330:16,17	battery (4) 157:17;180:6; 260:19;298:3	Behind (2) 7:12;350:17	biggest (4) 38:9;47:15;108:20; 114:2
autonomous (2) 66:11;220:20	bait (1) 343:16	batting (1) 168:19	belief (1) 111:22	bilateral (2) 33:5;304:5
availability (1) 166:3	balance (3) 43:12;295:5;298:4	battle (1) 32:1	below (3) 294:10,17;324:13	Bill (1) 81:19
available (11) 13:6,14;23:1;50:2; 54:2;55:13;101:20; 174:10;199:10;244:8; 288:1	ball (1) 339:22	Bayesian (2) 340:12;341:3	beneficial (2) 45:12;159:8	binding (2) 98:16;309:16
average (7) 92:19;93:4;255:22; 256:18;293:7;324:12, 13	bane (3) 78:20,22;79:1	BDI (2) 154:12,20	benefit (11) 89:19;107:2;139:9; 175:2;193:21;194:7; 195:4;200:19;252:20; 253:1,2	binds (1) 98:17
averaging (3) 335:2,2,3	bar (4) 274:1,5;289:19; 293:6	beard (2) 4:10,14	benefits (3) 46:9;189:22;197:6	biochemical (1) 307:3
aversive (2) 332:14,20	barely (1) 232:8	bears (1) 178:17	benign (1) 102:20	Biogen (2) 60:4;234:22
avert (1) 31:12	barriers (2) 183:10;323:19	beast (2) 255:7;283:6	besides (1) 356:8	biologic (1) 104:3
avoid (1) 184:20	bars (8) 273:20;274:15; 276:16;278:11,20; 289:17;295:8,9	beat (1) 254:2	best (15) 9:11,12;133:9; 148:12,15;159:10; 220:15;223:15;224:3; 266:8;281:6;354:11; 355:19;358:3;367:3	biological (2) 82:15,20
avoiding (2) 172:15;242:1	Barsky (1) 125:18	beautiful (1) 30:4	bet (2) 149:9;158:2	biologics (3) 75:20;215:4;250:5
aware (2) 159:14;221:11	basal (5) 310:5,6,7,8,10	became (1) 41:8	Bethesda (1) 264:4	biology (3) 82:13;109:3;240:7
awareness (1) 130:11	based (24) 10:15;29:1;56:7,21;	becomes (9) 19:7;23:21;110:13; 174:9;193:20;206:15; 209:8;234:22;310:11	better (59) 25:21;30:5;75:9; 87:9;91:11,15;93:1,4; 97:4;106:21;114:6; 116:11,11;118:6; 149:20;158:19,21; 164:5;180:14;191:13; 197:1;201:17;217:5; 223:4;229:22;235:9; 238:5;240:2;243:11; 244:6;249:1;250:2,4,	biomarker (1) 366:4
away (12) 6:3;24:7;72:20; 104:11;121:20;122:2; 200:6;215:3;217:9; 246:5;249:1;256:11		beds (1) 310:8	biopsies (1) 211:16	biomarkers (1) 363:10
awhile (1) 354:10				
axis (1) 133:6				
B				
back (89) 6:22;11:18;15:4,8; 19:5;26:5,14;39:1; 54:13;55:12;60:11;				

biopsy (1) 216:13	board (1) 321:18	306:4;314:2;318:1,3; 322:4;328:7;331:17, 21;333:5;348:16; 350:21,22;351:1	332:7;333:6,8; 334:11	240:12,14;352:2
biopsychosocial (7) 72:7;137:13,20; 138:2;139:22;147:17; 148:19	boatload (1) 195:16	bother (2) 232:6;367:17	break (15) 121:11;123:21; 197:8;202:1;272:4; 284:19;292:17;300:9; 306:6,8,10,14;355:17; 369:8,21	Brummett (1) 86:14
biostatisticians (1) 340:9	Bob (18) 4:12;8:2;16:8,19; 17:1,2,3;21:5;23:5,12; 25:10;41:22;43:2; 144:19;169:20; 171:21;245:3;348:8	bothered (1) 58:7	breaks (1) 10:11	bucket (2) 113:16;305:6
bit (54) 6:11;13:11;68:11; 71:14,15;93:4;96:21; 100:17;109:6;110:11; 125:2;128:16;130:3, 12;131:6;145:11; 149:6;151:12;152:17; 157:11;161:5;166:2; 169:5,11;170:22; 198:11;224:16;236:8, 10;238:5;247:10,11; 256:15;263:8;271:17; 284:17;285:15;286:3, 5;290:8;313:13; 319:22;324:4;328:10; 344:15;346:11; 350:11,12,18;355:17; 360:14;363:16; 371:10;373:5	bodies (1) 63:21	bothersome (2) 358:15;359:3	buckets (2) 267:11;272:15	
bits (1) 51:5	bodily (3) 130:11,21;358:1	bothersomeness (1) 359:8	breakthrough (1) 29:13	build (1) 232:13
black (5) 4:10;29:14,16; 236:11;273:22	body (25) 91:5,13,22;101:13; 117:19;181:4,13; 193:3;206:8,10; 223:14;224:14,17,21; 225:10;228:9;293:3, 15;295:8;327:16; 352:16;353:13,19; 354:17;356:8	bottom (8) 90:13;103:16; 137:3;268:22;276:16; 278:12;290:22;300:8	breaths (1) 156:14	buildup (1) 306:21
bladder (3) 95:4,10,12	BOLD (14) 310:3;342:21; 343:3,22;344:1,7,8,10, 12;345:19;346:9; 348:13;368:3,5	bottom-up (5) 96:18;105:3,9; 120:14;235:15	brief (9) 37:4;42:9;58:13; 116:18;228:5,10; 246:1;274:8;309:3	bullets (1) 270:8
blaming (1) 74:17	bolded (2) 273:22;287:6	bouts (1) 233:15	briefly (3) 86:13;147:18; 152:17	bunch (12) 81:9;107:1;153:16; 166:5;184:18;186:15; 188:17;208:9;268:16; 286:13;330:16;346:11
blanket (1) 214:7	bombarded (1) 68:19	bowel (16) 65:6;78:8,14,18,21; 110:10;122:16,17,18; 123:1;142:1;257:13; 274:17,20;275:6; 287:11	brigham (6) 69:7;124:3;144:19; 158:5;183:19;339:8	unionectomy (1) 122:6
bleeding (1) 177:1	bone (8) 73:19,19;80:19,19; 84:18,18;93:9,9	box (3) 29:14,16;236:11	brightness (2) 77:3;311:13	burden (3) 15:6;289:3;292:2
blinded (1) 362:13	boom (1) 178:4	boy (1) 241:13	bring (5) 8:10;215:16; 265:18;286:3;301:18	burn (1) 326:12
block (4) 237:14;311:16; 323:21;324:6	bootleg (1) 70:17	brain (83) 27:15;50:17;69:17; 93:22;94:10,13;97:14; 101:7;105:17;115:12; 116:1;118:19;120:18; 131:17;149:16;150:4; 153:16;154:14;158:2; 160:12,21;164:11,18; 166:9;168:4;211:6; 236:9;243:21;248:5; 262:11;303:15,22; 304:3,12;307:11; 309:7,9;310:6,11; 311:3,11,14,22;312:2; 313:20;317:16; 318:13;319:4,19; 322:17,21;323:22; 324:1,17,18;325:5,6, 21;326:5,6;331:4,12, 17,21;333:4,6;334:20; 335:5;336:9,21;337:8; 338:15,20;343:13; 344:21;345:10,20; 348:3,7;350:1;359:19; 367:20;371:15	bring (5) 18:12;25:11; 205:20;263:5	burning (1) 237:17
blocker (1) 330:10	borne (1) 207:18	bro (1) 311:3,11,14,22;312:2; 313:20;317:16; 318:13;319:4,19; 322:17,21;323:22; 324:1,17,18;325:5,6, 21;326:5,6;331:4,12, 17,21;333:4,6;334:20; 335:5;336:9,21;337:8; 338:15,20;343:13; 344:21;345:10,20; 348:3,7;350:1;359:19; 367:20;371:15	brings (2) 310:17;361:20	bursting (1) 68:6
blocks (4) 222:2;334:14,19,21	born (1) 120:9	broader (4) 76:14;77:15; 114:22;361:21	bring (5) 8:10;215:16; 265:18;286:3;301:18	
blood (19) 214:18;215:19; 216:3,4;233:4;237:15; 243:19;309:20;310:4, 7,13,16;344:18,21; 345:9,13,13,15;347:4	borrowed (2) 39:16;186:4	broadly (6) 59:6;61:10;77:19; 101:16;223:5;238:16	bringing (4) 18:12;25:11; 205:20;263:5	cab (1) 366:15
blow-up (1) 345:5	Boston (4) 62:15;102:2;119:2; 302:18	broke (3) 279:22;295:19,20	brings (2) 310:17;361:20	calculated (3) 316:15;333:22; 335:5
blue (6) 276:16;278:20; 293:6;295:8;312:9; 324:12	both (46) 5:18;20:13,14; 42:21;53:21;56:8,22; 68:4;72:14;79:21; 96:5;119:8;126:3; 129:16;133:20; 134:11;136:15; 153:14;155:17; 158:22;159:18,18; 160:8;175:2;210:20; 213:10;239:10; 248:19;251:22;262:4; 297:4;304:11;305:15;	brain-based (1) 337:2	broader (4) 76:14;77:15; 114:22;361:21	calculating (1) 311:20
blunt (1) 188:22	both (46) 5:18;20:13,14; 42:21;53:21;56:8,22; 68:4;72:14;79:21; 96:5;119:8;126:3; 129:16;133:20; 134:11;136:15; 153:14;155:17; 158:22;159:18,18; 160:8;175:2;210:20; 213:10;239:10; 248:19;251:22;262:4; 297:4;304:11;305:15;	brains (1) 50:21	broader (4) 76:14;77:15; 114:22;361:21	call (13) 5:12,13;77:13; 96:17;101:10;115:2; 148:15;226:20;228:7; 232:9;235:14;295:3; 368:22
		brain's (1) 114:16	broader (4) 76:14;77:15; 114:22;361:21	called (17) 5:10;27:19;82:9; 99:4;113:11;115:8; 197:12;218:7;302:4; 309:22;310:3;311:5, 16;313:3,4;315:21; 326:3
		brainstem (4)	broader (4) 76:14;77:15; 114:22;361:21	calling (4) 23:18;94:1;216:8; 229:12
			broader (4) 76:14;77:15; 114:22;361:21	calls (1) 8:6
			broader (4) 76:14;77:15; 114:22;361:21	calmly (1) 233:3
			broader (4) 76:14;77:15; 114:22;361:21	came (7) 11:19;33:10;45:6; 78:11;230:4;271:16; 288:12
			broader (4) 76:14;77:15; 114:22;361:21	campylobacter (1)

C

<p>122:20 can (252) 5:4,4,22;7:18;9:18; 12:2;13:1,6,21;14:1,6, 20;15:10,21;16:4,13; 20:3;28:7;35:17; 40:18,21;47:17;51:10, 12;52:6,20;53:6;55:1, 18,21;56:4,5,6;59:8; 61:13;66:12;67:15; 68:22;69:8,15;74:5,9, 22;75:22;79:6;80:15; 81:1,4,19;85:18; 87:10;90:13;93:20; 94:22;100:8;101:9; 103:20;105:2;106:18; 109:14,20;110:2; 113:18,20;114:13,21; 115:10;118:15; 121:14,17;123:13; 124:15;126:7;127:16, 21;128:14;130:15,18; 131:19;133:7;134:4; 135:13;136:11; 138:15;139:12; 140:10;141:13;143:5, 13;146:14;147:1,14; 148:8;149:11,13; 154:10;155:3,10,19; 156:4,4,5,6,7,8,8; 157:18,20;158:20; 159:4;164:4,20;165:3, 13;168:3;179:16,17, 19;180:10,14;182:14, 15;183:17;188:19; 189:9,20;190:10; 191:10,20;192:6,7,12; 193:8;195:16;196:7,9; 197:5;201:5,5,203:21, 22;207:15;210:20; 212:5,17;213:12; 215:16;218:18; 220:15;221:4,14; 222:11;224:15; 231:12,20;233:20,21, 21;234:3;236:17; 241:22;243:14,22; 244:3,22;250:5; 251:10;255:14;261:9; 262:5;264:1,22;266:6, 13,14,16,22;269:11; 270:19;271:18; 273:22;279:8,17; 287:21;288:4,7,19; 290:2;292:12;293:5; 308:11,12;309:6,12, 14,16,20;310:5; 311:12;312:1,18,22; 313:2,8;315:5,8; 320:16,19;321:4,8; 324:14,22;326:4,10, 13,14,14,19;328:8,16; 332:4,5,6,9;334:19;</p>	<p>335:3;338:19;341:7; 342:14;344:7,12; 348:13;353:7;354:14, 20,21;355:1,13,14; 357:20;358:6;362:8; 365:6;368:10;370:12, 22;371:19;373:1,5,7, 8,21 Canada (1) 143:20 cancer (2) 54:21;79:8 cannabinoid (1) 100:12 cannabinoids (1) 100:10 canonical (1) 325:9 capabilities (1) 191:11 capable (1) 72:16 capacity (2) 161:4;166:18 capillary (1) 310:8 capsaicin (28) 42:3;43:3;61:13; 121:21;122:1;229:10, 17,18,22;230:15,19; 231:2,5,18;232:22; 233:14,21;234:8; 236:22;245:13,14,22; 246:9;259:1;314:14, 21,22;316:1 capsaicin-induced (2) 315:13,19 capture (5) 48:14;53:7;57:15; 241:16;362:14 captured (4) 39:3;41:2,9;228:16 captures (2) 41:16;346:7 capturing (2) 53:11;364:11 cardiac (1) 243:21 care (9) 9:19;16:22;17:1; 23:1;45:15;116:13; 148:6;276:9;371:12 career (3) 38:10;44:11;114:2 careful (4) 6:11;86:3;109:6; 347:10 carefully (3) 129:6;254:5;346:13 carfentanil (1) 99:1 Carolina (1) 31:22</p>	<p>carpal (4) 104:4,5;321:12,16 carry (1) 86:1 CART (1) 340:12 case (28) 4:17;13:7;21:4; 141:10;146:10;155:6; 177:13;181:10;187:9; 204:18;218:12; 220:18;251:18; 252:13;259:22; 274:16;287:2;303:11; 313:17;318:20;319:6; 328:6;332:14;333:19; 335:15;364:12;365:5; 366:12 cases (23) 72:6;98:5,6;101:18; 162:21;167:7;186:8; 250:1;260:1;274:1; 286:14;287:9,13,17; 288:3;289:18,19; 290:1;295:9,11;299:5; 302:10;365:15 cat (1) 200:9 catastrophic (1) 164:8 catastrophize (5) 138:21;156:5; 164:2;337:17;338:8 catastrophizers (5) 141:16;144:6,12,15; 145:8 catastrophizing (85) 72:12,16;74:18; 75:2;86:21;88:5; 124:8;125:9;127:3; 128:7;137:22;138:4, 15,21;139:2,4,8,13,16, 21;140:6,14,21;141:1, 5,7,11,14,20;142:7,13, 18;143:2,7,13,15; 145:5,12,18;146:2,4,6, 8,15,19;147:3,9,14; 151:21;155:5,15; 159:17;160:12;161:1, 16;162:14;163:9; 164:19;166:6;167:7, 11,15;168:3;195:2; 238:19,22;247:22; 248:1,10;249:7; 250:11,13;252:10; 290:22;337:19,22; 338:5,10;361:4,6,6,11, 12,15,18 catching (1) 4:16 catechism (2) 111:10,11 categories (1)</p>	<p>272:18 categorizing (1) 271:14 category (5) 79:16;105:2; 277:16,21;370:8 caudalis (1) 348:19 causal (5) 219:6;340:11; 341:1,15,22 causality (6) 162:21;340:4,14,22; 350:4,18 causally (1) 20:11 cause (3) 29:9;108:13;243:14 caused (2) 72:5;109:6 causes (5) 20:13,14;109:21; 238:14;240:8 causing (2) 72:18;74:18 caution (1) 16:15 CBD (4) 92:11,11;93:3; 100:11 cell (15) 5:11;16:3;27:19,21; 29:5;55:18,21;56:20; 57:15;63:21;79:8; 90:21;96:9;237:12,12 cells (4) 27:22;28:7;216:14; 218:19 center (9) 104:1;108:15; 249:9;285:7,8;307:7, 8,9;321:4 central (230) 25:15;26:7,21; 30:13;34:11;35:8,22; 36:8,21;38:3,12,18; 39:5,7,20;40:3;42:17; 43:21;44:6,18;45:1,7; 46:18;47:9;48:1,11, 19,20;49:3,5,8,19,22; 52:14,17;53:3,15,22; 54:4,6,12,16;55:4,9; 56:13;57:18;58:10; 59:1,3,6,7,11,20;60:5, 5,10;61:3,9,17;62:3; 63:6;64:12;65:12,15, 19;66:15;67:13;68:1; 69:10,16;70:3;71:1,6, 20;72:9,21;77:7,10, 17;79:4;80:1,14,15; 81:5,10,14;84:5,9; 90:15;92:21;93:16; 94:1;95:20;96:3,4,7,</p>	<p>18;97:5,9,11,13,14; 100:22;101:10; 103:14;104:8;105:22; 106:21;107:12; 111:10;114:15;117:8, 15;118:19;119:21; 121:6;122:12;125:7; 127:3;131:16;173:5; 178:22;179:6;181:19; 190:14;205:10,12,15; 206:2,7,12;207:16,18; 209:7,16;210:12,13; 212:1,1,5,8,11,13,16, 19;213:8,11;214:5,9, 13;215:17;216:1; 217:11,19;219:13; 220:8,13,20;221:9; 222:21;223:8;224:3,4; 230:7,22;231:8; 232:16;234:10,14,16; 237:7;238:13;240:16; 243:13,14,15;244:10, 13,15;245:10;247:1; 249:8;254:6;255:19; 257:12,19;259:2; 260:17,22;265:19; 285:14,17;288:9,11, 14,18;289:7;294:20; 300:21;305:3,11,19; 307:17,19;308:4,6,15; 314:16;315:19;316:4; 320:5;322:18;323:2; 331:14,15;335:18; 336:9;337:3,6;338:13, 17;339:2;341:9; 349:3;351:3,5,8; 352:4;358:7;370:9 centralization (6) 66:4;68:18;218:7; 225:19;228:6;337:5 centralized (16) 64:4;86:1;89:4; 91:1;97:18;100:16; 134:22;140:2,4,7; 143:12;162:9;218:1; 221:5;223:16;370:9 centrally (6) 93:2;97:16;100:18; 116:21;171:3;244:4 centrally-acting (2) 177:8;186:3 century (1) 25:19 certain (22) 9:3;28:9;29:10,15; 45:18;46:15;59:13; 111:10;128:11;181:3; 209:11;218:8;220:5; 226:14;241:17; 269:22;276:7;308:10; 347:17;349:18;362:4, 5 certainly (28)</p>
--	--	---	--	--

57:19;62:9;63:10; 67:20;69:13;88:3; 120:13;121:15;181:6, 6,10;182:20;201:7,21; 204:18;205:4;206:11; 221:10;225:21;256:2; 280:15;282:22;286:1; 305:22;343:20; 354:14;357:17;358:5 cetera (7) 41:20;132:7; 144:11;223:1;248:11; 340:6;347:2 Chad (1) 86:13 chaff (1) 243:7 chair (2) 24:21;298:4 challenge (6) 59:5;61:22;74:4; 113:21;161:8;207:2 challenges (5) 65:3;190:18; 242:15;263:22;265:15 challenging (4) 17:17;161:7;191:8; 277:19 chance (7) 15:2;70:17;135:19; 169:3;203:4;261:10; 307:15 chances (1) 184:5 change (25) 38:15;40:8,10;50:5; 51:19,22;52:8;59:10; 60:15;61:17;67:2,13; 149:12,13;156:2; 192:16,22;206:4; 217:11,12;249:6,22; 277:14;372:5;373:13 changed (6) 37:3;40:13;49:21; 52:2;71:7;174:2 changes (51) 36:4;37:2,8,18,20, 22;38:1,3,18;39:2,4; 44:18;47:17;49:5,14; 50:16,17;51:4;52:20; 53:7,11;56:2,6,8,9; 57:3;63:21;64:4,8; 65:15;69:3,20;70:1,6; 163:17,17;164:9,11; 209:21;219:18; 239:22;240:1;246:8; 249:8;304:6,17; 342:13;347:4,9;367:8, 9 changing (6) 35:1;62:6;64:6; 174:9;282:21;301:15 channel (1)	51:9 chaotic (1) 324:15 characteristic (5) 19:22;20:1;127:12; 236:15;296:1 characteristics (1) 201:10 characterize (5) 33:21;109:19; 113:14;149:18;247:4 characterized (3) 28:6;53:7;183:4 Charles (1) 28:18 Charlie (1) 223:21 Charlie's (1) 224:10 chart (2) 88:20;264:16 chatting (1) 11:1 check (1) 353:13 checkbox (1) 353:21 checkerboard (1) 319:12 checklist (2) 129:14;147:19 checklists (1) 129:16 chemo-induced (1) 189:18 chewing (1) 245:9 chicken (1) 66:14 child (1) 77:16 childhood (1) 258:3 children (1) 108:6 chime (4) 262:5;342:3,7; 356:9 choice (2) 14:1;46:3 CHOIR (1) 354:6 choose (2) 299:15;313:7 Chris (4) 78:10;197:9;286:1; 295:18 Christensen's (1) 210:15 Christin (1) 339:13 chronic (147) 9:21;18:1,20;19:3;	36:20,22;54:8,14,17; 60:17;61:1;64:14; 65:3;66:1;67:8;69:21; 70:5;71:20;74:3,5; 75:15;78:11;79:5,21; 82:4,7;87:7;90:3; 92:20;94:22;96:12; 98:8;99:17;100:1,4, 21;101:2,8;103:2; 106:3;108:3;110:16; 115:1;122:5;126:18; 129:5;132:18;133:21; 134:12,13,15,21,22; 135:2;136:18;137:10, 21;138:16,19,22; 139:4;140:2,4,8,15, 17;141:18,21;142:16, 20;144:22;148:17; 149:18;150:13; 152:19,22;154:9,19; 155:19;162:9;164:3; 166:13;167:16; 170:10,12,21;173:8; 177:21;181:2,17; 197:10;209:3;211:12; 234:12,13;239:1; 252:8;254:11;255:16; 257:6;260:6;263:3,19; 269:19,21;270:17; 273:4,13,15;275:3,16, 22;276:10,15;281:2, 17;286:2;293:1; 295:1;300:22;304:21; 305:9;313:11;316:6,9, 12,16,19;318:16,19; 327:20;331:18; 336:11;337:10; 339:14;341:8,9;343:6, 17;345:4;355:12; 359:4,14;360:2,12; 369:10,22 chronically (1) 69:20 chronicity (2) 64:17;189:12 chronification (1) 101:11 Chung (1) 292:19 chunk (1) 371:4 Cincinnati (2) 117:3;190:13 cingulate (6) 315:4,13;318:22; 325:19;337:13;338:3 cingulated (2) 153:17;314:4 circles (1) 335:12 circling (1) 252:15 circuit (2)	27:13;28:11 circuitries (1) 338:21 circuitry (4) 329:7;337:6; 359:15,17 circuits (12) 27:5;48:16,20;49:9; 51:8;52:4,21;53:12; 56:5,8;60:10;66:11 circulated (1) 13:22 circulating (1) 246:11 circumstances (2) 37:21;225:21 citation (1) 269:9 cite (3) 245:17;267:18; 281:13 cited (2) 270:12;279:13 claim (2) 46:9;207:13 clarification (3) 212:10;213:20; 215:12 clarify (1) 346:4 clarifying (1) 285:20 clarity (1) 239:13 class (2) 172:13,14 classes (2) 106:7;251:21 classic (15) 72:10;73:11;74:13; 75:1;79:5;80:3;88:3; 94:12;110:16;214:14; 215:10;295:17; 362:14,15;368:9 classified (3) 301:22;302:7;305:4 classifying (1) 297:13 Claudia (1) 292:20 Claw (66) 55:11;70:22;71:3,9, 10;84:1;85:20;86:6, 12;89:2;102:17,19; 103:20;106:6;107:8, 10,22;108:2;109:10, 12;110:5;111:13; 112:12;113:17; 115:19;118:1,10; 119:4,15;121:12; 122:14;131:3;167:1; 180:19;192:11,14; 193:10,16;204:8,10,	16;207:22;210:7; 212:14;214:6;215:15; 216:3,9,19;217:1,4; 218:14,16;223:11; 242:18;249:13,16; 250:1;251:20;255:20; 258:1;259:8;319:9; 353:7;371:10;373:11 Claw's (3) 137:22;140:3;162:7 clean (1) 171:15 cleanup (1) 168:19 clear (18) 32:21;112:12; 123:4;193:20;205:1; 210:2,19,21;218:6; 235:10;238:12; 252:12;259:22; 263:11,16;264:12; 277:17;286:7 clearer (1) 196:7 clearly (28) 29:12;41:12;47:13; 48:6;55:1;63:11;67:6; 77:6;80:15,18;81:1; 95:1;96:11;98:22; 106:20;156:21; 159:13;166:1;170:18; 180:7;194:5;208:10; 213:9;247:19;329:8; 338:15;346:13;351:2 clears (1) 122:22 Cleland (1) 223:21 click (1) 354:19 clients (1) 264:5 Cliff (1) 179:1 Clifford (20) 25:22;26:1;58:5; 60:3;62:16;65:10; 71:13,15;72:13;96:20; 105:13;106:9;131:3; 162:18;167:2;205:16; 236:21;288:11;320:8; 363:13 Clifford's (1) 238:12 clinic (5) 225:11;271:12; 301:19;362:3;363:12 clinical (80) 9:5,11;11:11,17; 17:14,14;18:13;19:1, 11,16;26:22;37:15; 45:2;47:12;57:14; 58:1;62:18;63:11;
--	---	--	--	--

<p>71:1,6,19;72:20,22; 82:18;92:18;108:14; 110:8;114:21;126:14; 128:5;148:3;151:19; 157:15;173:22;178:2; 179:11,20;180:8; 187:4,6;188:1;195:3; 198:5,14,21;199:21; 200:15;204:1;223:14; 226:11;227:8;233:2, 10,17;234:19;240:10; 249:3;250:21;252:11; 255:18;257:9;288:16; 296:12;301:12; 312:17;320:3;341:21; 351:22;355:20; 357:15;360:12;362:2; 363:4;365:6,11,15; 366:21;371:12; 372:22;373:8</p> <p>clinically (13) 73:2;108:18;111:4; 118:13;120:21;135:9; 204:15;212:18;215:2; 254:4;308:10,12; 356:8</p> <p>clinician (7) 109:15;112:19; 168:21;184:8;254:3; 358:18;366:13</p> <p>clinicians (7) 37:12;71:7;72:4; 80:8;179:19;182:17; 351:5</p> <p>clinics (3) 280:9;282:1,1</p> <p>close (8) 67:1;70:10;236:4; 274:6;289:13;339:7; 348:9;372:12</p> <p>closed (1) 372:9</p> <p>closer (3) 159:9;306:15;322:1</p> <p>closest (1) 307:2</p> <p>cluster (5) 158:15,21,22;293:6; 303:1</p> <p>clustered (1) 167:22</p> <p>clusters (3) 159:5;302:21;321:5</p> <p>CNS (17) 32:13;52:4;64:5,5; 65:8;66:11;77:22; 84:11;96:22;108:9; 114:17;121:8;209:22; 211:19;218:2;221:2; 288:15</p> <p>co-author (1) 36:14</p> <p>co-chair (1)</p>	<p>4:8</p> <p>code (1) 7:7</p> <p>coding (2) 331:6;341:3</p> <p>coefficient (1) 142:8</p> <p>coffee (2) 6:8;10:11</p> <p>cogent (1) 71:5</p> <p>cognitions (2) 149:11,14</p> <p>cognitive (6) 72:12;126:4; 127:14;138:1;163:16; 334:22</p> <p>cohort (6) 90:8;129:4;229:20; 259:18;271:2;292:22</p> <p>cohorts (5) 106:19;108:14; 208:3;258:13;360:13</p> <p>cold (5) 330:13,19,22;331:4, 5</p> <p>collaborative (1) 150:1</p> <p>collaborator (2) 229:3;339:7</p> <p>collaborators (1) 58:15</p> <p>collagen (1) 102:8</p> <p>colleague (2) 149:19;153:6</p> <p>colleagues (6) 158:5;235:8;265:8; 306:1;307:2;339:5</p> <p>collect (8) 225:11,22;227:11; 259:13;324:5;332:4,7; 353:9</p> <p>collected (1) 142:19</p> <p>collecting (5) 158:7;226:2; 264:20;324:8;341:18</p> <p>collective (1) 158:2</p> <p>College (5) 26:10;37:12;45:5; 285:5,9</p> <p>COLLOCA (6) 203:11,12,13,13; 204:15;367:5</p> <p>color (1) 144:6</p> <p>color-coded (1) 312:2</p> <p>colors (1) 291:19</p> <p>Columbia (1)</p>	<p>60:11</p> <p>column (1) 290:13</p> <p>combination (3) 18:14;178:1;287:15</p> <p>combinations (2) 288:1,5</p> <p>combine (4) 175:2;274:10,13; 333:4</p> <p>combined (2) 269:3;304:16</p> <p>combining (1) 223:6</p> <p>comfortable (1) 263:20</p> <p>coming (17) 4:19;11:2;70:10; 85:15;90:10;93:6; 94:16;101:12;105:17; 114:13;179:6;199:13; 219:13;246:21; 280:17;283:10;365:22</p> <p>comment (12) 13:15;67:9;172:7; 203:21;234:6;245:6; 341:13;342:7,8,14; 367:5;368:10</p> <p>comments (9) 14:4,13;219:11; 229:8;261:22;346:15; 359:11;373:18,20</p> <p>committee (4) 8:5,11;9:2;25:10</p> <p>common (17) 14:19;88:11; 155:17,18;178:8; 243:18;244:1;276:20; 281:15;288:20;289:6; 294:19;295:12; 331:11;359:15,17; 368:22</p> <p>commonalities (1) 44:5</p> <p>commonest (1) 54:1</p> <p>commonly (7) 18:19;133:10; 137:20;157:1;251:21; 284:8;286:6</p> <p>Communication (3) 94:15;174:14;201:2</p> <p>community (6) 27:4;76:15;198:21; 199:4;295:22;325:18</p> <p>community-based (1) 362:6</p> <p>comorbid (14) 19:18;20:10;94:17; 102:21;118:4;130:8; 251:7;267:10;273:1; 276:20;283:9,20; 293:10;294:7</p>	<p>comorbidities (15) 85:10;109:1;148:4; 263:18;266:9,12,21; 268:9;269:19;271:5; 273:15;275:22;276:6; 280:3;281:3</p> <p>comorbidity (6) 18:9,10;253:7; 274:5;281:15;283:13</p> <p>companies (2) 91:19;200:10</p> <p>company (6) 91:19;92:3;178:16; 181:15;371:22;372:8</p> <p>comparable (1) 75:17</p> <p>compare (2) 185:6;319:17</p> <p>compared (12) 39:10;91:16;93:1; 151:7;154:8;268:4; 279:2,11;299:8; 301:11;303:7;361:5</p> <p>comparing (2) 359:6;364:5</p> <p>comparison (4) 70:4;153:10;282:6; 291:17</p> <p>comparisons (3) 269:8;297:17;312:6</p> <p>competing (1) 17:20</p> <p>complaints (1) 144:14</p> <p>complete (4) 60:18;68:8;195:19; 196:14</p> <p>completed (3) 267:4;337:15; 354:20</p> <p>completely (19) 41:10;50:13;51:19; 52:2;68:8;96:19; 184:8;195:12;207:8; 221:7;234:2;242:1; 318:15;325:6;342:16; 344:16;355:2,13; 371:12</p> <p>complex (1) 239:16</p> <p>complexity (2) 165:15;263:14</p> <p>complicated (4) 99:12;247:20; 251:9;276:22</p> <p>complications (1) 63:5</p> <p>component (12) 34:11;36:9;84:9; 108:16;137:19;220:9; 232:16;235:5;241:14; 324:21;349:3;359:2</p> <p>components (7)</p>	<p>41:5;67:10;79:4; 84:7;114:3;127:19; 356:1</p> <p>compound (2) 100:18;184:7</p> <p>comprises (1) 131:10</p> <p>compulsive (1) 277:12</p> <p>conceived (1) 126:22</p> <p>concentration (2) 310:9,19</p> <p>concentrations (1) 309:14</p> <p>concept (10) 18:8;28:22;45:9; 48:10;69:10;176:16; 179:2;194:18;225:19; 235:1</p> <p>concepts (5) 8:20;71:20;72:11, 12;308:21</p> <p>conceptual (1) 118:17</p> <p>conceptualization (1) 126:21</p> <p>conceptually (2) 58:7;182:12</p> <p>concern (1) 358:21</p> <p>concerned (3) 175:18;182:4; 207:16</p> <p>concerns (4) 7:17;173:1;175:16; 176:3</p> <p>conclude (3) 124:15;139:21; 153:22</p> <p>conclusion (3) 36:7;305:9;338:13</p> <p>conclusions (4) 36:2;197:16;278:4; 362:4</p> <p>concomitant (1) 309:20</p> <p>concrete (1) 263:11</p> <p>condition (28) 73:12;74:6,14;79:9; 82:3,4;90:18;134:7; 148:17;190:16; 223:15;228:21; 239:16,19;254:21; 290:2,6;291:3,5,7; 293:9;295:18;317:22; 318:2,18;319:18; 330:18;370:5</p> <p>conditioned (7) 133:11;298:19; 308:17;323:4;329:13, 16;330:1</p>
---	---	---	---	---

<p>conditioning (6) 40:7,11,13;330:5,6,14</p> <p>conditions (120) 9:21;18:1,3,11;19:3,9,17,18;20:11;48:20;59:14;61:4;71:21;72:22;74:3;76:4;78:4,6,7,12,14;79:6,22;80:2,3;81:1;82:8;90:12,20;92:18;96:13;97:22;98:3,8;99:8,17,19;100:1,3,4,21,22;110:16;114:14;126:14,17,20;128:11;130:8;134:15,21;135:1;140:15;141:21;153:1;155:20,20;167:16;172:2;173:5;210:19;221:4;223:10;225:13;240:7;276:8;281:18;283:9;285:15;286:1,7,16,17,19,21,22;287:5,10,10,15,19;288:4,7,21;289:10,12,15;290:18;291:10,16,18,21;292:1;293:2,8,10,17;294:3,7,17;295:1,3,13;299:10,12,14,20,22;300:5,10,17;301:1;304:22;305:10,12;318:14;352:7;355:22;356:2;358:20</p> <p>conduct (1) 225:2</p> <p>conducted (2) 60:12;225:6</p> <p>conducting (1) 263:6</p> <p>conduction (1) 321:13</p> <p>conference (2) 211:14;212:16</p> <p>confidence (1) 278:16</p> <p>confident (3) 164:8;278:4;281:12</p> <p>confidently (1) 281:14</p> <p>confined (2) 95:4,10</p> <p>confound (1) 31:4</p> <p>confronted (1) 62:17</p> <p>confused (1) 273:7</p> <p>confusing (2) 120:4;221:9</p> <p>confusion (1) 32:20</p> <p>connect (1) 49:9</p>	<p>connected (3) 102:5;299:19;328:2</p> <p>connection-involved (1) 160:14</p> <p>connections (2) 28:5;248:5</p> <p>connectivity (30) 93:20;94:18;116:6;150:3,4;151:4,11,13,16;161:19;165:4;323:22;324:1;326:22;327:4,15;328:4;329:3,4;336:19;344:7,8;347:11;359:22;360:11,22;361:14;365:5;371:19;372:5</p> <p>conscious (1) 112:20</p> <p>consecutive (1) 271:14</p> <p>consensus (7) 12:19,20,21;14:19;21:1;285:20;358:7</p> <p>consequence (11) 34:5;35:13;36:4,7;64:5;217:15;219:16;251:2;300:21;302:14;305:15</p> <p>consider (11) 11:11,16;12:16;13:3;18:12;20:5;37:13;127:2;157:21;159:6;341:1</p> <p>considerably (1) 276:3</p> <p>consideration (3) 17:1;172:8;192:9</p> <p>considerations (4) 11:11;14:20;172:3;213:22</p> <p>considered (12) 9:9;18:20;129:3;133:15;182:21;190:7,10;193:4;265:9;320:10;338:14;358:16</p> <p>considering (4) 19:16,18;66:18;236:14</p> <p>considers (1) 244:13</p> <p>consistent (5) 141:19;257:8;270:21;315:14,17</p> <p>consistently (5) 62:18;145:12;257:5;271:11;275:7</p> <p>constantly (1) 325:5</p> <p>constellation (1) 178:14</p> <p>constellations (1) 222:21</p> <p>constitute (1)</p>	<p>63:17</p> <p>construct (6) 11:7;77:14;126:13;156:22;157:22;158:17</p> <p>constructed (1) 254:5</p> <p>construction (1) 272:16</p> <p>constructs (6) 17:19;18:7;124:8;125:14;305:7;358:9</p> <p>consult (1) 171:17</p> <p>consulting (3) 91:18;264:3;372:14</p> <p>Contestant (1) 204:6</p> <p>context (12) 26:7,22;32:13;52:9;128:5;129:2;137:12;152:19;182:11;187:11;234:19;254:4</p> <p>contiguous (1) 81:16</p> <p>continue (2) 43:15;132:18</p> <p>continues (1) 43:13</p> <p>continuous (4) 237:2;317:2;330:18;351:17</p> <p>continuum (5) 85:8;87:13;88:1;244:7;351:14</p> <p>contracted (2) 321:22;322:10</p> <p>contraction (1) 29:9</p> <p>contradicts (1) 160:10</p> <p>contralateral (3) 230:1;237:3,5</p> <p>contrast (10) 125:7;175:13;177:3;215:1;310:3,5;315:6;316:16;326:20;328:2</p> <p>Contrasting (1) 317:9</p> <p>contribute (6) 27:6,15;42:21;47:2;50:22;271:20</p> <p>contributed (1) 47:7</p> <p>contributes (1) 283:12</p> <p>contributing (3) 50:17;96:15;142:15</p> <p>contribution (2) 93:17;358:10</p> <p>contributions (7) 72:9;80:14;90:16;92:21;108:10;118:19;</p>	<p>304:17</p> <p>contributor (5) 50:11;54:7;55:5;61:15;285:3</p> <p>control (13) 32:3;35:15;38:19;45:19;56:4;89:18;129:22;148:3;167:12;189:13;316:16;318:8;330:20</p> <p>controlled (5) 99:20;170:9;297:16;308:7,9</p> <p>controls (41) 134:4;136:5,8;140:20;141:19;150:14;151:1,7,9;153:11,21;154:8,20;286:13;293:16;295:9,11;296:6,22;302:5;313:11,16;314:19;316:9;317:7,15;318:4,10,12,17;319:2;331:3;332:16;333:5,17;334:7;335:12;336:13;364:6,8,13</p> <p>controversial (2) 46:6;176:5</p> <p>controversy (1) 344:2</p> <p>convenience (3) 271:13,15;281:22</p> <p>convenient (1) 228:19</p> <p>conversation (1) 238:10</p> <p>converse (2) 250:3;252:7</p> <p>convert (1) 207:15</p> <p>conveyed (1) 199:8</p> <p>conveying (1) 228:3</p> <p>convince (1) 199:18</p> <p>convincing (1) 127:7</p> <p>convulsive (1) 68:14</p> <p>co-occurrence (1) 302:15</p> <p>co-occurrences (1) 20:12</p> <p>co-occurring (2) 19:17;283:8</p> <p>co-occurs (1) 18:19</p> <p>Cook (1) 26:13</p> <p>cool (1) 78:17</p> <p>coordinates (1)</p>	<p>315:8</p> <p>coping (1) 290:21</p> <p>copy (1) 15:22</p> <p>cord (19) 30:7;31:4;36:4;50:18;55:20;56:15;60:14,22;165:8,10,20;166:12,17;178:13;236:10;322:22;331:16;338:14;352:5</p> <p>co-reviewers (1) 284:10</p> <p>Corey (1) 144:17</p> <p>corrected (1) 312:5</p> <p>corrective (1) 304:10</p> <p>correlate (5) 53:12;113:7;116:5;234:12;320:9</p> <p>correlated (12) 142:6;151:19,21,22;152:4,9;163:2;238:19;320:2;322:15;338:1,11</p> <p>correlates (5) 111:17;115:22,22;165:6;348:14</p> <p>correlation (4) 137:6;142:7;162:20;335:21</p> <p>correspond (1) 274:2</p> <p>corrupted (1) 207:1</p> <p>cortex (37) 150:17;151:17;153:17,18;154:15;165:6;304:5;314:4,5,8;315:3,12;318:22;319:21;320:2,12,14,22;325:12,19;331:8;332:5;334:11;336:3,20;337:11,13;338:3,4,16;348:18;349:1,4;350:7,9;364:1,12</p> <p>cortical (16) 49:10;50:14;55:20;215:3;248:9,9;303:18;308:18,20;320:11;321:17,18;322:15;327:7;334:8;373:6</p> <p>corticospinal (2) 50:9;66:8</p> <p>coughing] (1) 363:22</p> <p>count (5) 83:16;84:3;200:11;268:21;353:22</p> <p>counted (1)</p>
--	---	---	---	--

269:8 counteracted (1) 330:19 counterparts (1) 298:13 counterpoint (1) 203:5 countries (1) 271:10 country (1) 233:13 counts (4) 130:22;269:11,12; 274:2 couple (22) 78:9;79:15;95:21; 99:13;100:15;129:9, 12;136:1;145:10; 149:22;169:19;174:4; 208:9;222:15;244:2; 282:17;283:19;300:7; 301:8;342:3;345:3; 363:14 course (24) 34:4;73:6;108:14; 113:3;114:2;119:21; 131:1;133:5;149:5; 163:11;177:21; 230:13;246:3;250:16; 252:7,8;260:10;268:5; 281:9;284:7;288:10; 311:12;312:6;355:21 Court (2) 7:9,11 cover (3) 11:3;17:17;72:1 covered (2) 21:18,20 covering (1) 173:14 COWAN (1) 356:13 CPM (28) 133:11,22;134:10, 18,20;135:3,22;136:4, 17,20;137:6,7,12; 141:21;142:1,2,5,10, 18;143:3,5,8;235:2; 236:6;330:14,22; 331:10;338:17 CR (1) 177:16 crack (1) 223:11 cramps (1) 257:14 cranial (1) 105:16 crate (1) 330:16 crazy (1) 30:21 cream (1)	230:18 create (4) 155:5;183:9; 192:20;197:1 created (1) 186:5 creating (2) 107:20;371:1 credibility (1) 78:7 credible (2) 112:15;211:17 credit (2) 83:8;131:20 creep (2) 371:11;372:22 criteria (34) 19:8,15;48:2;82:18; 84:2,4,6;88:15; 177:16;179:16; 182:14;183:7;184:13; 189:6;197:3;201:18; 213:22;264:16,21; 267:5;269:16;270:6,9; 280:8,19;282:5,17,19, 21;302:2,3;369:3,21; 370:1 criteria-based (1) 264:12 criterion (3) 197:5;255:13;370:4 critical (3) 84:9;213:13;362:9 criticized (3) 58:14;77:10,11 cross (2) 206:5;359:22 cross-comparing (1) 364:15 cross-correlation (1) 360:4 crossing (1) 85:17 cross-sectional (7) 134:18;141:6; 154:22;271:6;280:7; 283:10;300:19 cross-sectionally (1) 373:14 Crosstalk (3) 216:5;252:17; 369:16 crowd (1) 309:3 CRP (1) 83:16 CRPS-1 (3) 239:12,19;240:2 crucial (4) 152:21;205:22; 226:13;348:10 crude (6) 163:12;230:6;	241:12;244:3;347:5,9 CSF (1) 115:9 CSI (1) 224:10 CTS (1) 322:5 cuff (10) 152:1;237:16; 241:17,19;317:4; 326:8,9,13,14;345:5 cumulative (1) 259:10 cup (1) 6:8 cured (1) 164:4 current (18) 54:5;98:1;101:19; 174:22;177:18; 178:20;184:5;236:22; 273:10;275:1,2,19; 276:10,14;278:13; 279:9;280:2;354:6 currently (5) 54:2;163:6;173:19; 177:9;185:15 curve (1) 366:10 curves (1) 130:16 cut (2) 23:16;185:8 cutaneous (5) 30:4;33:1;313:17, 18;316:22 cutoff (1) 297:12 cutout (1) 287:8 cut-out (1) 153:8 cutpoint (1) 354:11 cutting (2) 23:22;238:10 cyan (2) 312:9;324:12 cyber (1) 237:21 cycle (1) 208:20 cycling (1) 325:5 cystitis (7) 78:15;95:2;110:13; 214:21;259:17,19; 273:18 cytokines (2) 215:20;218:21	D2/D3 (1) 322:11 daily (1) 135:4 damage (7) 63:8;72:6,7;206:9; 221:13,18;227:9 damaged (1) 206:9 damaging (1) 206:1 damn (3) 27:19;29:5;55:18 Dan (28) 55:10;103:13; 109:14;119:3;131:3; 137:21;140:2;150:8; 162:6;166:22;168:13; 200:16;204:6;212:6; 215:13;226:1;242:10; 248:19;249:12;257:1; 286:4;295:16;319:8; 353:3,4;357:17; 360:13;371:9 Daniel (2) 71:9;367:6 Dan's (4) 187:20;189:9; 261:22;352:9 darker (3) 290:11;291:19; 299:13 darkness (1) 299:7 darn (1) 184:11 data (93) 9:6;12:3;32:16; 54:8;56:9;86:13;88:9; 98:5;100:2;106:6,10; 108:6;116:11;127:5; 17;130:13;132:1,12; 134:2;135:19;136:7; 139:5,19;140:16; 141:22;142:19; 144:18;157:6;158:7; 159:4;160:9;162:4,6, 7;181:11;184:3,21; 187:11,12;188:4; 193:5;200:16;207:18; 208:3,13;225:11,17, 22;229:7;231:12,17; 247:6;252:12;259:14; 267:11;269:3;270:9; 272:15,19;286:8,12; 287:3;289:11;290:9; 292:19;293:13;294:5, 11,12,12;295:19; 299:20;300:19;311:9, 10;324:5,8;332:4,5,7; 341:19;342:9,20,21; 344:7,20;349:19; 350:5;352:3;354:11;	356:2;359:1;371:4 database (1) 282:4 databases (2) 267:3;268:14 date (2) 111:6;119:15 daunting (2) 285:16;286:10 David (1) 135:11 day (10) 5:8;10:21;25:20; 87:1;88:17;185:13; 233:13;251:12; 343:11;355:6 days (10) 10:19,20;60:11; 72:2;76:12;99:22; 111:16;170:11; 174:11;253:14 day-to-day (1) 151:20 DC (3) 13:12;249:16;267:7 de (1) 65:18 deactivated (1) 325:4 deactivations (1) 312:21 deadline (1) 12:7 deadlines (1) 14:11 deafferented (1) 232:8 deal (4) 162:19;163:4; 165:15;346:18 dealing (4) 29:14,15;182:17; 351:6 dealt (1) 263:12 death (1) 254:3 debate (3) 10:22;48:18;211:14 debating (1) 20:20 decade (1) 126:13 decades (5) 49:22;55:8;174:4; 244:2;257:14 decerebrate (3) 30:15;36:20,22 decerebrating (1) 31:2 decide (2) 13:2;190:2 decided (7)
D				

<p>17:11;21:14;28:13; 36:14;38:6;283:22; 353:10</p> <p>deciding (1) 111:18</p> <p>decisions (2) 12:7;13:8</p> <p>decondition (1) 156:11</p> <p>deconditioned (1) 101:3</p> <p>deconstruct (1) 219:6</p> <p>decrease (5) 310:15,18,19; 327:12;328:17</p> <p>decreased (2) 302:9;304:7</p> <p>decreases (1) 304:4</p> <p>decreasing (2) 69:15;312:9</p> <p>deemphasize (1) 107:10</p> <p>deep (1) 326:19</p> <p>deeper (1) 296:18</p> <p>deeply (1) 113:1</p> <p>deep-tissue (2) 317:3,6</p> <p>default (10) 94:12;116:2;150:8; 161:18,19;162:8; 164:10,16;360:1,4</p> <p>defer (1) 249:12</p> <p>deferring (1) 235:8</p> <p>define (20) 29:12,19;48:1;59:6; 72:21;79:19;169:12; 179:13;180:7;188:13; 189:2,3,6,20;191:21; 193:14;201:19;214:1; 244:19;255:13</p> <p>defined (18) 29:3;31:8;32:5; 51:8,11,12;55:17; 56:2;76:13;77:19; 125:22;129:12; 156:20;180:14;220:2; 308:6;326:1;348:6</p> <p>defining (3) 180:9;188:15; 201:17</p> <p>definitely (8) 30:14;32:4;232:16; 270:17;272:10; 317:11;359:8;365:22</p> <p>definition (6) 30:19;49:7;131:4;</p>	<p>170:12;234:17;244:15</p> <p>definitive (2) 161:9;235:7</p> <p>degree (31) 55:3;62:22;64:21; 67:7;69:2;83:10,13; 84:5;114:6;116:4; 128:10,10;133:8,18; 135:5;136:13;144:7; 151:6;153:15;220:19; 228:16;247:3;291:7; 295:21,21;305:19; 337:21;338:6,8;357:9, 10</p> <p>degrees (2) 152:12;174:18</p> <p>delay (1) 349:14</p> <p>delayed (1) 143:22</p> <p>deliberately (4) 35:16;36:18,22; 227:19</p> <p>delighted (2) 24:21;228:22</p> <p>deltoid (1) 144:2</p> <p>demographically (2) 136:5;150:13</p> <p>demonstrate (1) 194:6</p> <p>demonstrated (1) 350:22</p> <p>demonstration (1) 234:14</p> <p>Dennis (7) 4:6;25:10;47:22; 50:20;61:9;71:11; 306:6</p> <p>Dentistry (2) 285:6,10</p> <p>deny (1) 282:14</p> <p>deoxygenated (4) 310:9,18,20;311:4</p> <p>Department (1) 339:16</p> <p>departments (1) 89:8</p> <p>depend (1) 179:11</p> <p>dependent (2) 159:21;310:4</p> <p>depending (12) 8:7;11:9;38:13; 161:5;173:16;265:4, 12;277:14;300:18; 305:16;355:9;364:22</p> <p>depends (5) 13:21;110:6;111:4; 214:6;340:22</p> <p>deployed (1) 123:7</p>	<p>depressed (3) 156:8;248:22;252:9</p> <p>depression (57) 20:14,16;72:11,15; 74:18;75:2;86:21; 88:4;116:13,14,15,15; 138:7;143:2;155:2,4; 168:7;186:10;238:20, 22;248:10;249:6,20; 250:2,7,10,12;251:7, 16,18;252:2,6,14; 253:6;257:2,4,7; 262:3,4,4;266:12; 267:21,22;268:3; 279:1,5,7,15;280:3; 281:3,5;283:11,14; 359:17;360:3,6;362:5</p> <p>depressive (2) 278:22;279:13</p> <p>deprivation (1) 253:10</p> <p>deprive (1) 253:12</p> <p>depths (1) 152:16</p> <p>derive (1) 159:1</p> <p>derived (1) 258:12</p> <p>describe (2) 184:12;279:8</p> <p>described (4) 44:8;67:6;170:7; 325:8</p> <p>describing (3) 67:12;122:13;197:5</p> <p>description (3) 49:2;130:5;337:9</p> <p>descriptions (1) 71:5</p> <p>descriptive (1) 274:12</p> <p>design (14) 12:1,11;19:20; 174:1;187:5,6;192:7; 252:19,22;311:15,16; 324:6;330:8;332:13</p> <p>designed (2) 24:9;253:4</p> <p>designing (3) 9:11;11:17;204:1</p> <p>designs (5) 323:13,21,21;339:1; 341:18</p> <p>desk (2) 5:7;7:3</p> <p>desperate (1) 7:2</p> <p>detail (2) 25:2;313:14</p> <p>detailed (1) 288:5</p> <p>details (3)</p>	<p>5:1,2;268:19</p> <p>detect (5) 47:15,17;52:20; 297:9,13</p> <p>detectable (1) 206:4</p> <p>determine (5) 234:10;235:18; 282:13;301:19;349:9</p> <p>determined (1) 265:12</p> <p>determining (1) 147:7</p> <p>develop (21) 12:17;60:17;65:4; 82:4;101:5;108:7,8; 116:17;123:2;144:13; 155:19;167:20; 170:16;171:20;173:4; 190:22;206:12; 210:20;228:5;305:21; 308:3</p> <p>developed (9) 13:20;82:11;126:7; 153:4;181:1;224:10; 301:21;302:5;373:9</p> <p>developing (19) 54:13;55:6;64:13; 67:12;76:5;82:6; 138:22;194:4;210:11; 223:7;301:4,14,18; 302:20;303:6,11; 338:22;354:18;358:4</p> <p>development (31) 45:7;54:7,17,20; 55:4;60:16,21;69:22; 91:21;92:4;122:10; 129:5,7,20;130:15; 147:22;148:17; 171:13;179:3,11; 196:5,7;197:13,14; 199:9;210:18;244:21; 301:10;302:15,16; 372:8</p> <p>device (2) 326:9,11</p> <p>Devor (1) 67:21</p> <p>diabetes (1) 57:8</p> <p>diabetic (6) 57:7,11;177:10,13; 178:8;255:7</p> <p>diagnose (2) 268:7;351:7</p> <p>diagnosed (10) 239:21;260:3; 263:10;265:13; 267:14;268:1;270:6; 279:15;280:13;283:15</p> <p>diagnoses (2) 73:9;368:8</p> <p>diagnosis (6)</p>	<p>110:3;115:18; 264:12;266:15;352:8; 373:16</p> <p>diagnostic (10) 52:17;111:2; 112:10;179:16; 264:21;269:16;282:5, 16,19;363:2</p> <p>diagnostically (1) 351:16</p> <p>diagram (3) 27:13;90:10;114:12</p> <p>diastolic (1) 160:4</p> <p>dichotomy (1) 212:8</p> <p>dictate (1) 273:18</p> <p>dictated (1) 273:16</p> <p>differ (7) 134:13;143:3; 183:21;272:3;314:19, 20;315:1</p> <p>differed (1) 38:13</p> <p>difference (21) 18:9;33:19;63:9; 92:15;104:14,21; 120:17;132:11; 162:20;198:17; 212:18;215:17; 317:16,18;319:4; 333:16;334:6;352:15; 364:7,10;368:12</p> <p>differences (16) 69:12;81:5;131:13; 142:10;159:16;208:8; 221:12;235:14; 316:10,13,17,18,22; 317:9,16;343:1</p> <p>different (146) 4:14;9:16,21;10:7; 17:18,21;18:7,14; 19:17;20:3;28:14; 31:14;37:1;40:14; 48:8;49:1;61:6,6,7,19, 21,21;63:4,6,12,12; 64:3;65:16;71:1;74:3; 81:18;89:13,14;90:7, 19;91:18;94:16,18,21; 95:2,9;96:2;98:2; 99:16;103:14;104:9; 105:8;114:17;116:20; 117:7;118:18;119:12; 120:19;121:2;122:18; 123:4,13;125:12; 127:19;148:9,11,20; 150:4,5;153:11;157:8, 10,19;169:5,7,13; 170:7;171:5;172:2; 173:4;175:9;178:1; 181:17,21;186:4;</p>
--	---	---	---	---

<p>190:22;195:13;208:4; 210:5;211:14,14; 213:14;214:13;215:8, 16;216:10,15;217:14, 20;218:20,22;219:15; 222:20;223:6;226:19; 227:21;228:12; 236:13;240:8,8,17; 242:8;243:3,10,13,22; 257:22;262:14; 273:11,14;277:10; 278:12;283:6;287:22; 288:7;293:2;299:19; 305:18;309:6,6; 318:14;319:11,11; 321:9;328:10;333:21; 337:21;338:16,20,20; 339:1;342:16,22; 348:3;353:1,6;357:14; 358:14;360:13;369:9; 372:19</p> <p>differential (8) 86:15;110:3,14; 207:19;213:18;224:9; 260:12;345:21</p> <p>differentially (1) 157:10</p> <p>differentiate (5) 212:17;248:3; 249:5;254:6;351:3</p> <p>differentiated (1) 232:2</p> <p>differentiates (1) 95:18</p> <p>Differentiating (1) 336:8</p> <p>differently (4) 117:9;209:3; 249:19;295:2</p> <p>difficult (17) 6:18;16:5;43:13; 65:21;66:19;114:19; 117:6;145:8;166:10; 201:6;266:6;274:13; 281:17;323:10,16; 341:7;346:18</p> <p>difficulty (2) 62:10;216:21</p> <p>diffuse (2) 77:17;181:13</p> <p>dig (1) 280:6</p> <p>digit (1) 322:2</p> <p>digital (1) 353:12</p> <p>digits (3) 321:20,21;322:4</p> <p>dinner (3) 7:10;11:1;374:4</p> <p>dinners (1) 10:11</p> <p>direct (9)</p>	<p>16:18;50:10,14; 70:4;218:10;266:6; 315:6;349:2,6</p> <p>directed (8) 76:6;93:3;97:16; 105:4;116:21,22; 119:19;121:5</p> <p>direction (4) 24:9;155:10;182:5, 7</p> <p>directly (7) 50:22;102:16; 105:17;144:9;231:3; 252:16;316:15</p> <p>director (4) 168:20;285:7; 307:6;339:14</p> <p>disability (3) 83:14;370:3,11</p> <p>disabling (1) 139:1</p> <p>disagree (1) 127:15</p> <p>disagreement (3) 20:22;77:13;343:6</p> <p>discern (1) 252:22</p> <p>discharge (2) 31:7;68:14</p> <p>discharges (1) 52:10</p> <p>discontinue (1) 139:17</p> <p>discovered (7) 26:8;31:6;32:9; 38:17;40:1,6;56:14</p> <p>discovery (4) 42:15;48:12;50:1; 57:18</p> <p>discrete (1) 204:20</p> <p>discretion (1) 306:11</p> <p>discriminate (2) 223:16;224:3</p> <p>discrimination (1) 325:13</p> <p>discuss (4) 8:9;10:14;49:6; 170:22</p> <p>discussed (8) 26:21;34:11;52:19; 197:22;234:7;253:10; 266:11;358:15</p> <p>discussing (4) 20:21;39:14; 197:18;248:12</p> <p>discussion (16) 10:21;12:18;24:18, 18;36:12;39:11;66:2; 137:22;142:3;149:4; 195:2;203:3;253:8; 254:19;308:5;339:10</p>	<p>discussions (2) 10:8;308:1</p> <p>disease (18) 19:1;62:19;63:2; 64:7;65:5;78:16,17, 17;79:8;90:21;96:9; 102:4;163:1;191:19; 214:15;215:11; 216:13;272:11</p> <p>diseases (3) 73:5;111:3;220:18</p> <p>disinhibition (3) 47:11;209:19;241:8</p> <p>disorder (20) 19:5;129:8,21; 147:22;250:21; 265:10;266:16;269:6; 272:3;276:21;277:12, 12,13,18;278:3,6,13; 279:1,13;281:16</p> <p>disorders (38) 191:5;263:2,14,20; 264:10,13;265:6,20; 266:22;267:12,15; 269:17,18;270:3; 271:5;272:13,20; 273:1;275:4;277:2,2, 6,7,21;278:19,22; 279:8,10,22;281:7; 282:16;283:16;351:4</p> <p>disparity (2) 74:8;81:2</p> <p>disproportionate (2) 52:22;53:13</p> <p>disputes (1) 127:17</p> <p>disputing (1) 112:18</p> <p>dissecting (1) 121:1</p> <p>dissed (1) 107:6</p> <p>dissociate (2) 168:1;258:8</p> <p>dissociated (1) 81:17</p> <p>distance (2) 322:10,11</p> <p>distances (1) 4:20</p> <p>distant (1) 371:17</p> <p>distinct (6) 127:1;133:15,16; 220:14;324:16;325:1</p> <p>distinction (4) 81:13;127:4;212:9; 267:9</p> <p>distinctions (1) 127:6</p> <p>distinguish (8) 4:12;230:7;231:10, 11;235:14;242:2;</p>	<p>254:20;368:12</p> <p>distinguished (6) 27:4;36:17;127:10; 285:4;298:12,19</p> <p>distinguishing (1) 170:13</p> <p>distorted (1) 85:8</p> <p>distortion] (1) 206:21</p> <p>distracting (1) 16:4</p> <p>distress (8) 142:14;154:6,17; 155:4;228:10;304:19; 305:5;370:3</p> <p>distressed (1) 154:12</p> <p>distressing (1) 359:10</p> <p>distribution (2) 109:17;292:14</p> <p>distributions (2) 134:5,13</p> <p>disturb (1) 126:12</p> <p>disturbance (2) 108:9;190:21</p> <p>disturbances (1) 359:14</p> <p>disturbing (1) 126:2</p> <p>diverse (3) 174:5;200:14;201:9</p> <p>diverted (1) 50:3</p> <p>divided (1) 361:11</p> <p>division (4) 23:11;168:19; 171:10,11</p> <p>divisions (2) 171:10;190:9</p> <p>DMN (3) 360:10,22;361:13</p> <p>doc (3) 26:14;41:3;366:13</p> <p>doctors (1) 191:10</p> <p>document (1) 170:6</p> <p>documented (1) 264:15</p> <p>domains (4) 199:19,20;227:21; 305:17</p> <p>dominate (1) 324:2</p> <p>dominated (1) 272:10</p> <p>DOMS (1) 143:22</p> <p>done (61)</p>	<p>12:9;19:4;21:9; 30:18;51:5;57:7; 58:15;22;80:17;81:19; 86:6;90:8;93:18;94:2; 100:15,15;106:13,14, 17,22;113:15;115:21; 123:17,18;129:9; 143:18;158:22; 159:11;167:19; 169:21;171:18; 174:21;179:20; 185:16,16;199:9; 201:20;210:15; 214:15;224:5;230:8; 233:8;236:8;242:12; 246:17;256:7,7;259:6; 260:11;284:3,22; 295:15;312:15;326:8; 334:15;340:20; 346:12;351:21;365:3, 7,17</p> <p>door (1) 7:13</p> <p>dorsal (21) 27:6;29:5;30:5; 31:12;39:2,4;41:5; 42:8;50:11,15;60:13; 66:8;68:5;69:18; 235:12;237:11,13; 238:3;331:20;333:19; 334:5</p> <p>dose (5) 170:14,14,15; 177:13;186:18</p> <p>doses (2) 45:19;175:17</p> <p>dots (1) 313:2</p> <p>double (3) 7:8;281:4;303:5</p> <p>double-blind (1) 177:12</p> <p>doubt (1) 164:11</p> <p>doubtful (1) 235:6</p> <p>down (23) 6:8;15:22;80:16; 103:17;161:14; 165:12;183:17; 233:20;268:21;270:7; 272:4;273:8;275:15; 277:11,13;279:22; 290:20;295:20; 335:14;351:13;369:8; 372:9,13</p> <p>dozen (1) 136:1</p> <p>dozens (2) 137:15;141:17</p> <p>DPN (1) 178:7</p> <p>DR (364)</p>
---	--	--	---	--

4:4;13:10;16:10,11; 17:8;22:6,10,11,18, 20;23:6,11,12;24:14, 22;25:9,18;26:2;31:1; 34:17,20;35:1;38:8; 39:18;44:13,17,58:5; 59:5,21;60:1,3;61:8; 62:15;63:15;65:10,21; 66:21;67:15;69:6,7, 13;70:9,15,22;71:3, 10;84:1,85;20;86:6, 12;89:2,102:2,17,18, 19;103:12,13,20; 105:19;106:6;107:5,8, 9,10,15,22;108:1,2; 109:8,10,11,12,14; 110:5;111:8,13,14; 112:12,17;113:17; 115:5,7,19;117:2; 118:1,9,10,22;119:2,4, 5,15;121:9,12,13; 122:14;123:18,20; 124:2,9,11,19;158:11, 18;159:12;161:2; 162:4,19;163:3;165:3, 16,18;166:21;167:1; 168:13,18,19;169:2, 19;170:4;173:19; 180:3,19;182:8; 183:19;184:10; 187:19;188:8,11; 189:8,14,16;190:12; 191:15;192:10,11,14; 193:7,10,12,16,17,18; 195:10;196:2;197:7, 14;198:10;199:7; 201:4;202:1;203:4,7, 11,12,13;204:3,4,6, 8,10,15,16,21;205:17, 19,20;206:13,14; 207:17,22;209:5,6,13; 210:7;212:6,14; 213:19;214:6;215:12, 15;216:1,3,6,9,17,19, 20;217:1,4,17;218:14, 15,16;219:11;221:8, 19;222:9,10,13,15,18; 223:11;224:18;225:7, 12,16;226:9,10; 227:17;229:5,6; 230:10,16,17,18,19; 231:20;232:1,6,21; 233:7,10,18;234:5,6; 235:2,4;236:17,18,19; 238:9;239:12,15,18, 19;240:12,13,14,19, 21;241:1;242:4,18; 244:9,17,18,22;245:5; 246:17,18;247:7,9; 249:11,13,16,19; 250:1;251:4,20; 252:18;253:5,21; 254:2,18;255:10,12,	20;256:22;257:10; 258:1,20;259:8; 260:14;261:1,3,6,16, 17;262:9,19;284:13, 14,15,21;285:13,19; 286:12;299:18;306:4, 11,13,18;307:2,14; 339:11;340:21; 341:12;342:2,6; 343:16,19;344:15; 346:4,6,7,16,17; 347:14;348:8;349:17; 350:21;351:11;352:2; 353:3,7;354:5,9; 355:1,16;356:11; 357:4,17;358:12,13; 359:1,12,16;361:20; 362:10,11,12,19,21, 22;363:1,4,13,14; 364:4,17,18;366:2,6; 367:5;368:6,7,15,18; 369:2,5,13,15,17,19; 370:14,17;371:10; 373:3,11,18,20;374:3 draft (4) 13:20;14:16;172:7, 7 drafts (2) 14:9;169:19 drags (2) 14:8;15:9 draining (3) 343:22;346:10; 348:12 dramatic (1) 167:10 drawings (1) 352:16 drew (1) 40:6 drive (13) 28:11;41:6;57:13; 63:18;66:6,12;117:12; 121:7;206:12;221:1; 269:11;275:20;304:17 driven (17) 28:17;35:7;38:3; 41:12;50:16;67:21; 96:10,18;97:12; 105:13;118:20;121:4; 215:5;219:20;242:5; 244:4;246:10 driver (1) 207:8 drivers (3) 38:12;55:1;256:20 drives (5) 49:11;103:3;149:8; 155:1;219:3 driving (8) 37:19;39:20;52:10; 68:15;96:22;162:22; 163:1;219:9	drop (3) 145:9;168:4;185:11 drop-down (1) 353:14 dropout (1) 186:19 dropouts (3) 184:18,20;185:8 dropped (1) 34:6 drops (1) 324:13 drove (2) 30:1;368:3 drug (36) 92:6,9;93:3;94:6; 97:1;98:19;100:8; 107:1;169:15;170:18; 175:15;177:8;179:2, 11;180:20,22;181:16; 182:18;183:2;185:10; 186:13,16;187:2; 190:3;191:18;193:22; 196:8,13;197:13,14; 199:9;252:3;371:22; 372:4,7,15 drugs (25) 9:8;75:11,19,21; 94:7;97:16,17,21; 101:19;105:21;106:7; 183:13;185:17;186:3; 188:16;194:19; 215:10;217:7;231:13, 17;248:14;250:7; 251:15,21;372:19 drug's (1) 191:11 dry (4) 78:15,16,19,20 DSM (2) 267:17;277:20 dubbed (1) 325:15 due (8) 38:17;102:9; 178:22;179:8;270:2; 333:13;341:22;363:21 dug (2) 263:13;266:7 duloxetine (15) 53:22;75:10;91:5,6, 9,10,14;92:9,22;93:1; 180:20;181:9;187:5, 22;188:3 duplicates (1) 268:13 duration (7) 37:7;177:2,6,12; 272:11;333:1;355:5 during (8) 10:10;33:19;60:16; 264:21;328:9,22; 337:18;372:7	Dworkin (12) 4:12;16:10,19;17:3; 23:6;70:9;187:19; 362:11,12,21;363:1; 369:19 dynamic (4) 52:22;64:6;164:9; 235:11 dynamics (1) 163:19 dysmenorrhea (1) 260:9 dystrophy (1) 239:21 E earlier (9) 108:11;117:12; 144:18;257:2,10; 279:14;297:6;319:9; 322:9 early (19) 39:12;42:15;44:5; 45:10;46:13;67:20; 76:12;91:21;111:2; 123:6;125:18;185:9; 196:4,6;197:1;286:12; 320:16;372:11;373:22 easier (2) 170:22;196:5 easiest (1) 47:15 easily (3) 239:21;254:14; 305:5 easy (9) 16:21;166:4;178:9; 225:3,10,22;228:19; 230:6;233:18 eccentric (1) 143:21 e-cigarettes (1) 264:7 ectopic (2) 67:19;68:6 Ed (2) 31:21;32:4 e-diaries (1) 225:9 editorial (1) 99:12 educated (1) 366:9 Edward (1) 22:3 Edwards (19) 94:3;124:9,10,11, 19;158:18;161:2; 162:4;163:3;165:16, 18;168:13;227:17; 235:4;244:22;245:5; 246:18;249:11;339:7	Edwards' (1) 195:2 EEG (7) 52:1;253:13; 309:13;315:15,16,17; 316:3 effect (24) 50:10;64:3;104:18; 136:6;146:7;182:15; 191:14;220:17;237:7, 21;247:14;249:6; 256:18;298:15,17; 303:12;319:8;322:18, 18;330:1,4,5,22; 332:20 effective (4) 43:11;76:5;101:19; 137:7 effectively (3) 136:22;173:3;201:8 effectiveness (1) 170:9 effects (13) 31:18;43:10,12; 139:18;144:16,21; 145:4,6;159:19; 203:16;222:8;235:16; 352:21 efficacy (4) 172:2;185:6,12; 199:6 effort (2) 128:18;266:3 egg (1) 66:14 Ehlers-Danlos (4) 90:21;102:4;103:4, 8 either (18) 16:17;24:7;72:6; 155:3,10;164:20; 181:13;185:5;197:3; 198:2;210:6;236:1; 254:11;264:15; 280:14;303:17;312:7; 365:4 elastin (1) 102:9 electric (1) 80:10 electrical (1) 35:9 electrographic (1) 111:16 electromagnetic (1) 309:10 electrophysiological (1) 321:14 electrophysiology (1) 27:8 element (3) 68:18;138:1;311:13 elements (17)
---	--	--	--	---

29:15;56:22; 127:19;140:1,8; 147:12;148:10;152:8; 154:6;155:12;157:9, 14,19;159:5;163:8; 228:17;241:16 elephant (1) 369:18 elevated (7) 116:19;130:7; 136:3,13;141:15; 154:17;336:10 elevation (5) 31:19;315:20; 316:3;319:19;334:7 elevator (1) 366:16 elicit (1) 59:3 elicits (1) 288:15 eliminate (1) 121:14 eliminated (1) 38:21 eliminates (1) 241:20 else (10) 14:8;23:16;54:5; 102:11;110:21; 112:10;157:18; 194:14;247:18;346:15 emails (1) 7:15 emerges (3) 130:13;146:8;147:9 emerging (5) 152:18;162:4; 208:12;370:20;373:3 emission (1) 309:17 emotional (8) 126:4;127:15; 138:1;154:6;163:16; 228:10;370:2,11 emotions (2) 149:12,14 emphasis (4) 8:1;9:10;90:14; 176:8 emphasize (7) 10:9;138:4;149:3, 22;154:3;166:16; 175:5 emphasized (1) 101:17 empirical (1) 247:6 enable (1) 30:6 enabling (1) 206:10 encapsulate (1)	338:9 encoded (1) 336:18 encoding (1) 338:5 encountered (1) 158:13 encourage (6) 10:9,17;13:15; 14:11;16:5;24:6 encouraging (2) 194:18;196:17 end (26) 9:13;11:5;13:4,16; 26:17;33:17,22;37:8; 48:18;85:7;95:21; 122:5;169:8;184:7; 185:12;187:16; 220:11;244:7;251:12; 256:14;263:17;266:5; 274:1;328:19;347:3; 368:4 ended (4) 35:1;44:11;264:19; 272:21 endogenous (7) 98:13,17;99:3,6; 133:2,3,11 endometrius (1) 78:15 endorphins (2) 98:15;309:16 endpoints (1) 198:12 ends (1) 122:7 engage (1) 25:20 engaged (1) 163:6 engineer (1) 307:3 England (1) 365:9 enhanced (1) 349:1 enhancement (3) 64:21;237:4;238:7 enjoying (2) 70:19;245:9 enkephalins (1) 98:15 enliven (1) 24:17 enormous (2) 43:19;44:8 enough (22) 11:6;12:18,19,22; 158:3;166:21;175:14; 185:3,4;186:15; 196:17;200:12;208:3, 18;225:22;234:13; 290:10;328:8;332:19;	342:9;348:21;372:16 enrich (4) 183:22;188:17,19; 192:18 enriched (1) 184:9 enriching (1) 184:17 enrichment (6) 184:19;185:2,15; 187:9;188:20,22 enroll (2) 196:14;201:17 enrolling (1) 201:9 entering (1) 133:4 enterprise (1) 112:11 entertain (1) 201:7 entire (4) 5:17;51:19;311:11; 348:7 entirely (9) 29:1;50:15;57:22; 73:22;94:15;97:3; 217:9,14;240:17 environment (2) 178:20;183:5 environmental (2) 126:10;304:16 epi (3) 219:7;300:22;369:5 epicenter (1) 89:6 epidemiologic (1) 138:18 Epidemiological (1) 355:11 epidemiologically (1) 258:12 epidemiology (1) 263:12 epidural (1) 233:6 epilepsy (2) 111:15;112:5 epileptic (1) 320:18 episodic (2) 332:16;333:19 equal (6) 87:21;273:2; 275:18;317:14;318:5; 333:20 equally (1) 334:14 equate (1) 364:16 equivalent (1) 245:16 ER/LA (1)	175:13 era (2) 100:6;193:20 Eric (6) 41:22;43:2,21;44:7, 9,20 error (2) 183:15;282:22 especially (12) 5:20;100:3,21; 124:13;167:15;196:4; 214:8;242:12;274:14; 294:2;341:7;347:6 essence (1) 223:15 essentially (6) 9:13;44:9;287:17; 289:14;296:3;303:8 establish (2) 251:10,11 established (1) 170:16 establishing (1) 48:2 establishment (1) 45:11 estimate (5) 51:14;265:5;266:9; 280:21;282:22 estimates (4) 263:17;264:22; 265:2;266:22 estimating (1) 271:20 estimation (2) 313:4;367:14 estrogen (1) 208:10 et (8) 41:20;71:11;132:7; 144:11;223:1;248:10; 340:6;347:1 Eva (1) 211:16 evaluate (3) 134:18;183:13; 231:13 evaluated (1) 153:15 evaluating (1) 184:6 evaluation (2) 170:9;226:20 even (61) 9:1;13:1;14:15; 35:19;36:10;42:22; 48:22;75:12,14;77:8; 82:20;85:16;89:19; 99:10;120:4;128:1,9; 129:22;131:9;132:8; 135:2;137:15;143:18; 145:19;148:2;166:19; 176:16;181:21;	182:17;186:14;191:7; 207:13;208:19;226:2, 7;227:5;230:8; 231:20;232:8;233:17, 22;235:13;236:4,8; 237:16;243:8;248:14; 249:4,17;251:8;254:4; 269:8;276:22;277:17; 293:11;294:16;324:4; 326:15;336:4;368:4; 370:21 evening (1) 11:1 event (10) 122:8;308:8;309:8, 19;323:12,14,15,21; 349:21;350:8 events (2) 123:14;309:11 eventually (3) 164:12;169:8; 236:12 everybody (6) 12:3;14:7;21:8,11; 264:9;351:13 everyone (11) 85:2;106:17,17; 124:11;157:16;169:2, 4;223:12,13;261:16; 262:19 everywhere (4) 71:7;111:12;112:3; 311:21 evidence (17) 105:20;121:9; 134:1;158:16;218:10; 221:6,13,15;227:8; 250:3,9,12;252:5; 257:1;305:15;349:2; 360:4 evolve (5) 35:6;37:5;61:12; 298:2;317:13 evoked (5) 317:3,6;323:20; 334:16;365:8 evolution (1) 189:11 evolutionary (1) 206:11 evolve (1) 267:7 evolved (3) 48:10;264:17; 282:17 evolves (1) 108:5 evolving (2) 264:21;308:5 Ewan (2) 266:4;284:11 exacerbated (1) 365:11
--	---	---	---	---

<p>exacerbation (1) 365:12</p> <p>exact (4) 191:17;211:9; 269:2;327:14</p> <p>exactly (19) 22:14;29:8;31:21; 39:22;42:7;47:4; 58:18,19;62:10;94:11; 101:13;102:17;116:7; 239:11;270:21;321:7; 353:4;361:13;369:6</p> <p>exaggerated (1) 49:11</p> <p>exam (1) 301:20</p> <p>examine (1) 297:9</p> <p>example (35) 18:17;33:17;57:6; 74:1;81:22;84:15; 97:1;114:1;121:13; 127:8;136:7;153:1; 164:2;167:9;174:22; 178:6;180:21;181:2; 191:4;192:15;235:11; 237:14;274:4;276:6; 287:7;290:13;293:5; 295:6;299:19;309:14; 320:21;323:7;331:18; 332:3;334:22</p> <p>examples (3) 189:17;205:14; 292:13</p> <p>exceeded (1) 297:12</p> <p>exceeds (1) 345:16</p> <p>Excellence (1) 285:8</p> <p>excellent (1) 109:14</p> <p>except (5) 121:2;167:7;250:8; 269:20;290:3</p> <p>exception (1) 258:11</p> <p>excitability (7) 35:8;36:3;38:18; 46:19;47:1;51:1;70:7</p> <p>excitation (1) 241:9</p> <p>excitatory (4) 28:4;234:18;347:1, 20</p> <p>excited (2) 51:4;57:22</p> <p>exciting (6) 41:21;42:12;56:20; 57:21;71:12,12</p> <p>exclude (7) 109:20;115:17; 214:4;235:21;255:14;</p>	<p>256:9,11</p> <p>excluded (7) 111:6;185:11; 268:15,18;269:14; 270:2,22</p> <p>excluding (1) 256:12</p> <p>exclusion (3) 19:7,15;213:22</p> <p>exclusive (1) 120:16</p> <p>exclusively (3) 43:4;53:6;289:14</p> <p>excruciating (1) 229:16</p> <p>executive (2) 8:5;9:2</p> <p>exemplified (2) 150:17,18</p> <p>exercise (5) 143:20,21;144:10, 13;258:15</p> <p>exercise-induced (1) 135:8</p> <p>exercises (2) 144:1,3</p> <p>exhibit (1) 305:10</p> <p>existence (5) 78:21,22;79:2; 234:13;276:5</p> <p>examples (1) 54:9</p> <p>exogenous (1) 98:18</p> <p>expand (6) 41:15;119:10; 183:20;184:4;232:15, 18</p> <p>expanded (2) 36:20;47:8</p> <p>expansion (2) 35:5;230:14</p> <p>expansive (1) 175:17</p> <p>expect (7) 15:10;79:11; 148:18;203:18; 207:19;244:18;367:20</p> <p>expectancy (5) 203:17,20,22; 204:21;205:5</p> <p>expectation (1) 68:6</p> <p>expectations (1) 261:18</p> <p>expected (1) 59:2</p> <p>expedience (1) 201:15</p> <p>expensive (1) 194:12</p> <p>experience (19)</p>	<p>73:13;76:16;113:5; 126:1;129:17;130:20; 137:16;139:18; 144:16;150:6;190:20; 191:13;196:15; 204:22;224:20;226:4; 250:21;263:6;367:19</p> <p>experienced (1) 74:22</p> <p>experiences (1) 357:19</p> <p>experiencing (7) 74:16;76:7;80:9; 81:4;101:14;293:12; 343:11</p> <p>experiment (6) 33:13,18,20;34:1,4; 245:12</p> <p>experimental (9) 59:3;151:11;152:2; 248:14;258:21; 311:15;338:22; 341:18,20</p> <p>experimentally (4) 42:5;65:22;204:17; 213:13</p> <p>experiments (2) 326:8;334:15</p> <p>expert (3) 268:1,4;279:15</p> <p>explain (3) 63:13;71:8;137:5</p> <p>explained (2) 113:11,14</p> <p>explaining (1) 124:7</p> <p>explains (2) 40:16;141:2</p> <p>explanation (1) 370:11</p> <p>explicit (1) 58:11</p> <p>explode (2) 80:7;353:9</p> <p>explore (5) 43:18;45:3;46:21; 50:7;241:10</p> <p>exploring (3) 27:5;38:11;56:9</p> <p>expose (1) 243:3</p> <p>exposing (1) 33:22</p> <p>exposure (2) 32:10;220:3</p> <p>express (4) 51:9;197:18;231:5; 358:21</p> <p>expression (1) 61:16</p> <p>expressions (1) 48:15</p> <p>exquisitely (2)</p>	<p>43:7;229:12</p> <p>extended-release (1) 175:1</p> <p>extension (1) 193:21</p> <p>extensive (1) 111:2</p> <p>extent (16) 60:22;119:11; 130:9;165:3;173:14; 174:7;212:5;213:12; 218:8;220:16;230:21; 231:15,17;232:18; 244:11;355:20</p> <p>extra (1) 196:21</p> <p>extraordinary (1) 29:13</p> <p>extrapolating (1) 172:2</p> <p>extrapolation (2) 174:1;178:3</p> <p>extreme (1) 128:10</p> <p>extremely (4) 56:20;57:20;58:11; 347:10</p> <p>extremes (1) 210:6</p> <p>eye (4) 70:21;78:15,16,18</p> <p>eyes (4) 70:22;78:19,19; 129:18</p>	<p>102:19;104:14;118:2; 175:21;184:15; 207:22;210:12; 220:15;227:2;235:7; 253:2;274:11;280:13; 285:21;333:14; 335:21;353:8;360:8</p> <p>factor (20) 20:13;54:17;63:20; 64:13,14;97:2;114:3; 126:22;135:10; 137:21;138:9;147:6; 148:6;158:22;163:1; 168:7;291:2,4,20; 305:14</p> <p>factors (51) 57:13;75:1;85:13; 88:4,6;101:12,12; 107:7,12,18,19; 108:12,15;127:1,15; 129:4,12;130:1,7,10; 137:16;138:11; 142:11;145:16;146:2; 147:11;148:21;154:5; 155:9;159:6,21; 161:11;163:16;172:3; 179:12;207:9;288:19; 289:2,3,6;290:7; 291:6,9,11,15;292:8; 297:16;301:12,12; 304:16;356:22</p> <p>fades] (2) 368:13,20</p> <p>fail (2) 209:10;240:10</p> <p>fails (1) 209:11</p> <p>failure (4) 62:17;64:18;75:8, 12</p> <p>fair (4) 115:5;166:21; 212:16;355:10</p> <p>fairly (15) 128:9;140:9,10; 153:4;168:6;173:20; 209:2;251:6;288:5; 299:15;303:12; 360:17;361:9;371:20, 20</p> <p>fall (5) 134:21;164:6; 232:3;253:14;325:2</p> <p>fallen (1) 325:16</p> <p>familial (2) 289:3;290:5</p> <p>familiar (9) 4:22;5:5;8:20;70:3; 131:10;160:3;280:11; 283:3;312:17</p> <p>family (7) 49:4;263:9;289:17,</p>
F				
			<p>face (3) 44:20,20;332:9</p> <p>faced (1) 190:18</p> <p>facial (4) 332:1,2,2,13</p> <p>facilitated (2) 40:22;303:2</p> <p>facilitating (1) 81:6</p> <p>facilitation (12) 44:1;45:11;47:10; 53:20;128:7;133:3; 134:8,16;155:15; 298:18;323:9;336:5</p> <p>facilitative (1) 254:21</p> <p>facilitatory (3) 50:10;133:14; 135:16</p> <p>fact (35) 11:19;14:2;20:3,11; 30:5;36:13;46:9; 52:11;66:7;74:20; 76:16;77:8,12;79:15; 90:20;91:7;101:18;</p>	

<p>20,21;290:1;366:13 famous (1) 32:3 fantastic (1) 165:18 far (10) 104:9;147:2; 178:15;207:15; 247:11;267:9;293:15; 351:13;355:18;373:14 FARRAR (16) 66:21,21;105:19,19; 121:13;159:12,12; 193:18,18;247:9; 249:19;342:6;344:15; 346:6;354:5,9 Farrar's (1) 346:16 fascinating (1) 165:1 fashion (1) 320:15 fast (1) 273:8 faster (1) 350:11 fatigue (8) 76:2;78:1;79:12; 84:11;108:8;126:18; 190:21;199:3 favor (2) 72:8;325:17 favorite (3) 14:22;18:18;168:13 FDA (10) 22:11,13,17;23:10; 174:14;190:8;197:12; 200:22;203:22;244:13 FDA-focused (1) 197:11 feasible (1) 187:10 feature (4) 39:19;95:18;253:7; 257:7 features (17) 41:16;47:21;49:17; 52:17;53:15;66:15; 79:3;108:3;220:6; 221:19;222:1;297:7, 20;298:7,20;342:22; 355:6 federal (2) 168:22;172:6 feed (2) 101:7;313:2 feedback (2) 70:9;247:14 feeding (2) 310:21;350:12 feel (13) 14:21;23:22;78:19; 109:20;113:6;240:9;</p>	<p>242:11,13;257:7; 263:20;278:4;281:12; 367:21 feeling (4) 48:18;56:17;319:3; 327:17 feels (3) 77:18;293:9;306:20 Feldman's (1) 211:16 fell (1) 160:6 felt (5) 32:5;230:1;232:8; 280:17;285:19 female (7) 93:1,5;208:22; 265:9;272:10;288:21; 289:11 females (7) 92:15,19,20;208:2; 231:12;289:9,14 fantanyl (2) 175:13,16 few (14) 52:12;128:22; 150:9;157:20;177:17; 203:9;276:11;279:20; 292:13;301:6,6; 307:21;323:5;329:15 fiber (3) 211:2,10,20 fibers (6) 67:22;68:16; 211:18;231:2;237:15; 241:19 fibro (4) 178:11;191:16,18; 356:3 fibromyalgia (163) 18:17;19:5;20:15, 17;58:17;65:5;73:7; 75:11;76:9,10,12,16, 18,22;77:2,16;78:7; 79:1;83:3,6,9,11,13, 20;84:22;85:3,5,7,11, 21;86:2,14,19;87:14, 18,19,20;88:12,14,15, 19,21;89:6,12,20,21; 90:6;91:2;93:17;94:8, 10,11,17;95:15;98:12, 13;99:3;102:21; 103:9;105:22;106:15; 108:21;109:3;111:3; 114:8;116:4,4;118:3, 4,11;120:9;122:15; 123:3;126:15;134:3, 15;135:1;136:1,3,9, 14;150:21;151:6,18; 153:10,19;154:2; 162:10;177:15;181:4, 14;191:5;206:16; 210:1,9;219:4;221:16;</p>	<p>223:21;224:7;248:21; 251:6;255:4,21,22; 256:7;263:1,9;265:2, 9,14,19;267:21;268:3; 269:6;270:6;272:4,12, 20,22;273:5,12;275:3; 276:3,7,15,19,21; 277:8;278:2;280:10, 14;281:2;282:9,12,19; 283:4,11;284:2;287:6, 7,9,13,14;288:2,3; 290:19;293:21;299:6, 7;316:18,21;317:8,14; 318:3,6,11;319:14; 327:21;328:21; 337:16;338:7;360:14; 362:15 fibromyalgianess (3) 228:7;248:20; 249:21 field (20) 25:14;27:12;28:8; 33:1;41:10;72:8; 75:17;77:13,15;159:8; 182:5,7;308:19; 310:20;311:1;312:15; 320:9;324:3;358:11; 365:18 fields (38) 30:4;31:9;32:17; 33:11,14,21;34:3; 35:5,39;12;41:4,15; 203:7;204:21;205:19; 206:13;215:12;216:1, 6,17,20;217:17; 218:15;221:8;222:9, 13;230:10,17,19; 236:17,19;239:19; 240:13,19;246:17; 256:22;261:3;338:19; 348:8 fifth (1) 321:3 fight (1) 223:3 figure (8) 136:22;139:15; 158:3;196:5;240:6; 243:20;266:8;366:18 figured (2) 4:13;209:2 figures (4) 271:18;272:17; 279:3;294:11 figuring (1) 114:6 fill (1) 87:2 filled (1) 173:7 filling (1) 7:15 FILLINGIM (17)</p>	<p>103:13;129:10; 209:6;284:21;285:12, 13,19;286:12;299:18; 341:12;351:11;355:1; 356:11;357:17; 361:20;368:15;369:2 final (10) 88:5,7;155:3,17,18; 156:18;243:18;244:1; 253:21;268:21 finally (4) 44:20;100:19; 110:13;167:3 find (19) 21:13;79:10,10; 82:1;86:4;121:18; 127:6;142:2;172:20; 183:16;247:5;303:19; 316:17;319:19;329:3; 330:4;346:17;360:18; 363:10 finding (13) 8:17;120:19; 141:16;211:12;219:1, 8;275:7;276:14; 277:3;279:19;295:12; 322:6;365:4 findings (23) 35:3;89:10;90:2,7; 98:11;149:22;150:20; 158:8;167:22;198:2; 269:13;271:18;273:3; 274:13;292:15;297:3; 301:7,14;303:17; 307:11;321:14; 359:22;362:6 finds (1) 60:19 fine (4) 15:14;20:22;154:2; 224:22 finger (1) 321:2,3,3,10 fingers (1) 321:9 finish (2) 140:10;373:21 finished (1) 265:22 fire (4) 40:18;114:16; 115:12;221:15 firing (2) 67:19;247:15 firm (1) 264:4 first (61) 6:14;10:21;14:9,15, 21;24:15,19,21;25:7, 12;26:14,15;27:2; 31:18;34:11;39:6,9; 41:3;59:22;60:16; 73:1;83:8;87:4;89:14,</p>	<p>17;93:17;123:9; 136:12;149:7;155:2,2; 160:5;171:21;175:21; 176:6;180:1;182:11; 184:2;196:3;197:11; 199:15;238:11; 243:18;250:17; 251:10;262:8;263:3; 285:20;290:13,15; 297:17;302:7;313:15; 328:15;329:1,22; 330:21;335:13; 341:17;350:20;367:10 fit (3) 18:7;255:18;335:8 fits (3) 165:6;286:6;371:4 Fitzgerald (1) 27:3 five (5) 8:7;81:22;82:5; 172:5;373:21 fix (2) 104:5,10 fixed (3) 59:10;177:13; 186:18 fixed-dose (2) 186:11;187:5 flag (1) 270:15 flattened (1) 335:16 flattered (2) 124:20,21 flavor (1) 57:17 flavored (1) 175:22 flavors (1) 103:14 flexion (3) 35:7;36:19;37:21 flexor (10) 28:16;29:7,9;30:3, 11;32:17,22;33:16; 39:3;42:8 Florida (2) 285:5,9 flow (12) 309:20;310:7,13; 344:18,21;345:9,13, 13,15;346:8,10;347:5 flu (1) 156:8 fluctuate (1) 355:7 fluctuations (2) 324:9,15 FM (1) 284:5 FMN (1) 28:15</p>
---	--	---	--	---

<p>fMRI (26) 93:18,20;157:17; 161:15;163:13;180:5; 181:22;236:8;310:1,3; 311:9;320:5;323:2,12; 332:3;334:15,18; 336:11;338:20;340:5; 349:19;350:5;363:2; 365:21;366:14;367:10</p> <p>fMRIs (1) 362:13</p> <p>focal (1) 356:1</p> <p>focus (14) 20:14;38:20;46:17; 49:4;50:15;57:21; 128:6;129:1;148:14; 150:14;166:7;195:20; 282:11;323:1</p> <p>focused (15) 145:14;170:20; 172:15;183:9;263:1; 264:11;265:10;266:1; 267:6,10;272:22; 277:6;280:10;282:9; 313:18</p> <p>focusing (4) 21:6;137:19;279:7; 310:2</p> <p>folks (3) 306:18;341:14; 346:4</p> <p>follow (8) 58:14;81:22; 119:19;244:22;245:8; 324:16;355:16;356:5</p> <p>followed (4) 129:6;132:14; 229:21;258:14</p> <p>following (6) 13:3;112:16; 216:21;217:2;254:18; 318:15</p> <p>follow-up (4) 111:8;212:6; 227:17;303:6</p> <p>Food (1) 169:14</p> <p>foolish (1) 165:19</p> <p>foot (5) 31:10;121:16,17; 122:6;201:9</p> <p>foothold (1) 118:16</p> <p>forbid (1) 15:3</p> <p>force (2) 186:17;370:15</p> <p>forced (3) 211:3;213:21; 280:17</p> <p>forearm (1)</p>	<p>144:11</p> <p>forest (1) 135:21</p> <p>forever (1) 107:11</p> <p>forget (4) 7:8;175:6;356:20; 368:1</p> <p>forgot (2) 14:22;260:1</p> <p>forgotten (1) 15:10</p> <p>form (3) 237:7;297:21; 299:21</p> <p>formal (1) 12:15</p> <p>formally (1) 66:19</p> <p>format (1) 24:11</p> <p>former (1) 192:21</p> <p>forms (1) 37:1</p> <p>formulation (1) 176:7</p> <p>forth (7) 197:20;199:1; 225:6;291:1;351:18; 355:8;362:7</p> <p>forward (7) 26:5;234:20;262:7; 264:1;267:2;286:3; 340:18</p> <p>found (32) 33:4;37:20;39:2; 47:4;50:1,9;60:15; 92:22;114:2;116:7; 192:19;211:18; 212:21;213:4;253:11; 259:21,21;268:12; 273:7;280:5;316:22; 318:3;321:7,15;322:9; 327:2;329:12;330:1, 21;333:15;335:11; 353:18</p> <p>foundational (2) 262:14;339:20</p> <p>four (6) 8:6;264:4;274:14, 19;286:19;326:15</p> <p>Framingham (1) 160:3</p> <p>frankly (7) 28:2,10;36:10;37:9; 45:15;59:18;68:7</p> <p>Fred (3) 83:4,20;87:12</p> <p>free (2) 138:19;260:7</p> <p>frequency (6) 130:20;160:15;</p>	<p>251:6;323:9;324:22; 332:18</p> <p>frequently (2) 18:11;129:17</p> <p>fresh (1) 26:16</p> <p>Frey (1) 296:16</p> <p>front (9) 5:7;6:5;7:3;10:2; 16:14;108:15;174:17; 293:19;353:17</p> <p>fueling (1) 279:5</p> <p>full (4) 157:17;241:14; 306:9;357:2</p> <p>full-text (1) 268:17</p> <p>full-time (1) 262:20</p> <p>fully (4) 220:20;221:5,11; 287:17</p> <p>fun (1) 246:16</p> <p>function (23) 29:12,17;31:3; 44:18;102:7;110:19; 135:5;148:4;160:13; 161:18;164:12;166:9, 19;205:21;206:7; 253:3;309:7;347:7,12; 349:20;350:2,10; 357:2</p> <p>functional (29) 53:10;76:2;93:13; 99:1;110:10;131:14; 149:16;150:3;204:13; 208:1;309:5;310:1; 312:18;320:17,20; 322:20;323:11;324:1, 2,8;336:10;359:12; 370:3,10;371:11,18; 372:10,21;373:4</p> <p>functioned (1) 29:6</p> <p>functions (1) 115:20</p> <p>fundamental (1) 97:14</p> <p>fundamentally (2) 215:8;216:15</p> <p>funded (2) 103:22;242:20</p> <p>funders (1) 339:4</p> <p>funding (2) 280:11;306:1</p> <p>funny (1) 169:14</p> <p>further (5) 115:14;195:22,22;</p>	<p>272:5;291:18</p> <p>Furthermore (1) 151:1</p> <p>future (10) 57:2;138:16; 228:20;301:4,9; 302:16;303:11; 338:21;358:4;371:18</p>	<p>92:17</p> <p>generalized (4) 277:13,17;278:9; 315:10</p> <p>generally (8) 138:12;173:21; 258:5;263:11;265:1; 312:11;315:20;369:11</p> <p>generate (2) 206:2;362:8</p> <p>generated (4) 34:4;40:7;42:2; 205:14</p> <p>generation (3) 28:11;42:22;62:12</p> <p>generational (1) 27:6</p> <p>generator (2) 255:1,17</p> <p>generous (2) 34:20;280:22</p> <p>genetic (8) 55:1;102:4,8,15,22; 207:8;289:3;304:16</p> <p>genius (1) 99:10</p> <p>Germany (1) 265:10</p> <p>gets (15) 35:18;125:22; 126:14;166:10;209:8; 242:14,19;248:16; 250:2;251:8;276:22; 299:12;316:7;348:18; 354:7</p> <p>Gewandter (1) 262:12</p> <p>GI (1) 122:19</p> <p>gill (1) 44:2</p> <p>GILRON (2) 254:18;255:12</p> <p>ginger (1) 313:4</p> <p>given (12) 45:17;57:17;59:15; 70:22;135:18;239:13; 266:10;281:8;319:15; 348:22;351:8;372:15</p> <p>gives (3) 89:7;236:8;282:7</p> <p>giving (11) 83:8;103:3;107:1; 157:15;164:2;199:4; 259:10;273:7;278:16; 281:12;366:8</p> <p>glad (2) 177:18;262:16</p> <p>global (2) 226:6;238:2</p> <p>Glutamate (2) 309:14;372:3</p>
---	---	--	---	--

<p>glutamatergic (2) 211:5,19</p> <p>glutamate (1) 237:19</p> <p>goal (2) 59:18;263:16</p> <p>goals (1) 266:19</p> <p>goes (13) 15:3;121:19;122:2; 123:8;151:12;193:21; 195:13,14;200:1,6; 217:9;246:4;358:5</p> <p>gold (1) 147:2</p> <p>Good (35) 4:4;23:2;25:9; 83:19;100:11;110:5; 116:9;124:11;134:6; 154:2;158:19;163:4; 174:15;182:6;190:5; 191:22;195:9;200:2; 204:11;206:13,14; 210:10;212:14; 222:15;242:19;245:9; 257:1;260:11;261:2; 262:2;312:13;343:4; 348:20;357:4;359:1</p> <p>gout (1) 255:15</p> <p>Gracely (1) 93:19</p> <p>grade (2) 25:16;100:12</p> <p>gradients (2) 310:21;311:1</p> <p>graduate (1) 26:13</p> <p>graduates (1) 36:17</p> <p>grain (1) 346:2</p> <p>grand (2) 21:10;89:7</p> <p>grant (3) 12:6,6;104:1</p> <p>granular (1) 243:12</p> <p>granularly (1) 354:4</p> <p>graph (1) 141:13</p> <p>graphical (1) 299:21</p> <p>grapple (1) 353:20</p> <p>gravitate (1) 116:20</p> <p>gray (3) 303:18;304:3,4</p> <p>great (25) 4:19;31:15;102:3; 106:5;167:1;182:8;</p>	<p>183:12;193:16; 195:11;197:2;201:16; 212:5;226:9;227:18; 230:10;231:16; 240:22;258:15;261:1, 3,6;285:3,13;306:4; 374:3</p> <p>greater (18) 37:6;55:3;130:7,8, 17;136:13;138:22; 139:18;144:7;237:17; 265:13;289:9;315:1; 318:7;322:12;329:4,5; 367:16</p> <p>greatly (1) 229:19</p> <p>Greenspan (1) 301:2</p> <p>gross (2) 185:2;347:9</p> <p>group (74) 21:9;62:20;74:2; 76:20;77:18;78:4; 81:20;92:6;93:5,5,19; 96:11;97:4,6;99:19; 100:9;104:13;115:2,3, 17;117:13;119:18; 120:5,12,20;123:8; 134:5;137:9;140:12; 141:2;142:9;143:1,6, 7,7,19;174:15,15,17; 181:11;211:16,17; 223:20;224:8;232:3; 240:7;262:15;263:22; 275:9;284:1;286:18; 295:20;296:3,5,6,13, 17,22;297:6,10,11,22; 298:12;301:22;302:3, 17,19;303:9;319:9; 329:20;330:1,5; 339:18;361:16</p> <p>grouped (1) 369:11</p> <p>groups (18) 94:21;95:1;96:1; 105:8;133:20;135:2; 136:15;143:10; 282:18;286:16;296:4; 298:20;299:8;301:21; 333:21;336:13; 364:15;365:22</p> <p>growth (2) 63:20;97:2</p> <p>guess (13) 4:8;88:19;106:8; 113:2;115:16;236:1; 248:22;249:17; 276:13;284:8;308:5; 344:5;366:8</p> <p>guidance (12) 11:13;169:16; 170:5;171:1;172:7,8, 10;198:3,4;199:4;</p>	<p>200:21;267:4</p> <p>guidances (4) 14:20;169:12; 173:12,13</p> <p>guided (1) 268:4</p> <p>guidelines (3) 12:14,15;98:2</p> <p>guitar (1) 80:12</p> <p>Gulf (3) 113:10;123:5,10</p> <p>gun (1) 291:2</p> <p>gyrus (4) 321:1,6,8;322:2</p>	<p>happens (14) 10:18,20;14:7; 37:11;51:8;164:21; 212:1;237:19;238:13; 246:4;255:8;310:15; 345:18;350:10</p> <p>happily (1) 124:20</p> <p>happy (4) 7:21;10:17;13:10; 112:2</p> <p>hard (11) 63:13;166:8;225:8; 226:7;251:19;254:14; 256:4;265:4;334:21; 340:2;368:12</p> <p>harder (1) 166:8</p> <p>hardly (1) 83:5</p> <p>hardwired (1) 114:12</p> <p>harm (1) 264:6</p> <p>harmonizing (1) 174:6</p> <p>Haroutounian (3) 222:18,18;358:13</p> <p>Harvard (2) 25:14;307:5</p> <p>hat (2) 83:17;236:20</p> <p>hate (2) 79:17;82:14</p> <p>hazard (1) 301:3</p> <p>head (10) 51:22;236:3;269:7, 7;275:9;294:2;301:9; 353:8,13,18</p> <p>headache (15) 20:7;126:16; 141:18;143:14; 275:11;276:12;281:6; 287:11,16,17,18; 289:21,22;293:6; 294:8</p> <p>headaches (1) 275:12</p> <p>heading (2) 126:19;134:22</p> <p>heads (1) 80:6</p> <p>HEAL (2) 242:21,21</p> <p>healing (2) 206:10,20</p> <p>health (3) 276:8,9;365:20</p> <p>healthcare (1) 99:11</p> <p>healthy (41) 61:12;134:4;</p>	<p>141:18;144:2;151:1,7, 9;153:10;154:8; 253:11;313:10,16; 314:6,13,18;316:9,12, 16,19;317:7,15;318:4, 8,10,12,17;319:2; 321:19;322:4;327:2; 331:3;332:16;333:5, 17;334:6;335:11; 336:13;361:8;364:6,8, 13</p> <p>hear (11) 9:15;22:3;65:11; 112:2;120:2;133:1; 222:19;223:2;242:13; 262:16;340:8</p> <p>heard (18) 10:14;117:12; 137:21;150:8;190:16; 199:22;248:2;257:11, 15;258:21;264:9; 283:18;285:21;286:4; 288:10,22;290:8; 305:2</p> <p>hearing (7) 18:18;20:20;70:19; 122:17;218:10; 225:16;242:4</p> <p>heat (21) 31:19;33:22;132:3, 15,16;220:8;241:12; 290:11;291:13; 293:14,18,20;297:4; 298:16;299:2,12; 300:13;301:7;313:19; 326:11;365:9</p> <p>heaven (1) 15:3</p> <p>heavily (1) 79:20</p> <p>heavy (1) 176:8</p> <p>height (1) 289:18</p> <p>heightened (8) 64:11;65:2;130:11; 210:3;221:2;253:15; 254:12;298:18</p> <p>hello (1) 169:3</p> <p>help (12) 7:3,21;8:19;9:13; 78:9;84:13;163:18; 167:4;182:5;193:14; 194:20;284:17</p> <p>helped (4) 76:14;94:3;167:20; 306:5</p> <p>helpful (7) 6:14;84:6;106:11; 196:3;213:15;270:15; 372:7</p> <p>helping (1)</p>
--	--	---	--	--

<p>14:18 helps (2) 197:1;257:4 hemodynamic (5) 309:18;323:13; 349:19;350:1,9 hemoglobin (6) 310:10,14,17,18,20; 311:4 Here's (7) 175:12;176:5; 177:8;193:5;199:8; 275:1;293:13 hernia (1) 132:14 herniorrhaphy (1) 132:13 herpes (1) 54:21 Hertz (26) 22:11;168:19; 169:1,2,19;170:4; 173:19;180:3;182:8; 184:10;188:8,11; 189:14,16;191:15; 193:7,12;195:10; 196:2;197:14;198:10; 199:7;201:4;204:4; 244:17;251:4 Hertz's (1) 23:11 hesitant (1) 350:18 heterogeneity (1) 62:19 heterogeneous (1) 201:11 heterosynaptic (5) 39:21;40:12;45:11; 47:10;53:19 Hey (2) 14:22;119:4 Hi (6) 117:2;119:2;169:2; 190:12;222:18;262:19 high (45) 31:11;33:2,12;37:4; 45:20;75:8;90:22; 91:2;98:14;102:20; 106:15;141:14; 142:22;143:1,1,2,2,6, 6,7;144:6,11,15; 188:7;207:5;251:6; 268:18;275:5;279:2; 295:21;296:3,6,13,17, 22;297:5;303:1; 304:18,19;332:19; 334:17;361:12,15; 367:21;372:2 high-dose (2) 232:22;233:14 higher (32) 68:11;89:20;92:19;</p>	<p>93:6;126:4;130:16; 139:13,15;140:20; 141:1;142:6;144:8; 145:5;181:8,14; 184:16;187:18;207:9; 268:3;278:6,20; 279:10,11;294:8,15; 296:17;297:21;298:6; 318:9,9;331:20; 344:21 highest (3) 143:15;145:3,7 high-level (1) 9:17 highlight (2) 131:18,20 highlighted (1) 145:2 highly (10) 18:16;95:8;137:5; 146:18;167:11; 196:17;213:1;220:2; 326:7;348:5 hijacked (1) 209:8 hind (2) 33:11;34:1 hindsight (1) 181:5 hint (1) 292:15 hints (1) 209:13 hip (9) 75:13;85:4;86:16; 87:10;88:10;89:16; 104:3,15;167:9 historical (5) 39:8;70:16;71:14; 112:9;156:19 historically (4) 78:6;82:21;260:11; 295:17 history (18) 60:5;65:11;67:17; 74:12;110:15;111:4; 148:3;171:7;177:19; 257:12;259:4,9; 260:22;289:17,20,21; 290:1,5 hit (3) 6:7;300:10;364:4 hits (1) 125:10 holding (1) 16:14 home (2) 281:1;327:10 homunculus (1) 320:19 honestly (1) 106:4 honor (1)</p>	<p>4:7 hope (8) 11:14;14:10;27:12; 57:17;70:16;121:6; 140:5;148:18 hopeful (1) 169:22 hopefully (11) 14:1;48:5;127:16; 139:12,20;146:14; 149:3;161:8;169:8; 173:15;312:11 Hopkins (1) 292:20 horizon (1) 371:13 horn (19) 27:7;29:5;30:6; 31:13;39:2,4;41:5; 42:9;50:11,15;60:14; 66:8;69:18;235:12; 237:13;238:3;331:20; 333:19;334:5 horsepower (1) 242:6 hospital (3) 45:5;124:3;307:6 host (2) 159:21;329:17 hot (1) 16:12 hour (3) 21:3;203:5;222:5 hours (9) 87:5;89:14,18; 144:4;215:21;218:19; 266:4;355:6;370:7 housekeeping (1) 5:2 hovering (1) 274:22 Howard (2) 39:11,15 Howard's (1) 245:11 huge (6) 103:5;148:19; 160:4;168:4;356:18; 358:10 hugely (1) 166:1 human (5) 56:20;166:4;167:3; 168:11;212:8 humans (15) 42:2,14,22;57:3; 67:4;81:15;153:4; 210:20;235:12,17; 236:7,10;238:16; 308:11;347:18 humorous (1) 25:6 hundred (7)</p>	<p>12:21;14:16; 184:12;243:13; 246:22;342:10;360:18 hundreds (2) 55:22;137:15 hurt (5) 73:15,16;298:6; 299:5,16 hurts (3) 121:18;300:14; 345:7 hyperactive (1) 98:14 hyperactivity (1) 94:12 hyperalgesia (23) 41:20;42:12;43:4; 49:12,16;53:2;69:9; 22;76:17;77:17;99:4; 118:6;134:9,16;156:7; 179:7;308:14;313:13; 314:11,15,18;315:7; 317:11 hyperalgesic (2) 140:19;315:14 hyperalgesics (1) 220:10 hyperconnected (1) 150:12 hyperconnectivity (1) 152:13 hyperelasticity (1) 102:6 hyperexcitability (7) 35:22;36:21;37:3; 38:13;39:5;47:8; 48:13 hyperexcitable (2) 37:22;41:8 hypermobile (3) 102:7,10,13 hypermobility (3) 102:20;103:2,8 hypersensitive (1) 319:14 hypersensitivity (11) 34:12;35:4;36:8; 41:17;43:6,20;64:12; 67:7;119:7,7;288:16 hypertension (2) 243:16;244:1 hypertonic (1) 345:6 hypervigilance (4) 127:4;128:6;152:4; 166:6 hypochondriasis (1) 125:21 hypomobility (1) 103:1 hypothalamic (1) 333:13 hypothalamus (2)</p>	<p>333:11;334:3 hypotheses (2) 227:13;372:2 hypothesis (2) 116:3;225:12 hypothesize (1) 105:7 hypothesized (1) 372:6 hysterectomy (2) 90:3;145:22</p>
I				
				<p>Ian (2) 253:22;255:11 IASP (3) 71:21;79:15;370:15 IBS (7) 18:19;19:5;20:6,15, 17;142:2;281:1 ICD-11 (2) 368:11;369:13 ice (3) 233:20;330:16,17 iceberg (1) 85:21 ICHD (1) 369:3 ID (1) 176:7 idea (33) 21:10;28:2,3,4,10; 57:12;70:21;83:20; 98:9;99:9;102:6; 112:3;180:4;195:9,11; 228:5;230:10;239:5; 254:3;263:13;274:9, 12;282:11;283:12; 308:2;309:4;320:8; 324:4,20;348:11,21; 353:11;359:20 ideal (2) 45:13;239:17 ideas (4) 25:20;45:5;120:2; 292:6 identical (4) 83:1;90:4;120:22; 136:10 identified (9) 31:1;41:3;98:11; 219:2;270:12;273:15; 302:21;337:22;360:12 identifies (2) 187:21;288:16 identify (16) 27:11;62:1;74:9; 75:22;79:6;84:13; 96:14;101:9;106:18; 118:13;161:15;162:7; 189:10;213:10; 227:15;371:2</p>

<p>identifying (7) 8:16,16;116:10; 167:4;219:5;236:5; 258:16</p> <p>idiopathic (11) 286:15;291:21; 292:1;293:17;299:12, 14,19,22;300:5,10,17</p> <p>ie (5) 80:12;98:19; 100:13;170:10;218:18</p> <p>ignore (2) 184:8;283:17</p> <p>ignoring (1) 184:10</p> <p>illness (1) 113:11</p> <p>illustrating (1) 53:21</p> <p>image (2) 115:12;311:10</p> <p>imaged (1) 343:9</p> <p>imagine (9) 14:6;52:7;84:15; 256:4;258:20;265:3; 268:2;272:2;321:4</p> <p>imaging (24) 53:10;94:10,21; 116:1;120:18;168:4; 207:18;208:1;223:1; 227:22;243:2;307:11; 309:21;312:13,15,19; 319:19;324:2;339:6; 342:20;351:2;371:11, 18;372:10</p> <p>imbalance (2) 207:7,18</p> <p>immediately (2) 222:2;237:19</p> <p>immediate-release (1) 175:12</p> <p>immensely (1) 205:4</p> <p>IMPACT (12) 4:9,18,21;8:4; 16:18;17:9,12;128:2; 186:6,6;199:20; 262:11</p> <p>I-M-M-P-A-C-T (1) 17:12</p> <p>IMPACT-ACTION (1) 339:18</p> <p>immune (4) 214:19;216:9; 219:21;220:3</p> <p>impact (8) 28:20;197:18,19; 248:9;264:22;356:17; 357:8,10</p> <p>impacts (4) 212:2;357:7,10; 359:7</p>	<p>impairment (1) 142:18</p> <p>impart (1) 332:8</p> <p>imparted (2) 308:7;309:10</p> <p>implications (13) 19:10;37:16;45:2,8; 48:3;58:2;97:11; 180:12;182:10;183:2; 189:5;213:18;244:20</p> <p>implies (2) 62:13;149:7</p> <p>imply (3) 54:6,15;352:20</p> <p>implying (1) 227:20</p> <p>importance (1) 108:17</p> <p>important (64) 12:9;18:8;20:9; 39:21;85:6,14;95:22; 96:16;100:20;107:13; 121:3,8;129:20;130:1, 6,10,14;133:1;134:19; 135:9;139:4;145:13, 19;146:9;147:6,20; 156:22;157:2;159:17; 160:8,17,19;161:12; 165:11,21;166:1,17; 179:15;190:20; 191:21;199:14,19,21; 200:18;201:3;226:15; 227:1;228:3;236:15; 239:9;252:8;262:14; 266:10;267:9;270:16; 284:9;285:1;313:22; 315:9;325:10;333:3; 348:11;355:4;370:21</p> <p>importantly (2) 179:17;314:7</p> <p>impossibility (1) 355:15</p> <p>impossible (1) 36:15</p> <p>imprecise (1) 227:13</p> <p>impressive (3) 168:6;291:13; 301:13</p> <p>improve (3) 9:19;182:14;186:9</p> <p>improved (2) 27:9;304:9</p> <p>improvement (1) 104:16</p> <p>improvements (3) 76:8;89:16;168:7</p> <p>imputed (1) 184:21</p> <p>inability (1) 199:18</p> <p>inception (1)</p>	<p>259:18</p> <p>inches (1) 232:19</p> <p>incidence (8) 130:17;263:17; 267:1;270:10;271:3,4; 281:17;301:1</p> <p>incident (1) 256:3</p> <p>incidents (1) 130:7</p> <p>inclined (1) 245:17</p> <p>include (15) 46:20;115:17; 126:3;127:13;146:21; 147:12;166:17;197:2; 220:10;277:4;283:4,7; 288:21;325:9,11</p> <p>included (18) 42:17;47:6,11,19; 195:4;198:13,14; 258:5;267:14;272:9; 277:22;279:20;280:8, 9,20;282:5;330:10; 368:21</p> <p>includes (5) 47:14;48:19;54:18; 239:19;240:2</p> <p>including (13) 124:13;146:2,22; 163:11;203:21;233:5; 239:22;256:15; 272:21;279:6;283:21; 338:16;368:8</p> <p>inclusion (7) 19:7,15;62:20; 197:3,4;255:13;267:5</p> <p>inclusion/ (1) 213:21</p> <p>inclusion/exclusion (2) 189:6;201:18</p> <p>incomplete (1) 226:21</p> <p>inconsistent (1) 303:16</p> <p>incorporate (3) 191:1;192:8;228:8</p> <p>incorrect (1) 82:19</p> <p>increase (20) 35:7,13;42:10; 87:14,20,21;215:20; 234:18;237:19; 246:12;309:20; 310:13,13,22;311:3,5, 6;328:4,17;336:6</p> <p>increased (11) 35:18;141:3;241:9; 244:10;276:18; 279:17;304:21; 305:11,13;308:18; 363:21</p>	<p>increases (13) 36:3;46:19;47:1; 151:5,13;154:18; 156:12;184:5;287:1; 289:11,12;304:3; 319:13</p> <p>increasing (6) 58:18;187:1;211:5, 18;312:7;327:14</p> <p>incredible (1) 75:18</p> <p>incredibly (2) 121:7;372:10</p> <p>inculcated (1) 112:1</p> <p>IND (1) 196:12</p> <p>indeed (7) 39:4;42:20;43:5; 46:9;47:4;54:1; 352:19</p> <p>indefinitely (1) 190:4</p> <p>independent (9) 66:2,13;88:2;96:12; 103:15;109:9;218:2,8; 324:21</p> <p>independently (1) 335:7</p> <p>index (16) 19:1;263:19; 264:10;266:15,21; 269:17;271:5;281:15; 283:8,16;287:5;290:2, 18;299:10;328:21; 329:2</p> <p>indicate (4) 50:4;178:21;183:2; 291:19</p> <p>indicated (6) 32:19;35:21;42:20; 46:2;88:20;177:10</p> <p>indicates (3) 66:10;253:14;293:6</p> <p>indicating (1) 64:11</p> <p>indication (17) 169:10;173:8; 174:6;175:1,7;177:15; 178:19;179:13,18; 180:11;181:2;188:15; 189:4,7;190:13; 191:20;200:18</p> <p>indications (17) 169:5;171:20; 172:16,21;173:11,20, 21;174:3,8,12;175:3; 177:9;178:7,14; 180:15;181:18;191:18</p> <p>indicators (3) 355:20;356:7; 357:15</p> <p>indices (1)</p>	<p>142:14</p> <p>indirectly (1) 308:13</p> <p>individual (24) 27:10;31:5;32:17; 47:16;56:17;62:1; 110:17,18;116:14; 131:12,15,21;132:10; 161:6;221:1;223:19; 299:9;330:3;334:19, 21;335:6,9;373:12,13</p> <p>individually (2) 128:18;289:10</p> <p>individuals (24) 9:20;48:9;54:16; 55:2,3,6;57:4,8;65:4, 7;76:1;78:5;96:13; 114:17;167:18;207:4, 11;210:3;214:20; 218:22;250:20; 302:19;351:6;372:17</p> <p>indolent (1) 123:15</p> <p>induce (4) 314:15;315:22; 330:17;332:19</p> <p>induced (6) 36:3;70:5;314:10, 10;318:9;337:16</p> <p>industry (1) 264:6</p> <p>inevitable (1) 204:22</p> <p>infection (1) 122:22</p> <p>infections (2) 122:18,21</p> <p>infer (1) 109:2</p> <p>inference (1) 340:11</p> <p>inferences (1) 341:22</p> <p>inferred (2) 308:13;315:5</p> <p>inflamed (1) 34:1</p> <p>inflammasome (1) 217:13</p> <p>inflammation (35) 32:11;63:14,15; 64:15,22;72:6;75:22; 94:5,14,17;100:12; 155:8;212:22;213:6; 214:11,12,14,22; 215:2,3,6,7,9,14,14; 216:12,16,17,18; 217:9,15;218:18; 219:8;220:6;241:22</p> <p>inflammatory (13) 32:10;60:20;61:1; 63:2,3;109:22;214:3, 10;216:7,14;217:21;</p>
--	---	--	--	--

<p>246:1,11 inflate (1) 326:14 inflated (1) 317:4 influence (8) 20:8;145:17; 156:15;164:21;198:1; 266:13;345:1;361:17 influenced (7) 87:4,8;117:21; 126:20;141:5,8; 143:13 influences (4) 140:7;141:10; 235:22;283:16 influencing (1) 141:11 influential (1) 162:9 inform (2) 22:8;266:15 information (26) 9:12;11:6;12:13; 13:17,18;16:13;40:3; 117:5;164:3;172:18, 19;174:7,9;187:1; 191:9;196:22;198:6; 199:10;224:21;226:3; 227:12;228:4;282:7; 292:12;343:13;348:18 informative (3) 195:18;196:22; 205:4 inherently (1) 93:10 inhibit (1) 51:8 inhibiting (1) 81:7 inhibition (10) 38:21;47:2,6;133:3, 12;134:8,9,14;142:16; 234:19 inhibitor (1) 91:20 inhibitors (1) 97:20 inhibitory (9) 28:4;47:7;135:17; 137:8;209:21;237:21; 304:8;347:1,19 initial (14) 48:12;50:15;57:18, 21;60:21;65:11;67:3; 111:9;143:17;188:22; 196:8;209:7;227:3; 268:10 initially (3) 46:17;138:19;343:9 Initiative (4) 17:13;242:21,21; 292:5</p>	<p>inject (4) 121:18;156:4; 233:22;314:13 injected (4) 122:1;230:15; 231:1;245:13 injecting (4) 91:20;121:21; 314:21,21 injection (5) 42:3;230:20; 232:12;316:1;345:6 injured (1) 67:22 injuries (1) 61:14 injury (18) 34:5;35:11,13,17, 20;36:2;37:1;47:5; 50:12;60:15;61:4; 67:18;68:5,10;153:2; 178:13;206:6,18 injury-induced (1) 36:19 innate (1) 127:12 inner (1) 152:9 innervated (2) 321:21;322:3 innovative (1) 87:1 input (50) 27:14;30:1,7;35:14; 40:7,7,9,10,11,13,17, 19,21;41:2;42:9;49:9; 50:14;51:15,17;52:10, 12;59:15;63:17;64:5; 65:17;66:3,5,17; 68:20;69:2;72:18,19; 80:4,13;96:10,14,19, 22;117:11;118:12,21; 205:11;206:3;210:17, 22;219:3;221:3; 238:14;318:9;319:3 inputs (11) 40:21;41:6,9,12,14; 52:16,16;56:2;68:13; 117:14;210:5 in-rush (1) 310:16 insight (3) 29:4;36:10;236:9 insightful (1) 261:19 insights (1) 40:16 insistent (1) 169:20 insomnia (1) 156:4 instance (3) 186:9;200:3;343:4</p>	<p>instances (1) 250:17 instead (9) 29:4,14;55:17,21; 62:2;134:9;183:15; 306:8;334:13 Institute (1) 153:12 instrument (2) 189:5;200:5 instruments (1) 270:4 insula (37) 94:12;116:3; 150:19;151:17;165:5; 314:2,3;315:2,2,12; 318:21,22;319:20; 320:2;325:20;328:6,7; 329:5,9;331:8;333:10; 334:3;336:3,15,16,19, 20,22;349:6,15;350:5, 10;360:5,11,22; 361:13;372:3 insult (3) 106:1;239:7,14 integrate (1) 14:13 integrated (1) 347:9 Integrative (1) 307:7 intelligence (2) 56:7;370:19 intelligent (1) 124:16 intended (1) 193:12 intense (3) 17:1;126:2;319:18 intensities (1) 319:11 intensity (23) 31:11;35:6;124:6; 165:9;199:17;230:21; 296:1;316:13;325:13; 348:14,15;352:13,17; 353:5,9;355:3;356:16; 361:6,14,19;365:7,16; 367:21 intensively (1) 49:22 intent (1) 9:18 intention (1) 221:11 intentionally (4) 10:12,19;290:9; 340:1 interact (2) 10:13;37:12 interacted (1) 45:3 interaction (1)</p>	<p>196:12 interconnected (4) 147:17;150:12; 151:9;168:10 intercorrelated (1) 152:10 interest (7) 9:4;11:13;15:12; 157:12;161:20; 189:17;284:15 interested (6) 32:2;53:4;117:9; 229:2;248:18;345:15 interesting (37) 10:16;24:2;53:9; 54:9;55:1;65:10; 170:6,8,12,20;171:9; 176:15;177:22;178:7, 13;200:21;208:7; 222:19;228:4;251:4; 267:20;278:20; 287:19;316:7;319:5; 320:1;322:8;329:11; 330:12;333:12,15; 334:12;345:3;346:1; 360:9;361:17;369:22 Interestingly (2) 136:17;328:8 interictal (2) 332:16;368:17 intermediate (3) 296:5;304:18,20 intermixed (1) 168:10 internal (1) 338:7 interpret (1) 225:3 interpretation (2) 19:13;204:2 interpreted (2) 179:4;221:8 interpreting (1) 344:19 interrelate (2) 155:15;228:1 interrelated (5) 125:13;133:18; 138:5;157:4;159:2 interrelationships (1) 164:9 interrogate (1) 113:1 interspersed (1) 332:22 interstitial (7) 78:14;95:2;110:12; 214:21;259:17,19; 273:17 intervention (3) 105:4;285:8;314:14 interventions (3) 76:6;250:4;366:5</p>	<p>interview (1) 267:15 into (59) 5:1;6:11;10:4;12:4; 25:2;58:10;72:8; 91:20;105:17;125:17; 131:5;142:21;148:6; 152:15;158:7;160:5; 169:10;172:8;176:2; 179:17,18;180:8,15; 186:18;187:7;192:9; 196:18;198:6,18; 200:11,14;203:19; 211:3;232:18;236:9, 13;238:18;255:18; 261:8;263:7;264:19; 266:7;268:19;277:21; 280:6;295:20;303:13; 307:22;313:2,9; 330:15;337:14;345:7; 351:19;361:11; 362:17;368:11; 371:11;372:22 intolerable (1) 132:7 intracellular (1) 27:11 intracellularly (2) 27:22;29:19 intradermal (4) 42:3;245:13;246:9; 258:22 intrigued (1) 343:1 introduce (8) 10:3,6;21:8,11; 24:15,17;25:12; 207:14 introduced (3) 28:21;45:19;50:20 introducer (1) 261:13 introducing (1) 39:15 Introduction (3) 4:3;53:3;262:20 introductions (3) 25:1,2,4 intuitively (1) 85:2 inventories (1) 129:13 inventory (2) 53:4;129:15 inverse (2) 137:4,6 invited (1) 124:17 invoke (1) 52:7 involve (1) 62:8 involved (14)</p>
---	--	--	--	--

7:14;15:13;20:4,8; 43:8;56:22;195:7; 203:22;213:3;245:12; 326:5;345:10;356:22; 371:6	173:8;224:2	junction (3) 325:20;332:11; 333:9	257:2,17;260:19; 296:20;311:10;313:1; 315:18;316:4;323:20; 324:2,10,16;325:1; 326:19;327:18;329:7, 19;330:15;331:9,11; 332:14;333:12,18; 334:8;335:13;338:4; 340:14;344:4;350:17; 359:18,22;362:14; 363:10;365:17;369:3; 370:10;371:19	32:4,8;138:8; 277:16;279:1 Labeling (7) 174:13;178:18; 188:14;190:19;192:5; 198:14;346:5 labels (1) 184:11 laboratory (6) 132:22;133:8; 136:8;140:15;143:18; 166:14 laboratory-based (1) 131:12 laborious (1) 119:18 labs (1) 326:16 lack (6) 15:12;77:12; 185:12;208:12; 234:19;239:13 lags (1) 365:18 LaMotte (2) 41:22;43:2 Lancet (1) 46:1 language (2) 174:7;191:17 Languidness (1) 129:15 large (25) 33:14;41:5;55:16; 60:21;67:21;117:1; 132:12;136:6;140:16; 158:13;205:12; 220:16;226:5;232:18; 237:21;282:3;283:21; 292:22;294:1,12; 302:19;307:8;343:21; 360:17;364:22 largely (4) 25:4;67:21;88:2; 209:16 larger (12) 41:15;85:22;194:1; 318:19;319:3;322:8; 328:22;350:12;361:8; 365:19,19;367:13 laser (1) 51:10 last (21) 4:9;8:3;38:22;50:8; 168:18;174:4;197:7, 10;200:5;214:10; 230:12;262:20; 267:19;306:19; 307:21;324:3;328:14, 22;348:9;367:6;370:7 lasted (1) 48:13 lasts (3)
involvement (1) 62:11 involves (2) 309:5;329:8 iPhone (1) 5:11 ipsilateral (4) 31:10;33:2;296:9, 10 IR (1) 175:11 Iraq (1) 123:10 Irene (1) 372:13 ironic (1) 56:13 irrelevant (1) 59:18 irreversible (1) 209:21 irritable (17) 65:6;78:8,14,18,21; 110:10;122:15,17,18, 22;142:1;232:2; 257:13;274:17,20; 275:6;287:11 irritableness (1) 232:9 Island (1) 339:15 isolate (2) 156:9;271:18 isolated (1) 356:4 isometric (1) 143:21 issue (13) 46:7;109:8;194:1, 14;209:15;225:2; 264:18;283:20;340:3; 342:16;357:12;362:9; 369:13 issues (11) 17:18;47:22;48:6, 10;161:22;171:4; 195:7;284:1;323:5; 340:22;341:8 Italy (1) 271:9 itching (1) 129:18 itchy (1) 358:1 item (1) 224:1 items (6) 126:8,9;130:18,19;	J Jack (1) 60:18 Jakita (1) 26:14 Jamison (1) 144:19 Jeff (1) 167:10 Jennifer (1) 262:12 jettison (1) 112:2 Jeungchan (1) 339:5 Jieun (1) 339:5 Jim (5) 69:7;183:19;247:7; 253:22;254:2 Joachim (3) 46:20;57:7;234:5 Joachim's (2) 241:1;245:9 job (8) 9:11;24:16;116:10; 149:20;158:19;164:5; 260:11;329:19 Joel (1) 301:2 John (26) 10:5;24:22;25:7,11; 26:17;30:9;31:16; 32:21;66:21;71:10; 105:18,19;109:13; 119:1;123:17;159:12; 165:2;193:17,18; 198:16;247:7;259:16; 261:7,10;342:5;353:7 John's (1) 346:16 joined (4) 26:9;38:10;262:20; 339:13 joint (8) 65:5;83:16;84:19; 129:8,21;146:17; 147:22;296:8 joints (1) 213:2 journal (2) 15:4;365:9 journals (2) 11:9;269:2 juices (1) 55:10 Julie (2) 7:3;210:14 jump (2) 131:5;355:1	Jung (1) 292:19 Jurgen (2) 60:8;226:17 juvenile (1) 283:4 K Kandel (3) 43:21;44:7,9 Kansas (1) 210:14 Karolinska (1) 153:12 Katz (11) 119:2,2,5;121:9; 167:10;225:7,16; 257:10;258:20; 260:14;359:12 keen (1) 65:13 keep (14) 9:18;116:11;130:1; 185:3;188:18;253:6; 262:6;269:22;306:21; 326:13,14,17;370:21; 371:8 kept (2) 229:13;253:18 ketamine (4) 43:10,15;106:9; 250:8 key (12) 20:1;35:3;36:1; 49:17;56:21;61:8; 194:14;196:20;284:2; 328:5;342:8;358:16 keynote (1) 103:4 kidney (1) 243:20 kilograms (1) 318:19 Kim (1) 339:6 kinases (1) 219:22 kind (72) 9:8;13:8;21:6; 27:13;43:2;57:20; 120:17;156:13;165:6; 169:13;171:13; 172:18,19;185:21; 188:8,11;192:21; 195:20;199:16;200:8; 214:11,12,14;215:2,8; 217:15,20;228:21; 233:8;237:9;238:4,9; 239:2;240:10,19;	King (3) 13:3;20:19;48:5; 55:13;105:13;190:6; 210:18;226:19; 259:12;326:21; 341:10;345:18;363:7, 9;364:21 King (3) 26:14;41:3;295:19 kit (1) 226:5 Kleykamp (5) 262:9,18,19;284:14; 369:5 knee (34) 54:19;73:20,21; 75:13;81:3;84:18,21; 85:4;86:16;87:9; 88:10;89:16;91:20; 92:13;93:9;104:12,15; 121:17;136:8;146:14; 167:10,13;250:5; 257:18;295:21,22; 296:9;297:1,10,18; 302:19,20;304:1,2 knew (5) 21:13;29:7;125:2; 180:22;196:15 knowing (3) 6:17;29:6;180:21 known (7) 220:1;239:20; 283:12;292:22; 320:13;327:7;348:12 knows (5) 22:4,20;211:17; 236:21;292:16 L lab (9) 12:5;26:9,11;30:10; 36:18;135:14;143:21; 144:3;318:1 label (14) 85:11;86:1;89:3; 174:16;175:13,13; 191:7;192:16,21; 195:13,15,17,19; 244:13 labeled (5)	

222:3,4;346:19 late (5) 26:10;125:17; 169:3;245:7;267:4 latency (1) 322:12 later (20) 10:6;25:19;71:15; 110:11;120:11; 129:11;133:17; 139:19;144:4;149:21; 172:5;194:21;195:5; 247:10;262:5;300:14; 301:22;302:2,3;364:5 lateral (1) 296:8 laughing (1) 84:2 Laughter (40) 13:9;25:17;30:22; 34:16;19,22;38:7; 39:17;44:12,16;83:22; 85:19;86:5,11;124:18; 162:3;165:17;168:16; 169:18;170:1,3; 173:18;180:2;188:10; 189:15;192:13;193:9; 196:1;204:5,9;205:18; 217:3;245:4;249:15; 285:18;286:11; 299:17;343:18;354:8; 362:20 launched (1) 25:14 laureate (1) 28:19 layered (1) 182:9 lead (4) 24:18;57:20;69:21; 210:18 leaders (1) 144:20 leading (2) 153:7;311:4 leads (12) 59:15;67:7,13;75:2; 87:20;102:13;224:9; 248:6;310:20,22; 311:3,6 lean (1) 268:7 learn (3) 23:3;263:21;266:2 learned (4) 69:9;172:9;205:4; 280:6 learning (11) 44:19;208:5;263:4, 13;264:17;267:7; 270:16;363:16; 364:17,18;365:14 least (43)	6:14;8:15;15:2; 29:11,16;39:7;43:15; 49:7;54:2;64:11,17; 65:1;66:11,12;68:12; 107:16,18;133:7; 155:16;163:18; 166:10;171:3;179:19; 196:8;207:15;209:13, 18;221:16;225:20; 228:16;231:8;237:7; 278:1;280:20;290:4; 291:11;292:13; 303:21;322:9;327:2; 351:22;363:17;367:18 leave (9) 5:13;14:15;19:8; 21:2;70:12;158:4; 188:20;195:9;283:22 leaves (1) 169:21 lecture (1) 46:10 led (9) 28:14;29:8;30:9; 32:11;34:10;42:18; 45:9;86:13;168:5 Lee (8) 22:5;75:17;84:1; 94:3;102:2;109:22; 212:21;339:5 leery (1) 177:21 left (21) 6:21,22;10:22;15:1; 21:12;31:16;55:9; 73:16;122:22;169:6; 170:2;245:14;246:9; 272:21;273:4;286:9; 287:8;292:7;293:15; 300:2;328:7 leg (11) 151:4;237:3; 245:15;296:9;317:5; 327:9;328:1,4;329:3, 4;330:17 legs (2) 330:15;353:16 length (1) 93:15 lengthy (1) 25:2 Lesley (6) 45:3;117:2;120:15; 190:11,12;262:5 less (20) 41:22;45:13;51:14; 67:11;80:21,21;82:2; 87:15,15;89:19;93:10; 137:8;139:14;160:18; 236:13;323:12; 335:15;342:10,11; 365:17 lesser (1)	175:9 lessons (1) 280:6 letter (1) 44:9 letters (1) 287:6 letting (2) 138:2;253:12 level (19) 45:18;126:3,4; 138:20;146:3;166:20; 184:13;191:6;220:22; 221:3;224:2;225:4; 310:4;315:9;324:14; 344:21;345:8;347:10; 354:1 levels (13) 68:9,11,20;98:15; 133:5;139:7;140:20; 142:22;145:4,5; 154:21;156:16;279:11 liberal (1) 270:1 liberty (2) 224:19;249:11 librarian (1) 267:5 life (12) 110:11;120:11; 151:20;164:5;197:19; 250:16;259:4;266:14; 356:17;357:3,7,10 lifelong (2) 257:12;260:17 lifetime (10) 260:10,22;273:10, 12;274:22;275:19,21; 277:9;278:5,21 ligand (3) 98:17,18;153:5 light (7) 6:9;33:16;119:9; 163:19;237:16; 358:19;359:13 lighter (2) 4:15;277:11 lights (3) 23:18;24:3;77:4 likelihood (4) 67:11;89:15;106:3; 313:4 likely (26) 21:4;52:14;82:3; 89:19;91:14;95:8; 132:17;134:14,16; 139:16;141:9;143:16; 148:9;155:3;157:5; 194:11,22;201:18; 242:20;250:22;252:2; 281:2;283:14;286:20; 297:14;300:11 likewise (2)	71:13;204:19 Lily (2) 91:4;181:7 Limbic (1) 129:15 limitation (2) 177:5;326:12 limitations (4) 176:11;308:11; 322:20;341:10 limited (4) 50:2;166:3;177:1; 281:4 line (6) 32:4;88:12,13; 138:8;147:2;296:8 linear (1) 300:4 lines (3) 32:8;198:8;335:9 link (4) 142:17;150:5; 253:17;289:7 linked (6) 126:14;139:22; 150:22;154:5;219:14; 253:9 linking (1) 359:22 links (1) 300:15 list (2) 15:18;161:9 listed (1) 176:10 listening (1) 22:4 lists (1) 268:12 literally (4) 55:22;116:17; 211:15,18 literature (29) 46:11;54:5;83:4; 103:6;125:5,17; 158:12;173:17; 221:13;236:21; 238:21;245:18,21; 257:8;262:2;263:15; 264:14,19;265:2; 266:10;273:16; 280:16;281:18; 282:20;283:5;329:18; 340:10;359:21;360:3 little (64) 4:15;6:11;13:11; 63:13;71:15;74:20; 93:4;96:21;100:17; 103:19;109:6;110:11; 130:3,12;131:6;135:4; 145:11;149:6;166:2; 169:3,5,11,15,17; 170:22;195:21;	198:11;224:15;229:3; 233:19;236:8,10; 238:5;247:10,11; 261:18;263:8;270:20; 271:17;272:14;280:4; 284:17;286:10;287:8; 291:13;292:8;299:7; 306:7;313:1,13; 319:22;321:5;324:4; 328:10;336:8;340:11; 344:15;346:11; 350:11,12,17;355:17; 371:10;373:5 Littleton (1) 26:15 live (5) 70:17;114:9;203:5; 247:3;357:2 lived (2) 75:3;76:11 lively (1) 261:17 living (3) 356:15,18;357:1 load (1) 361:7 local (8) 35:19;121:14,19; 221:22;222:2,4; 233:22;321:15 localization (2) 314:17;316:11 localize (1) 213:16 locally (2) 310:16;347:1 locate (1) 271:3 located (2) 265:16;325:12 location (8) 51:12;103:11; 143:17;254:22;294:4; 325:13;327:16;353:2 locations (7) 312:20;313:1; 352:10,14,22;353:2,6 Loggia (1) 153:6 logging (1) 369:7 logic (1) 201:15 logically (1) 100:8 logistical (1) 7:12 logistics (3) 7:18;17:5;24:11 lollipop (1) 176:1 London (1) 26:10
--	--	---	--	---

<p>long (20) 13:11;21:14;22:18; 33:8;58:16;67:17; 80:5;101:2;110:6; 130:19;152:20;170:5; 173:16;179:1;182:19; 185:4;186:19;232:10; 320:13;332:22</p> <p>long-acting (1) 175:1</p> <p>longer (12) 13:21;37:7;38:15; 66:5;75:22;142:10; 147:3;163:5;230:3; 302:3;370:1,10</p> <p>longitudinal (7) 112:9;119:20; 163:14;213:10;258:2, 4,10</p> <p>longitudinally (6) 168:2;243:5; 250:15;258:14; 373:12,17</p> <p>long-lasting (1) 153:1</p> <p>longstanding (1) 32:1</p> <p>long-standing (1) 229:11</p> <p>long-term (8) 39:22;40:5,14;43:9; 148:16,16;258:2,4</p> <p>look (96) 14:5;26:5;31:3; 37:18;55:18,22;63:1; 79:9;86:19;89:11,13; 92:18;94:18;97:17; 98:1;103:6,9;104:6; 106:5;108:4,5;111:3; 112:11;113:20; 119:16;128:19;129:7; 136:20;137:2,3;139:7; 145:17;150:3,6; 154:20,21;159:9; 160:7;168:3,4,4; 173:4;174:2;175:19; 187:8;191:16;201:3; 208:8;214:2;216:11; 223:18;230:13,20; 237:1;238:16,20; 240:5;243:4;250:15; 251:5,15;255:22; 256:19;258:14;266:9; 267:12;274:17; 279:20;287:19,21; 288:6;296:15;298:8, 22;299:11;300:2,7; 311:9;312:16;316:3, 20;317:21;318:13; 323:19,21;327:20; 328:20;329:2;330:3; 331:4;332:1;334:19; 337:2,8;343:5;371:15</p>	<p>looked (35) 31:21;36:18;86:14; 87:3;99:5;119:13,15; 122:15;136:16; 229:20;260:3;267:22; 269:5;275:16,21; 277:5;280:2,19;293:1; 294:12;295:19;298:2; 301:12;317:5;319:10; 321:13;332:15; 334:13;335:7;346:12, 13;361:3,12;369:21; 373:9</p> <p>looking (71) 26:5;29:1;32:13; 44:2,5;52:9;68:4; 71:19;79:20,21;82:10; 84:7;85:7;92:5;93:20, 21;106:22;110:20; 118:15;123:6,9; 144:21;153:14; 158:12;180:15;199:5; 205:8;214:9;224:2; 260:12;265:11;268:8, 12;270:14;271:2; 273:17;275:6;278:3,9, 14;279:12;284:4,7; 295:7;296:2;300:18; 303:14;311:12; 313:12,15;322:21; 325:18;329:7,18; 340:5;341:15;343:4; 347:15,22;348:1,2,3; 352:6;357:1;360:2; 364:14;372:17,18; 373:12,13,15</p> <p>looks (21) 48:7;52:11;58:19; 94:11,15;96:11;98:12; 99:2;120:19;203:17; 211:9;214:19;221:18; 244:4,6;278:5;286:9; 294:3;300:8;311:10; 372:14</p> <p>loops (1) 247:14</p> <p>lose (5) 147:15;184:22; 201:14;272:17;273:6</p> <p>losing (1) 187:1</p> <p>loss (5) 47:5,6;209:20; 227:7;238:2</p> <p>lot (122) 10:21;16:2;18:6,18; 72:1;76:11;78:9,10, 13;81:2,18;88:3; 90:19;91:10,18;93:22; 95:14;100:2,10;101:1; 103:9,21;107:6; 108:11,14;111:3,4; 112:21;114:17;</p>	<p>115:21;120:16; 122:15;123:5;131:8; 132:11;140:7;141:6; 150:10;155:8;157:1; 166:2;174:13;176:10; 180:13;181:11;192:3, 4;196:2;197:21; 199:15;205:4;208:5, 12;210:14;214:15; 224:15;226:3;229:10; 231:12;240:3;243:9; 250:9,18;251:1; 254:10;256:2;258:15; 260:6;262:13;263:4; 264:10,14;269:10,13, 14;277:22;278:16; 281:7;283:2,6;288:13, 22;293:10,22;305:2; 306:20,21;307:10; 308:1;312:15,19; 313:20;315:16; 322:20;323:1;326:4; 329:14;339:4,6,19,19; 340:10;341:4,5; 351:20;352:8;355:18; 357:8,18,22;359:7,16, 17;360:3,7;365:17,22; 366:19;368:20; 370:20;372:1;373:17</p> <p>lots (5) 134:20;152:16; 178:9;195:7;225:9</p> <p>loud (1) 126:11</p> <p>loudness (2) 77:4;80:10</p> <p>love (3) 99:20;120:2;366:17</p> <p>low (50) 33:6;40:19,20;68:9, 19;78:15;83:13;91:9, 11,15,17;100:12; 114:3,8;126:16;139:1, 2;140:17;141:16; 142:21,22;145:6; 154:20;174:20;178:3; 181:6;186:8;188:2; 200:11,13;221:3; 241:19;242:22; 255:15;287:11;290:3, 19;293:21,22;295:21; 296:5;302:13;303:7,8; 344:12;359:4;360:14, 16;361:9;365:12</p> <p>lower (18) 33:15;69:4;126:3; 151:4;153:9;221:14; 261:18;274:4,17; 276:2,3;280:4;310:20; 311:1;317:4;335:17; 344:1;361:7</p> <p>lowering (1) 237:3</p>	<p>low-grade (6) 214:12,22;215:9,13, 14;219:8</p> <p>low-intensity (1) 37:5</p> <p>low-threshold (1) 231:4</p> <p>lozenge (1) 175:22</p> <p>LPS (4) 156:4;214:18; 215:19;218:19</p> <p>Luana (1) 203:13</p> <p>lucky (1) 362:19</p> <p>lumbar (1) 359:2</p> <p>lump (4) 97:8;220:15; 240:12;254:13</p> <p>lumper (3) 240:5,13;261:21</p> <p>lumping (2) 240:17;242:2</p> <p>Lunch (6) 7:8;197:8;202:2,3; 226:2;369:21</p> <p>lupus (8) 62:18;63:1;75:19; 80:2;96:8;217:6,22; 256:9</p> <p>lux (3) 319:11,13,15</p> <p>lying (3) 265:20;324:7;327:1</p> <p>Lyrica (2) 178:6;191:4</p>	<p>major (13) 15:7;27:18;30:1; 38:20;39:19;40:2,15; 47:13;50:11;54:3; 201:12;278:22;279:13</p> <p>majority (5) 12:22;32:22; 265:17;272:6;282:8</p> <p>makes (13) 87:14;107:15; 118:5;120:4;208:22; 218:1;250:10,13; 252:2;281:8;323:10, 16;327:18</p> <p>making (10) 116:11;162:21; 198:20;250:10,12; 251:3;252:6;277:19; 278:4;297:16</p> <p>maladaptive (5) 149:17;151:6; 152:12;165:4;322:16</p> <p>maladaptively (1) 150:11</p> <p>MALE (5) 89:1;93:2;170:2; 207:11;370:16</p> <p>males (5) 92:15;93:5;208:2, 14;231:11</p> <p>male's (1) 93:6</p> <p>mammals (1) 44:6</p> <p>man (2) 38:9;128:15</p> <p>manage (3) 189:12,14,19</p> <p>managed (1) 225:3</p> <p>management (2) 178:22;179:5</p> <p>manifest (1) 179:6</p> <p>manifestations (6) 47:13;51:3;71:6; 114:18;179:15;245:20</p> <p>manifests (1) 55:11</p> <p>manipulate (1) 164:16</p> <p>manipulating (1) 163:15</p> <p>manipulations (3) 156:1;341:20,21</p> <p>manmade (1) 212:9</p> <p>manufacturers (3) 99:15;198:5,22</p> <p>manuscript (7) 11:7,20;13:1,19; 14:3;15:13;357:13</p> <p>manuscripts (2)</p>
		M		
		<p>machine (4) 363:16;364:17,18; 365:14</p> <p>mad (2) 269:11;275:20</p> <p>magnetic (3) 309:15;346:7,8</p> <p>magnitude (2) 135:8;347:17</p> <p>main (10) 90:17;95:17; 265:18;266:19;269:9, 15;272:18;276:13; 330:4,5</p> <p>mainly (1) 270:8</p> <p>maintain (1) 155:20</p> <p>maintained (2) 144:22;345:8</p> <p>Maixner (1) 81:19</p>		

<p>10:14;95:16 Many (54) 4:20;43:14;46:8; 47:12;51:6;52:11; 53:10,17;71:1;78:2; 83:3;88:19;96:1,20; 98:20;101:18;126:15; 131:9;133:9;134:21; 149:9;152:15;153:7; 160:3;165:10;167:7; 184:20;192:19; 196:19;198:12;200:1, 1;219:4;220:17,18; 232:13,19;233:2; 250:17;256:16; 258:21;265:20;266:4; 272:15;277:1;278:3; 295:13;298:10;306:1; 307:3;330:2;342:11; 355:21;356:21 map (29) 91:5,13,22;181:4, 13;193:3;223:14; 224:14,17,21;228:9; 290:11;291:14; 293:15,20;299:12; 320:19;347:11; 352:16;353:5,10,13, 20,21;354:4,6,7,15,17 MAPP (4) 94:19;95:17;162:6; 214:16 mapped (1) 321:10 mapping (1) 327:16 maps (6) 225:10;272:19; 293:14,18;299:2; 312:2 Marchand (1) 134:3 Marco (1) 153:6 Maria (1) 27:3 marker (4) 316:4;335:18; 360:10,11 markers (6) 214:3;238:17; 307:20;361:19;365:4, 6 market (3) 177:5;178:10; 194:15 Markman (55) 10:5;24:22;25:9,11, 18;59:21;69:6;70:15; 103:12;109:14;111:8, 14;112:17;115:5; 118:22;123:18,20; 124:2;165:3;166:21;</p>	<p>168:18;192:10; 193:17;197:7;202:1; 203:4,12;204:3,6; 207:17;209:5;212:6; 213:19;222:15; 224:18;225:12;226:9; 229:5;231:20;232:21; 233:10;234:5;235:2; 236:18;239:12,18; 240:21;242:4;247:7; 252:18;253:21; 255:10;261:1,7,17 marriage (1) 164:6 married (1) 124:20 Marsha (1) 67:21 Martinos (1) 307:8 Maryland (1) 203:14 masked (1) 320:21 Mass (4) 153:7,11;158:5; 321:4 Massachusetts (1) 307:6 massive (4) 52:16;68:14;207:7; 259:2 match (2) 183:13;318:18 matched (6) 136:5;150:13; 318:10;319:1;336:12; 362:16 matches (1) 192:16 matching (1) 179:20 material (1) 205:8 matter (12) 76:17;87:13,16; 129:11;134:5;251:17; 254:7;295:10;297:8; 303:18;304:3,4 matters (1) 254:10 Max (1) 121:20 maximum (1) 28:1 may (75) 8:11;9:9;15:7; 17:10;18:12,12,15,15; 27:5;36:11;37:15,19; 50:19;52:16;54:7; 55:5;57:14;61:19,20; 62:8,9;64:8,14;66:11; 69:17;79:18;90:18;</p>	<p>92:11;96:20;97:1; 98:10;102:9;145:2; 157:8;158:22;159:14, 21;160:1;161:21; 163:2;171:7;174:8; 175:9;193:22;200:19, 19;201:3,10;208:11, 11,14;213:17;215:5,6; 221:3;226:2,19; 227:13;233:15;239:6; 241:16;251:9,10; 253:2,8;256:10; 261:20;282:12;287:3; 294:14;305:18; 345:15;357:8,9; 371:11 Maybe (51) 23:3;65:8;68:11,17, 18;69:3;107:20; 112:7;117:12;128:10; 137:15;147:1;155:1,2, 2;218:11;228:8,14; 229:1;236:21;239:4; 249:1,2;252:18; 256:17;276:8;279:6; 280:12,12;282:10; 284:15,16;291:6,13; 292:3;294:19;299:4; 300:10;317:2;339:21; 342:17;343:19; 345:20;346:21; 350:12;354:12;355:3; 356:5;357:12;362:5, 19 Mayfair (2) 7:9,11 McGill (1) 297:20 McKenzie (2) 266:4;284:11 McMahon (1) 36:17 MD (1) 366:16 MD-PhD (1) 57:21 MDs (1) 174:17 mean (20) 19:10,12;103:20; 145:15;157:20;179:3; 183:11;184:19; 219:13;233:20;234:2; 237:6;255:14;272:1; 324:13;337:4;343:20; 347:11;363:1;366:6 meaning (2) 230:1;268:13 meaningful (3) 196:9;371:12; 372:22 means (16) 12:21;42:5;50:19,</p>	<p>19:51;7;82:15;109:2; 195:11;207:14;211:3; 219:2;228:3;268:5; 274:16;336:5;347:12 meant (1) 285:14 measure (77) 55:16;56:10,18; 64:21;74:5;82:8;84:4; 86:15,20;87:2,3,14, 20;90:6;106:15; 116:5;127:21;128:4, 14,19;131:7,12;133:2, 12,13;135:9,13; 138:11;144:3;145:16; 146:1,11,15;148:13; 152:3,5;153:3;157:13, 16,19;159:6;166:5,9, 19;178:2;181:4; 185:5;192:5;193:15; 197:3;215:22;223:8, 21,22;224:7,12;227:3, 10;228:10;231:8; 236:15;243:19;244:9; 245:14;248:16; 281:17;290:14;299:2; 300:2,18;305:17; 322:13;328:9;355:4; 356:21;358:10;359:6 measured (17) 128:8;146:19; 147:5;148:5;152:12; 156:16;160:2;176:18; 227:6,21;274:21; 275:2,12;284:6;299:3; 328:11;354:22 Measurement (2) 17:13;91:3 measurements (5) 163:10,12;179:21; 199:6;241:6 measures (44) 19:21,21;20:2; 64:11;83:17;93:21; 138:6;180:4,10; 190:22;192:7,17; 193:13;194:20;195:4; 222:20;223:4;224:16; 226:14,18;227:1; 234:7,9;239:9;241:12; 247:4;257:5;290:15, 16;296:3;299:1;300:8, 16;301:8;303:9,19; 304:12;346:20;347:7; 351:1,2,7,10;352:6 measuring (14) 132:21;160:12,16, 20,22;161:11;163:16; 249:4;308:8;345:13; 347:4,4;356:14;366:4 mechanical (7) 136:10;151:3; 296:16,21;298:14,17;</p>	<p>300:12 mechanically (1) 140:18 mechanism (15) 38:22;40:2;62:2; 77:7;100:7;194:10; 206:18;207:13; 209:11;220:1;231:9; 244:12,16;254:15; 343:5 mechanism-based (5) 115:6;179:2;292:6, 12;297:7 mechanisms (28) 28:21;37:14;38:11; 42:14;46:18;54:3; 55:12;72:3,15;79:7; 105:13;107:20,21; 137:8;148:21;155:18; 183:12;234:15;236:6; 240:9;242:9;243:4,14; 266:16;292:9;305:8, 19;330:11 mechanistic (6) 40:16;49:20;61:20; 62:14;209:15;213:16 mechanistically (11) 41:1;49:1;53:11,17; 69:8;70:5;210:5; 219:14;253:9;254:9; 298:21 mechanoreceptive (2) 31:9;40:19 mechanoreceptor (1) 40:20 mechanoreceptors (1) 231:5 Medial (2) 296:7;338:4 median (6) 272:1,14;321:15,21; 322:12,13 mediated (2) 160:14;337:7 mediates (1) 146:6 mediation (1) 341:1 mediational (2) 140:22;146:6 mediators (3) 32:10;219:21;220:3 Medical (7) 25:14;71:16; 113:11;167:18; 259:20,22;307:5 medications (1) 139:9 medicine (2) 57:4;365:9 medulla (1) 332:11 meet (3)</p>
---	--	---	--	---

<p>183:6;269:18;270:8 Meeting (40) 4:3,18;5:17;6:21; 7:6;8:1,2;9:15,22; 10:15,19;11:4,6,19; 13:4,11;15:15;16:18; 17:6,9,16;21:2,19,20; 22:7,22;52:19;57:20; 103:4;128:3;178:21; 184:13;197:13,15,17; 199:8;236:4;263:3; 358:6;374:6 meetings (8) 4:21;7:18;8:9,14; 11:5;16:2;23:7;128:2 MEG (1) 309:13 melts (1) 104:11 member (2) 26:18;27:4 members (1) 263:10 membrane (1) 70:6 memory (9) 40:2;43:9;44:2,14, 19;78:1;79:12;84:12; 108:8 men (5) 93:10,10;207:20; 265:13;272:8 menstrual (2) 110:9;257:14 menstruating (1) 208:19 mental (1) 365:20 mentally (1) 245:9 mention (5) 10:6;150:9;152:17; 283:18;303:21 mentioned (13) 102:3;141:4;180:7; 198:16;203:16; 241:17;264:2;267:6; 271:7;297:6;339:20; 349:20;363:15 mentioning (1) 278:11 menu (2) 173:3,8 mess (1) 33:7 message (4) 121:6;128:12; 291:22;355:10 messy (3) 239:16;249:5; 270:20 met (6) 44:20;280:8;302:2,</p>	<p>3,7;369:3 meta-analyses (1) 312:17 meta-analysis (7) 135:21;142:1; 279:16;312:16; 313:10,18;317:20 meta-analytic (2) 313:3;315:8 metaphors (1) 73:8 method (5) 186:2,7;187:3; 242:18;294:19 methodological (1) 282:2 methodologies (1) 341:2 methodology (3) 11:12;242:6,14 methods (6) 9:6;17:13;133:10; 305:18;338:20;366:8 metrics (6) 307:20;320:5; 323:2,22;336:9;337:3 MGH (1) 307:9 mic (5) 24:7,8;206:21; 368:13,20 mic] (6) 67:1;348:9;368:10; 369:15,17;370:16 mice (2) 50:10;347:16 Michigan (4) 71:5;89:5;91:13; 352:16 Mick (1) 143:19 micro (1) 154:4 microglia (3) 152:18,19;155:7 microglial (10) 152:21;153:3,15,20; 154:1,13,18,21;155:1, 5 microphone (6) 5:21;6:3;23:16,21; 70:11,13 microphones (4) 5:15;6:5,12;23:14 mid (1) 213:6 mid-1980s (1) 26:11 midcingulate (2) 154:14;331:8 middle (2) 272:2;290:22 middle-aged (2)</p>	<p>83:7;280:10 might (64) 11:16;26:6;67:9,10; 69:11;72:21;86:4; 99:6,8,17,18;100:11; 105:21;106:2;119:5; 121:5,7;132:2;144:5; 148:10;152:11;153:8, 22;155:16;159:8; 179:1;181:1;183:7; 185:11;192:18;193:2; 194:7,20;198:10; 223:5;228:1,7;231:16; 235:4;236:12,20; 240:7;246:19,21; 247:2;248:14;257:10; 265:3;268:2;272:2; 286:3;288:17,17; 289:6;292:8;297:8; 298:21;320:10; 335:19;337:7;340:13; 343:2,12;344:22 migraine (23) 20:6;47:20;126:16; 257:13;274:17; 332:15,17;333:14,16, 20;334:6;335:15,15; 337:1;364:8;368:8,9, 21,22,22;369:4,9,10 Mike (4) 222:17;229:5,6; 368:6 mild (1) 32:3 mildly (1) 354:9 milligrams (2) 89:17;90:5 milliseconds (2) 315:22;346:20 milnacipran (1) 94:7 mind (12) 9:18;11:18;35:1; 70:21;117:18;128:21; 130:2;253:6;262:7; 349:2;370:21;371:8 minimize (1) 108:17 minor (1) 15:5 minute (4) 155:11;161:17; 185:18;206:5 minutes (22) 35:18,19;48:14; 124:22;125:15; 128:13;149:1;228:15; 232:14;253:21;286:9; 306:9;326:15,15,18, 18;328:14,15;329:1,1; 345:20;373:22 miracle (1)</p>	<p>177:2 misinterpreting (2) 218:3;242:17 mislead (1) 196:20 misleading (1) 149:6 miss (1) 121:6 missed (1) 257:10 missing (2) 165:7;187:12 mistake (5) 38:6,9;97:8;108:20; 160:4 Mithcell (1) 121:20 mix (3) 147:10;148:7; 256:15 mixed (3) 90:15;106:7;118:7 mixture (1) 346:22 modalities (4) 223:6;228:13; 309:6;312:13 mode (10) 94:12;116:3;150:8; 161:18,19;162:8; 164:10,16;360:1,4 model (26) 31:1;32:12;37:15; 57:2;60:12,19;106:5; 118:17;137:13,20; 138:2;139:22;140:22; 146:22;147:17; 148:19;160:5;210:10, 10,11;211:15;304:14; 305:4;314:13;315:18; 365:12 modeled (1) 313:21 modeling (4) 340:21;341:1,3,15 models (26) 42:21;46:22;60:7; 72:7;88:5,7;146:6; 147:21;167:4;170:15, 17;210:8,8,13,15,16, 17,17;211:4,7;235:19; 257:6;305:21;308:12; 341:6;347:16 moderate (2) 303:2,7 moderately (5) 138:10;152:9,10; 155:16;299:6 moderator (6) 10:4;24:15;261:7,9, 11,14 moderators (1)</p>	<p>10:2 moderator's (1) 24:16 modest (3) 137:4;232:14; 301:10 modified (1) 304:14 modify (1) 230:9 modulate (2) 69:17;81:10 modulating (1) 165:8 modulation (13) 82:3;124:6;125:8; 133:11,12,16;134:7; 298:19;308:17;323:4; 329:13,16;330:2 modulators (1) 64:1 modulatory (5) 133:2;135:12,15; 295:4;314:7 molecules (1) 63:19 moment (4) 34:6;35:2;50:4; 289:8 moments (2) 346:7,9 Monday (1) 12:5 monitor (2) 111:15;248:5 monitoring (2) 111:15;112:5 month (2) 104:17;171:3 months (12) 8:15;13:21;119:20; 132:14,17;171:2; 266:7,8;302:1,3; 370:1,10 mood (12) 50:21;78:2;197:20; 249:6;250:21;267:11; 277:2,6;278:19,22; 279:10;359:13 morbid (1) 276:20 more (197) 12:3;16:20;23:2; 29:20;31:16;42:22; 56:11;64:19;67:11; 69:6;76:5,6,19;77:6, 19;79:11;82:2,3; 83:13,17;89:10,17; 91:12,13;92:8,20; 95:7,12,14;97:15; 100:8,16,18;101:4,5, 16,18;103:9,19,21; 104:12,17;105:15;</p>
---	---	--	--	--

108:9;113:1;114:1; 116:11,20,21;118:17, 18,20,22;119:10; 120:4;123:15;129:10; 130:3;132:16,17; 134:14,16;135:15,16, 17;137:7;138:10; 139:16;140:18; 142:17;143:16; 144:13;145:16; 153:20;155:2;157:1,8, 11;160:18;166:22; 167:8;168:9;170:10; 173:12;177:21; 179:17;181:13;183:9; 185:19,20;187:6; 190:8;192:10;195:3; 196:4,6,9,10;197:4; 205:19;208:16,19,22; 209:10;210:11;213:8; 214:20,21;215:5; 220:9;223:5,7;224:8, 13,16;227:17;229:16, 16;238:16;240:4; 243:12;244:4,5;245:6; 250:3;251:9,17;252:2; 257:3;258:13;260:15; 261:21;268:7,7,16; 272:8;275:1;276:9,11, 12,22;278:9,13;279:6; 280:13,15;281:15; 283:14;284:18; 285:20;286:20;287:3; 289:10;290:17; 291:13,20;292:1; 293:11;295:11;296:4, 13;297:4,14,18,19; 299:7,13;300:11; 301:13;302:14; 310:17;313:9;319:13, 13,16;322:10;326:21; 327:17;332:20;336:1, 2,3;337:2;338:22; 345:17;351:16,20; 356:4,15;358:15,16, 21;363:22,22;367:16; 373:6,17	121:16 most (69) 13:11;24:22;41:4; 65:14;66:15;75:6,14; 84:9;88:11;100:1; 106:8,18;109:1; 118:10;124:5,16; 129:19;130:6,14; 133:10;138:21; 144:16;145:8,9,13,18; 146:8;147:6,20;159:2, 16;162:14,15,15; 164:21;177:18; 179:15;194:11,21; 206:2;223:13;227:3,9; 236:11;247:15; 251:21;265:16; 267:17;270:2;271:8; 272:6,11;276:1,20; 277:19;280:9,10; 281:2;285:1;294:19; 302:20;303:4;317:19; 355:3;359:3,10;360:8, 16;369:5 mostly (1) 60:6 motor (15) 28:16;29:7,22; 30:11;31:5,6;32:17, 22;33:16;35:16;39:3; 42:8;123:2;327:11,13 mouse (4) 51:15;60:12;200:9; 253:11 mouth (2) 70:13;227:19 move (9) 24:7,8;87:18;182:5, 7;264:1;273:5; 287:16;351:19 moved (3) 36:16;277:20;286:2 movement (3) 29:10;86:3;298:2 moving (3) 51:21;100:6;101:4 MRI (18) 99:1;149:16;150:3; 204:13;309:22;310:1, 10,22;311:5,6,10,21; 320:17,20;323:11; 324:8,10;336:10 MRIs (2) 194:12;362:15 Mrs (1) 366:22 mu (2) 98:16,20 much (83) 10:12;16:20;25:3,8; 29:20;33:15;37:7; 38:15;46:4;56:11; 64:20;68:11,21;69:4,	4;71:10;84:20;85:22; 96:14;104:14;123:15; 124:12;132:17,17,17; 139:9;145:5;149:15, 20;151:13,19,22; 152:5;154:13;158:4,8; 173:9;176:13;179:14; 180:19;185:19;196:7, 9;203:18;207:9; 220:9;227:12;228:20; 237:17;240:4;241:11; 252:5;254:8;263:10; 264:18;265:13; 266:15;268:3;276:2; 285:1;291:1;293:20; 294:8;296:18;298:5; 303:13;307:14,22; 315:14,17;320:7; 322:7;326:12;328:13; 330:9;343:10;344:1,8, 9;351:16;354:15; 363:8,20 muddying (1) 145:11 Mueller (1) 249:14 Mueller's (1) 245:3 multicenter (1) 226:6 multidisciplinary (1) 309:2 multifocal (2) 91:12;92:8 multimodal (3) 228:5,14;235:5 multimorbid (1) 20:10 multimorbidity (2) 18:10,13 multiple (15) 53:20;158:14; 170:14;191:12,19; 269:13;275:6,12; 276:4;305:10;309:5; 312:5;335:1;338:15; 352:9 multisite (2) 200:12,17 multivariate (1) 364:20 Mun (1) 292:19 muscle (6) 29:9;129:17; 143:22;144:1;299:3; 345:7 muscles (3) 30:1;38:15;299:5 musculoskeletal (7) 137:10;141:14; 177:22;178:5;181:3, 18;183:3	must (4) 5:13;11:15;12:22; 26:3 mute (1) 5:12 mutually (1) 120:15 myelinated (1) 237:15 myofascial (3) 118:4,11;256:3 myself (2) 158:1;273:7 N N2 (2) 315:21;316:4 NA (1) 143:1 naive (1) 263:7 naloxone (1) 330:9 name (6) 4:5;6:16;25:11; 59:21,22;267:19 nap (1) 128:13 Napadow (17) 149:19;307:2,13,14; 340:21;343:16,19; 347:14;349:17;353:3; 359:16;362:19,22; 363:4;364:4,18;366:6 Naprosyn (1) 176:19 narrative (2) 165:7;274:11 narrow (7) 99:18;172:21; 173:1;175:15;176:4; 198:10;265:21 narrowed (1) 175:15 narrower (2) 60:6;179:5 Nat (5) 119:1,4;224:19; 354:16;359:11 Nathaniel (1) 119:2 national (1) 294:12 natural (1) 239:12 nature (11) 34:13;36:21;39:13; 71:17;94:15;135:16, 17;140:11;147:16; 246:10;341:2 near (5) 228:2;276:17;	342:9;363:2,5 nearby (1) 40:12 near-infrared (1) 373:4 nearly (2) 85:14;272:8 neat (2) 131:14;156:19 necessarily (11) 12:14;18:15; 105:11;109:5;183:6; 187:4;205:2;264:16; 275:7,18;276:5 necessary (2) 192:20;214:8 necessitate (1) 173:2 neck (4) 294:9,10,17;359:5 need (49) 5:3;7:17,20;12:10; 13:2;20:4;43:16; 52:15;68:13;85:16; 95:14;107:2;115:8; 128:13;131:4;138:4; 157:11;161:14; 172:11,18;175:4; 178:17;180:3,9;188:4; 191:20,22;198:10; 200:4;206:8;214:2; 220:21;233:5;248:15; 253:5;254:20;258:2,7; 282:10;305:1,7,20; 338:21;340:1;341:4,5, 17;346:1;355:10 needed (3) 183:15;187:18; 345:16 needs (8) 12:9;59:9;89:17; 106:13,17;113:15; 252:10;308:3 negative (4) 138:6;142:22; 143:6;361:18 negotiable (1) 201:5 neighbor (2) 24:6;149:19 neighboring (1) 40:10 neither (2) 89:12;368:3 Neogi's (1) 302:17 neonatal (1) 210:16 nerve (24) 35:12;47:5;50:12; 60:15;61:4;63:8,20; 67:18,22;68:5,10; 72:6;97:2;153:2;
---	--	--	--	---

206:17;227:9;321:13; 15,21;322:3,12,13,14; 332:10	neurology (2) 25:13;111:11	54:10	5;325:10;326:6; 337:10	non-responders (1) 225:15
nerves (1) 105:16	neuroma (2) 121:16;221:22	newly (1) 153:4	nociceptive (23) 60:7;72:3,17,19; 80:4,13;96:10,19,22; 103:2,10;118:12,21; 135:16;205:11; 210:17,21;219:3; 238:14;313:22; 316:11;331:9,12	nonresponsive (1) 90:5
nervous (48) 34:7;35:8;36:6; 38:3;40:4;49:5,8,19; 52:3;56:1;59:7,11,20; 61:18;62:6,12;65:15; 72:9;79:4;80:14,15; 81:5,10,13,14,15,17; 90:15;92:21;93:16; 97:14;114:15;117:15; 118:19;131:16;133:4; 165:22;211:11,22; 212:2;213:14,15; 216:1;217:19;221:17; 247:12,16;347:7	neuromatrix (1) 325:16	next (35) 11:3;12:6,6;21:3; 26:12;55:8;70:20; 82:4;103:4;124:2,22; 125:15;126:13; 128:13,22;139:1; 140:5;149:1;184:13; 203:4;261:10;262:8; 268:19;270:8;272:5; 275:15;276:20; 277:15;278:19; 284:18,21;294:9,9; 340:17;373:2	nociceptor (6) 48:15,20;52:21; 53:12;97:3;232:3	nonresponsiveness (4) 86:17,18;87:21,22
network (35) 7:6;56:7;94:19; 95:17;116:3;150:7,7, 8,15,16,16,18;161:18, 19,20;162:8;164:10, 17;207:20;214:16; 325:3,3,11,14,18; 326:4;327:10,11,11, 14,15;328:5;340:12; 360:1,5	neuron (4) 28:16;35:16;66:9; 238:8	next-door (1) 24:6	nociceptors (13) 28:22;32:6,10; 40:18;42:6,9;51:10, 11;57:1;63:17;67:20; 69:15;219:17	non-selective (1) 176:22
networks (20) 149:16;150:5,6,11, 15,22;151:5,8;152:13; 153:19;161:20; 164:11,18;324:17; 325:1,1,8,9,9;327:3	neuronal (9) 155:7;308:8;309:8, 11,19;323:14,15; 349:21;350:8	NHANES (1) 258:10	nociplastic (3) 71:22;79:17,19	non-specific (2) 130:9;176:21
neural (4) 56:7,21;133:6; 288:15	neurons (42) 27:10;29:7,11,20, 22;30:11;31:5,6,13; 32:18,22;33:4,16; 39:3;40:17;41:7,8,11, 11,14;42:8,9;47:7; 50:11;55:17,19,19,20; 63:22,22;64:6;68:15; 209:21;235:12,20; 238:2;346:21;347:20, 21;364:1,7,11	NIAMS (1) 104:1	node (1) 347:13	non-tissue (1) 206:1
neuralgia (6) 19:6;54:20;178:11; 229:11;233:1;362:16	neuropathic (26) 46:22;47:20;61:5, 15;66:3;67:18;72:3; 139:6,14;173:6,7; 177:14;178:12; 189:18;209:18; 221:21;227:4;241:21; 297:9,13,19,22;298:7, 12,20;321:11	nice (29) 4:10;12:8;130:5; 132:9,12;134:2;137:4; 142:19;193:7;245:11; 282:6;317:6,7,22; 322:17;326:9;329:19, 22;330:22;331:1,5,10; 333:7,10;334:5,15; 335:4,13;337:2	nodes (2) 325:19;328:5	non-transient (1) 293:12
neuroanatomical (1) 113:7	neuropathy (10) 57:7,9,10,11; 177:11;178:8;211:3, 10,20;255:8	nicely (12) 72:13;115:22; 116:1;143:18;150:8; 285:22;288:10;319:8; 322:3;323:10;338:10; 352:3	noises (4) 23:15;77:4;126:11; 358:19	non-white (1) 297:14
neurobiological (11) 37:14;42:13;51:3; 57:22;148:22;149:4; 152:11,14;157:6; 161:15;163:18	neurophysiology (1) 350:16	nickel (1) 161:14	non-centralized (1) 223:17	non-widespread (1) 243:9
neurobiology (9) 25:13;82:22;85:14; 116:14;149:7,12,13; 163:12;203:19	neuroplasticity (1) 322:16	night (5) 8:3;192:2;200:6; 230:12;253:13	node (1) 347:13	nor (2) 121:1;173:9
neuroimaging (19) 93:13;131:14; 292:15;303:14;307:7, 9,18,18;309:2,5; 320:10,17;322:21; 323:7;325:17;359:12; 362:1,6;372:21	neurotic (1) 83:6	nights (1) 13:7	nodes (2) 325:19;328:5	norepinephrine (1) 97:19
neurologically (1) 215:5	neuroticism (1) 138:7	NIH (1) 78:11	noisily (1) 23:15;77:4;126:11; 358:19	normal (11) 73:22;134:11; 205:10;220:22,22; 231:8;257:16;321:19; 345:11,17;351:3
neurologist (1) 240:4	neurotransmitter (1) 309:13	NMDA (9) 42:18,20;43:5,7; 53:18;60:13,22;61:7; 62:8	noises (4) 23:15;77:4;126:11; 358:19	normalgesia (2) 314:18;315:7
	neutral (1) 224:13	NME (2) 172:12,12	non-centralized (1) 223:17	normalized (2) 229:22;304:11
	neutralized (1) 165:14	Nobel (5) 26:18,20;28:19; 44:15,17	non-clinician (1) 226:12	normally (8) 40:17;41:4,7,12; 64:2;68:9,19,20
	new (23) 36:10;50:4;68:3; 71:21;79:16;82:4,7; 84:2;85:18;88:14; 104:2;172:13,13; 174:9;194:4;205:1; 233:3;239:1;259:18; 266:1;310:16;365:9; 371:4	Nobody (2) 173:7;301:16	non-drug (2) 100:9;101:15	North (2) 31:22;247:16
	newer (1) 361:8	nobody's (2) 23:18;113:5	none (6) 88:6;227:16;228:2; 232:12;264:7;287:18	nortriptyline (1) 139:10
	newest (1)	nocebo (2) 156:12;203:16	nonetheless (2) 84:1;124:21	nose (1) 358:2
		nociception (7) 28:22;56:22;255:3,	non-inflamed (1) 41:19	note (2) 289:3;314:7
			non-injured (1) 49:15	noted (8) 124:14;265:8; 270:13;275:3;282:9; 284:1;336:22;338:15
			noninvasive (1) 133:8	noteworthy (1) 142:9
			noninvasively (3) 153:3;320:17,20	Notice (2) 6:5;273:21
			non-irritable (1) 232:5	noticed (1) 361:4
			non-neuropathic (2) 298:1,13	noticing (1) 24:3
			non-opioids (1) 176:12	notion (15) 26:7;32:5;44:1; 45:20;47:9;52:2;53:5; 62:11;69:1;111:21; 113:21;127:17; 135:12;205:20;304:15
			non-pain (3) 126:17;127:13; 357:18	novel (3) 178:19;338:22; 348:10
			non-painful (3) 77:1;296:13;325:22	
			non-peripheral (1) 101:12	
			non-pharmacologic (2) 100:20;163:7	

<p>novo (1) 65:18</p> <p>nowhere (2) 363:2,5</p> <p>noxious (19) 30:20;31:11;33:20; 36:5;40:7,9;41:12,14; 49:12,13;63:7;109:18; 126:2;136:10;205:11; 206:1;220:8;245:18; 257:17</p> <p>NSAID (1) 176:22</p> <p>NSAIDs (5) 75:7,9;97:21; 171:11;220:15</p> <p>nuances (1) 161:5</p> <p>nucleus (7) 332:10;333:8; 348:19,22;349:8; 364:2,3</p> <p>nullified (1) 165:15</p> <p>numb (1) 121:22</p> <p>number (61) 14:6;17:18;46:12; 54:14;72:19;77:21; 82:7;85:22;125:12; 126:17;127:18;130:8; 20;134:17;138:13; 140:4,12;141:21; 143:10;146:1,21; 154:3;163:6;170:7; 171:9;173:14;174:14; 176:18;178:7;179:12; 181:17;183:15;185:8, 11;187:18;204:6; 210:12;228:18; 265:13;268:19;275:8; 281:4;286:14;289:12; 291:15;293:3;294:21; 299:11,22;300:4,16; 305:11;314:12; 350:13;356:8;364:7, 11;367:12,13;368:2; 372:2</p> <p>numbers (2) 174:20;274:1</p> <p>numerical (1) 368:2</p>	<p>OB/GYN (1) 90:1</p> <p>obese (1) 297:15</p> <p>objective (9) 11:4,5;12:12;83:17; 93:22;192:17;239:22; 366:18,21</p> <p>Objectives (2) 4:3;21:17</p> <p>observation (2) 222:1;257:9</p> <p>observations (2) 65:12,13</p> <p>observe (1) 367:18</p> <p>observed (1) 65:14</p> <p>obsessive (1) 277:12</p> <p>obvious (4) 36:11;276:1;283:9; 300:20</p> <p>obviously (9) 15:6;70:8,15; 168:21;233:1;244:21; 281:11;308:10;342:21</p> <p>occupational (1) 114:4</p> <p>occupies (1) 138:9</p> <p>occur (13) 18:11,15;56:3;61:4; 69:20;90:16;108:12; 206:10;215:21; 247:15;291:10;337:5; 372:19</p> <p>occurred (4) 33:17;40:4;230:11; 251:1</p> <p>occurring (3) 110:17;114:4; 213:17</p> <p>occurs (5) 65:19;122:8; 206:20;241:15;288:6</p> <p>odds (4) 286:17;294:6,8,15</p> <p>off (18) 7:20;23:16,22;24:4; 32:21;56:5;91:7;97:3; 172:10;177:5;234:2; 253:11;340:1;368:9; 369:15,17,19;370:16</p> <p>offer (1) 84:19</p> <p>often (27) 6:17;10:20;27:22; 76:7;81:12;90:16; 114:4;123:13;126:19; 145:9;164:22;196:10; 200:6;208:19;220:7,9; 222:3;245:6;257:3;</p>	<p>259:8;267:17;272:11; 274:16,21;284:6; 351:5;369:6</p> <p>oftentimes (1) 200:20</p> <p>O'Keefe (1) 26:17</p> <p>old (3) 72:2;138:17;177:17</p> <p>older (1) 176:13</p> <p>olds (1) 108:6</p> <p>omics (1) 243:2</p> <p>once (14) 23:14,20;89:3; 143:4;147:11;180:13; 229:22;233:19; 271:17;296:19;300:9; 328:12;338:13;367:15</p> <p>one (175) 9:20;11:8;17:17; 18:17;23:15;24:19; 27:21;31:13,17;35:3; 37:5;40:15;44:9;45:5, 10;47:10,14,21;48:10; 51:5,17;53:15;55:15, 21;59:16;65:2;73:14, 16;81:15,16;83:9; 84:17;89:7,9;116; 94:7;99:13;106:13; 115:9,16;117:17,19; 119:6,15;120:20; 121:13;127:12; 128:16;129:3;130:16; 132:12,22;137:19; 138:1;143:3,19; 144:20;145:7;148:1; 150:20;152:9;155:16; 157:4,12;159:20; 163:15;166:22; 171:10,19;174:14,19; 175:15,21;176:5; 177:3,22;181:1;182:2; 187:9;188:3,5;190:18; 193:19;197:7;199:19; 201:13;203:16;205:9; 206:22;211:22; 218:13;219:4;221:19; 223:12;224:5;226:13; 227:17;230:11;235:5; 236:20;237:1,7; 238:11;242:15;245:1; 247:16;251:14,14; 256:13;257:4;258:20; 260:14,16;269:9; 270:12;272:7;274:16; 275:11,15;276:22; 277:3,5,18;278:14; 279:13,19,22,22; 281:9,15;284:18; 286:3;289:4;292:18;</p>	<p>296:16;301:22;303:1; 305:1,5;307:2;312:13; 313:7;316:1;317:18; 322:1;323:18;325:3; 326:7,9;329:11,19; 330:15;331:13,22; 333:15;334:15; 335:18;339:22;342:8, 14,22;343:8,22; 345:12;353:1;354:13; 355:16,19;357:5,11; 359:3,9;361:4;363:17, 19;368:7</p> <p>onerous (1) 192:22</p> <p>ones (8) 33:14;34:4;90:20; 181:8;232:9;259:2,3; 358:16</p> <p>one's (6) 89:9;153:11,12; 167:19;300:5;303:15</p> <p>one-word (1) 163:3</p> <p>ongoing (18) 66:5;67:14,16; 72:18;75:22;80:4,13; 94:5;96:10,14,21; 97:12;118:12,21; 190:5;209:9;212:22; 255:2</p> <p>only (72) 6:6;10:10;27:20; 31:7;40:8,17;44:14; 45:17,21;51:20;63:16; 79:3;86:22;92:3,5; 105:6;106:14;113:18; 119:16;120:18; 124:14,15;125:3; 143:6,6,7;146:4; 153:2;154:16;172:22; 185:13;194:6;201:13; 218:18;222:4;241:13; 242:5;258:11;261:22; 262:3;263:9;264:11; 265:16;267:10,13; 269:9;272:7,9,22; 274:7,14,19;275:21; 276:18;277:5,6;280:7; 281:9;289:8;298:10, 11;315:5;316:1; 321:20;332:5;337:4,6; 342:13;353:15;355:3; 361:15;372:11</p> <p>onset (9) 67:2;113:8;122:12; 123:15;138:16; 143:22;238:22; 341:17;349:15</p> <p>ontology (1) 308:2</p> <p>open (6) 97:7;128:17;165:1;</p>	<p>247:17;320:18;335:12</p> <p>opened (1) 68:12</p> <p>opening (1) 203:8</p> <p>OPERA (2) 82:1,9</p> <p>operate (1) 220:13</p> <p>operated (1) 84:21</p> <p>operates (2) 56:1;346:18</p> <p>operating (1) 61:21</p> <p>operation (1) 46:3</p> <p>operationalize (2) 225:8;244:20</p> <p>operationalizing (2) 224:21;226:4</p> <p>ophthalmologists' (1) 78:21</p> <p>opinions (1) 171:17</p> <p>opioid (28) 69:22;70:1,5;87:4,6, 7,15,21;89:13;90:4; 98:13,16,17,19,21; 99:6,14;100:5;142:20; 143:8;144:22;145:4; 174:11,12;185:17; 187:15;193:20;330:10</p> <p>opioid-induced (3) 69:9;99:4;156:7</p> <p>opioid-related (1) 144:21</p> <p>opioids (17) 43:17;54:1;69:14; 75:7,9;86:17;97:21; 98:5,8;99:9,14,17; 136:18;143:4;174:10, 22;186:2</p> <p>OPPERA (31) 129:2,11,21;130:6, 15;147:18,21;158:18; 159:9;258:8,11;286:8, 13;289:10,16;290:9; 291:12;293:13,14; 294:5,11;295:6;299:1; 301:1,13;304:14; 305:4;341:14;357:22; 362:2;369:2</p> <p>OPPERA-2 (1) 287:4</p> <p>opportunity (2) 233:12,16</p> <p>opposed (6) 31:12;122:10; 173:6;183:14;185:21; 220:8</p> <p>opposite (1) 60:18</p>
--	--	---	--	--

<p>optical (2) 68:3;309:21</p> <p>options (1) 158:14</p> <p>optogenetically (1) 56:4</p> <p>optogenetics (1) 51:6</p> <p>oral (3) 142:20;143:8;145:4</p> <p>orange (1) 290:12</p> <p>order (9) 133:13;168:1; 237:12;248:13;283:8; 330:17;341:22; 351:14;355:2</p> <p>orders (1) 347:16</p> <p>organization (1) 44:17</p> <p>organized (1) 320:14</p> <p>organoids (1) 57:1</p> <p>original (8) 39:13;49:2;199:20; 244:14;301:1;304:13; 305:4;337:9</p> <p>originally (4) 51:2;55:14;82:11; 360:19</p> <p>originates (1) 218:2</p> <p>orofacial (1) 130:9</p> <p>orthopedic (1) 84:16</p> <p>osteoarthritis (36) 47:20;73:6,11;74:1, 12,13;75:7,10;80:19; 81:2;83:12;88:22; 89:3;92:1,5,8,14;96:8; 97:5;100:14;104:3; 106:20;118:5,12; 120:6,10,12;181:10; 255:6;286:4,5;295:16; 297:10,11;303:12; 367:7</p> <p>osteoporosis (1) 240:1</p> <p>others (14) 62:10;76:21;81:19; 93:12;115:7;125:19; 126:18;135:11; 140:12;208:6;245:5; 278:6;280:4;289:5</p> <p>otherwise (4) 106:2;218:20; 234:20;372:9</p> <p>ours (2) 144:19;358:17</p> <p>ourselves (1)</p>	<p>266:20</p> <p>out (124) 4:10;5:8;7:3,21; 14:9;15:1,9;19:8; 22:7;30:4;32:14;34:8; 36:20;38:12;46:6; 47:22;55:11;56:8,11; 72:5;73:17,18;74:5,9, 20;75:12;77:2;80:16; 81:11;82:17;83:20; 85:17;87:2;88:16; 92:14;95:16;99:13; 104:21;109:9;110:8; 111:9;112:6;114:6; 115:2;117:10,15; 120:2;125:21;126:5; 129:19;136:22;145:9, 15,18;150:1;152:16; 156:13;158:3;159:5, 13;160:6,8;163:22; 172:17;174:3;176:22; 185:8,11,21;188:19; 196:5;199:7;205:7; 207:3,12,18;209:3; 215:16;218:18;227:2, 15;229:7;230:2; 240:6;243:20;244:11, 19;245:2;251:19; 260:21;263:15,21; 264:3,14;265:7;266:5, 8,20;269:19;276:8; 277:18,20;278:15; 279:9,12;283:22; 290:10;294:21;318:1; 320:19;321:8,10; 324:22;325:17;326:2, 2;329:20,20;339:21; 347:19;352:22;353:1; 366:19,22</p> <p>outcome (14) 19:21,21;20:2; 115:20;116:9;190:22; 191:2;193:13,15; 194:13;197:3;199:6; 222:22;283:19</p> <p>outcomes (24) 20:8;86:15;130:5; 134:19;145:13; 146:13;148:11,13,16, 16;157:3,10;163:18; 177:7;185:4;204:2; 224:9;258:6;260:13; 267:10;268:8;279:21; 281:10;284:9</p> <p>outliers (1) 274:20</p> <p>outlined (1) 72:13</p> <p>outlining (1) 72:14</p> <p>outpatient (2) 271:12;280:9</p> <p>output (6)</p>	<p>29:15;30:8;32:13; 41:7;55:19;56:14</p> <p>outside (5) 6:21;230:14;231:1; 232:19;317:5</p> <p>over (78) 10:11,18,20;24:7; 34:4;35:12;58:19; 73:5;82:4;89:22; 92:17;114:2;122:10; 125:6,11,15;126:13; 128:13;139:1;140:5; 147:4;149:1;155:12; 163:10;169:15,17; 190:8,18;201:15; 205:8;213:3;219:21; 245:9;253:13;260:9; 272:6,14;280:21; 287:16;303:6;304:14; 311:14,18;312:2,7,9; 313:2,10;314:1,2; 315:21;317:4;320:15, 22;323:19;324:11; 325:2;327:3,9,12; 328:6;330:22;331:20; 332:8,10;333:9,11; 335:8,10,20;338:4; 341:16;345:9,19,21; 348:7;354:21;360:17</p> <p>overall (3) 148:2;223:8;248:22</p> <p>overkill (1) 354:4</p> <p>overlap (12) 17:19;128:9,16; 148:20;157:20; 195:14;228:1;286:1; 288:6;346:13;358:8; 360:7</p> <p>overlapped (1) 269:1</p> <p>overlapping (32) 18:1,21;19:3;71:19, 21;78:11;79:5,22; 82:7;96:12;98:2,8; 100:1,22;110:16; 127:2;147:12;167:16; 228:17;285:15;286:6, 19,21;288:21;289:12, 15;294:3;300:22; 304:21;305:9;352:7; 368:13</p> <p>overlaps (1) 138:10</p> <p>overly (1) 248:17</p> <p>over-report (1) 276:7</p> <p>over-the-counter (2) 229:17;230:18</p> <p>overuse (1) 275:10</p> <p>overview (4)</p>	<p>60:4;266:19; 307:17;308:22</p> <p>own (11) 34:18;39:16;55:10; 107:21;136:8;138:9; 203:10;212:9;280:19; 287:22;370:22</p> <p>Oxford (1) 28:18</p> <p>oxygenated (4) 310:9,14,17;311:4</p> <p>oxygenation (2) 310:4,15</p>	<p>121:15,17,22;122:6; 124:6;125:4,8;126:15, 16;128:7,11;129:5,18; 130:8,11;131:13,17; 132:3,7,8,15,19,20,22; 133:2,3,3,11,12,12,13, 16,19,21;134:7,7,9,12, 14,15,21;135:1,2,4,6, 12,15;136:11,18; 137:8,10,13,17,20,21; 138:16,19;139:1,4,6, 14;140:2,4,8,14,15,17, 18;141:3,14,18,21; 142:7,15,16,21; 143:11,12,14,16,16, 17;144:4,7,8,13,22; 145:22;146:7,16,20; 147:5,7,17;148:4,17; 149:18;150:6,13; 151:11,18,19,21; 152:1,4,12,19;153:1; 154:9,19;155:14,19; 156:3,12,16;162:10, 11,12;163:12;164:3,8; 165:8,12;166:13; 167:12,16,18,20; 168:8;169:13,16; 170:18,21;173:6,7,8,9, 10;175:5,14;176:8,15; 177:14,19,22;178:3,5, 12,22;179:8;181:3,7, 13,18;182:18;183:3; 189:18;190:15,17,21; 197:10,19,21;199:2, 16;200:11,12,13,17, 17;204:22;205:14,21; 207:11,13;208:22; 209:4,19;210:15,20; 211:6,7,12,13;214:20; 215:7;216:8,11;218:1, 8;219:9,10;221:21; 222:2,3;223:14,17,17; 225:18;226:20,21; 227:4;228:21;229:14, 19;230:3,3;231:10,18, 19;232:7,15,17; 234:12,13,16;237:2, 17;239:1;241:18,21; 242:3,22;243:8,9; 244:5,10;248:6,22; 249:8;250:2,6,10,13, 16,17,22;251:2,3; 252:6,8,15;253:7,15; 254:11,12,22;255:8, 16,16,17;256:3,16; 257:3,4,6;258:6,7; 259:9;260:6,7,7; 262:3,4;263:3,19; 266:14;269:19,21; 270:17;273:4,13,15; 274:18;275:3,10,16, 22;276:10,15;281:2,8; 282:1;285:6,7,15,22;</p>
---	---	--	---	---

P

package (1)

page (1)

paid (1)

pain (760)

<p>286:2,7,15,17,19,21, 22;287:10,10,11; 288:4,7,15,21,22; 289:4,5,12,15;290:4, 18,19;291:3,5,7,9,15, 18,21;292:1,6,7,14,19; 293:1,4,7,8,10,11,12, 17,19,22,22;294:1,3,4, 7,9,9,16;295:1,4,4,7, 18,21,22;296:1,3,5,6, 7,12,13,16,17,17,22; 297:4,4,5,6,7,8,8,9,13, 13,18,18,20;298:2,6, 12,16,18,19,20;299:3, 10,12,14,20,22;300:1, 3,5,5,10,12,13,17,22; 301:7,8,14,15;302:8, 11,12,14;303:1,4,7,8, 16,18;304:8,19,22; 305:6,9,12,13;307:7, 10;308:16,17;312:15, 21;313:11,18,19; 314:5,7;315:11;316:6, 9,12,16,19,21;317:1,2, 3,6,14;318:5,7,11,15, 16,20;319:2,7;320:3; 321:11;323:4,8; 325:10,13,15,17; 326:9,9,11,13,19; 327:4,5,12,20;328:3, 13,18,22;329:13,16; 330:2,19;331:2,4,5, 18;332:1;334:16,16; 335:3;336:11;337:9, 10,19;339:14;341:7,8, 9;343:6,10,17;345:4; 348:16;352:10,16,17, 22;353:15;354:1,2,12; 355:5,6,11,12,21,22; 356:1,3,4,8,15,15,16, 19,21;357:1,3;358:5; 359:2,3,4,5,7,9,14; 360:2,11,12,14,16; 361:9,12,14,19;365:7, 8,10,10,11,11,12,13, 16,18,18;366:3,4,22; 367:14;368:1,11,13; 369:22;370:9</p> <p>PainDETECT (1) 86:21</p> <p>pain-free (3) 133:21;136:4; 150:14</p> <p>painful (10) 57:11;62:21;110:9; 132:16;151:3;234:3; 304:21;311:18; 325:22;367:17</p> <p>painometer (5) 363:6,7;366:2; 371:14;372:20</p> <p>pain-reducing (1) 304:10</p>	<p>pain-related (3) 52:13;145:13;157:3</p> <p>pain-relevant (1) 153:16</p> <p>pains (2) 66:1;275:11</p> <p>pain-sensory (1) 319:7</p> <p>paints (1) 90:15</p> <p>panacea (1) 344:5</p> <p>Panel (9) 203:3,15;229:8; 234:6;235:9;339:10, 12;340:16;356:6</p> <p>panels (2) 24:18;300:8</p> <p>panel's (1) 223:3</p> <p>panic (4) 277:12;278:3,6,12</p> <p>paper (23) 25:15;28:13;30:9, 12,13;34:11,13;35:3; 39:1,6,13;71:17; 116:1;265:7;268:6; 281:13;282:10; 283:22;288:13; 292:21;360:20,20; 365:8</p> <p>papers (16) 30:18;38:5;53:20; 54:14;88:6;159:10; 199:20;212:20; 259:19;278:1;294:21; 312:19;313:10,11,21; 361:1</p> <p>parabrachial (1) 349:8</p> <p>paradigm (4) 134:10;156:12; 184:5;254:16</p> <p>parallel (1) 272:16</p> <p>parallels (1) 70:2</p> <p>parameter (1) 311:5</p> <p>parameters (6) 58:11;59:1,2,8; 371:1,6</p> <p>parenteral (1) 176:7</p> <p>part (45) 8:5;32:9;37:17; 38:19;52:14;62:22; 64:6;68:17,18;78:3; 86:2,8,9;87:17; 109:11;110:6;112:7; 124:14;139:21; 149:18;160:17; 170:21;188:20;</p>	<p>199:17;204:22;206:9; 209:14;214:1;232:1; 238:11;241:4;242:20; 246:18;253:17,19; 262:11;307:9;324:17, 18;330:9;339:18; 344:6,20;356:18; 371:3</p> <p>partially (1) 325:15</p> <p>participant (3) 272:1;367:11;368:5</p> <p>participants (4) 271:11;275:8,13; 367:12</p> <p>participate (2) 94:3;209:22</p> <p>participated (1) 179:22</p> <p>participating (1) 99:7</p> <p>particular (31) 9:22;10:3;14:3; 17:16;20:10;21:19; 28:8;32:6;35:15; 57:14;119:12;139:6; 186:16;194:19;195:1; 223:10;251:18; 281:15;287:1;290:2,5, 14;300:1;313:18; 317:20;324:17,18; 341:15;344:20;348:9; 358:20</p> <p>particularly (15) 41:21;46:21;71:12; 99:8;146:11;147:10; 157:5;161:12;162:8; 172:18;196:11; 201:11;221:21; 290:18;301:9</p> <p>pass (1) 125:17</p> <p>passed (1) 315:8</p> <p>past (3) 17:9;19:4;21:9</p> <p>Pat (8) 26:12,12;32:1,2; 34:14;36:13;38:6; 39:1</p> <p>patch (1) 232:22</p> <p>patches (1) 233:14</p> <p>patent (1) 91:7</p> <p>path (2) 164:20;234:20</p> <p>pathogenesis (1) 99:7</p> <p>pathological (8) 65:7;66:12;70:1; 205:2;207:1;209:8,10;</p>	<p>303:4</p> <p>pathologically (2) 206:15,19</p> <p>pathology (3) 31:17;322:13,14</p> <p>pathophysiologic (2) 152:22;154:1</p> <p>pathophysiology (1) 20:7</p> <p>pathway (7) 63:7;155:4;234:18; 243:18;244:1;331:11; 364:1</p> <p>pathways (3) 155:17,19;332:8</p> <p>patient (39) 20:6,7;46:4;48:3,4; 57:13;62:1,4;78:10; 89:11,12,17,19; 108:22;109:17; 112:21;113:3,4,8; 141:2;192:1;197:6,12; 199:15;200:18; 203:17;213:1;232:22; 234:11;248:21; 250:16;252:9;254:11; 269:3;271:19;343:10; 345:8;351:9;354:18</p> <p>patient-focused (2) 197:12,14</p> <p>patiently (1) 222:17</p> <p>patient-reported (5) 115:20;116:9; 147:7;194:13;222:22</p> <p>patients (191) 9:13;20:2;37:11; 45:8,12,16;47:19,19; 58:17;62:20;64:10; 65:1,8;67:6;71:8; 74:17;76:7,16;77:3; 80:8,19;83:6;90:22; 91:11;92:5;94:5;99:3; 103:9;106:19;107:17; 110:4;115:9;116:6; 120:13;121:15;122:4; 132:13;133:21;134:3, 12;135:2,22;136:3,8, 9,14,18,21;137:2,10; 139:3;140:17,18; 141:14;142:20,22; 143:14,15;144:21; 145:3,6;149:18; 150:12,21;151:6,10, 18;153:10,20;154:9, 16,17,19;162:10,11, 13;164:22;166:12; 179:16;182:13,18; 183:3,13;187:21; 188:2;190:20;191:13; 194:10;196:14,15; 197:18;198:18,22; 200:1,13,14;206:16,</p>	<p>17;209:4;221:16; 226:12;227:16;229:9, 10,20;231:10,21; 233:3,5,13;234:4; 236:16;241:6,20; 249:20;251:5;255:21; 256:1;260:20;262:2; 265:11;267:21;268:4; 269:7;270:13,20; 271:11,16;276:7,19; 280:9;281:21;288:17; 304:2;313:11;316:6, 10,12,19;317:8,14; 318:4,6,16,20;319:14; 320:3,19;321:11,12, 16,22;322:5;327:21, 21;328:21;329:6; 331:18;332:15,17,21; 333:5,14,17,20;334:6; 335:15,16;336:11,13; 337:1,3,16,21;338:8; 341:8,9;349:2;354:9; 356:3;358:16,21; 360:18;361:9;362:14, 15;364:5,8,13;366:20; 367:7</p> <p>patient's (6) 154:12;163:8; 266:13;358:17; 365:11;367:16</p> <p>patients' (1) 318:12</p> <p>Patrick (1) 26:10</p> <p>pattern (14) 29:10;32:7;58:18; 94:10;111:12;112:4; 116:7;160:15;294:13; 317:7,8;319:1;364:20; 371:4</p> <p>patterns (9) 32:2,52:15;94:18; 104:10;150:4;166:9; 316:9;371:3;372:18</p> <p>paw (4) 31:10;33:2,12;34:1</p> <p>paying (1) 24:1</p> <p>PBR-28 (1) 153:5</p> <p>PCA (2) 45:18;46:3</p> <p>PCC (2) 338:2,12</p> <p>PCS (3) 157:16;337:20; 361:7</p> <p>PDF (1) 86:7</p> <p>peak (3) 315:21;316:4;344:3</p> <p>peaking (4) 323:14;349:21;</p>
--	--	--	--	---

<p>350:6,20 pectoral (1) 144:1 pelvic (4) 90:1,3;94:22; 162:11 pelvis (1) 95:6 Penfield (2) 320:16;321:7 Pennebaker (1) 129:15 Penney (1) 356:12 Pennsylvania (4) 66:22;105:20; 159:13;193:19 penny (1) 34:6 people (229) 4:11;6:18;10:15,22; 14:6;16:2;19:8;21:22; 22:13,17;23:11,15; 51:6;53:5;55:10;63:2, 12;70:10,18;73:18,21; 74:16;75:6,12,21; 76:1,21;77:20;78:19; 79:8,10;80:11,18,22; 81:20;82:2,16,20; 83:11;84:5,11,14; 85:9,11,17,22;87:2, 15;88:10,13,16,16; 89:3,11;91:15,16; 92:1,7;93:8;94:22; 95:1,8,10,12,18;96:8, 17;97:4,6;98:4,7,12, 14;99:9;100:12;101:2, 9,21;102:21;103:7,17; 104:1,7,10,15,22; 105:9,15;106:14; 107:1;108:21;111:15; 112:1;113:17,22; 114:11;115:2,3,12; 116:10;118:3,10,18, 20;119:18;120:5,7,7, 10;121:6;122:21; 123:1,6,8;124:17; 126:9;128:4;129:6; 130:19;132:4,6; 133:19;134:6,8;135:4, 14;138:18;139:9,16; 151:2;155:19,21; 156:4;164:1;166:4; 167:15;174:17; 176:10,19;177:2; 178:9;181:8,12,19; 183:6;184:12;185:3,9, 11,20,21;186:12,15; 188:17;194:4,18; 196:19;198:4;199:9, 18;200:4;201:8; 203:9;210:20;211:2; 212:15;213:8;215:17;</p>	<p>216:11;219:10;236:1; 239:5,7;242:22;244:5; 247:18;250:6;255:14; 256:2,15,19;257:5,11, 16,21,22;258:3;259:9; 260:6,17,18;274:7; 280:13;291:17; 292:22;293:2,3,5,12, 16,18,21,21;294:1,7; 295:1,2;296:11; 297:19;298:7;301:14, 17,21;302:21;306:21; 342:11,14,15,15; 352:15,21;353:15,18; 356:9,15;359:10; 367:19;372:4;373:21 people's (7) 137:16;155:7; 156:2,16;250:2,10; 259:11 peptides (1) 64:1 per (2) 41:13;90:5 perceived (1) 58:19 percent (32) 12:21;14:16;30:17; 73:18,21;75:13,20; 80:18;91:15;95:3,5,6; 120:8;122:21;123:1; 182:22;185:1;186:20; 187:17;227:6;232:22; 242:14;246:22;255:4; 259:21;265:3;269:15; 272:7;274:6;280:3; 287:13;297:11 percentage (3) 144:8;273:21;274:2 percentages (1) 276:2 perception (2) 18:5;318:15 percept-matched (3) 317:12,21;318:2 perfect (2) 235:19;347:5 perfectly (5) 138:8;228:2;236:5; 246:7,15 performance (1) 298:3 performs (1) 223:4 Perhaps (16) 20:14;70:18; 129:10;148:11,13; 183:8;189:18;190:8; 214:1;233:15;236:13; 245:2;253:18;280:11; 333:13;357:6 period (12) 60:21;122:11;</p>	<p>186:19;187:16; 188:22;242:12;303:6; 326:18;328:9,14,15; 345:19 periodic (1) 8:6 periodically (1) 6:2 periods (6) 101:3;110:9; 183:22;332:22;333:1; 337:18 perioperative (1) 242:12 peripheral (67) 32:11,14;35:12,20; 36:9;39:10;47:5; 63:16;65:16,20;66:3, 13,17;72:17,19;73:12; 74:14;81:13;96:19,21; 97:12;104:6,11; 109:20;117:14,15; 121:7;173:6;177:10, 14;178:8;206:17; 211:11;212:1,8,18; 213:2,10;214:3;216:3, 4,7;217:18;219:3,13, 15;220:12,16;221:9, 17;222:7,11;230:7; 237:6;239:14;244:12; 245:10;246:10;247:1, 16;254:6;256:20,21; 321:15;322:14,18; 331:15 peripheral/central (1) 254:19 peripherally (9) 76:6;93:3;105:4; 116:22;119:19;121:4, 4;171:2;205:14 peripherally-based (1) 295:18 periphery (21) 49:10;66:6;72:5; 74:5,9;80:17;81:7,8, 11;85:16;93:7; 100:13;117:21;212:3, 4;218:3,9,12,17; 239:22;245:20 Perl (1) 31:21 permission (1) 15:19 persisted (2) 37:8;302:12 persistence (1) 35:21 persistent (5) 37:19;54:18;55:6; 106:3;301:22 person (13) 21:11;25:19;28:21; 73:13;84:21;90:18;</p>	<p>91:13;111:5;183:16; 255:18;283:15; 356:18;357:1 personal (1) 15:12 personality (3) 267:12;277:3,5 personally (3) 44:10;246:14;350:3 persons (1) 23:17 person's (2) 81:4;101:13 perspective (7) 63:11;70:16;71:14; 160:22;247:12; 358:17,18 persuasive (1) 246:7 perturbations (1) 126:11 PET (7) 98:22;153:5,15; 157:18;163:13;180:5; 309:17 pharmaceutical (1) 264:6 pharmacokinetics (1) 175:18 pharmacologies (1) 61:22 pharmacology (1) 61:6 phase (7) 92:4;196:6,13; 197:2;208:20;270:14, 21 phenomena (5) 49:4;50:20;70:2; 88:2;105:6 phenomenon (19) 39:10;42:1;43:20; 44:7,22;46:12;47:3; 48:7;49:11;84:13; 156:22;219:7;232:12; 248:9;300:22;308:13, 15;323:7;338:14 phenotype (15) 57:14;78:3;79:10; 81:21;84:14;85:9; 95:7,13;103:18;123:6; 163:1;226:16;241:6; 260:16,20 phenotyped (1) 129:6 phenotypes (5) 95:3;119:6,11; 304:18,20 phenotypic (3) 115:14;226:22; 236:15 phenotypical (1) 234:9</p>	<p>phenotyping (3) 128:2;226:11;363:3 philosophical (1) 32:1 phobias (1) 277:10 phone (1) 5:11 phones (1) 16:3 photos (1) 16:3 PHQ-9 (3) 116:12,16,18 physical (4) 135:5;162:16; 228:12;298:3 physically (2) 124:16;156:10 physiological (1) 245:19 physiology (3) 18:2;20:4;208:16 pick (6) 5:15,22;100:8; 306:14;324:22;347:19 picked (3) 19:4;309:12,21 picking (2) 185:20;363:15 picture (1) 131:19 pictures (1) 312:3 piece (3) 113:5;266:17;345:2 pieces (1) 249:7 piggyback (1) 238:9 pile (1) 250:18 piles (1) 362:18 Pill (13) 82:9,9;129:14; 130:4,13,16,19; 147:19,19;148:1,14; 157:16;357:21 pinch (1) 33:22 pinky (1) 322:3 pinprick (1) 328:11 Pittsburgh (3) 107:6;158:6;261:12 place (5) 170:5;247:12,15; 281:9;312:13 placebo (1) 104:18 placebo-controlled (1)</p>
--	--	--	---	---

177:12 plaintiff's (2) 22:19;23:1 plan (3) 8:13,14;192:8 planning (2) 12:17;162:1 plasticity (13) 34:7;36:6,19;39:19; 42:16;43:1;44:6; 49:18;63:18;64:7; 69:18;241:15;308:19 play (6) 61:1;63:14;101:14; 111:7;253:12;337:14 playbook (2) 245:3,6 played (1) 263:15 player (1) 165:21 playing (1) 114:15 plays (3) 61:7;152:21;165:11 pleading (1) 246:21 Please (10) 5:7,12,13;6:4; 59:22;70:12;262:16; 273:9;285:11;372:12 pleased (1) 44:19 pleasure (2) 26:2;307:15 plenty (1) 10:7 plot (3) 137:3;139:13;144:6 plots (2) 135:21;154:10 plug (2) 146:4;161:21 plus (4) 91:15;186:14; 231:4;240:2 pm (5) 202:2,3;203:2; 306:16;374:6 point (43) 14:18,22;39:8;48:5; 61:8;64:9;74:20;84:3; 90:14;109:5;121:18; 135:15;137:16; 184:19;185:18;212:7, 13,14;220:18;224:13; 241:1;244:19;247:18; 252:20;264:3;265:6; 266:5;268:6;269:9,19; 277:18;300:9;301:16, 17;342:18;348:9,10; 353:10;355:14;357:4; 361:21;364:4;373:15	pointed (5) 47:22;92:14;99:13; 111:9;117:15 pointing (4) 7:1;82:17;159:13; 359:18 points (7) 36:1;76:14,15; 163:10;177:20; 242:16;363:14 poked (2) 83:21;296:19 poking (5) 178:16;295:10; 296:11,12;297:1 polytrauma (1) 123:12 pontomedullary (2) 332:11;333:9 poor (1) 76:2 poorly (5) 101:4;113:11,14; 163:5;165:16 popular (1) 176:2 popularized (1) 135:11 population (42) 18:16;120:9;132:2, 8;133:22;134:11; 160:2;173:1;179:13, 17;180:7,10;182:15; 183:1;184:1,15,18; 185:13;187:14; 188:13,17;189:3,21, 22;193:14,22;194:7, 21;197:6;201:10,13, 17,19;214:2,4;258:13, 19;272:10;274:6; 276:9;294:16;342:16 population-based (2) 73:19;282:3 populations (10) 33:3;55:17;103:15; 170:19,19;172:19; 209:12;271:19;284:5; 360:15 pordensation (1) 60:9 portable (1) 373:5 portion (2) 185:13;338:5 positive (4) 43:17;227:5,6; 336:4 positron (1) 309:17 posits (1) 137:14 possibilities (1) 110:4	possibility (6) 36:5;46:22;56:19; 66:10;68:12;235:21 possible (9) 10:13;29:18;55:16; 128:1;153:3;226:18; 236:4;246:22;357:14 possibly (3) 57:3;228:3;271:19 post (4) 23:6,9;26:14;41:3 postcentral (2) 321:1;322:2 posted (1) 86:9 poster (1) 77:16 posterior (10) 314:3;315:2; 318:22;333:10;334:2; 336:3,16,22;337:12; 338:3 posteriorly (1) 294:2 post-exercise (1) 144:4 postherpetic (7) 19:6;54:20;178:11; 229:9,11;233:1; 362:16 post-injury (2) 41:17;43:20 postoperative (7) 43:16,17;45:14; 46:14;135:6;146:7,20 postoperatively (2) 46:5;132:18 postsurgical (2) 132:19;145:22 post-surgical (2) 43:6;61:14 post-synaptic (1) 38:22 post-translational (3) 219:18,20;220:4 potent (1) 134:7 potential (16) 51:13,18;67:8; 146:12;147:13; 149:17;185:19; 189:10;247:13; 281:20;317:19; 335:18;337:1;346:19; 360:11;366:3 potentially (9) 37:15;45:6;185:10; 196:20;207:14; 231:21;233:6;240:14; 331:17 potentiation (4) 40:1,5,15;43:9 power (4)	23:2;158:2;201:16; 203:16 powerful (1) 217:7 powering (1) 186:21 practical (2) 183:11;351:20 practice (8) 110:8;114:22; 180:9;187:4;233:2,10; 366:13;372:22 pragmatic (3) 173:21;176:13; 254:15 praise (1) 25:21 preceding (1) 350:8 precise (2) 367:14;369:12 precisely (3) 236:5;247:1,5 precision (1) 57:4 preclinical (5) 37:15;42:21;69:19; 211:4,15 predict (15) 86:17;88:7;135:3,7; 138:15;145:21; 147:21;148:11; 157:10;187:21; 226:19;365:6,15; 372:3,18 predicted (3) 86:16;301:9;341:16 predicting (4) 146:13;188:3; 194:10;225:14 prediction (3) 121:10;366:8,9 predictive (12) 83:14;132:9,19; 138:14;145:17;147:6, 14,15;161:3;225:19; 247:5;341:3 predictor (18) 82:6;86:15;130:14; 134:19;139:5;145:12, 19,20;146:5,9,18; 147:4,10,20;148:1,12; 300:21;302:16 predictors (11) 128:20;129:20; 146:12,21,22;148:2,9, 15;157:2;303:10; 358:3 predicts (7) 74:6;119:13;129:7; 138:9;146:20;238:22; 260:12 predisposed (1)	239:6 predominance (1) 289:11 predominant (2) 62:22;72:9 preemptive (1) 45:9 preexisting (2) 130:10;239:2 preferentially (1) 92:10 prefers (1) 26:4 prefrontal (3) 314:8;337:11;338:4 pregabalin (5) 53:21;75:10; 139:11;191:4;372:1 preliminary (1) 231:17 prelude (1) 102:14 premenstrual (1) 208:20 premier (1) 129:4 premise (1) 161:3 preoperatively (1) 132:15 preparation (4) 28:1;30:14,20;44:3 preparations (1) 30:18 prepared (2) 13:1;23:8 preparing (2) 43:14;46:10 prescribed (1) 177:4 prescribing (2) 174:18;191:9 presence (20) 52:22;53:13;54:15; 55:2;59:17,19;61:10, 13,16;64:10,12,15; 144:4;226:19;227:4; 241:8;252:1;254:22; 286:22;366:4 present (16) 22:12;61:12;62:10; 86:12;117:8;127:17; 191:9;206:19;241:13; 242:3;264:20;270:9; 271:8;272:18;275:17; 307:16 presentation (13) 5:22;26:1;62:16; 71:9;124:10;140:3; 163:9;169:1;262:18; 263:18;273:8;285:12; 307:13 presentations (2)
---	--	---	---	--

<p>9:16;225:17 presented (6) 65:15;134:2; 247:21;260:2;342:21; 368:19 presenters (1) 157:7 presents (1) 110:22 president (1) 99:11 press (1) 39:7 pressed (1) 166:16 pressure (25) 58:16;113:6;160:5, 6;233:4;237:1,16; 243:19;295:7;296:7; 299:2;300:3,5;301:8, 15;302:8,11,12,13; 303:1;306:20;317:12, 13;318:5,9 Presumably (5) 69:16;139:17; 145:7;163:14;182:16 presume (1) 122:9 presumed (1) 126:3 pre-synaptic (1) 38:20 pretreatment (1) 139:7 Pretty (27) 25:3;30:21;54:22; 115:21;116:9;154:4; 174:4,19;175:17; 176:20;210:10,19; 213:9;218:6;220:1; 228:20;235:10;246:4, 5;252:12;259:13; 262:2;268:18;300:3; 312:3;319:5;330:8 prevalence (32) 263:17;264:22; 267:1;270:10;271:6, 20;273:10,12,21; 275:1,2,20,22;276:2, 10,15,19;277:9;278:5, 13,21,22;279:10,11, 17;280:18,21;281:13; 282:13;283:1;286:15; 294:8 prevalent (1) 18:16 prevent (4) 45:6;189:11,19; 190:4 preventative (2) 189:13;190:3 prevented (1) 45:10</p>	<p>prevention (2) 190:7,9 previous (3) 143:5;233:15;361:5 previously (4) 196:15;265:14; 325:15;335:22 primarily (4) 97:19;185:16; 289:1;292:11 primary (26) 27:14;37:18;38:2; 39:5;50:16;143:17; 146:8;150:17;151:17; 165:5;191:2;221:14; 238:7;320:11,14,22; 325:12;327:6;329:10; 331:19;333:18; 334:10;336:20; 338:16;368:11;369:22 primed (2) 214:19;216:10 principally (2) 310:1;313:19 prior (1) 171:5 priori (2) 225:12;372:2 privilege (4) 25:12;70:15,18,19 Prize (3) 26:18,20;44:15 PRO (14) 181:20,22;182:16, 19;185:19;187:20; 188:2;192:15,16,21; 242:5,5,14,18 probably (52) 5:5;74:2;84:8;85:3; 92:9;93:3;95:11,13; 96:7;98:16;99:22; 100:16;106:18; 133:18;134:4;136:21; 140:7;147:16;148:21; 150:5;151:5;152:7,8; 157:8;158:18;159:10; 161:12,16;162:1; 164:5,12;165:11; 166:2;174:15;212:14; 229:3;235:4,22; 243:13;254:13;256:7, 12,16;262:5;306:20; 312:16;341:13; 342:11;350:1;351:12; 366:12;372:15 probe (1) 316:2 probes (1) 328:12 probing (1) 84:10 problem (26) 27:18;62:19;66:14;</p>	<p>72:5;89:2;103:5,7; 104:6,11;106:16; 114:22;115:3;162:19; 163:5;177:1;187:7,12; 222:13;243:20,21,21; 260:5;283:9;341:4; 343:22;370:13 problematic (3) 114:11;122:7; 329:17 problems (17) 7:16;32:6;78:1,1,2; 79:12,12;84:12,12; 99:14;108:9;118:13, 14;197:19;226:13; 329:14;358:2 procedure (1) 143:20 procedures (1) 133:17 proceeding (1) 30:14 proceeds (1) 171:22 process (30) 13:18;15:9;59:11; 67:5,10,14;79:18; 96:22;97:12,13,13,14; 117:8;122:12;160:13, 15,17;179:9;180:1; 192:14,20;193:4; 216:7;217:21;219:20; 221:17;244:4;248:15; 282:20;357:16 processed (1) 27:14 processes (11) 126:5;131:6;133:2, 14;135:13;137:11; 152:15;169:7;209:10; 240:17;371:6 processing (16) 131:17;249:8; 313:22;315:11; 316:11;325:10;326:6; 329:9,10;331:9,12; 337:9,10;359:19; 360:1,5 processors (1) 350:15 produce (9) 42:10;64:1;66:9; 68:17,21;69:2;155:7; 164:18;206:4 produced (5) 35:17,19;37:1; 38:15;199:20 produces (4) 63:16;143:21; 237:16;245:19 producing (2) 34:5;36:6 product (4)</p>	<p>98:2;172:17;176:6; 190:1 production (1) 63:19 products (13) 9:8;168:21;171:2,8; 173:4;174:3;175:8,8, 12,17;176:13;191:17; 194:15 professional (3) 111:22;267:16; 270:5 professor (7) 25:13;71:3;124:4; 262:10;285:4;307:4; 339:16 profile (5) 135:12;303:5; 304:7;351:12,15 profiles (1) 303:1 profiling (1) 233:8 profound (9) 28:20;35:13;37:2, 22;47:17;52:7,10; 64:8;97:11 profoundly (1) 212:2 progesterone (1) 208:11 program (5) 91:21;92:4;188:20; 196:20;372:9 progress (1) 8:9 progression (1) 103:16 progressive (1) 363:22 pro-healing (1) 206:18 proinflammatory (2) 215:20;218:21 project (2) 27:2;229:1 projection (2) 347:1;349:6 prolonged (3) 37:2;222:7,11 prominent (8) 79:4;85:10;92:20; 101:14;107:17; 108:22;109:3;114:15 prone (1) 135:16 pronounce (1) 267:19 proof (1) 235:1 properties (8) 27:12;28:7;30:11; 31:5;38:1;41:11;</p>	<p>55:19;149:17 property (1) 28:8 proportion (6) 93:6;141:2;287:8; 289:19,22;303:7 propose (1) 119:5 proposed (3) 40:1;112:10;128:3 proposing (1) 116:8 proprioceptive (2) 30:2;126:10 PROs (4) 192:17;193:1; 223:20;244:3 prospective (4) 129:4;134:17; 138:17;341:19 prospectively (2) 238:21;259:14 PROSPERO (1) 267:2 protect (2) 206:8;208:14 protected (1) 120:10 protecting (1) 206:9 protective (1) 205:21 protocols (1) 58:9 proton (2) 371:20,21 prototypical (1) 288:20 prove (4) 66:20;155:9; 188:16,21 proven (1) 157:2 provide (4) 9:19;14:3;198:4; 207:12 provided (1) 158:6 provocation (1) 326:9 provocative (2) 234:3;241:4 provoke (2) 52:13;232:7 provoked (1) 44:8 pseudospecific (1) 172:16 psychiatric (12) 108:22;263:19; 266:12;267:10,15; 268:8;269:17;270:3; 279:7,21;280:2;</p>
--	---	---	---	--

<p>281:10 psychiatrist (2) 125:18;261:21 psychiatry (1) 71:4 psychological (28) 72:11;75:1;85:10, 13;88:3,6;107:6,17; 108:12,15;142:11; 154:17;289:2;290:7, 14,15;291:2,4,6,9,11, 15,20;292:2,3;301:11; 304:18;305:5 psychological/psychiatric (1) 109:4 psychologist (4) 85:16;246:21; 262:9;285:6 psychometrics (1) 351:21 psychophysical (2) 133:16;146:22 psychophysically (1) 152:6 psychophysics (2) 124:5;223:1 psychosocial (11) 124:6;130:14; 142:14;145:16;146:1; 147:11,20;148:6; 154:5;155:8;160:13 psychosomatic (2) 18:3;51:2 psychosomatically (1) 126:20 psychotropic (1) 43:10 PTSD (6) 123:11;277:19; 278:2,14;281:3,3 public (1) 168:22 publication (3) 34:10;271:7;360:8 publish (2) 94:9;195:17 published (25) 28:13;30:12;34:12; 46:1;50:8;54:15; 71:17;95:16;172:6; 259:19;266:21;269:1; 271:3;280:1,16; 282:18;292:21;294:5; 301:2;302:18;312:20; 329:15;330:3;343:20; 365:10 publishing (1) 229:9 PubMed (1) 125:5 puff (2) 332:14,18 pull (2)</p>	<p>83:20;268:21 pulled (2) 267:20;268:14 punctate (1) 316:2 pure (3) 119:6;256:8,21 purely (3) 47:9;255:4;338:14 purple (3) 274:5;277:11; 289:18 purport (1) 210:8 purposes (3) 194:1;236:2;363:3 pursuing (1) 225:22 push (2) 76:18;344:15 put (37) 5:3;6:8;11:18; 14:20;15:20;17:11; 24:7;27:12;89:3; 91:22;105:2;113:17; 128:18;151:1,10; 156:15;160:4;161:14, 21;166:8;195:15,18; 196:6,21;221:22; 224:14;229:17; 236:19;255:20;260:8, 19;292:5;305:6,21; 330:15,16;354:9 putting (8) 85:17;91:5;180:4; 224:19;227:19; 232:21;241:17,19 p-value (2) 146:17;147:4</p>	<p>qualitative (1) 352:7 qualities (3) 292:14;297:8;355:7 quality (3) 261:19;266:14; 284:4 quantify (1) 47:18 quantitative (17) 58:8;76:22;80:20; 131:8,22;181:22; 274:10;294:18,22; 296:2;298:8,10,22; 302:22;303:10; 304:11;351:1 quarter (1) 288:3 questionnaire (6) 53:6;88:18;138:12; 249:21;259:11;297:20 questionnaires (3) 166:5;223:1,20 quibble (1) 344:5 quick (6) 158:11;172:6; 227:17;245:1;246:1; 280:5 quickly (6) 27:18;94:19;140:9; 246:4,5;368:15 quirks (2) 160:2;161:6 quit (1) 164:5 quite (32) 4:22;36:11;42:15; 46:6;51:4;53:8;56:13; 92:13;94:18;104:9; 125:2;128:16;136:6; 151:12;157:11; 160:15;161:5;164:8; 182:9;192:22;208:4; 210:5;219:14;220:14; 234:3;238:12;275:8; 286:3;288:8;290:8; 301:10;312:14 quote (4) 127:8;142:3; 288:12;316:7 quote/unquote (2) 211:20;327:10</p>	<p>radiographic (3) 74:16;367:8,8 radiographs (1) 73:22 radiology (1) 307:5 raise (1) 17:2 raised (2) 61:9;345:17 raises (1) 220:19 Ralph (1) 94:3 ramble (1) 161:17 ran (3) 156:13;264:19; 360:17 random (2) 324:15;366:13 randomized (1) 99:20 range (10) 47:19;48:8;174:2; 175:16;179:14;214:3; 235:11;241:14; 271:21;358:1 rapidly (3) 71:22;250:6,8 Rappaport (1) 169:20 rare (1) 272:7 rarely (1) 125:4 raspberry (1) 175:21 rate (9) 83:16;132:4,16; 135:4;187:17;353:14, 15,19;354:19 rated (3) 132:5;200:6;319:12 rates (9) 75:8,13;90:22; 92:19;102:20;186:8, 19;267:22;268:2 rather (19) 11:15;26:3,5;50:2; 62:5;64:20;73:8; 106:22;108:13; 116:21;127:5;180:21; 189:13;227:13;240:5; 272:1;275:5;279:2; 358:17 Rathmell (6) 69:7,7;183:19,19; 254:2,2 rating (4) 319:15;331:2; 354:7;368:2 ratings (2)</p>	<p>132:3;136:11 ratio (6) 311:3;334:1,7,9; 335:22;364:14 rationale (2) 347:21;367:3 ratios (2) 301:3;348:4 rats (4) 30:15;36:20;153:2; 347:15 raw (1) 332:3 RDC (1) 267:7 reached (2) 45:18;191:6 react (4) 111:20;240:21; 242:10;257:19 reaction (2) 239:7;261:22 reactions (1) 340:15 reactivity (1) 29:8 read (7) 11:19;130:4; 174:16,19;184:11; 233:3;287:4 readily (2) 187:2;318:10 reading (1) 211:16 readings (2) 8:17,19 ready (1) 179:10 real (14) 26:2;33:7;51:1,3; 56:1;65:10;112:14,17, 18;113:3,3;114:7; 217:18;307:15 reality (3) 82:12;183:4;349:17 realize (3) 8:14;12:20;285:16 realized (4) 33:10;34:7;39:9; 277:3 realizing (1) 74:14 really (131) 9:17;16:4,5;21:16; 23:10;24:1,16;32:18; 34:6;37:9;51:16; 56:16;70:20;72:10,13; 73:8;75:6;76:5;78:2, 17,20;79:20;81:16; 82:9;84:20;85:8,13; 86:3,22;93:14;94:19; 95:22;96:13;99:2,5, 16,18;107:2;110:5,20;</p>
	Q			
	<p>Q&A (10) 58:4;102:1;158:10; 180:18;284:16,20; 306:19;307:12; 339:10,12 QST (26) 94:20;115:22; 133:8;135:14;148:5; 157:17;166:13; 167:22;180:5;227:22; 243:2;292:14;295:2; 299:2,9,19;300:16,18; 301:5;304:6;340:5; 351:11,12,14,22; 356:2 quadriceps (1) 296:9 qualification (2) 179:22;193:12 qualifying (1) 192:15</p>			
		R		
		<p>RA (5) 75:19;94:4,11; 215:5;250:5 radicular (5) 142:21;359:2,2,5,9 radiograph (1) 81:3</p>		

<p>111:1;112:15;117:13, 17,19;119:11;121:3,5; 126:12;128:14; 131:14;138:5;139:22; 148:16;149:8;151:13; 154:11;156:1,19; 157:12;158:6;161:7; 164:7,14;166:4,10; 170:13;172:15; 175:18;176:1;188:3; 191:2,6;195:8;196:3, 7;201:12;204:11; 208:4,7;210:11; 214:17;216:15;217:7; 222:19;223:2;234:1; 235:13,18;239:9; 245:8;251:17;256:12; 257:1;258:15;259:14; 262:13;263:14,16; 265:9;266:6;267:20; 270:9;271:21;278:7; 279:8;281:7;282:19; 286:2;294:13;298:9; 307:22;312:3;319:22; 323:10;331:10;340:7; 341:6,19;343:5;350:7; 351:15;353:11;354:3; 359:9;362:19;366:22; 368:15;370:6;372:7, 14</p> <p>reason (25) 15:11;22:1,16;23:4; 27:20;34:13;40:20; 64:16;91:9;92:3; 96:16;105:12,14; 174:8;186:1;194:4; 199:17;207:5;246:12; 260:14,15;269:15; 280:12;317:19;348:17</p> <p>reasonable (7) 14:12;16:12;70:12; 153:21;166:11; 180:11;248:2</p> <p>reasons (7) 145:7;183:8;186:4, 17;276:4;329:18; 350:13</p> <p>reassignment (1) 156:3</p> <p>receive (2) 40:17;318:4</p> <p>receiving (1) 231:22</p> <p>recent (24) 46:11;56:9;66:7; 92:13;94:14;100:14; 125:5;127:8;135:21; 139:5;140:16;141:22; 144:18;149:22; 150:20;152:17;167:9; 176:5;277:19;283:22; 287:3;337:15;360:8, 16</p>	<p>recently (11) 51:6;94:9;134:2; 153:2;200:1;211:1; 253:9;292:21;294:6; 302:18;359:20</p> <p>reception (1) 182:2</p> <p>receptive (10) 28:8;30:4;33:11,14, 21;34:3;35:5;308:19; 320:9;338:19</p> <p>receptor (18) 27:11;32:17;33:1; 41:4,10,15;42:18; 43:5,8;60:13,22;61:7; 98:16,18;219:21; 231:6;232:9;309:16</p> <p>receptors (4) 42:21;53:18;62:9; 98:21</p> <p>recess (3) 123:22;202:3; 306:16</p> <p>reciprocal (1) 141:9</p> <p>recognize (1) 48:1</p> <p>recognized (1) 39:18</p> <p>recognizing (1) 29:2</p> <p>recommend (4) 8:11;98:4;128:8; 228:20</p> <p>recommendations (6) 11:10,16;12:16; 14:19;161:9;198:21</p> <p>recommended (1) 128:3</p> <p>reconcile (2) 242:16;305:20</p> <p>record (6) 27:10,20,22;29:18; 186:5;235:20</p> <p>recorded (4) 6:13;29:7;33:3,13</p> <p>recording (4) 29:5;68:3,4;235:11</p> <p>recordings (1) 27:11</p> <p>records (3) 259:21,22;260:4</p> <p>recovery (1) 64:18</p> <p>recreate (1) 56:21</p> <p>recruit (2) 178:9;200:12</p> <p>recruited (4) 271:12,16;281:21; 293:1</p> <p>recruiting (2) 200:14;362:3</p>	<p>recruitment (1) 361:22</p> <p>red (8) 88:12,13;278:11; 295:9;312:7;313:1; 324:11;331:7</p> <p>reduce (8) 43:16;69:16; 105:21;106:2;121:14; 231:14;354:13;368:2</p> <p>reduced (11) 46:5;134:20;136:4; 141:20;142:2,5; 253:16;303:17; 308:17,17;336:21</p> <p>reduces (1) 60:20</p> <p>reducing (1) 46:13</p> <p>reduction (16) 35:5;41:18;47:2; 48:21;51:9;139:14; 142:18;143:8;219:16; 220:7;264:7;331:1,6, 6,7;335:19</p> <p>reductions (2) 142:15;167:11</p> <p>redundancy (1) 269:4</p> <p>re-examined (1) 302:1</p> <p>refer (3) 12:8;73:5;334:8</p> <p>referable (1) 178:20</p> <p>reference (2) 268:12;286:18</p> <p>referred (1) 175:22</p> <p>referring (1) 306:22</p> <p>refers (3) 237:11;308:6;346:5</p> <p>refine (1) 266:17</p> <p>refining (1) 282:20</p> <p>reflect (11) 56:16;183:1;187:4; 188:14;199:22; 200:22;234:10;241:8; 288:18;305:18;337:19</p> <p>reflected (3) 35:4;173:21;197:5</p> <p>reflecting (2) 154:5;158:16</p> <p>reflection (2) 66:16;69:22</p> <p>reflective (1) 314:16</p> <p>reflects (3) 171:4;237:7;289:19</p> <p>reflex (11) 28:20;29:1;30:3; 36:19;37:3,21;44:3; 51:21;56:14,16; 239:20</p> <p>reflex-evoked (1) 56:12</p> <p>reflexion (1) 37:3</p> <p>refuse (1) 156:10</p> <p>regard (1) 275:21</p> <p>regarded (1) 7:17</p> <p>regarding (1) 62:2</p> <p>Regardless (3) 76:10;87:22;90:17</p> <p>region (5) 95:5;213:7;319:21; 353:13,15</p> <p>regional (6) 110:12;114:1,5,7; 122:6;295:18</p> <p>regions (16) 153:16,17,18; 154:14;304:3;314:19; 315:1;318:21;332:6; 333:11;334:2;336:2; 337:8,14;353:16; 356:9</p> <p>registered (1) 267:1</p> <p>registration (3) 91:6;256:1,6</p> <p>regressing (1) 222:10</p> <p>regression (1) 335:8</p> <p>regular (3) 11:8;233:17;371:19</p> <p>regularly (1) 354:21</p> <p>regulars (1) 110:18</p> <p>regulation (1) 165:12</p> <p>reinforcement (1) 200:2</p> <p>reintroduced (1) 50:6</p> <p>rejected (1) 360:21</p> <p>related (39) 9:5;11:12;18:21; 20:11;67:11;102:8; 126:15,17;127:1,13, 14;129:22;131:16; 140:21;141:20; 151:15;152:18;162:6; 167:12;174:18;191:5; 213:1;264:8;266:2; 267:11;275:10,10;</p>	<p>276:13;292:8;305:8; 323:13,21;346:8,9,17; 357:6;359:7;361:14; 369:7</p> <p>relates (3) 181:22;311:22; 329:3</p> <p>relationship (14) 30:7;74:15;139:8; 140:13;154:11; 159:22;164:17;167:5; 213:5;225:18;283:16; 300:4;303:17;359:13</p> <p>relationships (6) 136:16;149:10; 163:20;165:21; 283:13;357:5</p> <p>relative (11) 136:4,14;139:2; 140:19;141:15; 150:13;158:19;310:8; 334:3,9;348:2</p> <p>relatively (2) 125:4;368:16</p> <p>relax (1) 261:10</p> <p>release (1) 69:15</p> <p>releasing (1) 98:14</p> <p>relevance (2) 132:10,19</p> <p>relevant (6) 20:6;135:9;227:1; 298:21;326:7;348:5</p> <p>reliable (2) 180:10;200:4</p> <p>reliably (1) 136:2</p> <p>reliance (1) 241:11</p> <p>relief (3) 168:8;222:3,12</p> <p>relieve (1) 90:9</p> <p>relooked (1) 46:10</p> <p>remain (1) 148:8</p> <p>remains (3) 146:5;147:6;148:1</p> <p>remapping (1) 322:16</p> <p>Remarkably (1) 316:8</p> <p>remember (10) 6:12;17:10;21:21; 113:9;169:20;177:16; 260:2;276:14;369:6,7</p> <p>remifentanil (1) 156:6</p> <p>remind (2) 23:13;155:21</p>
---	--	--	---

<p>reminded (2) 6:1;31:20</p> <p>reminds (1) 70:20</p> <p>removal (1) 237:20</p> <p>remove (3) 31:3;233:21;363:18</p> <p>removed (3) 60:13;268:13; 345:14</p> <p>removing (1) 185:9</p> <p>renormalizing (1) 302:11</p> <p>reorganization (1) 211:11</p> <p>reorganized (1) 171:15</p> <p>repair (2) 104:5;132:14</p> <p>repeat (1) 44:10</p> <p>repeated (9) 31:19;33:20;40:4; 59:15;66:2;103:1; 229:14;323:17;335:20</p> <p>repeatedly (1) 246:17</p> <p>repetitions (2) 335:2;341:5</p> <p>replaced (3) 87:9,9;167:13</p> <p>replacement (2) 146:14,17</p> <p>replicate (2) 322:7;330:13</p> <p>replicated (2) 90:2,7</p> <p>report (18) 137:17;143:16; 144:7,8;145:3,6; 151:20;162:14; 195:19;198:2;259:12; 266:14;271:6;289:20; 290:1;297:18;318:6; 328:21</p> <p>reported (18) 269:2;271:4; 272:11,13;273:11; 275:19;293:2,3,7; 297:12,19;298:7; 318:11;329:6;331:2; 338:9;345:8;348:15</p> <p>reporting (9) 113:4;268:6; 270:19;291:16; 293:16,18,22;294:1; 353:6</p> <p>reports (1) 296:17</p> <p>represent (2) 49:18;223:8</p>	<p>representation (2) 322:15;327:8</p> <p>representations (7) 308:20;320:11; 321:11,17,18,22; 322:1</p> <p>representative (6) 90:11;157:21; 159:7;203:22;342:15; 362:8</p> <p>represented (3) 274:15,19;276:16</p> <p>representing (2) 273:20;296:20</p> <p>represents (3) 54:16;127:11;366:3</p> <p>request (2) 22:16;23:10</p> <p>requesting (1) 22:19</p> <p>require (4) 15:7;84:3;200:22; 269:21</p> <p>required (6) 23:6;31:11;35:6; 198:15;201:5;269:18</p> <p>requirement (2) 46:13;66:5</p> <p>requirements (2) 89:13;270:1</p> <p>requires (1) 16:22</p> <p>research (19) 9:6,6;11:12;12:9; 26:15;76:14;89:6; 113:19;197:10; 198:21;270:11; 273:18;285:8;286:2; 323:1;339:4,14; 351:17;359:18</p> <p>research-based (1) 292:11</p> <p>researcher (3) 73:4;142:9;358:18</p> <p>researchers (5) 80:6;139:7;142:2; 146:1;279:6</p> <p>researching (1) 199:5</p> <p>resembled (1) 29:21</p> <p>resistance (1) 86:2</p> <p>resolution (10) 33:9,10;104:7; 209:11;344:9,11,12; 348:20,21;365:1</p> <p>resonance (1) 309:15</p> <p>respect (6) 89:15;92:16;100:4; 101:17;342:1;349:13</p> <p>respected (2)</p>	<p>177:3,6</p> <p>respond (27) 95:9,11;104:15; 105:3;112:3;126:10; 167:2;182:16;183:7; 184:15;185:5;187:22; 188:2;194:11,22; 215:9;232:5;244:6; 249:11;252:2;256:21; 257:3;295:2;325:21; 345:1;356:11,14</p> <p>responded (2) 94:6;372:4</p> <p>responder (2) 186:22;187:15</p> <p>responders (3) 184:1;225:14; 227:16</p> <p>responding (1) 89:15</p> <p>responses (3) 183:17;185:14; 188:5</p> <p>response (87) 17:7;24:13;30:20; 31:12,20;35:7,14,16, 18;37:4,6;40:18;44:8; 49:12,13;56:16;59:16; 67:2;119:13;132:3; 144:12;186:8;187:17; 188:7;207:1;225:20; 229:10,22;238:15; 239:6,18;241:18; 245:11,20;246:2,11, 11;253:16;259:3; 304:8;308:9;309:10, 11,13,18;312:8,10,21; 313:15,16;314:5; 316:3;317:6,17; 318:13;319:5,20; 320:1,21;321:2; 323:14,20;331:4; 333:4,6,13,17,21; 334:18,20;335:6,9,16; 336:6,11,19;338:2; 343:14;345:21;348:1; 349:1,19;350:2,10; 366:5;373:19;374:1</p> <p>responses (19) 29:2,3;48:22;56:12; 131:13;135:7;137:17; 142:5,10;251:16; 301:5;304:12;322:21, 22;337:7;338:15; 348:2;356:2;368:5</p> <p>responsible (3) 57:12;62:2;219:10</p> <p>responsive (3) 87:15,16;248:17</p> <p>responsiveness (7) 87:4,6,7;92:16; 100:5;221:2;372:18</p> <p>rest (6)</p>	<p>175:6;287:14; 325:6;327:1,13; 339:11</p> <p>resting (5) 324:5;326:20; 327:5;328:3;333:1</p> <p>restricted (4) 33:1,11;48:12; 210:4</p> <p>restricting (1) 173:2</p> <p>restrictions (2) 31:10;269:20</p> <p>restrictive (1) 34:3</p> <p>Restrooms (1) 6:20</p> <p>result (5) 46:19;219:17; 312:1;331:10;361:13</p> <p>resulted (1) 178:2</p> <p>results (7) 63:19;67:18;136:2; 196:16;270:18;298:9; 312:4</p> <p>retain (1) 221:3</p> <p>retention (1) 40:3</p> <p>rethink (2) 69:1;282:11</p> <p>retirement (1) 83:20</p> <p>retrieved (2) 268:11;280:7</p> <p>retrogradely (1) 63:20</p> <p>retrospectively (1) 259:12</p> <p>return (1) 355:15</p> <p>returned (1) 345:10</p> <p>returns (1) 345:17</p> <p>reuptake (1) 97:20</p> <p>reveal (2) 59:9;61:13</p> <p>revealed (5) 34:9;35:9;37:14; 42:7;53:16</p> <p>revealing (3) 59:14,17,19</p> <p>reveals (2) 52:3;59:10</p> <p>reversible (1) 209:18</p> <p>review (19) 127:9;141:22; 262:22;263:8;264:11; 265:15,22;267:2;</p>	<p>268:15,17;270:19; 279:12;280:20;282:6; 283:7,21;311:2; 313:21;316:8</p> <p>reviewed (1) 281:19</p> <p>reviewer (1) 360:21</p> <p>reviewing (2) 198:7,19</p> <p>reviews (4) 263:6;284:4;326:5; 339:19</p> <p>revision (1) 277:20</p> <p>revisions (1) 15:5</p> <p>revisit (1) 370:12</p> <p>rheumatoid (19) 73:7;75:16;80:2; 83:12,15;94:13;96:8; 104:2;116:5;120:6,13; 212:21,22;213:3,12; 217:6,21;256:9; 265:11</p> <p>rheumatologist (7) 62:17;73:3,3,10; 102:12;215:1;216:21</p> <p>rheumatologists' (1) 79:1</p> <p>rheumatology (4) 71:3;111:10;116:2; 282:1</p> <p>Rhode (1) 339:15</p> <p>Rick (1) 93:18</p> <p>ridiculous (1) 355:2</p> <p>right (47) 17:8;21:12;44:15; 53:8;73:14;77:12; 82:11;84:18;87:12; 88:13;90:12;104:21; 105:6;109:10;111:13; 114:21;117:1;118:9; 120:17,21;123:12; 130:18;131:5;137:3; 139:15;144:1,7;147:2; 153:9;161:14;183:5; 187:14;204:16; 215:15;221:19; 242:19;243:8;244:3, 15;245:15;287:7,16; 291:18;292:10; 299:13;328:7;333:8</p> <p>rise (1) 325:2</p> <p>rises (1) 324:12</p> <p>rising (1) 221:21</p>
--	--	---	---	--

<p>risk (33) 54:7,13,17;55:2,6; 57:5;64:9,13;65:9; 129:4;130:6,10; 137:21;138:22; 148:20;162:22;175:2; 185:8;189:10;193:21; 207:5,10;244:9; 288:19;289:6,9;301:4; 302:20;303:6,11; 304:21;305:14;358:4</p> <p>risks (4) 54:19;175:9; 189:21;287:1</p> <p>Rob (7) 167:1,6;195:1; 235:2;247:21;339:7; 362:10</p> <p>Robert (1) 124:10</p> <p>robust (1) 188:7</p> <p>robustly (3) 156:15;187:22; 188:5</p> <p>Rochester (3) 17:4;262:10;339:17</p> <p>rock (1) 86:4</p> <p>rodents (1) 42:14</p> <p>Roger (9) 82:11;103:12; 129:10;158:21;209:5; 284:21;285:11,12; 350:22</p> <p>Roger's (2) 130:4;131:18</p> <p>role (11) 61:1,7;63:14; 101:14;114:15; 152:22;154:1;165:8, 11;278:1;346:14</p> <p>rolling (1) 339:22</p> <p>room (21) 5:13;6:21;7:10; 10:22;14:5,15;17:8; 21:7;25:19;70:12; 149:9;156:13;158:2; 223:12;264:9;317:5; 330:20;340:9;369:18; 373:7,7</p> <p>Rooms (2) 7:6;13:6</p> <p>root (1) 108:13</p> <p>Roughly (2) 297:11;323:15</p> <p>rounds (1) 89:7</p> <p>Rowbotham (11) 229:6,6;230:16,18;</p>	<p>232:6;233:7,18;368:7, 18;369:15,17</p> <p>ruin (1) 164:4</p> <p>rule (2) 244:11;258:12</p> <p>run (4) 140:22;146:5; 187:7;350:15</p> <p>run-in (2) 183:22;184:12</p> <p>running (1) 326:21</p> <p>runny (1) 358:2</p> <p>rush (1) 257:19</p>	<p>319:1;327:14;345:9; 359:4;361:13;372:13</p> <p>sample (17) 158:13;265:4; 269:3;271:21,22; 274:3;275:13;278:7, 16;280:1;281:21; 282:3;295:22;298:21; 302:22;362:8;368:16</p> <p>sampled (1) 265:12</p> <p>samples (6) 136:21;137:2; 139:3;141:18;142:16; 362:7</p> <p>sampling (5) 271:13,14,15; 281:22;282:13</p> <p>Samumed (1) 91:19</p> <p>Sandkuhler (1) 60:8</p> <p>satisfying (1) 244:12</p> <p>saw (12) 31:19;39:3;73:12; 88:18;186:7;260:4; 265:1;276:14;284:8; 334:5;361:13;367:6</p> <p>saying (25) 18:22;107:12,13; 108:4,18;118:2,7; 169:20;198:20,22; 199:7;200:16;201:2; 204:16;216:6,9,22; 217:2,4,17;218:4; 240:12,19;253:18; 366:7</p> <p>scale (9) 87:11,17;126:6; 132:6;151:21;200:6; 337:20;361:7;368:2</p> <p>scan (5) 180:5;317:5;320:4; 328:19,19</p> <p>scanner (10) 113:18;151:2,10,19; 152:2,6;166:9;324:7; 329:17;337:17</p> <p>scanners (1) 371:19</p> <p>scary (1) 233:19</p> <p>scatter (3) 137:3;139:12; 154:10</p> <p>scattered (1) 271:9</p> <p>scenarios (3) 65:14,18;71:2</p> <p>Schedule (2) 171:11,12</p> <p>scheduled (1)</p>	<p>13:4</p> <p>scheme (1) 185:2</p> <p>schizophrenia (1) 267:13</p> <p>Scholz (6) 46:20;60:3,3;234:6; 244:9,18</p> <p>School (3) 25:14;71:16;307:5</p> <p>Schrepf (1) 214:15</p> <p>science (4) 80:6;179:10;235:8; 236:19</p> <p>scientific (2) 171:21;172:9</p> <p>Scientifically (1) 195:10</p> <p>scientists (1) 65:14</p> <p>score (16) 87:19;88:12;89:21; 106:15;130:17; 139:13,16;154:12; 181:3,8,14;188:2; 249:21;258:7;296:1; 300:1</p> <p>scored (1) 87:10</p> <p>scores (5) 87:3;93:15;151:22; 154:20;188:7</p> <p>scoring (1) 91:2</p> <p>Scott (1) 342:4</p> <p>screen (9) 5:3;116:12;135:18; 153:9;182:13;226:18; 228:5,8,14</p> <p>screening (2) 110:19;256:11</p> <p>search (3) 125:5;267:3;268:10</p> <p>season (1) 7:21</p> <p>second (11) 86:8,9;180:3; 237:12;245:1;296:19; 321:2;328:12;344:13; 364:4;370:2</p> <p>secondary (12) 41:20;42:12;43:4; 49:15;53:2;217:19; 220:10;314:3,15; 315:3,12;350:6</p> <p>Secondly (1) 261:20</p> <p>second-order (1) 238:8</p> <p>seconds (11) 58:12,17;67:3;</p>	<p>300:14;311:11; 323:15;344:11,13; 346:19;349:21;354:20</p> <p>section (1) 142:3</p> <p>sedimentation (1) 83:15</p> <p>seed (1) 328:1</p> <p>seeing (16) 89:8,9;105:7,7; 135:19;173:15,16; 215:19;225:17;247:9; 276:17;281:1;335:10; 348:5;364:9;371:4</p> <p>seeking (1) 276:8</p> <p>seem (17) 36:11;53:8;61:1; 84:12;97:22;104:13; 105:9;136:19;142:14; 175:4;195:3;215:3; 254:7;290:17;291:10; 300:17;305:10</p> <p>seemed (3) 176:19;218:5; 343:10</p> <p>seeming (1) 257:2</p> <p>seemingly (1) 257:16</p> <p>seems (29) 46:14;63:13;64:19; 65:1;69:4;101:1; 117:6;125:16;153:21; 154:2;157:5;162:7; 194:16;209:20; 214:12;216:10,15; 225:21;226:13; 231:16;235:10;237:6; 238:12;239:5;246:16; 248:1;340:9;359:9; 363:17</p> <p>segment (1) 193:2</p> <p>segmentality (1) 294:14</p> <p>segregating (1) 225:14</p> <p>segueing (1) 78:4</p> <p>seizure (1) 111:17</p> <p>select (3) 7:5;159:5;187:14</p> <p>selected (2) 45:19;46:5</p> <p>selection (4) 182:13,18;226:16; 281:20</p> <p>selective (1) 53:19</p> <p>selectively (2)</p>
--	--	---	---	--

<p>51:7;164:16 self-report (8) 82:8;112:22; 115:18;227:22;228:9; 264:15;270:3;279:14 self-reported (3) 268:1,2;290:5 self-selects (1) 282:2 seminal (1) 25:15 send (2) 14:9;366:14 sensation (5) 27:16;227:8; 237:18;300:8;351:8 sensations (5) 126:1;127:13; 130:21;232:14;300:12 sense (21) 12:14;29:16,22; 45:12,22;56:1;57:19; 60:6;65:12;105:11; 107:16;112:20; 159:11;196:8;233:19; 274:3;281:8;327:18; 343:9;362:9;367:15 senses (1) 357:20 sensitive (25) 6:6;24:5;43:4,7; 56:11;77:3,5;80:22; 81:21;93:11,11; 105:15;140:19; 208:17,19,22;209:1; 227:3,9;229:13; 295:11;296:4,14; 299:15;343:21 sensitivities (1) 79:13 sensitivity (51) 41:19;42:10,11; 47:18;49:15;53:8; 66:17;77:21;79:13; 80:16;105:10;120:20; 132:8,20,22;133:20; 140:14;141:3;148:5; 156:3,13,16;182:14; 186:9;225:5,8;228:11; 234:21;241:2,7;242:8; 244:10;253:15; 254:12;289:1,4,5; 295:4;301:8,15;303:2, 5,8,8,16,19;344:17; 351:9;358:19;363:8; 366:10 sensitization (207) 17:22;25:16;26:7, 21;30:13;32:11,14; 39:8,11,20;42:17; 43:21;44:7;45:1,7; 46:18;47:9;48:1,11, 19;49:3,22;52:15,18;</p>	<p>53:4,16,22;54:4,6,12, 16;55:5,9;56:13; 57:18;58:10;59:1,3,6; 60:5,6;61:4,10;62:3; 63:6,16;64:13;65:12, 19;66:16;68:2;69:10, 16;70:3;71:1,6,20; 72:21;77:7,10,18; 80:1;84:5,10;94:2; 95:20;96:3,4,7,18; 97:5,9;101:10;103:14; 104:8;105:22;106:21; 107:20,21;117:8; 119:21;125:8;127:3, 10,11,12,14;131:2,5; 155:14,22;156:17; 178:22;179:7;181:19; 190:14;205:10,13,15; 206:3,7,12;207:16; 209:7,16;210:12,13; 212:5,11,12,13,17,19, 19;213:2,8,11,11,17; 214:5,9,13;215:18; 217:11;219:12,15; 220:16,20;221:10; 222:21;223:9;224:3,4; 230:8;231:9;234:11, 14,16;235:15;237:8, 10,22;238:2,4,6,13; 239:2,3;240:16; 243:14,15;244:11,14, 15;245:11;247:2; 248:4;254:7,21; 255:19;257:12,20; 259:2;260:17,22; 265:19;285:14,17; 288:10,11,14,18; 289:7;294:20;300:21; 305:3,11,13,14,20; 307:17,19;308:4,6,12, 16;313:8;314:10,16; 315:19;316:5;320:6; 323:3;331:14;335:19; 336:9;337:3,6;338:13, 17;339:2;341:9;351:4, 5;358:7,14;370:9 sensitized (1) 231:7 sensitizing (1) 239:6 sensory (39) 17:22;18:2;49:9; 58:8;76:22;77:1,21; 79:13;80:20;82:10; 93:11;105:10;119:8; 120:19;126:4;131:8, 22;153:17;182:1; 208:16,17;209:1; 226:4;228:12;294:18, 22;296:2;298:9,11,22; 302:22;303:10; 304:11;327:11,13; 336:16;351:1;355:7;</p>	<p>357:19 sent (3) 8:18;205:8;360:20 separate (16) 117:16;119:6; 220:12;234:15,17; 243:6;247:1;253:19; 255:6;259:1;268:14; 269:2;277:2,21;358:9; 369:10 separated (1) 322:4 separately (6) 127:22;128:4,8,14; 157:14;208:2 separates (1) 225:4 separating (2) 171:13;245:10 separation (4) 210:16;321:19; 322:10,11 Serge (1) 134:3 series (12) 38:5;42:19;86:6; 94:2;103:22;213:9; 243:3;311:21;312:4; 313:6;323:17;332:21 serotonin (1) 97:19 serve (1) 184:21 service (1) 168:22 session (13) 5:18;10:4;22:11; 24:16;124:13,14; 218:6;261:3,6,8,14, 17;262:8 sessions (3) 10:3,10;222:20 set (19) 24:9;32:14;34:8; 40:16;52:12;59:13; 76:20;125:13;126:8; 131:10;156:11;189:6; 200:14;253:3;261:18; 267:2;326:7;342:22; 347:9 sets (10) 29:3;32:5;38:13; 108:6;159:1;208:3; 241:21;294:12,13; 358:22 setting (27) 31:17;43:16;45:13; 46:22;50:12;54:18; 56:2;57:6;59:4;64:7; 65:3;67:17;69:14; 106:8;114:5;176:9; 179:8;189:17;205:22; 206:16,17;207:2;</p>	<p>209:19;233:17; 240:10;323:7;352:1 settings (6) 46:15;62:8;85:13; 220:17;248:14;271:12 several (8) 8:12;13:6;55:8; 215:16;223:6;260:1; 288:16;304:3 severe (6) 73:21;74:7,10; 135:4;175:14;297:19 severely (1) 248:21 severity (5) 146:20;147:7; 151:20;199:2;360:2 sex (5) 208:8;209:4; 288:22;289:8;362:16 shade (1) 290:11 shading (1) 299:13 Shannon (2) 262:12;339:15 shape (1) 93:21 share (5) 22:16;23:10;67:15; 148:21;157:6 shared (2) 42:13;109:9 shares (1) 156:22 Sharon (7) 86:7;169:1;180:19; 187:19;197:10;204:3; 248:12 Sharon-Bob (1) 249:13 Sharon's (1) 245:2 sharp (1) 125:7 shed (2) 163:19;359:12 sheet (1) 5:6 Sherrington (1) 28:18 shift (2) 270:16;327:3 shifting (1) 327:9 shifts (1) 206:8 shigella (1) 122:19 shingles (1) 255:7 shock (1) 68:8</p>	<p>shooting (1) 201:8 short (4) 21:2;116:18; 297:21;298:3 shorter (1) 177:2 short-lived (1) 220:5 short-sighted (1) 165:19 shotgun (1) 196:10 shoulder (2) 144:10;255:15 show (34) 42:1;59:12;85:1,5; 92:12;132:10;134:8, 14,16;136:3;139:19; 140:5;141:15;151:14; 154:18;188:6;224:8; 252:19;253:2;257:15, 17;271:17;273:3; 274:12;286:8;293:18; 294:22;303:17;304:2; 315:1;321:22;331:18; 348:13,22 showed (19) 37:1;42:13;67:21; 83:11;84:17;91:10; 98:22;116:2;142:9; 144:17;200:16,17; 211:4;294:13;304:1; 318:22;335:22; 336:10;352:3 showing (11) 39:4;85:1;88:9; 94:4;95:21;115:21; 222:6;265:4;278:18; 300:20;367:1 shown (15) 42:8;43:3;80:18; 93:16;102:19;135:3,7; 141:17;143:5,10; 156:2;181:21;252:1; 299:21;327:19 shows (5) 58:18;143:8; 238:21;258:22;291:14 sickle (3) 79:8;90:21;96:9 side (11) 35:20;72:20;73:1; 88:13;139:18;144:16, 21;145:4,6;237:5; 296:11 sides (1) 281:12 sight (1) 237:18 sign (4) 5:7,8;176:17;229:2 signal (15)</p>
---	--	---	--	--

<p>201:14;278:15; 310:10,22;311:6,21; 312:6;324:11,12,13; 346:9;348:14,22; 350:14;372:10 signaling (3) 63:19;165:12; 288:15 signals (2) 60:9;133:4 signatures (1) 56:10 significant (18) 137:6;142:11; 145:19;146:3,18; 147:3;148:1;301:7; 304:2;316:10,13,17; 317:9,15;319:4;331:1; 342:13;370:2 significantly (11) 46:5;142:6;294:15; 302:9;304:8,9;305:13; 318:7,19;325:17; 361:7 sign-in (1) 5:6 signs (8) 18:14;176:14,16; 198:13;222:22; 288:17;305:10;358:22 similar (13) 31:14,21;44:22; 68:10;70:7;175:11; 197:17;265:5;297:3; 312:18;316:8;327:22; 365:12 similarities (2) 43:19;69:11 similarly (2) 168:6;279:9 SIMON (11) 22:6,18;62:15,15; 102:2,2,18;222:16,18; 227:18;358:12 Simon's (1) 241:5 simple (3) 110:19;193:2;225:2 simpler (1) 354:15 simply (3) 182:12;198:5,17 single (19) 34:13;51:13;62:4, 13;69:14;82:8;91:17; 103:11;121:18; 130:14;147:6;170:14, 15;227:5;351:6; 353:9;367:11;368:5; 373:15 sink (1) 34:17 sit (1)</p>	<p>233:3 site (10) 35:11;39:5;91:17; 213:6;220:6;225:4; 230:15;245:21;354:1, 13 sites (15) 91:12,16;143:16; 144:9;153:11,14; 177:20;213:7;293:3, 11;295:7;296:13; 353:19;354:19,20 sitting (3) 16:13;26:12,17 situated (1) 137:12 situation (7) 26:3;35:15;68:22; 187:2,13;255:9; 280:12 situations (1) 255:18 sizable (1) 217:8 size (7) 93:21;135:18; 187:1;274:3;280:2; 308:19;320:9 sizes (6) 136:6;271:21; 278:7,16;281:21; 338:19 skeptical (1) 350:4 skin (6) 38:16;61:12; 121:21;229:18;230:2; 231:8 skip (1) 199:16 skull (1) 320:18 skunk (1) 83:21 Slade (1) 294:5 sledgehammer (1) 185:19 sleep (20) 78:1;79:12;84:11; 108:9;190:21;191:5; 192:2,16;197:20; 199:3;200:3,5,5; 253:10,12;283:18; 284:1,4,6;341:16 sleeping (2) 51:22;101:4 slide (18) 17:10;86:8,9;88:9; 90:21;111:9;131:19; 138:3;143:5;156:15, 18;268:19;272:5,17; 275:18;277:15;</p>	<p>278:19;280:1 slides (12) 15:20;16:4,6;95:22; 128:22;137:18;140:6, 9;145:10;269:11; 277:4;287:21 slightly (1) 297:15 slog (1) 72:20 slope (7) 296:18,19,21;297:4; 335:17;336:1,4 slow (2) 273:8;323:13 slowly (2) 122:10;345:16 small (15) 41:6,14;137:19; 211:2,9,17,20;229:18; 268:11;271:22;272:1; 278:7;281:21;290:9; 368:16 smaller (2) 286:14;314:11 smallest (1) 52:6 smart (1) 158:3 smartphone (1) 5:11 smirking (1) 75:3 Smith (3) 262:12;339:15; 366:22 smoking (1) 291:2 snapshot (1) 280:5 SNE (1) 65:8 Snowden (1) 22:3 SNR (3) 334:17;335:4;344:1 SNRIs (3) 106:10;252:1,13 socially (1) 156:9 software (1) 313:5 sole (3) 145:19;146:9; 147:10 solve (1) 115:15 somatic (12) 82:10;126:1;128:6; 129:1;130:11;148:14; 166:6;240:15;289:2; 290:16;291:10;305:2 somatization (12)</p>	<p>18:4;82:12,13,14, 17,21,22;125:20; 128:22;129:13; 148:14;155:14 somatomotor (4) 150:7,15,16;325:11 somatosensory (43) 125:1,16,22;126:6, 21;127:9,20;129:1; 131:1;140:1;148:10; 150:17;151:17;152:8; 154:7;155:13;156:18; 157:9,22;165:6;210:4; 304:5;305:2;314:4; 315:3,12;320:12,14, 22;325:12;327:6; 329:10;336:20; 338:16;350:6,9; 355:19,22;356:7; 357:6,15,20,21 somatopic (1) 320:15 somatotopically (1) 348:6 somebody (16) 7:2;14:8;16:14; 22:3;23:20;160:6; 180:5;182:11;199:13; 258:22;291:16; 292:16;293:9;326:12; 366:14;368:10 somehow (9) 90:15;165:14; 179:4;183:4;248:16; 252:14;260:21; 285:19;305:20 someone (40) 6:9;11:19;26:4; 70:4;74:22;76:18; 80:9;84:17;85:2,4; 87:8,13;89:4;94:13; 95:15;98:18;103:10; 108:2;110:7,22; 112:13;122:20; 166:10;167:12;168:3; 190:15;217:6;221:1, 20;224:19;243:17,22; 252:2;255:3,7;281:12; 342:4;352:21;353:1; 373:15 someone's (5) 74:10;100:8; 149:11;243:19;371:15 sometimes (18) 9:16;15:3;17:19,19, 20;83:19;121:19; 145:18;147:9;167:14; 251:19;253:8;265:3; 277:14;326:15;336:4; 365:19;369:9 somewhat (7) 17:20;46:16;65:16; 125:3;186:8;296:5;</p>	<p>300:17 Somewhere (4) 33:5;309:9;311:2; 366:13 soon (4) 39:13;108:7; 121:22;235:12 sophisticated (1) 223:7 soreness (1) 143:22 sorry (5) 162:2;268:10; 298:15;346:6;363:15 sort (52) 16:16;17:15;75:16; 77:16;81:2;85:2; 103:2;104:20;105:11; 114:12;118:18; 126:16;129:18; 132:10,20;159:1,11; 164:6;169:6;193:1; 196:9,11;198:10; 208:15;209:8;217:20; 223:3,7;235:7;237:20; 242:5,7;243:17; 250:18;255:6;260:21; 272:19;280:18; 288:20;298:18;300:9; 308:8,19;312:8; 314:14;324:6;328:17, 22;332:19;334:4; 362:17;368:21 sorts (16) 126:14;134:19; 135:13;138:5;141:17; 142:14;143:12; 144:16;147:13; 152:14,22;163:10,13; 165:21;371:1,5 sought (1) 167:18 sound (3) 119:9;161:10; 246:20 sounds (4) 188:11;191:15; 197:4;227:19 source (2) 255:2,5 Sp5 (5) 332:10;333:7,21; 334:4;364:11 space (7) 70:13;138:10; 157:1;280:15;354:7; 358:5;360:6 spaced (1) 58:17 spaces (1) 354:7 Spain (1) 58:16</p>
--	--	---	--	---

<p>span (3) 153:18;174:4; 282:20</p> <p>spans (1) 264:20</p> <p>spatial (3) 316:11;348:20; 365:1</p> <p>speak (6) 6:11,16;21:5; 124:17;225:1;307:10</p> <p>speaker (7) 25:12;70:20;124:2; 168:18;284:18,19,21</p> <p>speakers (12) 5:19;8:16;10:7; 15:19,20;24:17;25:3; 203:6,7;261:2,13; 306:5</p> <p>speaker's (1) 262:8</p> <p>speaking (4) 6:17;23:20;71:22; 265:1</p> <p>special (2) 246:20;284:10</p> <p>specific (28) 9:7;19:5;22:16; 24:10;116:3,6;125:4; 128:20;155:18;159:5; 164:14;188:12; 189:16;211:12;223:9; 224:16;237:10,11; 244:16;245:21; 271:19;331:16;337:2, 18;342:20;347:20; 349:3;358:21</p> <p>specifically (17) 53:12;62:5;163:8; 179:8;238:6;251:15; 270:13;273:17; 282:18;292:10; 319:20;321:12;329:4; 336:11,22;338:11; 339:5</p> <p>specificities (2) 242:3;366:10</p> <p>specificity (7) 234:21;241:2,7; 242:8;351:10;363:9; 367:11</p> <p>specified (2) 270:7,18</p> <p>specify (2) 271:3;282:4</p> <p>spectroscopy (4) 309:15;371:20,21; 373:4</p> <p>spectrum (2) 135:15;232:4</p> <p>spend (8) 13:12;124:22; 128:21;137:18;</p>	<p>145:10;149:15; 161:13;338:22</p> <p>spending (1) 4:20</p> <p>spent (2) 174:13;354:17</p> <p>spike (1) 233:4</p> <p>spin (1) 346:5</p> <p>spinal (22) 30:7;31:4;36:4; 38:19;50:18;55:20; 56:15;60:14,22;72:14; 77:7;165:8,20;166:12, 17;178:13;236:9; 332:9;333:7;338:14; 352:5;364:2</p> <p>spinalized (1) 30:16</p> <p>spinalizing (1) 236:1</p> <p>spite (2) 184:17;357:3</p> <p>split (7) 138:19;142:21; 154:16;171:9;212:13; 273:2;277:1</p> <p>splitter (1) 240:5</p> <p>spoke (1) 361:21</p> <p>spondylitis (1) 75:19</p> <p>spontaneous (3) 31:7;67:19;68:9</p> <p>spontaneously (1) 221:15</p> <p>spot (4) 58:6;155:3;224:19; 228:22</p> <p>spread (6) 41:19;42:11;49:14; 230:20;231:14;237:17</p> <p>spreading (2) 121:14;231:19</p> <p>square (3) 218:13,15;229:18</p> <p>SRINIVASA (1) 350:21</p> <p>stable (2) 99:10;103:17</p> <p>stage (1) 268:18</p> <p>stand (1) 17:12</p> <p>stand-alone (1) 73:9</p> <p>standard (9) 35:14;45:15; 177:11;187:6;236:5, 14;246:19;253:16; 297:12</p>	<p>standardized (8) 131:11;132:3; 151:2;166:13;226:20; 267:16;270:4;301:20</p> <p>standards (1) 172:6</p> <p>standing (3) 6:22;7:13;298:4</p> <p>standpoint (3) 97:10;213:16; 320:10</p> <p>stands (3) 178:18;326:2,2</p> <p>stark (1) 89:10</p> <p>start (31) 9:9;51:21;64:1,6; 71:15;85:17;101:4; 105:15;108:7,8; 180:14;184:14; 186:21;203:8;204:3,7; 222:16;232:14,15; 243:6;244:8;253:11; 273:11;277:10;296:2; 312:13;339:21;340:1; 344:22;353:18;369:19</p> <p>started (15) 4:10;27:5;32:20; 38:10;47:16;55:12; 72:20;74:17;76:21; 77:9;80:5;91:5; 171:13;264:5;324:2</p> <p>starting (6) 100:9;108:5;110:8; 168:11;224:13;273:4</p> <p>starts (2) 233:20;348:12</p> <p>state (32) 32:19;36:21;47:8; 50:21;59:6;63:4; 100:16;101:9;102:10, 13;103:3;115:1; 164:19;167:8;170:8; 201:6;211:12;214:10; 254:21;304:19;310:5, 12;314:20;315:14; 324:5;326:20;327:4,5, 5;328:3,3;343:13</p> <p>stated (1) 218:7</p> <p>statement (4) 214:8;252:4;343:8; 344:6</p> <p>statements (3) 337:20,22;338:10</p> <p>states (5) 90:14;97:18;99:16; 118:8;258:5</p> <p>statistical (6) 192:8;311:20; 312:4,5;340:18,21</p> <p>statistically (2) 141:1;342:13</p>	<p>statisticians (2) 342:1,2</p> <p>statistics (3) 274:10;340:11; 341:13</p> <p>status (1) 76:3</p> <p>stay (6) 5:21;13:16;103:17; 173:17;186:18;190:3</p> <p>stayed (1) 302:13</p> <p>stays (1) 159:20</p> <p>steeper (2) 296:22;297:4</p> <p>stem (3) 56:20;57:15;69:17</p> <p>step (3) 226:21;309:4; 340:17</p> <p>steps (1) 345:14</p> <p>stereotyped (2) 29:2,21</p> <p>steroids (1) 215:4</p> <p>Steve (6) 36:16;37:17;39:1; 59:21;60:1;158:11</p> <p>stew (1) 55:9</p> <p>stick (1) 223:5</p> <p>still (32) 67:16;75:20;76:1; 77:12;83:5;92:3; 93:19;94:5;111:7; 117:4;121:7;124:20; 170:16;184:18,22; 185:12;187:14,16,17; 188:21;220:18;243:7; 249:2;277:21;294:15; 300:14;302:2;308:3; 345:22;355:12;362:8; 367:16</p> <p>stimulate (2) 214:18;218:19</p> <p>stimulating (4) 35:11;215:19; 311:18,19</p> <p>stimulation (23) 35:10;131:12; 166:14;215:21; 229:14;237:18; 312:22;313:19; 317:21;319:7,10; 321:2;332:2,3,12,15, 18,22;334:14,20; 336:15;343:14;367:17</p> <p>stimulations (2) 314:6;334:21</p> <p>stimuli (35) 29:3;31:8,11,11,19; 33:20;36:5;37:5; 49:12,13;77:2,21; 105:10,16,16;119:8; 136:11;206:1;208:17; 300:13,13;323:17; 325:22;326:1,3;332:8; 333:2;335:3,6,20; 336:16;341:5,7; 343:12;344:20</p>	<p>stimulus (3) 30:20;31:20;35:6; 40:8;58:12,16;59:2; 63:7;65:20;67:3,14; 132:4,4,5,15,16; 136:12;144:13;151:3, 3;152:2;205:11; 245:19;257:18,19; 308:7,9;311:18;312:8, 10;315:22;318:7; 319:16;323:9;327:8, 18;330:6,6,14,18,18; 332:13;334:17; 335:14,14;336:7,12, 12;348:13,15;349:13; 352:14,17</p> <p>stimulus-matched (3) 317:22;318:2,18</p> <p>stomach (1) 99:21</p> <p>stood (2) 205:7;278:14</p> <p>stop (4) 101:4,20;209:10; 311:19</p> <p>stopped (1) 300:13</p> <p>stops (1) 23:20</p> <p>stories (1) 263:9</p> <p>story (1) 152:18</p> <p>straight (2) 22:15;132:21</p> <p>straightforward (4) 140:11;291:22; 323:6;330:8</p> <p>strange (1) 361:2</p> <p>strategies (1) 290:21</p> <p>strategy (2) 179:19;267:3</p> <p>stratified (1) 361:10</p> <p>strength (2) 314:22;348:1</p> <p>strengths (1) 348:2</p> <p>stress (9) 123:4;142:7,13; 210:9,11,17;245:19;</p>
---	---	---	---	---

246:10;341:16 stressed (1) 101:5 stressors (1) 123:14 strictly (1) 308:6 stringent (1) 236:14 strong (7) 82:19;162:21; 290:4;299:9;303:12; 334:17;372:10 stronger (5) 88:3;290:12; 291:19;292:2;293:20 strongest (2) 82:6;291:8 strongly (16) 24:6;77:18;98:4; 116:5;127:15;131:16; 138:5;139:22;142:15; 143:12;154:5;157:3; 164:20;258:16; 290:17;299:4 struck (1) 32:18 structural (2) 211:10;303:22 structure (4) 164:12;166:19; 303:15;309:7 structured (3) 10:1;267:15;268:7 struggled (1) 207:6 stuck (1) 78:12 student (1) 26:13 studied (14) 30:3;31:4;32:18; 60:7;82:17;21:91:9; 137:20;140:13; 176:14;204:12,18; 289:15;291:11 studies (181) 19:8;33:4;42:20; 43:14;46:8,12;47:12; 53:10;58:9,22;64:17; 67:20;69:19;72:14; 73:19;74:2;76:20; 79:21;80:17;81:18,19; 86:7,13,20;87:1; 88:11;90:1,6;92:22; 93:15;94:2,9;98:22; 100:14;103:22; 106:16;108:11;129:4; 131:14;132:9,11; 134:18;135:6;136:1; 138:14;141:17; 143:19;145:14; 146:11;149:16;150:1,	2,10;152:20;153:7; 154:4;158:13;159:18; 162:5;163:7,14,21; 166:4,18;167:3,9; 168:2,11;173:22; 177:11,16;178:3,4; 181:21;185:17; 194:20;196:19;205:1; 208:5;211:1;213:10; 215:16;223:18;224:1, 5,8;225:5,9;226:6; 232:2;233:7;242:11, 17,20,22;243:10; 258:3,4,10,21;264:12; 265:16;267:6,14; 268:8,22,22;269:5,8, 15,16;271:1,2,4,8; 272:4,6,9,11,21;273:5, 11,13;274:4,14,19,21; 275:1,5,6,16,19,21; 276:11,18,22;277:9, 14,16;278:3,8,9,14; 279:2,6,20;280:7,20; 281:4,8;282:3,4,8; 283:10;303:19;313:9, 12;314:11,12,12; 315:6,17;316:15; 317:19;320:16; 329:12,15;330:2,14; 339:7;342:10;345:4, 19,19;346:12;353:12; 355:11;359:8;361:5; 368:19;369:5 studies' (1) 271:6 study (129) 12:11;19:3,20; 29:11;30:6;31:16; 32:21;36:16;37:17; 39:18;41:2;44:2;46:1; 50:8;51:9,17;60:12; 65:22;66:7;82:1,12; 88:17;90:19;92:13,14; 93:17;94:15;104:22; 105:5;106:13;117:5; 118:2;129:3,11,22; 130:6,15;132:13; 138:16,18;139:5,7; 140:17;144:17,19; 145:21;146:13; 147:18;154:8;158:18, 20;160:4;161:6; 169:13;170:17;171:1; 174:1;179:17;181:7; 185:3,4;186:18,21; 187:10,15;188:19; 192:7,18;195:14,15, 16,19;196:6,13,17,18; 214:2,4,7;225:1; 226:21;253:9;259:16; 260:5,8;265:10; 267:18;269:7,13; 270:11,12;272:8;	274:7,16;275:11; 277:5;281:9;286:9,13; 287:4;295:6;299:1; 301:2,13,17;302:18, 21;303:9,22;305:16; 313:8;317:3,12,20,22; 322:8,9;329:19;330:7, 12;337:15;345:5; 354:22;360:16;361:8; 362:1,2;368:5;371:21 studying (9) 19:2;30:10;34:7; 43:22;44:21;56:14; 134:6;229:8;333:14 study's (1) 147:21 stuff (12) 141:6;149:8;190:8; 192:4;195:16,20; 236:22;260:9;340:20; 341:3;346:1;358:8 stupid (1) 76:15 style (2) 138:8;166:14 sub (1) 331:2 subacute (1) 123:15 subacutely (1) 110:22 subcategories (1) 240:6 subclinical (1) 252:14 subcortical (1) 332:6 subgroup (4) 188:4,5,5;316:18 subgroups (2) 173:10;316:20 subject (3) 67:5;324:7;330:3 subjects (17) 144:2;314:6,13; 316:12;318:8,16; 321:20;322:5;327:1,2; 328:13;330:15;336:2; 338:6;351:3;361:15; 368:16 subject's (1) 335:9 subliminal (2) 41:5,9 submitted (2) 11:8;198:20 submitting (1) 194:19 subpopulations (1) 201:12 subscale (1) 129:14 subscales (1)	297:21 subscribe (1) 137:14 subsequent (2) 14:10;246:8 subsequently (1) 181:7 subset (10) 101:9;106:14,22; 116:10;181:18;217:8; 349:1 subsets (2) 79:7;97:9 substance (1) 267:13 substantial (4) 128:10;141:2; 262:2;288:8 substrate (1) 152:11 substrates (4) 148:22;149:5; 157:7;161:16 subtle (1) 142:17 subtleties (1) 161:5 subtype (1) 232:10 success (1) 184:6 successful (2) 75:14;201:19 sudden (3) 126:11;160:6; 232:11 sufentanil (1) 176:6 suffered (1) 78:6 suffering (1) 321:16 sufficient (12) 51:18;52:7,13,16; 66:9;68:16,21;69:2; 188:6;206:3;221:3; 348:20 sufficiently (1) 38:8 suggest (13) 105:21;106:11,11; 131:15;136:2;138:14; 141:7;150:11;162:5; 178:14;181:12; 194:12;279:16 suggested (6) 54:11;66:22;67:9; 152:20;159:15;221:20 suggesting (8) 38:2;100:2,15; 214:1;245:18;282:10; 302:13;304:9	suggestive (2) 351:4;357:16 suggests (6) 118:3;150:21; 194:3,9;239:1;245:22 suitable (1) 175:10 Sullivan's (1) 143:19 sum (2) 269:10;275:17 summaries (1) 199:11 summarize (1) 274:9 summarized (1) 288:13 summarizes (1) 54:8 summary (2) 280:18;336:8 summate (1) 136:13 summation (60) 49:14;53:1;58:9,20; 59:13;64:20;133:13; 134:1;135:22;136:4, 14,17,19;137:7,9,12; 141:4,8,12,15;147:1,5, 13;148:12;152:5; 159:17;162:15; 228:11;234:8;235:18; 236:7;238:17;241:12; 245:15;246:13; 296:15,21;297:3,5; 298:10,11,14,16,17; 303:3;304:7;308:16; 323:3,8;328:9,11,16, 20,22;329:2,5,8; 332:20;336:18;338:18 summer (1) 197:11 super (2) 172:5;248:8 superimpose (1) 343:2 superimposed (8) 80:1;90:13,17; 94:11;95:20;106:20; 123:11;214:10 superior (1) 224:6 supervised (1) 176:9 support (3) 179:10;180:11; 338:20 supported (2) 179:2;221:7 supporting (1) 98:5 supports (1) 257:1
--	---	--	---	---

<p>supposed (3) 58:10;238:17,18</p> <p>suppress (2) 136:20;143:5</p> <p>suppression (1) 54:3</p> <p>supraspecific (1) 172:16</p> <p>supraspinal (2) 72:15;332:6</p> <p>sure (26) 4:14;5:7,20;6:11; 11:3;22:14;44:11; 52:18;84:19;96:3; 102:10;112:19; 131:20;140:9;158:20; 159:7;160:9;171:17; 197:5;222:13;239:9, 10;280:14;293:8; 364:10;370:13</p> <p>surface (1) 373:6</p> <p>surgeon (1) 84:16</p> <p>surgery (18) 47:14;75:15;86:18; 87:2,5,15,22;88:17; 90:8;105:1;106:2; 122:5;146:19;147:5,8; 148:13;156:3,9</p> <p>surgical (4) 90:8;132:11;135:6; 257:18</p> <p>surprise (4) 60:14;306:11,13,13</p> <p>surprised (10) 43:13;51:16;133:1; 163:22;205:5;276:12; 278:8;279:19;360:19; 363:16</p> <p>surprises (1) 259:6</p> <p>surprising (4) 46:17;222:1;227:7; 292:4</p> <p>surprisingly (9) 30:2;33:8;37:10; 125:3;148:18;184:17; 290:3;293:20;299:4</p> <p>surrogate (3) 84:4;222:20;223:4</p> <p>survey (2) 174:15;270:3</p> <p>susceptibility (3) 57:13;65:2,6</p> <p>suspect (7) 137:14;149:9; 155:9;164:13,20; 185:7;259:15</p> <p>sustained (4) 326:19;327:4,5; 328:2</p> <p>sustaining (1)</p>	<p>68:1</p> <p>Suzie (1) 89:22</p> <p>sweating (1) 240:1</p> <p>Sweden (1) 153:13</p> <p>swelling (1) 240:1</p> <p>Swett (3) 30:10;31:16;32:21</p> <p>swim (2) 34:17;210:9</p> <p>switch (2) 56:5;247:10</p> <p>switching (1) 261:9</p> <p>sympathetic (1) 239:20</p> <p>symptom (9) 129:13,14,16; 130:22;147:19; 189:13;227:5;284:2; 289:2</p> <p>symptomatic (1) 199:14</p> <p>symptomatically (1) 115:13</p> <p>symptoms (39) 18:14;20:16,16; 77:22;79:7;84:11; 96:15;102:14;109:17, 19;110:7;111:1; 113:21;130:9;162:16; 176:14,16,18;190:14, 17,20;191:1,12; 198:13;210:21; 222:22;227:7;228:12; 249:1;266:13;290:16; 291:10;292:3;297:10; 301:18;305:2;358:1, 15,22</p> <p>synapse (7) 40:5,5;237:11; 247:13;331:19; 333:18;334:10</p> <p>synapses (2) 40:8,13</p> <p>synaptic (8) 39:19;40:21;42:16; 43:22;63:18;69:18; 70:6;241:14</p> <p>syndrome (20) 62:21;65:6;78:18; 90:22;102:4;104:4; 109:22;113:10; 121:15;122:2,6; 126:18;142:1;164:3; 274:17,21;287:11; 321:12,17;368:14</p> <p>syndromes (6) 18:21;53:14; 109:16;113:9;143:12;</p>	<p>162:10</p> <p>synthesize (1) 14:13</p> <p>system (57) 34:8;35:8;36:6; 38:4;40:4;49:5,8,19; 52:3,10;56:1;59:7,11, 20;61:18;62:7,12; 65:16;67:13;72:9; 79:4;80:14,15;81:5, 10,13,14,15,17;90:16; 92:21;93:16;97:14; 98:13;99:6;114:15; 117:16;118:19; 131:16;133:4;165:22; 211:11,22;212:2; 213:14;214:19;216:2, 10;217:20;221:17; 247:12,16,20;347:7, 13;357:21;363:20</p> <p>systematic (9) 141:22;262:22; 263:6;265:22;267:2; 270:19;279:12;284:4; 339:19</p> <p>systematically (1) 163:15</p> <p>systemic (2) 92:11;246:1</p> <p>systems (3) 112:1;133:18; 213:15</p> <p>systolic (1) 160:5</p>	<p>193:19;200:9;212:7; 236:13;238:12;264:8; 265:21;266:5,16; 271:17;273:8;277:22; 279:17;285:14,21; 286:4,5;289:8;292:17; 306:19,22,22;307:16; 308:22;309:4;310:2; 313:13;315:16;320:7, 8;330:9;331:13; 357:13;360:9;361:22; 370:20;371:10</p> <p>talked (22) 103:13;105:14; 106:9;107:11;110:1; 155:13;171:1;172:1, 11;247:21;283:2,11; 295:16;305:22;313:7; 319:8;320:6;322:19; 337:12;355:18; 357:18;360:13</p> <p>talking (52) 8:21;9:9;17:21,22; 18:2,3,4,6;20:20;73:9; 82:13,16;83:2;108:20; 113:10;123:16;125:1; 127:18;128:22; 130:22;131:5;149:15; 153:19;155:22; 190:13,14;191:16; 195:1;212:10,11; 217:10;218:17;226:1; 248:8;253:6;258:9; 260:16;262:21;279:5, 14;285:2;289:1; 295:13;307:21;352:9, 12;355:17;360:22; 363:19;364:22; 369:20;370:7</p> <p>talks (6) 131:3;205:3,9,9; 238:10;307:21</p> <p>tap (1) 58:10</p> <p>tapping (1) 238:18</p> <p>target (5) 20:15;144:1;163:8; 178:8;251:3</p> <p>targeted (4) 144:9,12;169:9; 197:1</p> <p>task (4) 298:4,4,5;370:15</p> <p>tasked (1) 307:17</p> <p>tasks (1) 334:22</p> <p>taught (4) 73:11;75:5;76:11; 124:5</p> <p>taxes (1) 7:19</p>	<p>TDCS (1) 164:15</p> <p>teach (2) 76:14;80:8</p> <p>team (1) 26:18</p> <p>tease (7) 55:11;56:8;112:6; 120:1;207:3,12; 251:19</p> <p>teased (1) 38:12</p> <p>teasing (1) 109:9</p> <p>technical (1) 193:7</p> <p>technically (1) 27:17</p> <p>technique (1) 164:15</p> <p>techniques (9) 27:9;68:3;94:21; 131:11;164:14; 204:13;292:11; 309:21,22</p> <p>technologies (5) 50:5;309:12;363:7; 373:3,11</p> <p>technology (7) 50:2;55:15;56:17, 21;57:16;311:8; 346:18</p> <p>tegmental (1) 314:9</p> <p>telling (1) 280:18</p> <p>tells (3) 91:4;211:13;243:17</p> <p>temperature (1) 330:20</p> <p>temporal (64) 53:1;58:9,20;59:13; 64:20;133:13;134:1; 135:22;136:3,13,17, 19;137:7,8,11;141:4, 8,11,15;147:1,4,13; 148:12;152:5;159:17; 162:15;163:19;167:5; 228:10;229:14;234:8; 235:18;236:7;238:17; 241:12;245:15; 246:13;283:8;296:15, 21;297:3;298:10,11, 14,16,17;303:2;304:7; 308:16;323:3,8;328:9, 10,16,20;329:5,8; 336:18;338:18;344:9, 10,12;348:21;355:5</p> <p>temporalis (3) 299:3;300:3,6</p> <p>temporally (1) 347:6</p> <p>temporary (2)</p>
T				
		<p>T2-star (1) 311:5</p> <p>table (3) 6:7;146:15;263:5</p> <p>tables (1) 312:20</p> <p>tactile (6) 42:11;50:12;53:1; 66:9;220:9;241:20</p> <p>tail (1) 33:6</p> <p>tailor (1) 209:3</p> <p>take-home (1) 128:12</p> <p>talk (69) 9:16;18:20;19:12; 47:14;71:13,18;73:1, 6;76:9;81:12;93:12, 14;100:19;103:19; 110:2;122:16,17; 127:22;128:12;131:2; 137:22;141:10;149:1; 157:8;161:22;167:1; 169:4,6,11;173:10; 174:17;185:18;</p>		

<p>220:5;241:15 temporomandibular (13) 65:5;129:8,21; 147:22;263:1;265:6, 20;269:6;272:3,12,20; 275:4;279:21 temporoparietal (1) 325:20 tend (4) 26:4;159:2;276:7; 358:21 tended (1) 335:16 tendency (4) 6:3;126:1,9;228:6 tender (8) 76:13,15,19;80:21; 82:2;84:3;177:20; 213:7 tenderness (2) 213:2,6 tens (2) 48:14;326:15 tension (2) 368:22;369:10 term (29) 39:7,15;48:11; 71:22;77:9;78:11,12; 79:17;82:14;96:4; 125:2,4,6,16,21; 156:19,20,21;163:5; 237:9,10;238:4,4,6; 243:15;248:4;308:4; 325:16;357:7 terminal (1) 38:18 terminologies (1) 125:12 terminology (4) 4:8;17:18;113:12; 240:15 terms (43) 46:4;64:9;70:6; 77:8;125:7;130:12; 144:20;147:20;157:1; 159:16;160:12;172:1; 173:20;174:16;182:9, 18;195:5,11;200:18; 203:17;222:21;223:6; 224:20;225:5,13; 235:1;242:7;248:10; 249:5;292:18;297:6; 312:12;333:5;334:18; 344:16,17;347:12; 351:21;355:15;359:5; 363:11;365:16,20 terrible (1) 74:15 terribly (2) 292:4;299:8 terrific (4) 140:3;161:2; 183:18;235:6</p>	<p>Terry (1) 44:4 test (14) 59:19;229:10; 230:6;231:13;232:19; 233:18;234:3,8; 254:17;311:20;312:1, 4;366:18,21 tested (1) 132:15 testing (17) 58:8;77:1;80:21; 131:8;134:10;182:1; 226:4;254:12;294:19, 22;296:2;298:9,22; 302:22;303:10; 304:11;351:1 testosterone (3) 208:11,12,13 tests (7) 59:8,8;110:19; 131:22;194:12; 298:11;312:5 thalamus (5) 314:1,2;331:8; 336:14;349:8 Thanks (18) 23:12;25:10;71:10, 10;124:9,12,12;138:2; 158:4,8;166:21; 180:19;197:9;261:16; 284:10,13;285:13; 306:18 That' (1) 306:4 THC (1) 100:17 theme (1) 47:13 theoretical (3) 189:8;221:6;245:12 theory (7) 32:3;38:20;127:5; 135:13;349:9,17; 364:15 therapeutic (5) 48:4;189:11; 193:22;194:7;207:14 therapies (6) 54:10;75:5;100:9, 20;101:16,18 therapy (6) 43:11;111:18; 145:1;190:5;194:11; 256:21 there'd (1) 50:14 therefore (6) 15:15;21:12;28:6; 64:2;174:2;201:12 thickness (1) 303:18 thinking (19)</p>	<p>18:8;19:14;66:18; 70:8;167:17,21,21; 169:7;194:17;209:6; 213:14;230:12; 283:20;331:22;340:2; 345:6;352:5;358:19; 368:18 third (6) 20:12;71:16;79:16; 90:11;106:19;321:3 thirds (1) 361:11 Thompson (1) 7:14 though (23) 9:1,8;36:11;75:14; 89:19;99:2,5,10; 101:1;105:9;122:4; 128:9;138:7;160:10; 176:16;182:22;191:7; 194:3;200:3;227:5; 251:4;252:19;269:9 thought (24) 27:5;31:15;32:12; 36:12,15;45:14;51:2; 72:4,10;113:13;125:2; 170:8;172:21;205:3; 225:1;259:17;263:10; 265:14;314:15; 329:19;332:19; 339:21;340:17;371:22 thoughts (4) 223:3;249:9;343:8, 15 thousand (1) 271:22 thousands (6) 55:22;68:14;125:9; 129:5;137:15;365:1 threat (1) 13:14 three (12) 8:6;15:3;28:2;73:5; 95:2;103:21;106:8; 266:7;267:3;300:10; 370:1,3 threshold (19) 33:2,12;37:4;40:19, 20;41:13,18;48:22; 206:5;219:16;220:8; 221:14;237:4;241:19; 247:14;295:9;299:3; 300:6;302:14 thresholds (8) 33:5;237:2,2;295:7; 296:7;302:8,11,13 throat (1) 358:1 throughout (1) 271:9 throw (2) 148:6;219:11 thrust (1)</p>	<p>226:22 thumb (1) 318:6 thumb-squished (1) 318:5 thus (2) 102:10;256:20 thyroid (1) 110:19 tie (1) 69:8 tied (1) 24:1 tight (1) 154:11 times (13) 6:15;8:7;59:15; 89:18;108:12;127:20; 138:22;199:16; 283:19;286:20; 296:19;323:5;352:8 timing (1) 61:5 tiny (11) 51:14,14,17;52:6, 12,16;68:11,13;96:21; 117:11;241:14 tip (1) 85:21 tired (1) 354:10 tissue (8) 34:5;35:11,17; 49:15;61:14;102:5; 206:6;326:19 title (1) 268:15 titles (1) 277:14 titrate (1) 186:13 TMD (60) 78:14;82:7;130:7, 15,17;270:7,13; 272:22;274:18;275:4, 16,22;276:10,16,19; 281:1,6,8,10;282:19; 284:5;286:14,17,20; 287:2,12;289:17,18, 19,20;290:13,19; 294:6,9,15;295:9,11, 12;299:5,5,7;301:4,5, 10,14,17,18,20,22; 302:1,2,4,4,5,8,12,15, 16;341:17;358:4 TMS (1) 164:15 TNC (2) 349:6,15 today (21) 26:22;73:6;74:2; 183:21;197:22; 212:10;217:10;</p>	<p>238:11;248:2;262:21; 263:14;264:8;265:19; 274:12;282:15;285:2; 288:22;307:10,16; 367:6;368:19 today's (1) 218:5 Todd (1) 245:5 toe (1) 255:15 together (23) 13:19;18:7,11,13, 15;19:19;25:11; 27:13;28:11;69:8; 80:11;97:9;110:17; 159:3;162:17;171:14; 220:13,15;240:7,18; 260:19;292:6;305:21 told (2) 26:19;337:18 tolerate (3) 185:5,10;186:12 tolerated (1) 187:3 tomography (1) 309:17 tomorrow (6) 13:5;161:13; 213:20;357:13; 369:20;370:12 ton (1) 137:5 tone (1) 212:2 took (5) 33:8;41:21;159:9; 266:4;330:16 tool (4) 174:14;192:3; 193:13;267:17 tools (10) 55:13;128:15; 166:3;191:22;196:22; 347:15,17;351:17,22; 366:1 top (7) 103:17;132:6; 148:2;275:9;277:9; 299:2;343:12 top- (1) 300:2 top-down (8) 105:2;117:13,13,20; 120:7,14;235:15,22 top-down/bottom-up (2) 117:4;239:4 topic (11) 8:22;11:9,13;15:12; 17:16;71:11;179:14; 263:11;265:18;283:2, 5 topical (3)</p>
--	---	---	---	---

230:16;232:11; 245:13 topics (11) 8:4,11,16,21;9:3,3, 4:15:19;18:18;21:18; 262:15 Tor (2) 318:1;365:8 Torebjork (2) 42:1;43:3 total (4) 32:19;33:3;146:13, 17 totally (3) 73:17;87:12;168:14 Toth (1) 144:17 touch (6) 33:16;48:6;161:22; 229:13;237:16;358:20 touched (1) 140:3 touch-evoked (1) 232:17 touching (1) 229:13 toward (4) 115:6;228:6; 302:10;362:5 towards (6) 100:6;116:20; 268:7;328:18;362:4; 364:1 tower (1) 80:10 toxic (1) 348:6 toys (1) 253:13 trace (1) 114:13 track (4) 214:12;306:15; 321:8;323:10 tracking (2) 260:11;311:7 tracks (1) 335:10 tract (3) 50:10;66:8;122:19 trade-off (1) 282:3 Traditionally (1) 175:3 traffic (1) 123:2 train (1) 136:10 trained (5) 73:2,10;114:11; 267:16;270:5 training (3) 111:11,11;285:6	trait (1) 167:8 transcript (4) 22:7,9;23:8;199:12 transcription (1) 63:22 transcripts (1) 23:7 transducer (1) 219:19 transferred (1) 27:15 transformed (1) 41:10 transient (6) 104:16;205:22; 209:17,19;302:4,10 transition (3) 34:2;64:10;260:5 translate (3) 169:9;180:8,15 translated (2) 179:16,18 transmission (2) 237:20;238:7 transmitter (2) 69:15;160:14 transmucosal (1) 175:12 transported (1) 63:21 trapezius (2) 213:7;296:10 trauma (5) 103:1;123:5; 259:10,11;275:10 travel (1) 84:12 treat (23) 75:19;97:15; 106:14,17;108:16; 115:13;116:16; 118:14,16;119:18; 120:21;145:8;175:5; 183:15;187:18; 191:19;215:4,11; 217:7;248:21;250:1; 251:7;262:3 treated (10) 45:10,21;75:21; 95:14,14;108:4; 183:14;187:21; 249:20;251:11 treating (7) 98:7;118:5;189:22; 250:20;251:17;252:6, 13 treatment (29) 9:20;20:13,15; 45:17;46:13;54:9; 62:4;95:11;97:10; 98:1;115:7;119:14,19; 139:6,17;142:20;	145:4,9;177:10;184:2; 191:14;199:14; 213:18;224:9;228:21; 257:3,4;304:10,10 treatments (15) 9:8;95:9;101:17; 116:21,22;121:5; 139:15;144:17;163:7, 11;169:9;209:3; 243:3;244:21;266:18 treats (1) 215:2 tremendous (2) 74:8;103:7 trend (1) 302:10 triad (1) 123:12 trial (27) 11:17;12:1,17; 18:13;19:1,11;92:12; 179:20;183:14;184:5; 186:11;187:6;188:1; 198:14;200:15;204:1; 223:14;224:14;227:3; 249:3;252:12;254:5; 255:19;256:13; 296:17;362:2;373:8 trials (41) 9:6,11;11:12;17:14, 14;19:16;58:19;62:18, 21;63:11;91:6;99:15, 21;106:21;128:5; 157:15;161:10; 170:15;178:2;184:9; 191:3;195:3;198:5; 199:6,21;200:10; 228:18,20;240:11; 252:19,21;255:21; 256:1,6,8,14;297:5; 312:17;341:21; 372:11,12 tricky (1) 109:11 tricyclics (4) 97:19;251:22; 252:12,21 tried (9) 10:12;175:2; 226:17;269:22; 272:16;275:9;330:13; 343:11;354:3 trigeminal (9) 68:5;332:8,10; 333:7;348:19,22; 363:20;364:2,3 trigger (10) 52:5,6,6;66:13; 68:1;69:3;210:2; 212:5;222:7,11 triggered (1) 123:13 trouble (3)	43:7;217:1;236:3 TRPA-1 (1) 219:18 TRPV1 (2) 42:4;220:7 TRPV-1 (1) 219:18 true (15) 60:8;117:11; 134:11;144:15; 145:15;163:3;164:13; 166:15;238:13; 251:20;276:5,6; 280:14;341:22;363:21 truly (4) 121:14;178:19; 221:4;234:10 trunk (2) 353:17,17 trust (4) 5:14;135:20; 262:11;366:20 try (43) 5:14;10:9;53:6; 59:22;71:14;72:20; 80:7;118:13;125:14; 128:1;137:1;160:11; 166:16;168:11; 169:12;171:19; 189:18,19;192:12,15; 203:19;207:3;213:16; 227:11;242:2;249:17, 18;251:2;259:11; 260:21;269:10;273:6; 274:9;275:17;282:15; 284:3;307:19;308:21; 323:19;330:11;365:3, 15;366:7 trying (31) 9:14;27:21;79:18; 80:11;108:17;116:17; 128:18;145:21; 157:13;170:16; 171:15;187:9,10,13; 189:16;193:10;194:9, 14;195:5;198:11; 212:12;235:17;239:8; 247:19;249:5;263:22; 266:8;271:2;329:16; 347:18;363:10 T's (1) 7:8 Tuhina (1) 302:17 tunnel (4) 104:4,5;321:12,16 TURK (11) 4:4,6;13:10;16:11; 17:8;22:10,20;23:12; 24:14;261:6;306:11 turn (7) 42:18;56:11;80:15; 97:3;169:6;227:14;	294:18 turned (8) 30:3;46:6;73:17; 125:5;145:15;160:8; 176:22;227:2 turning (1) 234:2 turns (6) 51:21;73:18;74:20; 77:2;117:10;163:22 tweezer (1) 185:20 two (66) 10:14,19,20;15:2; 28:1;54:9;69:11;72:2; 84:7;89:11;96:2;97:8; 103:14,21;104:9,21; 105:8;106:7;118:22; 119:6,11;123:17; 126:13;130:6;133:15, 16;150:14,22;153:11; 161:17;171:10; 177:11,15;192:10; 210:6;213:14;218:15; 221:12;240:16; 241:21;242:16; 251:21;253:17;266:1, 19;269:5,8;270:8; 275:5,21;276:18; 280:20;284:4;286:16; 290:15;294:12;296:4; 298:19;301:21; 304:17;317:9;318:14; 343:2;362:17;364:15; 368:7 type (22) 5:12,9;19;12:17; 57:8;92:20;119:14; 175:11;179:10,12; 183:9;216:16;229:12; 271:14;275:11,13; 281:18;282:7;309:11; 340:18;344:2;352:3; 369:10 types (21) 77:1;96:2,5;119:8; 123:13;133:15;182:3; 273:14;275:12; 277:10;278:12; 341:21;347:15,21; 350:4,18;351:22; 364:19;365:15;369:9; 372:19 typical (1) 311:15 Typically (4) 8:12;314:12; 334:15;335:1 tyrosine (1) 219:22
		U		

UCL (1) 27:2	138:8;145:12;146:5,9; 148:8;228:4	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	valuable (1) 8:12 value (4) 226:7;301:16; 344:18;352:18 values (2) 351:18;353:5 Vanderbilt (1) 60:2 vanilloid (1) 231:6 variability (9) 124:7;131:15,21; 135:3;151:12,14; 160:1;330:4;349:22 variable (2) 275:8;284:8 variables (2) 147:14;159:2 variance (3) 74:21;88:8;137:5 variant (1) 309:22 variants (2) 109:9;352:16 variation (3) 9:5;132:7;133:20 variations (1) 156:21 varied (1) 265:2 variety (12) 9:21;133:5;140:1; 144:8;146:12;171:17; 176:14;186:3,17; 205:1;295:1;304:15 various (8) 63:4;127:20; 155:12;163:10; 227:21;228:17; 271:19;305:17 vary (7) 11:10;130:12; 133:19;161:4;241:3; 300:17;349:12 vast (2) 32:22;364:7 Veasley (8) 78:10;197:9,16; 198:16;200:8;286:1; 339:13 vehicle (1) 239:12 veins (1) 343:22 velocities (1) 321:13 venous (1) 346:10 ventral (3) 314:8;338:2,12 ventrolateral (1) 314:8
ulnar (1) 322:3	uniquely (5) 127:22;128:19; 138:15;148:11;157:13	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	use-dependent (3) 48:13;63:18;209:17 useful (10) 8:12;11:14;23:3; 26:6;182:17;195:18; 201:7;225:13;258:6; 344:19 useless (1) 235:1 user (2) 184:7,7 users (1) 9:13 uses (3) 131:11;143:20; 344:4 using (33) 4:8;27:10;53:10; 55:15;56:20;57:1,15; 74:1;80:5;82:14; 98:22;105:20;131:18; 135:14;153:4;163:13; 177:16;180:10;185:2; 201:18;224:12;257:5; 264:16;267:15;270:6; 271:12;296:16;299:1; 340:18;344:3;345:4; 353:5,5 usual (3) 62:15;66:14;326:21 usually (8) 6:20;8:14;13:20; 85:12;208:1;219:17; 220:4,6 UTI (1) 260:3
ultimately (3) 311:7;341:19; 366:19	unit (2) 112:6;373:5	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	valid (1) 236:14 validated (8) 126:7;128:15; 133:9;180:4;192:5,6; 224:11;228:18 validation (3) 182:19;234:7; 351:21 validity (1) 225:20 Valorie (5) 6:22;7:2,13,14,18
umbrella (1) 134:22	United (1) 258:5	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	V
unaffected (2) 230:2;297:2	units (2) 111:15;249:9	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	
unanesthetized (1) 30:15	univariate (3) 146:3,16;159:19	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	
unanimous (1) 98:7	University (22) 4:6;17:3;26:10; 31:22;37:12;45:5; 60:2,12;66:21;71:4; 89:5;105:19;107:5; 159:12;193:18; 203:14;261:12; 262:10;285:4,5,9; 339:17	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	
unbiased (3) 226:18;227:12; 371:3	unlike (1) 29:19	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	
uncertainty (1) 247:3	unmodulated (1) 133:5	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	
unconnected (1) 151:10	unoccupied (1) 98:20	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	
unconscious (1) 112:21	unknown (1) 210:1	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	
under (9) 37:20;121:21; 126:19;134:22; 196:12;238:1,3; 306:20;366:9	unless (4) 165:13;214:17; 242:17;364:6	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	
underestimate (1) 346:22	unpleasant (4) 109:19;130:21; 319:13;367:22	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	
undergone (1) 122:5	unpleasantness (1) 319:16	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	
underlying (18) 19:22;38:11;40:2; 42:16;72:2;77:14; 85:14;90:11;100:7; 102:22;158:17; 173:22;240:6,8;243:4; 254:15;329:8;360:2	unpublished (1) 67:16	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;309:12,21;315:8; 320:18;321:5,8;323:5; 331:20;334:11; 339:12;340:20; 353:19;355:16;356:5; 360:19;361:20;364:1; 368:4;371:7	181:20;186:2,7,14; 191:2;192:21;193:13; 205:6;224:8,11;225:9, 10;228:18;234:17; 239:20;264:11;267:6; 274:10;280:19; 294:22;315:18;317:3, 13,21;318:1;332:12; 341:14;344:7;351:17; 353:22;354:6,21,21; 357:22	
underneath (1) 86:4	unreal (1) 114:7	22;194:9;198:8; 203:8;205:20;228:19; 229:2,21;232:13; 235:8;240:10;241:13; 244:22;245:8;247:2; 253:3;254:16;256:14; 257:15,17;258:22; 261:15;262:16; 264:13,19;265:8; 269:12;271:22; 272:21;274:5;276:17; 280:15;283:5,10,19; 284:17;286:4;306:5,7, 14;		

<p>veracity (3) 113:20;114:20; 259:14</p> <p>versa (3) 117:22;212:4;364:9</p> <p>version (5) 14:10,14,21;177:18; 293:14</p> <p>versions (1) 14:10</p> <p>versus (42) 94:17;111:6;114:7; 117:19;118:20; 170:14;172:12,13; 207:20;215:18; 231:18;241:8;255:3; 258:17;259:3;260:18; 268:1;279:14;295:21; 308:11;314:21;315:7; 316:16,18;322:22; 327:4,13;328:3,14,19; 329:1;330:6;331:5; 340:3,14;344:3;346:8; 347:20,20;362:6; 364:8,12</p> <p>vessels (1) 310:21</p> <p>via (4) 138:12;155:3; 349:8,9</p> <p>vice (3) 117:21;212:3;364:8</p> <p>video (2) 22:10;324:10</p> <p>videoed (3) 21:21;22:8,12</p> <p>videotape (1) 23:9</p> <p>videotaped (2) 5:19;124:15</p> <p>view (5) 39:8;48:5;85:8; 112:9;242:16</p> <p>viewed (1) 295:17</p> <p>vigorous (1) 48:18</p> <p>virtually (1) 98:3</p> <p>virtue (2) 61:15;69:14</p> <p>visceral (2) 173:9;210:15</p> <p>visit (2) 39:12;302:7</p> <p>visitor (1) 30:10</p> <p>visual (4) 105:16;136:7; 319:10;336:15</p> <p>Vitaly (16) 93:12;149:19; 153:6;157:7;161:21;</p>	<p>162:2;292:16;306:20, 22;307:1,13;346:10; 350:22;352:3;362:12; 371:13</p> <p>voice (6) 6:6;23:14;24:2; 89:1;170:2;370:16</p> <p>volitional (2) 112:22;114:3</p> <p>volume (3) 303:18;304:4; 311:13</p> <p>volumetric (1) 304:12</p> <p>von (1) 296:16</p> <p>voted (1) 79:15</p> <p>voxel (2) 311:13;346:20</p> <p>voxels (1) 365:1</p> <p>VTA (1) 314:8</p> <p>vulnerability (1) 55:4</p>	<p>358:12;359:1;362:10; 363:13;368:6;369:13; 370:14,17;373:3,18, 20;374:3</p> <p>Wash (2) 222:19;348:7</p> <p>Washington (2) 4:7;13:12</p> <p>waste (1) 370:8</p> <p>waters (1) 145:11</p> <p>watery (1) 129:18</p> <p>waves (1) 67:22</p> <p>waving (1) 7:13</p> <p>way (101) 6:22;7:1;9:1,22; 12:20;24:10;27:12; 33:15;51:1,11;57:4; 59:16;62:13;63:10; 80:21,21;81:16;86:7; 95:18;96:14;104:19, 20;105:5;112:6; 113:19;114:6;119:16, 17;120:1;121:1; 150:22;152:15,16; 160:7;164:19;167:17, 20,21;172:10,17; 175:20;178:15; 179:18,20;180:9; 185:15,16,22;186:9; 188:13,15;196:9; 201:6,7;208:15;211:8; 214:1,19;219:9;221:9; 223:16;224:11; 227:12,18;231:13,16; 234:1,21;242:15; 243:12,16;244:3,19, 20;245:6;258:8; 259:5;266:7;269:22; 270:18;277:13; 282:13;283:6;287:19; 303:6;322:17;326:21; 331:3,22;335:1; 336:16;344:22;347:6; 349:13;354:3;363:17; 366:4,21;371:12; 372:21;373:1</p> <p>ways (9) 61:21;120:2;129:9; 149:6;227:22;229:4; 230:11;243:22;268:7</p> <p>WDR (1) 235:20</p> <p>weak (1) 301:6</p> <p>weaker (1) 290:21</p> <p>Web (2) 22:21;199:11</p>	<p>website (5) 15:17,18,20;16:7; 172:11</p> <p>week (2) 60:16;103:4</p> <p>weekend (1) 13:12</p> <p>weeks (10) 14:7,8;16:8;37:8; 122:8;186:12,12,13, 13;222:4</p> <p>weeping (1) 233:5</p> <p>welcome (1) 4:18</p> <p>well-meaning (1) 84:16</p> <p>weren't (7) 37:20;144:9;233:8; 270:4;273:17;281:7; 284:7</p> <p>Westin (1) 7:6</p> <p>whacking (1) 185:21</p> <p>what-have-you (1) 259:1</p> <p>what's (47) 8:10;11:4;19:1,7; 53:9;54:9;80:12,12; 81:6,7,10;85:15; 113:7,14;121:8; 125:11;166:11,19; 179:14,15;183:21; 191:21;197:12; 199:14;212:3,4; 217:19;218:2,8,16; 240:6;251:4,11; 266:17,19,20;279:5,9; 284:3;307:1;315:20; 317:1;350:19;352:19; 358:7,8;368:11</p> <p>whatsoever (4) 28:2;73:20;220:17; 317:10</p> <p>wheat (1) 243:7</p> <p>whereas (17) 32:4;95:12;159:18; 163:1;209:18;222:4; 224:9;232:8;287:15; 291:3;302:11;309:16; 318:8;319:1;322:2; 335:11;346:19</p> <p>whereby (1) 31:2</p> <p>Whereupon (4) 123:22;202:3; 306:16;374:6</p> <p>whichever (1) 248:4</p> <p>whiskers (1) 51:21</p>	<p>whisper (2) 5:14;24:5</p> <p>whispering (1) 5:16</p> <p>whole (23) 29:20;42:19;46:17; 81:9;114:16;121:16, 17,17,19;122:1; 153:16;176:10; 184:19;188:17; 214:18;215:18;240:3; 277:15;282:21; 342:22;346:11; 359:20;372:1</p> <p>whomever (1) 189:1</p> <p>who's (12) 6:17;24:12;70:4; 125:18;174:16;177:4; 189:10;222:16; 248:21;255:4;339:16; 358:3</p> <p>whose (2) 29:11;302:12</p> <p>who've (3) 167:18;179:22; 233:14</p> <p>wide (6) 132:7;133:20; 176:2;235:11;271:21; 357:22</p> <p>widely (7) 53:9;106:8;129:3; 156:20;175:19; 181:20;249:22</p> <p>wider (2) 146:11;321:17</p> <p>widespread (45) 48:8;65:3;66:1; 76:2,13;79:11;84:8; 92:2,2,6;94:6;95:7,13, 19;104:7,12;109:16, 18,18;110:3,14; 112:13;113:22; 121:22;143:11; 144:13;162:12; 177:19;179:8;197:20; 200:17;214:20;216:8, 11;223:17;225:18; 231:10;243:8;244:5; 254:11;255:16; 256:16;288:22; 316:20;355:20</p> <p>widespreadness (3) 248:7;249:2;292:18</p> <p>WiFi (1) 7:5</p> <p>willing (2) 160:15;246:15</p> <p>win (1) 26:20</p> <p>wind (5) 127:18;228:18;</p>
	W			
	<p>Wager's (2) 318:1;365:8</p> <p>wait (2) 16:6;23:18</p> <p>waiting (4) 52:5;222:17; 243:11;284:14</p> <p>walk (1) 275:15</p> <p>walking (1) 298:5</p> <p>Wall (4) 26:10;32:1;34:14; 36:18</p> <p>Walters (1) 44:4</p> <p>wander (2) 5:21;6:3</p> <p>wants (3) 22:12,21;23:17</p> <p>War (6) 113:10;123:5,7,7, 10</p> <p>warrant (1) 175:14</p> <p>Warren (1) 259:16</p> <p>WASAN (35) 65:10;107:5,5,9,15; 108:1;109:8,11; 142:19;158:6;261:11, 16;284:13,15;306:4, 13,18;339:11;342:2; 346:4,7;355:16;357:4;</p>			

235:8;241:13;247:2 windows (1) 242:13 wind-up (3) 235:19;237:5; 246:13 wish (1) 203:18 wit (1) 261:19 withdrawal (2) 44:3;51:20 within (23) 35:8;36:4,6;38:3; 49:5,8,18;50:18;59:7, 11,20;61:17;63:3; 65:7;67:3;135:2; 137:12;139:3;232:4; 234:16;285:9;288:15; 357:20 without (15) 29:6;31:4;72:18; 85:5;92:2,5;134:13; 176:3;201:17;210:21; 215:18;251:16;295:2; 330:6;331:5 witty (1) 261:17 WNT (1) 91:20 woke (1) 45:17 Wolfe (4) 83:4;87:12;265:8; 282:10 women (15) 83:7;90:2;93:11; 207:9,20;208:16; 259:18;265:10,16,17; 272:6,9;280:10;282:9, 11 Women's (3) 124:3;144:19; 183:20 wonder (8) 83:19;114:20; 182:22;236:12; 246:19;249:9;343:14; 352:18 wonderful (5) 32:12;62:16;262:1; 342:12;367:19 wondering (12) 4:17;63:3;67:9; 102:3;180:20;181:15; 193:1;195:6;223:2; 233:11;254:20;352:12 wooden (1) 330:15 woods (1) 230:3 Woolf (35) 26:1,2,3;11:34;17,	20;35:1;38:8;39:18; 44:13,17;59:5;61:8; 63:15;65:21;67:15; 69:13;115:7;131:3; 162:19;189:8;205:17, 20;206:14;209:13; 219:11;221:19; 222:10;226:10;232:1; 241:1;253:5;346:17; 363:14;364:17;366:2 Woolf's (1) 320:8 word (6) 34:14;76:9;85:18; 174:11;205:5;219:12 words (4) 35:10;85:17; 226:15;227:19 work (72) 4:22;7:20;24:10; 27:17;28:10,17;29:1; 30:14;31:21;32:9; 44:13;46:19;51:5; 53:17,22;57:7;58:2, 15;60:8;67:16;71:19; 75:9,11,11;91:4,4,14, 22;92:7,9;93:4;97:4, 17,22;98:19;99:17,18; 100:10;113:15; 115:15,21;117:1; 121:5;124:7;126:5; 131:9;157:11;158:7; 171:6;173:1;188:16, 18,21;201:13;210:14; 214:16;225:11; 249:16;262:14;264:7; 285:1;288:13;295:15; 303:14;312:15; 339:20;340:17; 351:20;352:9;365:17; 372:1,16 worked (11) 4:12;49:21;75:5; 91:14;92:13;93:1; 181:9;190:21;243:9; 262:22;264:6 working (16) 27:2;93:2;117:4; 123:6;161:13;173:12, 13;174:6,13;229:2; 234:22;282:18;284:1; 292:20;323:18;372:15 works (7) 52:3;91:10;92:7; 175:4;181:17;191:4,7 workshop (3) 171:21,22;172:9 workup (2) 111:2,5 worried (5) 22:2;176:1,11; 182:4;346:1 worry (4)	86:10;113:22; 114:20;117:17 worsening (1) 107:19 worth (5) 66:18;70:8;128:18; 225:21;226:2 wrap (2) 149:2;155:11 wrapping (1) 236:3 wrist (1) 322:14 wrists (1) 321:14 write (1) 77:9 writes (1) 174:19 writing (5) 12:6;113:9;125:19; 169:16;171:22 written (1) 10:15 wrong (2) 73:17;83:7 wrote (3) 44:4;99:12;360:19 X X-axis (1) 299:21 x-ray (5) 73:13,14,15;74:21; 84:17 Y Yarnitsky (1) 135:11 Y-axis (3) 273:14;300:1; 322:11 year (9) 8:7;50:8;54:15; 71:16;108:6;139:1; 177:17;262:21,22 years (36) 4:9,13;12:2,2; 41:22;46:11;71:18; 78:9;79:15;81:22; 82:5;94:20;99:13; 103:21;122:11; 125:12;129:7;138:17; 167:17;169:16;171:9; 172:5;177:17;180:22; 190:19;200:2;226:17; 229:21;257:14;264:4; 271:7;272:14;304:14; 307:3;324:3;373:2 yellow (4) 147:2;289:22;	312:7;324:11 Yep (1) 158:21 yes/no (2) 193:10;353:22 Yorker (1) 233:3 younger (1) 297:15 YouTube (1) 70:17 Yvonne (2) 94:3;212:20 Z Zero (4) 89:1,2;132:5; 286:16 Zhigang (2) 50:9;66:7 zoster (3) 54:21;229:20; 233:15 0 0 (4) 87:10;200:6; 286:15;354:11 0.002 (1) 146:18 0.4 (1) 142:8 0.9 (1) 147:4 06 (1) 171:14 1 1 (9) 75:12;183:17; 202:2;286:17;311:11; 353:2;354:1,11,12 1:00 (1) 370:12 1:20 (1) 203:2 10 (24) 12:2;41:22;51:14, 18;58:19;73:20; 94:20;136:10;148:2; 200:6;228:15;272:22; 277:9;287:13;296:19; 324:3;345:20;352:22; 353:1;362:13,15; 366:22,22;373:2 10:08 (1) 123:22 100 (3) 132:6;255:4;272:1 100,000 (1)	346:21 10-11 (1) 108:6 10th (1) 136:12 11 (2) 265:3;333:1 11th (2) 335:14;336:7 12:00 (1) 7:9 12:09 (1) 202:3 12-20 (1) 278:8 125 (1) 268:17 12-week (2) 177:12;187:16 13 (5) 87:17;88:12;110:8; 122:11;275:18 14 (2) 274:7;354:13 14-second (1) 332:22 15 (5) 73:21;74:2;228:15; 270:7;300:13 150 (1) 313:10 15-20-year (1) 110:15 169 (1) 268:16 17 (1) 297:11 17.5 (1) 280:3 170 (1) 286:20 180 (1) 315:21 19 (1) 169:17 1930s (1) 321:7 1979 (1) 26:11 1980's (1) 39:13 1983 (1) 25:15 1989 (1) 39:6 1990s (1) 44:5 1992 (1) 171:4 1-point (1) 87:14 1st (1) 336:6
---	---	--	--	--

	13:20;14:7,8;16:8; 75:12;87:19;92:4; 138:22,22;149:1; 170:11;171:12; 183:16;196:6;197:2; 311:11;321:6,20; 345:14;370:1,10; 371:16	171:12 4-week (1) 372:11	272:14;353:16; 354:13,19,20;371:16 70 (2) 271:22;274:6 700 (2) 88:10,16 70S (1) 125:17 75 (1) 269:15 7th (2) 23:17;25:16
2		5	
2 (19) 14:7;57:8;58:12; 170:10;183:17; 196:13;204:6;311:11; 321:6,20;328:14,15; 329:1,1;344:13; 345:14;353:16,16; 354:12	3:18 (1) 306:16 30 (15) 35:17;58:17;71:18; 73:18;75:13,20; 124:22;184:22; 280:21;306:9;342:12, 14,14,15;354:20	5 (18) 12:2;13:21;16:8; 88:12;89:18;91:16; 161:11;253:14,21; 321:6,20;322:2; 323:15;345:19; 349:20;352:22; 371:16;373:2	8
20 (7) 74:2;75:13;95:3,5; 138:17;169:15;342:11		50 (5) 75:20;95:6;184:12; 272:6;274:22	8 (8) 90:5;122:21;123:1; 180:22;229:21; 232:22;352:22;353:1
200 (3) 156:14;313:9; 315:22	300 (1) 259:18	500 (1) 132:13	8:03 (1) 4:2
2000-2010 (1) 229:9	30-year (1) 74:12	50-60 (1) 186:20	80 (3) 242:14;276:17; 364:22
2005 (1) 171:14	31 (1) 87:10	50-ish (1) 256:2	806 (1) 268:11
2006 (1) 322:6	32 (1) 313:11	54 (1) 130:19	80s (2) 125:18;126:7
2007 (1) 280:1	33 (1) 270:5	55 (2) 88:16,19	8th (1) 23:17
2011 (1) 288:12	35 (1) 353:19	5-second (1) 58:16	
2014 (2) 172:7;322:8	37 (1) 272:21	5th (1) 136:12	9
2018 (1) 271:8	3-point (1) 87:19		9 (4) 275:16,18;313:12; 344:11
20-30 (1) 167:17	3T (1) 371:19	6	90 (4) 89:17;187:17; 227:6;242:14
20-minute (2) 306:9,14		6 (24) 23:15,15,18;87:19; 119:20;120:8;122:8, 18,21;123:1;132:14, 17;171:2;183:16; 199:20;222:4;259:19; 268:22;302:1,3; 323:15;326:18,18; 349:21	90s (4) 113:9;264:18,20; 271:7
20s (1) 110:12	4		9-10 (1) 8:15
20-second (1) 333:1	4 (10) 13:20;16:8;149:1; 272:18;273:13;286:9, 15;293:7;302:21; 345:19	60 (4) 35:19;91:15;95:6, 16	92 (3) 170:5;171:1;271:8
22 (1) 271:22	4.5 (1) 318:18	63 (1) 280:2	99.9 (1) 30:17
23 (1) 4:9	4:50 (1) 374:6	64 (2) 354:7,14	
23rd (2) 4:18;8:1	40 (6) 73:18;75:20;80:18; 125:6;259:21;364:22	65 (1) 196:15	
24 (7) 87:5;89:14,18; 144:3;215:21;218:19; 355:6	400 (1) 196:14	65-patient (2) 196:17,19	
25 (1) 128:13	400-patient (1) 196:18	683 (1) 268:13	
28 (1) 125:15	41 (3) 268:22;271:1;280:7	6-minute (2) 328:14,15	
2's (1) 171:11	47 (1) 270:2		
2-stimulus (1) 134:10	48 (4) 87:5;89:14,18; 144:3	7	
2-to-3-day (1) 170:19	49 (1) 268:12	7 (8) 111:16;180:22;	
3	4's (1)		
3 (22)			