Brain, Behavior, & Mind 2026 Spring Conference

Center for the Study of Traumatic Stress

Department of Psychiatry

Uniformed Services University

April 21, 2026

CONFERENCE TRANSCRIPT

Disclaimer: All statements, opinions, and assertions expressed during the Brain, Behavior, and Mind 2026 Spring Conference are those of the speakers and attendees, and do not reflect the official policy or position of the Uniformed Services University of the Health Sciences or the Department of War.

WELCOME & CONFERENCE ANNOUNCEMENTS

00:05:29.110 --> 00:07:24.239

James Naifeh: Welcome to the Brain, Behavior, & Mind 2026 Spring Conference, sponsored by the Center for the Study of Traumatic Stress of the Uniformed Services University, in collaboration with the USU Department of Psychiatry, the Neuroscience Program, Center for Deployment Psychology, Department of Family Medicine, USU Brain and Behavior Hub, and the Henry M. Jackson Foundation for the Advancement of Military Medicine. My name is Jamie Naifeh, and I'm a member of the Center for the Study of Traumatic Stress and the Department of Psychiatry at USU.

Before we move on today, I just want to note that we have an ASL interpreter with us today. We will post instructions for how to activate that in the chat. You can choose not to, or turn it on or turn it off at any point. And we will continue to post those instructions throughout the day.

The purpose of Brain, Behavior, & Mind events is to bring together diverse speakers and attendees to consider the substantial breadth of research that can inform our understanding of how life events, and the stress resulting from those events, can alter and injure brain function; with a range of cognitive, emotional, and behavioral consequences that include everything from posttraumatic stress disorder, to adjustment disorders, to transient stress reactions, with downstream risks such as impaired job performance, family dysfunction, substance abuse, and suicide. Our ultimate goal, of course, is improved prevention, treatment, and recovery.

We are grateful to all of you for contributing to the tremendous growth of Brain, Behavior, & Mind. This 2026 Spring Conference was record-breaking, both in registrations and poster submissions. We will continue to try to reach new audiences, both to educate and to learn from professionals with diverse knowledge and perspectives.

00:07:24.650 --> 00:09:15.750

James Naifeh: Before moving on to today's speakers, I'll go over some important Conference-related information. You can find the Conference agenda on the Brain, Behavior, & Mind website. Throughout the day, we will post Conference-related information and links in the Zoom chat. This morning, there are two presentations, followed by a Question & Answer panel with our two morning speakers. The afternoon, we'll have three more presentations, followed by a second Question & Answer panel. There will be breaks in the morning and afternoon, as well as a break for lunch. During the breaks, we encourage you to visit our online poster gallery with

submissions from fellow conference attendees, including the winners of our poster contest. You will find all poster submissions on the Posters page of the Conference website.

Please use the Q&A feature at the bottom of the Zoom window to submit questions to our speakers. You can submit questions at any point during the day, before and during the Question & Answer session of the speaker you'd like to ask. When submitting your questions, please specify whether you are submitting your question for a specific speaker, or for a couple of speakers, or for all the speakers in the panel.

Continuing education credits are available for this event for physicians, psychologists, and social workers. We will provide more information on that throughout the day, including posting information and links in the chat.

Lastly, a disclaimer. All statements, opinions, and assertions expressed during the Brain, Behavior, & Mind 2026 Spring Conference are those of the speakers and attendees, and do not reflect the official policy or position of the Uniformed Services University of the Health Sciences or the Department of War. With that said, we would like to start by sharing a message from COL Vincent Capaldi, Chair of the USU Department of Psychiatry.

COL VINCENT F. CAPALDI, II, MD

WELCOME

Total Conference Timestamp: 00:10:16.140 --> 00:13:45.399

Within-Segment Timestamps below

***Video with Department of Psychiatry, USU application information*

00:00:44:01 - 00:02:24:20

Vincent Capaldi: Good morning and welcome. On behalf of the Department of Psychiatry at the Uniformed Services University and the Center for the Study of Traumatic Stress, it's my privilege to welcome you to the Brain, Behavior, & Mind Spring Conference. This conference continues a long-standing tradition, now in its 19th year, of bringing together leading voices across neuroscience, psychiatry, psychology, and public health to tackle some of the most complex challenges in brain and behavioral health.

What makes today particularly compelling is the extraordinary group of speakers that will guide us through these challenges. We begin with Dr. Husseini Manji, whose work continues to push us towards meaningful advances in serious mental illness, reminding us that progress in this space is not only scientific, but also societal in responsibility. Following that, Dr. Kerry Ressler will take us into the neuroscience and genetics of fear, helping us understand the biological foundations of PTSD, an area central to both clinical care and operational readiness.

And moving to the afternoon, Dr. Bridget Callaghan will expand our lens to examine the generational impacts of diversity, how experiences in early life shape the long-term trajectories of brain and body health. Dr. Sharon Dekel will then challenge us to reconsider trauma through a different, but highly relevant, context of childbirth, highlighting what it can teach us about stress, recovery, and resilience across populations.

00:02:24:22 - 00:04:13:03

Vincent Capaldi: We'll close out the day with Dr. Bruce Perry, whose work on neurodevelopment and [his] Neurosequential Model have fundamentally influenced how we translate neuroscience into real-world clinical practice, particularly for those exposed to early adversity and trauma. Throughout the day, these sessions will be complemented by moderated panel discussions and opportunities to engage with emerging research through our poster presentations, ensuring that this is just not a passive experience, even though it is virtual, but an interactive and collaborative one.

Taken together, today's agenda reflects a deliberate progression from molecular and genetic mechanisms to developmental and intergenerational processes to apply clinical frameworks. It's a reminder that problems that we face in brain health do not exist in silos, and neither can the solutions. Equally important is the community gathered here. This conference is designed to connect leaders across disciplines and institutions, united all by a shared goal, advancing actionable knowledge that improves care, strengthens resilience, and ultimately enhances readiness for those we serve.

So, as we begin, I encourage you to fully engage, listen critically, ask questions, think about how the insights shared today can be translated into your own clinical practice, your research, your leadership environments. Thank you for being part of this effort and for the work that you do every day in advancing brain health and behavioral health. We hope that this will be the start of conversations, and we invite you to download our smartphone application to help us stay connected using the QR code shown on your screen. Thank you and welcome to the conference.

00:13:49.840 --> 00:14:05.100

James Naifeh: Thank you, COL Capaldi, for that lovely introduction to this event. Hopefully people have a chance to check out our new USU Psychiatry Department app. Next, a few words from Dr. Stephen Cozza, Director of the Center for the Study of Traumatic Stress. Dr. Cozza?

STEPHEN J. COZZA, MD

WELCOME

00:14:06.720 --> 00:16:06.810

Stephen Cozza: Thank you, Jamie. Good morning, everyone. As the Director of the Center for the Study of Traumatic Stress, it is my pleasure to welcome you to the Brain, Behavior, & Mind 2026 Spring Conference. We are joined today by a truly global community. I'm thrilled to share that we have over 4,600 participants registered for this event, representing all 50 states in the U.S. and 94 countries worldwide. This Conference, formerly known as the Amygdala, Stress, and PTSD Conference, is presented by our Center within the Department of Psychiatry at the Uniformed Services University.

As we gather today, I want to reflect on the vision that drives our work at the Center for the Study of Traumatic Stress. It is a vision of a nation uniquely prepared to mitigate the impact of trauma, disaster, and war. We operate as a multidisciplinary team of nearly 120 professionals, comprised of research and prevention scientists, educators, and clinicians, all working together toward the goal of ensuring resilience is a measurable reality for the communities we serve.

Our Center's mission is fundamentally tied to the health and readiness of our men and women in uniform, as well as their families and the communities that sustain them. Beyond our commitment to the military, our University embraces a vital public purpose. We strive to extend the expertise of the Center to support the broader nation. This work is intentionally cross-informing. The lessons we learn in supporting our service members directly benefit the health of the entire country, just as our findings regarding the traumas that impact the general public inform how we better support and care for our service members.

00:16:07.390 --> 00:18:12.640

Stephen Cozza: We link this public purpose to our responsibility to bring this knowledge to the broader professional community, which is why we are pleased to offer this event today with Continuing Education credits at no cost to our participants. To learn more about what we do, I encourage you to visit our website at www.cstsonline.org, where you can access information

about our research, summaries of our forums and workshops, and our library of educational fact sheets.

Today's Conference explores new insights into health and illness by integrating knowledge from genes to community, and moving research from the bench to the bedside. We have an excellent panel of speakers joining us to cover a variety of critical topics. Their presentations will span from the genetics of fear to what we can learn from childbirth about stress, recovery, and resilience. We will also explore the application of neurodevelopmental frameworks in clinical practice, specifically looking at how understanding the brain's sequential development can transform our therapeutic approaches.

In addition to our featured speakers, I'm excited to announce that participants can engage with nearly 70 virtual scientific poster presentations highlighting the latest research in the field. Following our morning and afternoon presentations, you'll have the opportunity to pose questions to our speakers during our live, moderated panel discussions. We believe that these interactive sessions are vital for the exchange of ideas, and I encourage you to actively engage with the content and our professional panels.

I am truly enthusiastic about the day ahead, and look forward to an exciting day of learning for all of us as we continue to push the boundaries of science and clinical care. Thank you.

00:18:16.390 --> 00:18:17.910

James Naifeh: Thank you, Dr. Cozza.

HUSSEINI K. MANJI, MD

PRESENTATION

00:18:18.340 --> 00:20:15.961

James Naifeh: Our first speaker today is Dr. Husseini Manji. Dr. Manji is Co-Chair of the UK government's Mental Health Goals Program and Professor at Oxford University. He also serves as Adjunct Professor at Yale University and Visiting Professor at Duke University. Previously, he was Global Therapeutic Head for Neuroscience at Johnson & Johnson, where he oversaw the discovery, development, and launch of several transformative treatments for serious neuropsychiatric and neurodegenerative disorders. Before joining industry, Dr. Manji was Chief of the Laboratory of Molecular Pathophysiology and Director of the Mood and Anxiety Disorders Program at the U.S. National Institutes of Health, which, at the time, was the world's largest program of its kind.

Dr. Manji has been elected to the U.S. National Academy of Medicine and serves on the NIH Novel and Exceptional Technology and Research Advisory Committee, the World Dementia Council, the World Economic Forum, Global Future Councils, the Board of Mass General-Brigham, the Board of Trustees of Harvard University/McLean Hospital, the Board of the Dana Foundation, and the Scientific Advisory Board of the Stanley Center at the Broad Institute of MIT and Harvard. He also chaired the National Academy of Medicine's Neuroscience, Behavior, Brain Function, and Disorders Group, and co-chairs the Healthy Brains Global Initiative.

Dr. Manji has received numerous awards for his outstanding contributions to neuroscience and medicine, including, but not limited to, the National Academy of Medicine International Mental Health Prize and the NIMH Director's Career Award. He was also named one of the inaugural “Health Heroes” by *Oprah* magazine. He has authored more than 350 publications, advancing neurobiology and treatment of severe mental illness.

We will now begin Dr. Manji's presentation, which is titled, “The Quest to Make a Real Difference in Serious Mental Illness: A Shared Societal Responsibility.”

Total Conference Timestamp: 00:10:16.140 --> 01:08:52.130

Within-Segment Timestamps below

00:00:03.930 --> 00:00:58.550

Husseini Manji: Thank you very much, James and Holly, for the kind introduction, and the privilege to participate in this important Brain, Behavior, and Mind Conference. I think it's a very timely event…

While I'll display a few grim statistics… We all recognize how challenging our diseases and disorders are. [But] I really think this is mainly about a message of hope, that we are making progress; and although we've got a long way to go, we will see improved treatments and improved outcomes for our patients. And so, hopefully, most of what I'll be presenting are exciting innovations that are happening, or will happen.

This is my disclosure slide, and I think, most importantly; I was the head of Neuroscience R&D at Johnson & Johnson for about a dozen years. So, any slide where I've depicted data that was gathered while I was the head of Neuroscience at J&J, I've indicated on that slide that this was done while I was the head of J&J, okay?

00:00:58.970 --> 00:02:43.609

Husseini Manji: So, as I said, I'll start with a few grim statistics; and unfortunately, I think most of you probably know these. But what's shown here is the data from the World Health Organization Global Burden of Disease Study. And on the left, they basically tried to quantitate all the illnesses affecting mankind. And they were actually kind of struck to find that mental illnesses were by far and away the leading cause of disability. This slide shows in the Western world, North America and Western Europe, but now it's true worldwide. And one of the big reasons for this is that, by and large, serious mental illnesses strike individuals when they're relatively young; so usually late adolescent or early 20s, and then they're lifelong, so they've been called the chronic diseases of the young. And not only are they highly disabling, they're also unfortunately fatal. So today, we think that someone with a serious mental illness lives almost 15 years shorter than someone without it, and I'll come back to it, but we think most of that is because of comorbid cardiovascular and metabolic diseases and disorders.

Additionally, they affect social functioning, occupational functioning, scholastic functioning; and especially in our ever-increasing knowledge-based economy, they have a huge impact on people's ability to function at work; and in fact, have a huge impact on overall productivity. On

the right-hand side of the slide, you see some of the individual diseases and disorders, and you can see that major depressive disorder is number one there. There's grim statistics too under it. It's the fact that not only do people die from some of the comorbid physical health conditions, but many people die, unfortunately, from suicide.

00:02:43.610 --> 00:04:31.389

Husseini Manji: And so, these numbers are probably an underrepresentation, because sometimes people don't acknowledge that the death was by suicide. And so, in the US, it's thought that there's at least 45,000 deaths by suicide every year; which means that there's only three forms of cancer that have a higher annual death rate. And then the third bullet there is something that's really tragic. It's thought that globally, [for] young girls and women 15 to 19, suicide is either the second or the third leading cause of death.

On the bottom left is a report from the World Economic Forum from a few years ago that basically indicated that mental illnesses alone were going to cost society more than, basically, you can see there, cancer, diabetes, and chronic respiratory diseases combined. So, we clearly need to spend more time and effort and money on developing better treatments. One of the things that has unfortunately happened, and you may be aware that, until recently, most large pharma companies actually left the space. And the main reason they left this space, despite the unmet need, was the concern that it was actually just too complicated.

And there's no doubt these are very complicated conditions. So, if you look on the left, we know there's a strong genetic component, but then the genes interact with environmental factors. Those bring about changes in cell function. The cell's function changes then bring about changes in circuit function. And then that relates to our complex clinical symptoms, mood, anxiety, psychosis, ability to experience pleasure, sleep, appetite, etc. So, in contrast to something like, say, oncology, where you could do a tumor biopsy and see what's going on, this is much more complex. And so, that's one of the reasons companies had left.

00:04:31.390 --> 00:06:20.540

Husseini Manji: The pendulum is swinging, because companies are coming back; and I think the main reason the pendulum is swinging for some of the things shown on the right… that while we have a long way to go and, as I said, it's not like oncology where you can do a biopsy, we're actually making a lot of progress. And I was delighted when I was at J&J to basically make the case that we are making progress, and we can help people even today, let alone the future. So, what I'm going to be doing is giving you some examples of what I think are some of the most

exciting advances, and I'll be starting with some of the advances in these things we call plasticity pathways.

So, what's shown on the left is sort of what people had previously thought, that depression is basically a serotonin deficiency. And this cartoon is basically a tongue-in-cheek approach to say that, when you were depressed, you'd go to your psychiatrist, and they would top you up with serotonin, and that sort of took care of things. Today, we know that's an overly simplistic view and, rather, we know that most of these diseases and disorders arise from impairments of what we call synaptic and neuroplasticity.

Now, you'll hear many different definitions of synaptic plasticity, but one way to think about it is the strength of the information flow through specific synapses. And one way to emphasize that is, all of you listening to this talk today, a year from now, you'll remember that we heard this talk on serious mental illnesses, new treatments, etc. You may not remember every single detail, but you'll remember a lot of it. And that's because some of this information is becoming permanent in your brain through changes in the synaptic plasticity. So, you're basically strengthening and weakening certain synapses, or the flow through certain synapses, to make this information more long-term.

00:06:20.580 --> 00:08:16.629

Husseini Manji: And what's shown on the right is sort of a cartoon depicting our real major advances over the last 20 years or so, to understand some of the mechanisms by which synaptic plasticity will regulate. And what you can see there are these molecules, in particular AMPA receptors or NMDA receptors, moving into or out of synapses. So, very specific synapses that you'd like to strengthen, these receptors actually move into or out of the synapse. So that raised a lot of exciting thinking; could these things, these synaptic plasticity changes, could they be relevant for psychiatric disorders?

And I think we all know that the animal models for psychiatric disorders are far from perfect. But what's shown here are some of the animal studies that really tried to be very rigorous; and they were showing that when you basically induce certain stress models that, sort of, bring about animals' behavior that they become depressed, depressed-like, you bring about changes in something called long-term depression, which is kind of the opposite of long-term potentiation. And that, interestingly, if you pretreat with one of these molecules, an NMDA antagonist, you actually block that.

What's shown in the middle is something similar, with this learned helplessness paradigm; and what's shown on the extreme right is something, when you treat animals, you can show some of the opposite changes. And what I'm summarizing on this slide is about 15 years of work; and

there's no doubt this is a simplification, but it tended to suggest that when you make animals depressed, you see what's known as a reduced AMPA relative to NMDA throughput. And by contrast, when you treat the animals and they show behavioral improvement, you see the opposite. Increased AMPA or NMDA throughput.

00:08:16.920 --> 00:10:17.579

Husseini Manji: So that got myself and a few others to start to think about… One of the questions people had is, why does it take 4 to 6 weeks for our antidepressants to work? Because you're increasing intrasynaptic levels of molecules like serotonin or norepinephrine, shown in the top right-hand with the red circle. That happens within hours. Why does it take 4 to 6 weeks for people to get better?

And so, one of the hypotheses we had was that it's just an upstream effect. You're increasing serotonin or norepinephrine. It's got to go through all these intracellular changes to ultimately bring about changes in AMPA or NMDA receptor function, and that's potentially one of the reasons why things take so long. That led to the obvious question; well, if that's the case, and AMPA and NMDA receptors are the correct targets, what if you hit them directly?

A, would you have antidepressant effects? B, would you have antidepressant effects that work rapidly? Because, as I suggested, you know, the other drugs seem to work through a long cascade, eventually changing them. And then, thirdly, would these treatments work even in people who had failed medications like Prozac? Because, if you've got a problem in any of the steps in the pathways shown on the right-hand side, you can increase serotonin all you want. It's not going to change these things. So, when I was at the NIH, we wanted to directly test this hypothesis in patients by using either an AMPA or an NMDA drug.

We were delighted that just a little bit earlier, John Krystal's group with Rob Berman at Yale had done a pilot study using very low-dose ketamine as an NMDA antagonist. And they were struck to find that they, in fact, did see an antidepressant effect, and it tended to occur rapidly. So, when I was at the NIH and I was heading up something called the Mood and Anxiety Disorders Program, we decided to do a more thorough study here.

00:10:17.640 --> 00:12:06.419

Husseini Manji: So basically, we wanted to look at treatment-resistant depressed patients. The usual definition of that is that you've failed two previous antidepressants. Now, most of you may know that the NIH is a place where, you know, a lot of patients who have not responded to anything are referred there. So, the patients we recruited into our trial had failed, on average,

six antidepressants. They had failed electroconvulsive therapy, some of them had failed electroconvulsive therapy, and they had been consistently depressed for three years by the time they came into the study. They were given either intravenous low-dose ketamine or low-dose placebo.

And these were the results, which really surprised a lot of people. So, on the left, you see the results with low-dose IV ketamine. You can see, starting within two hours, about 50% of people are starting to show a response; and at one day, 70% of this highly treatment-resistant population were classified as responders. By contrast, if you look on the right end, I've got that blue dashed line there to make the point that it's not from the same study. The data on the right is from the STAR*D study, which you may know looked at 4,000 people with depression, and then treated them sequentially with different drugs or additions, etc. And if you look at the population that would be treatment-resistant, that's the improvement you see at eight weeks. So, you see less than a 20% response at eight weeks, compared to the 70% response we saw within one day with low-dose ketamine.

So, these were very exciting findings. The NIH Director at the time called it the biggest breakthrough in psychiatry in 50 years, etc. And so, I was quite excited about this.

00:12:06.420 --> 00:14:06.300

Husseini Manji: But I didn't think IV ketamine was going to necessarily be the practical drug, because in many places you need an anesthesiologist present, intravenous administration is complicated, etc. I had thought that one of the reasons you see these rapid responses, the main reason is that you're hitting the right target. But I had thought that the rate at which the drug gets into the brain may also be important. And so, I started to wonder whether you could use an intranasal delivery, sort of deliver the drug intranasally, you don't need IV, and it gets into the brain rapidly, and might you see a robust antidepressant response?

Now, a problem you run into there, and anyone who's taken a nasal decongestant knows, that you deliver a very small amount of drug. So, you actually couldn't deliver sufficient, regular ketamine through the intranasal formulation. But when I was at J&J, we did these studies to show that the S version of ketamine; and as you probably know what's shown in the bottom right, most molecules come in two flavors, S and R, so that the S version was three times more potent at the NMDA receptor than the R-ketamine. So, you could potentially get away with a very small amount of drug that you could deliver intranasally. And so, we thought, okay, let's try if we can deliver low-dose S-ketamine through the intranasal formulation, and does it work?

Now, sometimes, and my heart goes out to patients who are really concerned [about] why it takes so long to develop treatments; and of course, when their loved ones are suffering, they'd

like a treatment tomorrow. But I'm one of those people who thinks that, when you're trying to develop a treatment that you're going to ask someone's loved one to take, you can't cut corners. You really need to do things thoroughly to show efficacy, safety, dosing, etc. And so, this is just an example of some of the steps we had to go through.

00:14:06.370 --> 00:15:52.500

Husseini Manji: So, as I said a moment ago, our hypothesis was that low doses of S-ketamine might be antidepressant. And if the hypothesis was correct, the S-ketamine should work at about a third of the dose of regular ketamine. So first, we tried to demonstrate that, on the extreme left using low doses of intravenous S-ketamine, and you can see this robust and rapid antidepressant effect. And interestingly, you're seeing these effects at about 0.2 milligrams per kilogram, which is almost exactly about a third of what was being done with regular ketamine, which is 0.5 milligrams per kilogram.

Now, I'm sure most of you are aware that conditions like depression, and especially treatment-resistant depression, patients have a lot of recurrences and relapse. Some of the data suggests that if you can put people in remission, then they're less likely to relapse. So, in the middle panel, we wanted to both figure out what an intranasal delivery… what dose and specific intranasal device would be, and wanted to go with doses that put people into remission.

Then, on the right-hand side, we were going to be using these plasticity treatments, and it was completely different from what we'd been used to in psychiatry, which is take a pill once a day or once a night, etc. Here, because it's plasticity pathways, we were fairly sure that you give the drug…Even though the drug only lasts in your system for about three hours, the benefits are going to remain there long after the drug is gone from your system. And we did studies to show that you see this robust benefit, and it sort of gradually starts to come down, so that by about one week, it's more or less gone.

00:15:52.510 --> 00:17:40.990

Husseini Manji: So, we designed this paradigm where for the first four weeks, you got it twice a week. And then, once you were better, you were maintained on once a week, once every two weeks, once every three-week dosing, whatever you needed. I should point out that when we were developing this program, the FDA had come up with this new designation called Breakthrough designation; and it's basically a designation for treatments that could be markedly better than the existing treatments, and for conditions where you have a major unmet need.

And at the time we were developing these programs, I think there had only been two or three drugs in oncology and infectious diseases that had received Breakthrough designation. We were delighted that we got Breakthrough designation as the first drug in neuroscience for this.

Here's some of the Phase III data. So, on the left, you can see with this administration paradigm I mentioned, about 70% of patients show response. And most of that is seen within 24 hours, and about 50% of people go into remission. Once again, next to that, just for comparison, is the STAR*D data. Again, just pointing out the dramatic contrast.

One of the things that also was done, was after people got better, we wanted to show that you can maintain them better by intermittent administration. When we went to the FDA for approval, we had one year of data to show that we could keep people in remission, or markedly responsive, over one year, with once every two weeks, once every three weeks administration.

J&J's recently published six-year data, and it's kind of remarkable that a condition as difficult as treatment-resistant depression, you can keep people well for so long with only once every three week or so administration.

00:17:41.590 --> 00:19:47.579

Husseini Manji: Now, when we'd done these studies, we'd obviously looked at the overall response to the antidepressant treatment, but we also looked at some sub-items, and it was very interesting that suicidal ideation was dropping rapidly. It may or may not surprise you to know that every previous trial of an antidepressant has actually excluded suicidal patients, and one of the reasons they do that is they don't want a suicide to happen during their study.

When I first suggested at J&J that we should do a study in actively suicidal patients, you can imagine the legal folks said, what are you talking about? You know, we don't want a suicide to happen on that study. And I basically said, look, we do cancer studies. Some of cancer patients are unfortunately going to die from their illness. We don't say we're not going to study you because you have a bad illness. I assure you we'll do this very carefully, we'll put in all the safeguards to minimize the likelihood of suicide. I want to do the study. So, this was a study we did; and Carla Canuso and my group deserve a lot of kudos for this, was basically take people who were actively suicidal. They were either in an inpatient unit or they were in an emergency room. If they were in an emergency room, with their consent, they were admitted to the inpatient unit.

Then they were given the best standard of care or intranasal esketamine, and we saw this rapid and robust effect on these patients who were at active risk for suicide. This was the second Breakthrough designation that the FDA gave us, and this was the second approval.

Now, brief segue, because I'm sure most of you know there's a lot of excitement about psychedelics; and although S-ketamine Spravato is not a psychedelic, sometimes it gets lumped in. And one of the reasons is because it causes these transient dissociative effects, which are nothing like the mystical experiences; but nevertheless, you do have the dissociative effects. So, on the left shows you the time course. When you give someone esketamine, at about 30 minutes, you'll see this increase in dissociation that'll go down, and then the antidepressant effects will start to kick in for two or more hours.

00:19:47.690 --> 00:21:32.989

Husseini Manji: We did a lot of studies to show that the magnitude of dissociation was completely unrelated to your antidepressant effect. And that's shown in the middle panel. There's a scale that's developed for posttraumatic stress disorder, something called the CADSS scale. And if you have less than a score of four on that scale, you're basically thought to basically not have any dissociative-like symptoms. On the other hand, more than four, you do have symptoms. And as you can see in the middle, whether you had less than four or more than four, you basically almost had an identical responder rate of about 70%.

So, with S-ketamine, we're absolutely convinced that it's this thing, you know, we're enhancing synaptic and neuroplasticity, which is the beneficial effect. It happens to cause dissociative effects, but that's not related to the mechanism. And I think, as I'll come to in a couple of slides, I think that raises the question for the psychedelics. Is the mystical experience necessary for therapeutic effects? And it may be different for things like depression, or for PTSD, where often it's a psilocybin, for example, or NMDA plus psychotherapy; but I'll come back to that. So here's some of the data with ketamine in rodents. So, on the extreme left, you can see… and this is really elegant work from Conor Liston's group… when you stress animals, you actually cause a shrinkage of parts of the brain. So, there are these things, those kind of knobs shown on the left. They're called dendritic spines, and when you stress animals, you actually cause a retraction or shrinkage. You then treat these animals who you stressed and caused a shrinkage with ketamine, and 24 hours later, you see a reversal of the atrophy.

00:21:33.290 --> 00:23:19.750

Husseini Manji: Then the very elegant work they did is they used a genetically engineered approach to stress the animals, to cause the dendritic retraction. Give them ketamine, but block; use a genetically engineered way to block the regrowth of these dendritic spines, and ketamine's long-term beneficial effects were actually gone. So, it really does suggest that these dendritic spine changes are necessary for the sustained effects of ketamine.

Now, similar studies have been done with psilocybin; and what you see here is the studies with psilocybin, and Alex Kwan has done some great studies. I think what I should emphasize is that these studies were done in normal rodents. The previous study was taking rodents who were quite, quote-unquote, normal, stressing them to induce these dendritic changes, and then giving them the drug. These are basically baseline rodents who are given psilocybin. But what you see on the left in the graph, you see an increase in the number of spines.

In the middle panel, you see an increase in the width of the spine. And there's a lot of data to suggest that the width of the spine is important for some of these long-term changes. So, it's an interesting dissociation where you see the number of spines remaining elevated for quite a while. The width of the spines that we think are the most functional spines are actually coming down somewhat rapidly.

So, there's a lot of interest in the field to ascertain. Can you bring about beneficial effects without the mystical or hallucinatory effects? Because if you could, you could have a take-at-home medication. And people are looking at different things.

00:23:19.750 --> 00:25:11.450

Husseini Manji: One approach is on the right-hand side. So, we now know that many receptors, and the 5-HT2A receptor, which psilocybin works on, is one example. It regulates multiple intracellular pathways, and two big ones would be the G-alpha-q pathway, which activates phosphoinositides, and the beta-arrestin pathway, which regulates MAP kinases. And it's interesting that some molecules for the 5-HT2A receptor bring about more or less of G-alpha-q or beta-arrestin. And in animal models, you can show that that allows you to dissociate the antidepressant-like effect from behaviors that you think are predictive of the sort of psychedelic, hallucinatory-type effects, etc. But, until we have human clinical data, we won't know whether this is possible or not.

Now, one of the things I'd mentioned in one of my earlier slides is we think this is all a balance between AMPA receptors and NMDA receptors. Our hypothesis was that when you give an

NMDA antagonist, like esketamine, you disinhibit glutamate terminals, so you've got a burst of glutamate release that then acts on ample receptors to basically start this cascade.

If this hypothesis is correct… if you block AMPA receptors, do you block the therapeutic effects of an NMDA antagonist? And that's shown in the middle. What you can see is that NBQX is an AMPA antagonist. And at doses that NBQX does nothing on its own, it completely blocks the antidepressant-like effects of ketamine, suggesting that AMPA throughput is critical.

00:25:11.460 --> 00:27:11.090

Husseini Manji: On the right-hand side, there's a lot of excitement in developing a subtype of NMDA receptor which might have fewer side effects, and NR2B is one of them. And once again, you see similar things. You see the antidepressant effects of the NR2B antagonist, and then the complete blockade with an AMPA receptor antagonist. So, this suggested, as I said, that AMPA throughput is important. Like, does it really happen in patients?

Now, obviously, you can't stick electrodes in patients' brains to directly measure AMPA currents. But there's this technology called magnetoencephalography, where you can stimulate parts of the brain and look at what is often looked at synaptic potentiation, which is largely thought to be mediated by AMPA receptors; and there you can actually see the degree of synaptic potentiation in people is directly correlated with the antidepressant effects of ketamine. So, it suggests that this AMPA potentiation really is very relevant, and as you may know, there's a couple of companies developing AMPA-positive allosteric modulators. So, we may have a new class of drugs working in AMPA receptors.

I think one of the things that might also happen in the future is that you might use some of these drugs as what we might call plasticity enhancers; but then you stimulate very specific brain circuits, so that the plasticity effects happen, especially in those circuits. And the ways that could be done could be with transcranial magnetic stimulation, electrical stimulation; you know, although it's preliminary, there's data on focused ultrasound. And the bottom right, CBT, cognitive behavioral therapy, is basically a retraining of the brain. So, you're basically engaging specific circuits and training them. So, could you give the plasticity-enhancing drug and then do the CBT, and ideally do it through digital means so you can reach a lot of people to really make this stick. I think those studies are ongoing.

00:27:11.440 --> 00:29:10.469

Husseini Manji: Now, I think all of you know that we're, more and more, getting into the mode of one-size-fits-all. That's a useless approach. We really need to start to target more specific people, or more specific illness domains, rather than trying to take all comers and treat everything. So, what's shown on the left, I think as all of you know, if you look at the, for example, classification of depression in DSM; it's basically a checklist. Depressed mood and anhedonia, sleep too much, sleep too little, eat too much, eat too little, you know, etc., etc. And I think it's highly unlikely that a single magic bullet will treat everything. On the other hand, as a field, what we've been able to do is map some of these domains I've shown on the left onto specific circuits, neuronal circuits.

And the idea there is that if these domains can be mapped onto specific neuronal circuits, if you target those circuits, will you really see an improvement in those domains? And I'll give you a couple of examples.

So, one of these pathways and circuits is something called the orexin system. It's very implicated in sleep-wake cycles; but if you look on the right at that table, you can see it's also related to a lot of categories that we think are actually quite important in subtypes of depression.

And so, our thinking when I was at J&J was that… Can we look at depressed patients who are characterized by what we call hyperarousal? They can't sleep, they have a lot of rumination, they're revved up; and would they respond to an orexin antagonist? This is some of the early data that suggests that… so on the left… These are depressive symptoms without… you've taken out the insomnia factor, because you know this is going to help insomnia; and you've also used another medication that treats insomnia, and you can see that this is giving you an antidepressant response.

00:29:10.470 --> 00:31:23.649

Husseini Manji: Even if you've taken out the insomnia score, and an insomnia drug doesn't do it. And on the right, if you look at just the six core depressive symptoms, once again, you see this effect. So, it's not just an effect of people sleeping better. J&J's completed one Phase III study, which is positive, and there's another one study underway; and hopefully, if it's positive, we'll get a new drug.

Now, here's a sort of unfortunate negative example. I was very excited about this, but it didn't work. So, anhedonia, as you know, is a domain that is present in major depressive disorders, schizophrenia, bipolar, substance abuse, etc. And a lot of work has looked at the circuitry underlying anhedonia. And data suggested that these molecules called kappa antagonists might

prevent these anhedonia symptoms. So, when I was at J&J, we did a lot of work on what you might call experimental medicine models, where we weren't trying to just look at overall double-blind, placebo-controlled clinical trial, but looking at, what would a kappa antagonist do to the fMRI brain imaging signal on a reward task? So, there's something called a probabilistic reward task, and then on the bottom right, on an anhedonia scale. So, this thing seemed to work in three out of three.

And then a Phase II study was done, and it was basically done as an adjunct to antidepressants. As I mentioned a moment ago, my thinking is that these novel drugs that might be working on certain domains, they might not treat the whole syndrome, but they might treat certain aspects really well. And as you can see on the right, there seemed to be a very good effect of this medication called aticaprant. And then, as you learn, about 90% of things in medication development unfortunately fail. And J&J's Phase III studies on this drug… And Numora is a biotech, had a similar drug, both failed. So, whether it was the ability to sensitively measure anhedonia, whether the hypothesis was wrong, etc., but unfortunately, this isn't going to become a new drug anytime soon.

00:31:24.180 --> 00:33:08.589

Husseini Manji: I think one of the other important things is to identify subgroups of people with certain kinds of what we call biomarkers. Can you see, do you belong to a neuroimmune subtype, do you belong to a hippocampal plasticity subtype, etc.? I think one of the things that I think is very important…In our research settings, we could probably do all the bells and whistles. So, as I mentioned, at the NIH, we were doing magnetoencephalography. But in the real world, for example, rural Alabama, you're not going to be able to send your patient for magnetoencephalography. So, you've got to think about inexpensive, routine, and practical biomarkers.

And what's shown on the left would be potentially blood-based measures. And some people might think, wow, are you really going to pick up things in the blood? And I think Alzheimer's is an interesting example where, for years, we did a lot of work on brain imaging and spinal fluid; and now there is a plasma test, plasma phosphor-tau217, which is amazingly accurate.

The second one next to that would be computerized behavioral tests you could do at home. As you all know, there's a lot of excitement about wearables; and then next to it, on EEG caps you could send to people's homes. And I think, what's shown on the right is an example where you've taken people who do this computerized test at home, and they show impairments of verbal memory. So, these are depressed patients who are showing impairment of verbal memory, and our hypothesis is that these people have impairments of hippocampal plasticity.

And if you use a drug that increases brain-derived neurotrophic factor in the hippocampus, those patients specifically should respond, and the trials are ongoing.

00:33:08.970 --> 00:35:15.990

Husseini Manji: The other big area… I'm sorry to go back a bit… that's also gotten a lot of excitement is the idea that there might be immune involvement. Now, one of my first slides, I mentioned that our patients, unfortunately, have very high rates of comorbid illnesses, as shown on this slide. And when you look on the right-hand side, you can see that when you're measuring something called CRP, which is C-reactive protein, which is basically a rough measure of degree of inflammation and depressive symptoms, you see a linear relationship, suggesting that, at least in some people, the CRP, or the inflammation, could be driving the depression.

Here's a study we did on the left-hand side; again, when I was at J&J. So, we basically took large databases from J&J, GSK, and others, and asked the question: if you have an autoimmune disease, and you were treated with a specific cytokine, those are shown on the left. If you had a subgroup of people who had prominent depressive symptoms, did the depression get better? And the answer seemed to be yes. So not every cytokine, but TNF-alpha, IL-12/23, and IL-6, the depression got better.

Now, an obvious concern is, well, wouldn't you feel better if your rheumatoid arthritis got better, if your ulcerative colitis got better, etc.? So, what this slide is showing you is patients who were non-responders for their primary autoimmune disease. So, their rheumatoid arthritis didn't get better, their ulcerative colitis didn't get better, and so on, and yet their depression got better. So, it's not just secondary to an improvement in their physical symptoms.

What's shown on the right is that in some cases, you may be able to just give a drug, and a lot of it doesn't have to cross the blood-brain barrier. If it's a monoclonal antibody that has to cross the blood-brain barrier, there's a number of exciting technologies which are now allowing you to deliver protein or gene products across the blood-brain barrier. So, I think in the future, if we identify something as a very important target in the brain, we will have mechanisms to get it across the blood-brain barrier.

00:35:16.150 --> 00:37:04.050

Husseini Manji: The last point to make about this sort of immune slide is that we've known about autoimmune diseases forever, right? Rheumatoid arthritis, […], arthritic colitis, multiple sclerosis. Now the data's starting to suggest that a potentially substantial subgroup of people we today call schizophrenia or potentially bipolar psychosis may actually have an autoimmune

disease, where they have antibodies against specific receptors in the brain. And the data's suggesting, and we're trying to figure out exactly what percentage of people is this, 5% of people, etc., but the data's suggesting that you can treat these people; and that slide on the top right-hand corner, or the figure on the top right-hand corner, is from a woman who talked about her own autoimmune psychosis. She'd sort of bounced around on a number of antipsychotics which weren't helping.

And then, immunoglobulins and plasmapheresis really basically got rid of her symptoms. There are now certain kinds of antibodies, or antibody strategies, including [those] that have been developed for myasthenia gravis, that could well work here. So, if we're able to accurately identify who has an autoimmune psychosis, we could potentially help them with these novel treatments.

The last part of the presentation, I'd briefly like to touch on bipolar disorder. I think you can see on the left that bipolar disorders, arguably, are most recurrent illnesses. And I'm actually using the term manic-depressive illness, and that's basically an old definition, which basically thought that patients with what we call bipolar disorder and patients with familial recurrent depression, they sort of belonged in the same family of manic-depressive illness. For some reason, some of them didn't have the manias, but they all had these recurrent illnesses.

00:37:04.200 --> 00:30:00.779

Husseini Manji: On the right is the data that I thought was remarkable with lithium. So lithium, the molecule is shown there. It's basically like table salt. It's in the same area of the periodic table as sodium, and yet at something like 150th of the concentration of sodium in the body. For the people in whom it works, it has a remarkable beneficial effect. So, what you're seeing there, is you spend about a 4.5-fold reduction in the time spent in mania, and a 2.5-fold reduction in the time spent in depression. And it really looked like lithium's best effects were prophylaxis. It keeps people well. So that begs the question, if we could understand how this simple molecule, as I said, looks like table salt, is bringing about these profound beneficial effects, could we come up with better treatments? And that's what's shown here, and this basically summarizes 15 years of work that tried to marry two kinds of research. One was to take post-mortem brain from bipolar disorder patients and ask the question… we look at bipolar disorder compared to controls. What genes do we see turned on or off? And obviously, in a post-mortem brain, you have to control for a lot of things. What medication have they been on? Have they been on substances? What's the post-mortem interval delay, etc.? And on the right was taking rodents and treating them with either placebo, in this case saline, or chronic lithium, and asking a similar question- What genes are turned on or off? And then trying to compare the two to look

for overlaps. And what was interesting is that the biggest class of genes that seemed to be turned on by the treatments and were reduced in bipolar disorder were molecules we consider neurotrophic molecules; molecules whose job it is, we think, to help nerve cells grow and survive.

00:39:00.960 --> 00:40:46.769

Husseini Manji: Now, could that actually be relevant for bipolar disorder? Because bipolar disorder is not Alzheimer's disease, where a lot of neurons are dying. The data over the last 20 years is suggesting very much yes. So, what you're seeing on the extreme left is this study that Wayne Drevets had done in either bipolar patients, what I mentioned, familial recurrent unipolar patients; and was struck to see that there was about 40% less gray matter in a part of the frontal cortex, the subgenual prefrontal cortex. Now, the MRI scans tell you that there's less gray matter. It doesn't tell you why.

So, then you go to post-mortem studies, and the cartoon shown in the middle tries to depict it. It's kind of a good news, bad news situation. The good news is that when you count the number of neurons, you haven't lost that many neurons; so it's not like Alzheimer's, where a lot of neurons have died. But what you do see on the bottom of the middle panel is that the neurons are shrunken. So, there's less of these dendritic branches, and those knobs there that almost look like Shrek's ears, those have retracted. So, it suggests that if the lithium is increasing neurotrophic factors, it could actually be very relevant for bipolar disorder.

On the right, you're seeing one of the specific molecules that lithium is turning on. It's a protein called Bcl-2, and it's thought to be arguably the most important neuroprotective protein, and it works at the level of the mitochondria and prevents cell death. And as you can see on the right-hand panel, what you're looking at is staining for Bcl-2. You can see in the anterior cingulate, or the dentate gyrus, or the striatum, you're seeing this robust Bcl-2 upregulation.

00:40:46.960 --> 00:42:34.809

Husseini Manji: Another molecule which talks to Bcl-2 was also upregulated. It's called BAG-1. It had these two very important functions that we thought made it relevant. One is that it interacts with Bcl-2 and potentiates Bcl-2's neuroprotective protein. Secondly, it interacts with the glucocorticoid receptor and regulates the movement of the glucocorticoid receptor. And you may be familiar that the glucocorticoid receptor is one of these receptors that sits on the cell surface. When the hormone, like cortisol, binds to it, it actually moves to the nucleus or the mitochondria. And BAG-1 regulates this. It sort of attenuates, reduces the amount of

glucocorticoid receptor that moves to the nucleus when you sort of overstimulate. So now this question was, if lithium is increasing this, does it actually affect glucocorticoid receptor movement? And the answer's a resounding yes.

If you look on the extreme left, the blue, where it says DAPI, is a stain that stains nuclei. Next to it, in red, are glucocorticoid receptor staining, and next to it, in sort of pink-magenta, is the overlay. So that shows, basically, the glucocorticoid receptors that have moved to the nucleus. Just below that is after chronic lithium treatment. You see that high-dose glucocorticoids aren't able to move these glucocorticoid receptors to the nucleus as much as they could without lithium, and that's shown in the middle panel. And then on the right, a lot of studies, it's about 10 years of work, showing that lithium really regulates this mitochondrial function.

00:42:34.920 --> 00:44:18.649

Husseini Manji: So, it suggests that these molecules, like Bcl-2 and BAG-1, could be involved in what we sometimes call risk or resilience. Are they sort of helping you be resilient against illnesses, or are they putting you more at risk? And it's well enough to show things in a test tube; then, does it really happen in animals? And that's shown here. So, on the left, these are animals that have been genetically engineered to have lower levels of Bcl-2. Then these animals are stressed in this learned helplessness model to make them depressed. And what you see on the left, is if you have normal levels of Bcl-2, and then you stress the animals, about 50% of them become depressed.

By contrast, if you have genetically lowered the levels of Bcl-2, about 100% of those animals become depressed. So, it really looks like if you lower Bcl-2, you make these animals more likely to develop depression.

On the right, you're looking at almost an opposite effect, which is increasing, genetically engineered, increasing the levels of the BAG-1. And what you do there is you make the animals depressed; and then you see if you've got more BAG-1, do you recover faster? And that's what you see on the right. In the blue, these are animals with normal levels of BAG-1. They remain depressed for several days.

By contrast, when you've genetically engineered BAG-1 to be higher, these animals recover very rapidly. So, it suggests there could be something to the idea that these are risk-resilience molecules, and hopefully down the road, we'll get new treatment.

00:44:18.920 --> 00:46:05.340

Husseini Manji: One of the things that I'm sure all of you are familiar with, is that while I've shown you a lot of work about, okay, we can manipulate these things in cells, we're talking about treating people who have to function in society. It's not about just treating neurons, right? And so, I think in the future, optimal outcome will be a little bit more holistic. You have the drug, which does the basic effects at the biology level. But then you'll need interventions to enhance scholastic and occupational functioning. On the bottom right, remote monitoring to potentially pick up likelihood of relapse, patient management program. And then you may be aware that there's some excitement recently about the ketogenic diet potentially helping in bipolar disorder. And the ketogenic diet exerts major effects on the mitochondrial level; so, if it's working, it could well be through that mechanism.

The very last thing I'd like to talk about, and the title of my presentation… basically the last part of it was a shared societal responsibility. And I think that's very important, and I think HIV/AIDS is a great example of the progress we can make when we're willing to work together. So, these are patients, these are companies, these are academics, these are FDA, etc.

So, what's shown on the right is when HIV/AIDS first came to North America. We were seeing this ever-increasing mortality rate. And then, by all these people coming together and working together and developing novel treatments, you can see that we really made an impact on the number of people dying. And now, in most Western countries, HIV, you basically have a normal lifespan than someone who doesn't have it. So that's a remarkable testament to what can happen when we work together.

00:46:05.350 --> 00:48:35.689

Husseini Manji: More recently, a similar type of thing has happened in dementia, where a lot of stakeholders have been brought together. On the bottom, you can see some of the stakeholders that have worked together to develop biomarkers and endpoints, etc. And you may know that there's two FDA-approved drugs, one from Eli Lilly and one from Eisai/Biogen. And I can almost guarantee they would not have been approved if this group hadn't done this sort of work. So, I think we really need the same sort of effort in mental health.

And I'm doing something like that in the UK. And the only reason I'm doing it in the UK… you know, UK has very good life sciences, but we have fantastic life sciences in the US. One of the things the UK has that, with the exception of, for example, the VA in our country, they have this National Health Service, where 60 million people are all under the same health insurance and very good electronic medical records. So, my thinking was, if we do some of these small-scale studies, we find something, we can quickly get into the population to see, does it work? And

these were, I organized at 10 Downing Street, this roundtable discussion. These are some of the stakeholders. And what we've also done recently is develop a major collaboration with our French colleagues. I'm definitely showing this slide in part to show off the photo of me with Michelle Obama, and me with Justin Trudeau. But these discussions with them were for exactly this sort of thing, to get people excited about different countries even working together, and I've obviously had a lot of discussions with the U.S. as well.

So, to conclude, I do think that, as we all know, unfortunately, serious mental illnesses really are one of the most challenging, not only health, but also economic and social justice issues of our time. After a long hiatus, I think we're finally turning the corner in terms of novel mechanisms that'll hopefully really help our patients. Clearly not all of them will work. As I said, if we can really sort of narrow down specific targets, focus on biomarkers, focus on specific domains, we'll do even well. And I think any of you who are interacting with legislatures, one of the things I try and do is to really emphasize to them that investing in mental health research and novel treatment-resistant treatment development will actually be cost savings to the healthcare system, and ultimately even facilitate economic growth. So, thank you very much for your attention, and I look forward to the Question & Answer period. Thank you.

01:08:57.319 --> 01:09:10.179

James Naifeh: Thank you, Dr. Manji. What a wonderful presentation to start us off today. Please submit your questions for Dr. Manji using Zoom's Q&A feature, and for any of our subsequent presenters.

KERRY J. RESSLER, MD, PHD

PRESENTATION

01:09:10.609 --> 01:10:39.519

James Naifeh: Our next speaker is Dr. Kerry Ressler. Dr. Ressler is the Chief Scientific Officer at McLean Hospital and Professor of Psychiatry at Harvard Medical School. He is an international leader in understanding the biology of fear and posttraumatic stress disorder. He's a member of the U.S. National Academy of Medicine, a prior Howard Hughes Medical Institute investigator, past President of the Society of Biological Psychiatry, and the American College of Neuropsychopharmacology. He has authored more than 600 manuscripts, with over 75,000 citations, focused on the molecular, cellular, and circuitry neuroscience of fear; focused primarily on amygdala function, as well as human psychobiology of stress and trauma, with more recent work examining the interaction of stress, trauma, and addiction. He has served on the Board of Scientific Counselors for the U.S. National Institute of Mental Health, the Scientific Advisory Board of the National Center for PTSD, and the Army STARRS project.

In addition to his own preclinical and clinical labs, he is the co-leader of multiple national consortia, such as the Psychiatric Genomics Consortia for PTSD and the Aurora Study, which are focused on deep phenotyping and understanding biomarkers and the genetic architecture of PTSD and stress-related disorders.

We will now begin Dr. Ressler's presentation, which is titled, “The Neuroscience and Genetics of Fear: Towards an Underlying Biology of PTSD.”

Total Conference Timestamp: 01:10:45.220 --> 02:0:10.569

Within-Segment Timestamps below

00:00:46.830 --> 00:01:26.899

Kerry Ressler: Thank you so much for having me today. I'm Kerry Ressler. I'm calling in from McLean Hospital, Harvard Medical School in Boston, and I'm really delighted to be part of the Brain, Behavior, and Mind Conference this year. I'm going to be talking about… really an overview of the neuroscience and genetics of fear that's made tremendous progress as a field over the last 20 or 30 years; and I think it's really leading us to exciting new insights and opportunities for posttraumatic stress disorder and other stress and trauma-related disorders.

To start with my disclosures, I'm on several scientific advisory boards, and consultation is listed here; but none of these are related to any of the work I'm going to talk about specifically today.

00:01:28.090 --> 00:03:29.060

Kerry Ressler: So, as Sandra Galea, the former Dean of the BU School of Public Health, said, trauma is a foundational driver of the health of the public. And while we'll talk more specifically about posttraumatic stress disorder today, I think it's important to remember that trauma, particularly childhood and developmental trauma, are some of the highest risk factors for all psychiatric disorders, from depression to PTSD to addiction to psychosis, as well as metabolic and cardiovascular conditions. So, there's a lot of data that I'm not going to talk about today; how PTSD and trauma exposure increase risk for cardiovascular risk, cancer risk, metabolic syndrome, diabetes, and others. So, it's really critical that we better understand this and have treatments, both for chronic PTSD, but ideally in the early aftermath of trauma. And one of the things I'll talk about as we go, is one of our dreams would be able to prevent the development of PTSD from happening in the first place.

But I want to start by getting us all on the same page. Again, I think it's a conference that's related to this, so I won't spend much time, but just to remind you that PTSD is clinically important. It affects 5-10% of the population, generally about 50% more women than men, as well as much higher rates in people who have been highly exposed to trauma, in addition to veterans and people who live in at-risk communities; for example, some of our work in inner-city Atlanta. And in highly traumatized populations and war-torn populations, you can see rates of PTSD up to 25 to 30%; so it's quite prevalent.

On that note, I'm going to talk about PTSD as one thing; but we of course know that, as with many psychiatric, and probably all psychiatric disorders, there's not one biological pathway to get to this disorder. There are likely multiple different ones that lead to multiple subtypes or biotypes of these disorders. And by understanding the biology, neuroscience, and genetics better, we'll be able to better understand the specific subtypes of PTSD, enabling better targeted treatments.

00:03:29.410 --> 00:05:27.700

Kerry Ressler: Additionally, one of the critical components of posttraumatic stress, and why I think it's perhaps more tractable than some of our other psychiatric disorders at this stage in our science, is that we know when it starts. And I'll walk through more why that's powerful from a scientific and, ideally, an interventional perspective later on.

Again, reminding you that PTSD requires having a Criterion A, exposure to trauma, where one is exposed to death, threatened death, actual serious injury, or threatened violence, and then has ongoing symptoms of re-experiencing, avoidance, negative alterations in cognition and mood, and sympathetic hyperarousal. And I'll particularly talk about those that are most specific to PTSD today, some of the mechanisms we think underlie re-experiencing, avoidance, and the hyperactivation of PTSD.

Just a couple slides on current treatments, because, on the one hand, our current treatments work moderately well, and can make many people better, but they don't work very well for getting people to remission and for making people well. Our best scientifically validated treatments are our cognitive behavior therapies, particularly prolonged exposure and multiple versions of combinations of CBT and PE, including STAIR, cognitive processing therapy, EMDR, and DBT-PTSD, all of which have some combination of skills training, emotion regulation components, and exposure therapy.

Importantly, the components that interfere with exposure, and thus extinction, and I'll talk later about extinction as the Pavlovian-defined concept of recovery from threat or fear over time, which is really the underlying basis of exposure. And the way these generally work is, we have a little diagram here, and you can't quite see my light blue line, but the therapist comes in for the first time, for example, or the patient comes in and talks to the therapist.

00:05:27.710 --> 00:07:20.900

Kerry Ressler: And the therapist will say, tell me about your trauma. Tell me what happened. And the patient will say, well, I don't want to talk about the trauma. Well, this is the way it

works. And so, again, there needs to be a psychoeducation component initially. But when they are ready, they will start talking about the trauma, and what'll happen is, the first time they talk about it, it'll be very high, and the therapist may say, tell me on a 0 to 100 scale how anxious or nervous are you are right now. And 100 might be, I'm having a panic attack, I gotta get out of the room. 0 might be, I'm so bored, I'm falling asleep.

And so, they'll go from a low level to a very high level, but the trained therapist is going to help them stay there, help them tolerate it, while staying with the narrative, staying with the theme. And over time, over minutes to an hour, those emotions will come down. And the patient will say, you know, I survived that, and it wasn't maybe as bad as I was afraid it would be. So they come back the next time, and then they say, tell me again about what we talked about last week. And they will, and they'll find that while it's still very upsetting, it won't be as upsetting as the last time. You don't get as high of a distress rating. Do that several times until that particular memory is less threatening to them, and less activating of all of the hyperarousal symptoms. And then they'll say, let's go to the next, what therapists call a hot spot; the next area that you're feeling really traumatized about, or that's really distressing you. And so that's the basic process. It usually, in research, takes 12 to 16 sessions. In real life, it can take longer.

And I'll talk about how we could improve extinction today; how do we understand how it works, as one of the components. The other side, of course, for treatment of PTSD is medication. And unfortunately, we still only have two FDA-approved medications for PTSD, that's SSRI, sertraline, and paroxetine.

00:07:21.550 --> 00:09:12.279

Kerry Ressler: I won't go through much else, I think you'll hear more, but we don't tend to use benzodiazepines. They can decrease anxiety in the short term and decrease the fear response in the short term; but in the long term, if anything, they can impair the natural recovery or the extinction process. And then there's a whole lot of off-label drugs that are used to really treat the emotional dysregulation components of PTSD, the depression components, the hyperarousal components; but none of them really target the underlying memory.

What we have, then, is sort of a conundrum, where we have psychotherapies that work for some people when done by the right trained therapists, and we have medications that really help with some of the symptomatic components, but don't get at the underlying memory. And the goal of neuroscience is to figure out, how can we come up with better treatments that are really targeting the biology and targeting the right person, and maybe even can be used for prevention.

One last area of a lot of excitement that I'm not going to talk much about today, but I'm going to hint at the end, is the psychedelics and MDMA, the entactogens and the [psychoplastogens]. And again, this was one of the most famous studies so far, by Lykos Therapeutics, and MAPS, where it was shown that MDMA combined with a form of therapy led to a more rapid improvement. In the discussion, we can talk more about where the field of psychedelics [is]. Medicine is hopefully going to start a PTSD trial with psilocybin soon; and there's been quite a few things, and I'll mention them as well as with ketamine. And there's excitement here, and then a lot of potential worry as well, so more to talk about. And as we better understand the neuroscience and neurobiology, we'll better understand where these fit.

00:09:13.450 --> 00:11:00.850

Kerry Ressler: So, to briefly summarize where we currently are… PTSD, as with most psychiatric disorders, is really targeted by a combination of psychotherapy and medication. Some of the prior VA work suggested- start with psychotherapy, but most people, will combine medication relatively early on as well. But the only, again, really approved medications we have are the SSRIs. So where do we go from there? We need research.

So, what I'm going to talk about today about is, how we can use learning theory… And a great deal of work over the last decades that has helped us to better understand the neural circuitry of fear, to better understand the process of posttraumatic stress disorder, PTSD, is tractable from this shared neurocircuitry that's really shared from mice and even lizards all the way to humans. We know when it starts. It starts at the time of the trauma.

That both gives us the ability to follow it longitudinally, and I'll tell some stories there, as well as potentially to intervene early after the trauma to prevent consolidation. And it also involves learning and memory, which is one of the areas that there has been the most progress in neuroscience. And so, our goal is to have a molecular neurobiology of PTSD that can both lead to predictive biomarkers for understanding specific biological subtypes, or treatment response biomarkers, as well as novel interventions.

So, PTSD, while we often think about it, or at least when I first came into the field, I thought about it as someone was fine, and then this horrible thing happened to them, and then they were changed. And of course, it's not that way. And by understanding the time course, and the time course of risk, we can begin to start to understand how people have individual differences in their development of PTSD, as well as how there might be biological subtypes.

00:11:01.190 --> 00:13:08.220

Kerry Ressler: So, first of all, I'll remind you that about 5-10% of the population develops PTSD after a trauma. So, if we think about the big picture question of why, given a significant life-threatening trauma, do 5-10% of people develop PTSD, but the vast majority actually recover. They may have symptoms early on, and that might be acute stress disorder, but they recover over weeks and months, to the point that this is still a bad memory for them, a fearful memory, a negative memory, but not one that is clinically impairing. So, what's the difference between PTSD, where someone will say something like, not only did I have a bad memory, this sort of became an emotional black hole of memories for me, and everything gets sucked into it, and it has become my life, to- that is just a bad memory that I can talk about or not.

So, the first thing is pre-existing sensitivity. I'll show you later that genetics is involved; and we now know that the genetic risk for PTSD is around 30-40% of the heritability for PTSD is heritable. And that's about the same percentage as we see for depression and addiction. And PTSD and addiction are similar in that we think that you have a genetic predisposition for how you will respond to the trauma, or an addiction, how you respond to the drug of abuse; but if that exposure never occurs, then you don't see that genetic risk play out. The second half of the gene by environment, or nature and nurture issue is the environment, of course. And we know, in particular, that developmental trauma, childhood trauma, early life stress, are some of the biggest risk factors, as I mentioned earlier, for everything in psychiatry, but in particular for PTSD. And animal models and human data suggest that, essentially, with early life stress, you're sensitizing these threat and fear systems concretely, sensitizing the amygdala response for how it responds to later future traumas, increasing the likelihood. And so we can kind of think about PTSD, or the trauma response, as a dose-response curve.

00:13:08.220 --> 00:15:14.439

Kerry Ressler: And the more genetic risk you have, the more trauma exposure early in life you have, the more sensitive you become to later adult trauma and pathology from there. We then also know that what happens around the time of the trauma, both the traumatic event itself and the hours and days following, can make a lot of difference. So, first of all, some of the best data suggests that it's interpersonal trauma that increases the risk the most for PTSD, compared to, say, incident trauma, et cetera; from whether it be natural disaster or motor vehicle accident.

Also, the peritraumatic components, like peritraumatic dissociation, peritraumatic distress are more associated with later PTSD. And then being surrounded by support, trusting support, senses of safety, being able to talk without retribution or judgment or shame, having contact

and support by loved ones; those are all things that are supportive and support resiliency or recovery, and not PTSD, in the aftermath of trauma. We also imagine that they're based on preclinical models, many molecular events that are happening in these hours and days after in the brain that lead to synaptic plasticity and synaptic sensitization of that trauma memory, that we're starting to better understand.

And then in the days to weeks following trauma, this early stress memory gets transitioned to a long-term chronic PTSD. And that difference is maybe one of the most important things, because it may be that window of the first weeks where we can prevent a lot of people from developing chronic and disabling PTSD. And in part, what we see there is people express the fear of this traumatic event, and how that expression then gets replayed into their memories makes a big difference. So, for example, those who recover will discriminate fear. They'll say, okay, I was attacked down that dark place at that night. But not all dark places are bad, et cetera, et cetera. There's good and bad in the world, and I can discriminate those two things.

00:15:14.530 --> 00:17:27.879

Kerry Ressler: Those who are more likely to develop PTSD readily generalize these threat responses. There was an attack down that dark alley by that man. First, I didn't want to think about that man or that place, but then I didn't really want to be around men in general. I didn't really want to be down that part of town. I didn't want to go out at night, then I didn't really want to leave my house, and now I'm kind of stuck in my bedroom. So, the world has become less and less safe as they generalize the fear response.

Furthermore, those who develop PTSD are more likely to sensitize fear. Doc, every time I talk about it, it gets worse and worse. Why would I want to do this exposure therapy thing? And the idea there is that people seem to get more… the fear gets worse over time.

And, I'll talk at the end about reconsolidation versus extinction; but we think that this clinical idea of sensitization may map onto the neurobiology of reconsolidation, where any time a memory trace or a memory engram is reactivated, it can be strengthened. And that is in contrast to those who recover naturally through this process of extinction. And I mentioned extinction related to exposure therapy, but we think a lot of natural recovery is natural extinction. Talking to your friends, talking to your family, going by the places, letting yourself think about it; and in all of those cases, not having the bad thing happen. Repeatedly exposing oneself to the memory without the negative event. And so, this extinction versus sensitization conundrum may be a really critical component about who's able to recover versus who doesn't.

So, I'm going to talk briefly about trauma memories broadly in the neuroscience, as well as the more recent data with genetics, and some of the exciting places, from our group at least, where the large-scale genetics is intersecting with our understanding of the neuroscience.

Then I want to talk a little bit about this idea of sensory systems. Our work is a lot focused on the amygdala and the limbic systems, but we know clinically that people talk about it, the fear and the threat, in a very sensory way as well. And people like Bessel van der Kolk is famous for *The Body Keeps The Score*. And so, I think there's some really interesting data starting to show that the primary sensory systems are also very much altered with trauma, and that may give us new targets for treatment.

00:17:28.349 --> 00:19:26.320

Kerry Ressler: And finally, we want to come back to this idea of extinction and recovery, and how, by better understanding extinction, we can come up with new treatments and interventions. So first, just reminding you of the limbic system, which is really the memory system in the brain, and particularly the amygdala and the hippocampus. The hippocampus [is] more associated with contextual memory, and the amygdala more with cue-specific and threat memories. And these are constantly modulated by many brain regions, including the insula, many cortical areas, and in particular, the prefrontal cortex.

What we know in animals, and looks like it occurs in humans as well, and really throughout mammals, is that when a previously neutral stimulus, in the lab it might be a sound, a tone, or a smell; and in the lab it might be a foot shock in a mouse or a rat… When those two are paired, we get active plasticity within the basolateral amygdala, and then transferring to the central amygdala, which then sends projections to many parts of the brain.

And this plasticity includes BDNF-dependent plasticity, NMDA plasticity, a variety of other glutamate and calcium-dependent plasticity, and we know it occurs with increased spines and increased axon spinal synapses. So, all of that basic neuroscience of synaptic plasticity is happening in the amygdala early after a basic Pavlovian, conditioned fear stimulus, fear conditioning. And all the data suggest that in humans, when you have a traumatic event occur, that's activating the fear conditioning process in the brain. Now, that is not all of PTSD. Obviously, PTSD is the whole range of stress- chronic stress, inability to recover, comorbidity, all of these other things. But this core component of what's happening early in the trauma gives us a lot of ability to make progress in understanding what's happening.

00:19:26.430 --> 00:21:35.950

Kerry Ressler: Most importantly, what was shown, really, in the 90s and 80s, through people like Mike Davis and Joe LeDoux and Mike Fanselow and others, is that hardwired projections from the amygdala, that can be shown anatomically and then can be functionally understood via electrical activation or chemical activation, that hardwired activation of the amygdala leads to a whole set of symptoms that look just like a panic attack. Increased heart rate, blood pressure, GI distress, panting, respiratory distress, hypervigilance, arousal, the increased startle response, freezing in rodents and social freezing in humans, and the paraventricular hypothalamic response of HPA cortisol activation. So, all of that, kind of everything we think about in the negative affect space, as well as in the panic attack space, can be activated through the amygdala projections. So that, the way we think about it, then, is with what this plasticity in the amygdala is doing at the time of the trauma, is essentially connecting these previously neutral cues- a specific person, a smell, a sound, a place- to this hardwired shock, unconditioned stimulus, so that in the future, the previously neutral cue activates the whole hardwired panic threat response.

So, how can we better understand the full temporal component of it? I was fortunate enough to be part of a study initially at Emory, and then with Sam McLean at UNC, and Karestan Koenen and Ron Kessler at Harvard, that became called the Aurora Study, which is one of the largest studies so far of prospective understanding of what happens in the aftermath of trauma. So, we identified people in about 20 different emergency department sites around the country; and we, shortly after they came into the emergency room, collected blood and collected a whole series of data. And then also enrolled them for up to a year wearing wearable devices, EMA phone-based tools, and pretty much threw everything that we could, six years ago, at them technically, to really understand what happens in the early aftermath of trauma, how does that lead to long-term risk, etc.

00:21:35.950 --> 00:23:07.250

Kerry Ressler: And there have been many, many papers and really a wonderful group of colleagues. I'm just going to hit a few highlights. So, some of our early work from the emergency room suggested that the early data and prior data, that amygdala showed to be hyperactive in laboratory settings and people with PTSD, that we could replicate that in these longitudinal prospective studies. Jenny Stevens, now one of the co-Directors at Grady Trauma Project in Atlanta, showed that amygdala activation two weeks after trauma, so when we would still call it this acute stress or early stress period, predicted PTSD symptoms three months and 12 months later. Similarly, the dorsal anterior cingulate that often goes along with amygdala and insula also

showed the same relationship. So, that early amygdala hyperactivation was associated with long-term risk consistent with the rodent models of threat conditioning.

In contrast, the hippocampus, generally encoding contextual memory, but critically involved in the contextual component of extinction or inhibition of fear memory, it had the opposite effect. So, higher hippocampal activation to an inhibitory task, like a Go/No-go, was associated, actually, with less PTSD symptoms at three months and six months later. So, the push-pull of the amygdala and hippocampus is predicted in animal models and in cross-sectional PTSD studies, [and] appears to be occurring early on in the aftermath of trauma, and predictive of later.

00:23:08.050 --> 00:25:21.249

Kerry Ressler: One of the most potentially scalable findings that we were excited about is the idea of hyperactivation of the adrenergic circuit. So, using the sympathetic measure of skin conductance, we could measure people's skin conductance in the aftermath of trauma, say, in the ER while they're telling us about their trauma. And what we found, and this is Becky Hinrichs and Tanja Jovanovic, who's now leading the Detroit Trauma Project at Wayne State, was that, again, in the hours after trauma, their skin conductance, when asked about their trauma, predicted PTSD symptoms very robustly up to six months later. Notably, in Aurora, we did the skin conductance during the demographic section instead of during the trauma, when they were talking about trauma, and we actually did not see nearly as strong a correlation. So, we have to trigger that trauma a little bit to be able to see this cue.

So, that's just a highlight of some of the main players; the amygdala, the hippocampus, the sympathetic nervous system. How is our understanding of genetics starting to play into our understanding of the biology of PTSD? So, the Grady Trauma Project in Atlanta was one of the founding cohorts with the Psychiatric Genomics Consortium PTSD Initiative, led by Caroline Nievergelt, Karestan Koenen, Murray Stein, and Israel Liberzon, and has made great progress in about the 15 years since it started. So, it went from a few thousand samples, or maybe 10,000 or 20,000, when we thought that would be sufficient, to now well over a million, and also includes the Million Veterans Program sample summary data. And it's very exciting, because we now have a full GWAS with very many skyscrapers, if you will, in the Manhattan plot analogy, associated with PTSD longitudinally from across the world. If you follow genetics of any of the psychiatric disorders, we still have a long way to go in having sufficient numbers of non-European ancestry to really have strong signals; so most of these initial data are the European subset.

00:25:22.800 --> 00:27:44.859

Kerry Ressler: So, I wanted to just point out a few of the genes that we're particularly excited about. So, first, that was seen when we had only about 1/10 of this sample size was the corticotropin-releasing hormone receptor, and I'll talk about more about that in a minute. I want to also talk about FoxP2, which is one of the top candidates, now in the larger subset; and is a very interesting gene for reasons I'll get into in a minute. Both of these are highly associated with amygdala activation.

Estrogen receptor is very interesting, given the sex difference we see in PTSD. Catenin (CTNND1) and WNT3 pathways are very interesting; both that they're very much involved in synaptic plasticity in the amygdala, and they're some of the main understood targets of lithium. GABA receptors and glutamate receptors and NCAMs are all involved. And so, we could go on and on. But the point is, there's a lot of exciting potential stories in these common variants. And the field is starting to do rare variant sequence analysis as well, and Adam Maihofer and Caroline Nievergelt [have] also shown the burden of rare variants increases in PTSD as well. So, to just move along and show a couple highlights. So again, CRHR1 is the primary receptor, excitatory receptor, for the corticotropin-releasing hormone released by the hypothalamus. As well as the amygdala and BNST; and from the hypothalamus, it activates the pituitary to release ACTH, which then causes the adrenal to release both cortisol, adrenaline, and the stress response.

So, it's long been associated, obviously, with this, and shout out to Rachel Yehuda and many others who did early work showing dysregulation of the cortisol and HPA systems, as well as Charlie Nemeroff in PTSD. More, very recent work also in collaborating with Niko Daskalakis, shown here, now at BU, along with Charlie Nemeroff and Joel Kleinman at Lieber Institute for Brain Disorders.

have focused on the molecular post-mortem analysis of PTSD. So again, another new area of great excitement in the field of psychiatry is really starting to use bulk sequencing, other omics, and single-cell sequencing to better understand our psychiatric disorders.

00:27:44.860 --> 00:29:23.960

Kerry Ressler: And, I encourage you to look at this. It came out in *Science* this past summer. There's a huge amount of data in it across all omics- proteomics, transcriptomics, and epigenetics- in those with PTSD versus depression versus controls. But one of the take-home messages is, both, we see a number of very interesting genes in the amygdala, hippocampus, and prefrontal cortex, including ones related to inflammation, TNF, a variety of other cytokines, the cannabinoid receptor, and FKBP5 and CRHR1 in different kinds of analysis, and FKBP5 is one of the main downstream regulators of glucocorticoid response. So, human brain biology is also

seeing these differences in HPA regulation associated with inflammatory dysregulation that we're also seeing at the genetic level.

Just to show briefly a few slides of probably many hundreds, if not thousands, of papers that have shown associations over the decades between HPA and CRF and CRH in the amygdala, and the role of fear conditioning. This is work we did when I was at Emory with Charlie Nemeroff, showing that overexpression of CRF in the CRF neurons in the central amygdala led to increased startle response; again, one of the signatory symptoms we see in PTSD. And if we over-activate the CRF neurons by knocking out specific GABA receptors only in the CRF neuron population, we didn't see an increase in fear learning per se, but we saw a deficit in extinction. Again, coming back to this theme of inability to recover, or delays in recovery from fear, or extinction of fear, is one of the hallmarks.

00:29:23.990 --> 00:31:41.779

Kerry Ressler: We also saw over-activation of the CRF system, as well as hyperactivation and dysregulation of the HPA axis system, so genes that are now meeting genome-wide significance, such as CRHR1 receptor, are associated with both preclinical data of hyperactivation of this system and post-mortem human data seeing similar findings.

A new finding that's not yet published that we're particularly excited about looks at a different role for the amygdala CRH neurons than has previously been really looked at. And it's asking the question of: what other roles are there for the central amygdala CRH neurons? They certainly are associated with threat response and with fear; but Emily Newman had a fascinating observation that they appear to be particularly important in animals with a history of stress and their own aggression to conspecific animals.

And this raises a question that we don't talk so much about; but is that the cycle of violence, and that so many of those who are perpetrators of violence have been victims of violence themselves. And that those with PTSD do seem to have a higher rate of impulsive or aggressive behavior. And what we found in the Grady Trauma Project was that, and I think the important point here societally is, that this is a treatable condition.

And if we treat PTSD, it may help both that generation and the next generation.

But to show you the data a little bit. So, Emily was looking… what we're seeing here is a close-up in the background of the central amygdala, and specifically green are the cells in the central amygdala that express the CRH gene. And using a tool called chemogenetics with calcium imaging; we used a GRIN lens, basically an implantable microscope in the mouse's brain that can look at calcium activation of genetically modified animals in which the increased calcium

release causes increased fluorescence in those cells that express it. And the CRH cells specifically express GCaMP, the calcium indicator. And what she saw here is that at baseline, those CR8 cells aren't very active.

00:31:41.930 --> 00:33:44.529

Kerry Ressler: If they're being attacked and are having an immediate defensive response against the attack, they don't get an E. They aren't active, in the dashed line here. But in the solid purple line, if it's a prior stressed animal that is now actively initiating attack to an opponent, whether that be a submissive opponent or an aggressive opponent, the CRH neurons were active. So, CRH is not just the readout of stress; it may be partly correlated with the attack behavior.

Emily went on to do many experiments, which I would love to share with you, but I don't have time, so I'll just show you the money experiment, where she shows causally that inhibiting the CRH neurons completely ablates this stress-related aggression. So, in this case, she used a genetic virus… this is called chemogenetics, and it's using an inhibitory virus that's activated by this drug DCZ, deschloroclozapine.

If she's looking at animal approach behavior and inhibits these cells, she sees no effect. If she's looking at the initial contact behavior, she sees no effect. But if she, then, specifically inhibits these cells prior to attack, it completely blocks the active attacks. Let me just see if this plays.

So, this is an animal with saline. And you can see the attack behavior there. So again, the C57 animal comes up, smells the other one, and starts to attack in this animal with a previous history of stress. This animal is given DCZ to specifically inhibit the CRH neurons and nothing else. He approaches, he contacts, he sniffs, he explores, and he never turns into attack. And that's actually the same animal with saline versus with the DCZ. So, targeted inhibition of the CRH cells inhibits that switch to stress-related aggression.

00:33:44.710 --> 00:35:40.149

Kerry Ressler: And, so again, I just said this, that a subset of the CR8 cells are active during social investigation and aggression. Blocking them blocks that, and it also raises the question of our concept of suicide; is one that historically was associated with aggression turned inward. And in our post-mortem data, increased CRH in the central amygdala is one of the highest associated with suicide history, or death by suicide, suggesting that perhaps targeting the CRH system may be particularly important in suicidality.

And finally, for one more example, I want to talk about FOXP2. FOXP2 is a gene that was associated with language, but [we] never really understood how. And there's also associations with amygdala function in language, and I want to propose something briefly here. FOXP2 is also most highly expressed in the brain in these intercalated cells that surround the amygdala. It's sporadic throughout the cortex, but not very strong. But almost every cell in these intercalated neurons, which essentially surround the amygdala and help suppress amygdala activation, express this FOXP2 transcription factor.

What, Olga Ponomareva, whose work is, showed is that if we knock out the FOXP2 gene, it very strongly decreases fear acquisition and fear expression, and enhances extinction. And she also showed, in these animals that have knocked out this gene, they have a hyperactivation, physiologically, of the intercalated cell masses. So, it looks like FOXP2 normally is involved in decreasing this activity, and increasing it may protect from the fear and threat response. What's interesting is FOXP2 is also a target of lithium, and this may have a very specific dynamic regulation in the intercalated cells of the amygdala threat response, tying together our top genetic hit of PTSD with one of the core circuits involved in fear and threat behavior. So stay tuned for more.

00:35:40.510 --> 00:37:15.539

Kerry Ressler: I want to briefly go through, in my last 15 minutes, a couple other stories. Again, in the PTSD literature, Bessel van der Kolk brought out the concept of the body keeps score; that people remember the trauma as much in their body. But of course, your arm, or your leg, or your physical body isn't remembering it, it's your brain regions.

There's a long history of understanding the role of sensory cortical plasticity in development, but some examples that if you reactivate with strong emotional learning, that there's plasticity in cortical, in adults as well. And just a few pieces of data from our group. In this work at Emory, Orion Keifer did multiple days of fear conditioning to an auditory tone. And we did this to be able to say, could we replicate any of the findings in the human literature looking at gray matter density; in this case, a 9.4 Tesla high-field MRI? And we found gray matter changes in multiple brain regions throughout the amygdala, the insula, but interestingly, also in the auditory cortex in these tone-shocked fear-conditioned animals.

When we then looked at a marker of cell expression in those cells in the auditory cortex, we found a significant increase in the number of spines in the auditory cortex in animals that had been tone shock conditioned, but not those who were without. So again, this is adult animals, relatively rapid plasticity, increasing the representation of the tone, the previously conditioned stimulus, following tone shock conditioning.

00:37:15.750 --> 00:39:10.610

Kerry Ressler: In another example, the olfactory system. The olfactory system is quite plastic throughout life. Individual neurons in the nose are specific to different odorant receptors in expression, and those odorant receptors are specific to different odorants. If you look at the axons coming in from the nose to a very specific glomeruli in the olfactory bulb, and you train the animal to be afraid of that odor and not a different odor, you see this robust, and this is all adult animals, again, a robust increase in the number of neurons in the nose and the size of the glomerulus that represent that olfactory cue. Again, that happens within weeks following olfactory fear conditioning, in the same way that within weeks we can see increased spines in the auditory cortex with auditory fear conditioning.

And, what's interesting and hopeful in the olfactory space, is we actually see this recovers with extinction; so that the sensory systems seem to be dynamic based on the robustness of the threat or fear cue. And then finally, in humans, Nate Harnett at McLean and at Harvard has been studying the role of the ventral visual stream. And again, we found out about this because we were just looking at all the players in the limbic system, and the visual cortex kept popping up. And so, Nate explicitly did what's called a multimodal analysis, combining structural gray matter volume, peel surface area, and functional activation and connectivity. And across this multimodal approach, saw very robust effects of increased signal in the visual system in patients after trauma in Aurora who went on to develop… as a biomarker of those who went on to develop higher PTSD symptoms.

So, to restate, higher structural covariance of the visual system is associated with more PTSD susceptibility in the aftermath of trauma.

00:39:10.860 --> 00:41:00.869

Kerry Ressler: He went on to replicate this in another cohort; so this was initially our Emory cohort. He replicated an entirely separate cohort in the larger scale Aurora study. And interestingly, he found that this structural visual connectivity and covariance was most associated with nightmares' intensity, frequency, and severity. So humans, who are primarily visual animals, seem to represent at least some of these visual traumas in their visual cortex structurally, in addition to all the other areas we've talked about. And I think that's interesting, because it suggests that neural processing in the sensory systems upstream of the amygdala and the limbic systems also represents a critical component of sensory-specific threat coding, and may be an important area for us to further understand things like eye movement desensitization and things like sensory-focused transcranial magnetic stimulation.

And I want to wrap up, then, with coming back to recovery and extinction from fear. So, I started with this model of how extinction works in the therapy. This is really built on decades of work for how we understand extinction of a conditioned stimulus in animal models. And that extinction requires plasticity by itself. So, this was first shown by Michael Davis's group; Bill Falls, at Vermont now, who showed that learning to inhibit fear, extinguishing fear, requires active plasticity. It's a new learning event. So, what I'm showing here is rats in red, rats that have been trained to be afraid of a light, and every time they got a light, they got a shock, and then they measured that fear with startle. If those rats then receive 60 lights in the absence of any shock and then retested, they had very little. So that's your extinction curve, that's the recovery from fear, that's rat exposure therapy, if you will.

00:41:01.020 --> 00:42:57.649

Kerry Ressler: If you then give the same rats the same training and the same extinction, but you do it with AP5, which is a blocker of the NMDA receptor. And this is the NMDA receptor expression in the amygdala, and the amygdala and the hippocampus are the two places in the brain that have the highest NMDA receptor expression, and I'll come to in a minute, D-cycloserine as a modulator of NMDA. But if you block NMDA function at the time of extinction, and then you retest them off-drug, the animals are just as afraid as they ever were. So, extinction exposure therapy is an active plasticity-related learning event requiring NMDA receptors.

If you then block NMDA, if you do the opposite and ask, can we activate NMDA, in this case with D-cycloserine, which is a partial agonist, we can enhance extinction. So this is giving a partial exposure, 30 lights in the absence of shock with saline, and you get a partial extinction. If you do that at the same time with these D-cycloserine-enhancing exposed NMDA function, you get better extinction, and it's durable.

We then first showed that this worked in humans, with Barbara Rothbaum at Emory, that doing a virtual reality exposure to fear of heights, combined with D-cycloserine versus placebo in two sessions over two weeks, gave as much improvement in fear of heights as normally six to eight sessions of exposure therapy. So this was very exciting. It was easily available as a generic drug, because it was used for treating tuberculosis because of the serine moiety.

So, there was a whole period of about five years in the mid-2000s, that D-cycloserine was shown to enhance extinction and social anxiety across cohorts and continents in exposure and response prevention in OCD, as well as in people with severe PTSD, as well as in panic disorder. So, it was a very exciting time. It suggested that we could translate our understanding of NMDA-dependent plasticity from mice or rats to humans.

00:42:57.850 --> 00:44:50.559

Kerry Ressler: And then, it stopped working, or at least it didn't work as frequently. As the sample sizes got larger, as people were starting to source D-cycloserine from multiple places, and the timing of giving the drug was different, and the doses were different, it was failing to replicate. So, the question was, well, were these all just file drawer effects and false positives, which we knew everybody in the field trying this out, and we didn't think that was the case. There was something else going on. So, at about the same time, Barry Everitt, who's a leader in learning and memory field, explicitly tested this in rats, and he said, well, perhaps D-cycloserine is enhancing two different kinds of memory at the same time.

So they gave D-cycloserine to rats that had been trained to associate, say, its home with a fear. But in one of those sets of animals, they did a normal, full-on extinction paradigm, where they got a lot of exposures without any unconditioned stimulus. The others only got a very short few to reactivate reconsolidation. And what they found is that D-cycloserine enhanced both memories depending on which was the prevalent. In extinction, the animals showed less fear over time than the normal extinction group. You enhance the extinction memory. In reconsolidation, they showed more fear over time beyond those who got saline, showing further enhancement of reconsolidation.

That suggests that anytime you reactivate an emotional memory, it has the possibility of being strengthened or being weakened, in part through a new extinction memory. But our field hasn't focused on that. As the D-cycloserine field started focusing more on that timing and dosing, et cetera, more positive studies have come through. And working with people like Jonathan Downar and Alex McGirr in Canada, they've shown that D-cycloserine can enhance the efficacy of TMS in depression, and we're doing studies now in PTSD. So, if you take some other plasticity-dependent somatic therapy, can you enhance it?

00:44:51.790 --> 00:47:16.450

Kerry Ressler: The idea that timing, dosing, and exposure may be critical is really important. I showed the exciting MDMA results earlier. Ketamine, as you're familiar with, activates NMDA-dependent plasticity through primarily initially blocking a subset of GABAergic cells that lead to a hyperglutamate-dependent plasticity of the pyramidal cells, and that has been shown, primarily by Adriana Fedr and others to enhance exposure therapy. But whether it be the psychedelics, whether it be ketamine, whether it be MDMA, this is probably a truism; that we have to make sure we're enhancing the right memory when we bring these things, or the risk could be high.

So, I want to end on this point. That neuroscience is bringing us the ability to target specifically the extinction neurons, or the fear-off neurons. Because the problem with the prior stories is that plasticity, NMDA plasticity, can target both the original fear memory and lead to enhanced reconsolidation, or it can target the extinction-inhibiting fear memory and target extinction. But we can't necessarily control which of those is happening.

But it is now understood that there's different kinds of cells within the basolateral amygdala, and some we can think of as fear-on cells that learn to associate fear and mimic the extinction in terms of, they don't fire when the animals extinguish, but others that specifically are holding the fear or safety or inhibitory memory.

If we could target just those extinction or fear-off neurons with plasticity, then we could potentially have a valence-specific plasticity enhancer, and not worry about which memory are we enhancing.

And we now know that there's hundreds of specific cell types throughout the brain and dozens within the amygdala. And, a number of findings have suggested there are specific cell populations that have specific molecular markers that allow us to target the extinction neurons. And this is one piece of data in rodents suggesting that one subset of neurons in the amygdala, marked by the PHI-1 developmental marker may specifically be a fear-off population. It only marks a subset of the CaM kinase pyramidal neurons, but when you activate it, you block the flow through in the amygdala. Interestingly, these cells don't project to the central amygdala like the canonical pathways, they just project primarily to the accumbens and the infralimbic cortex.

00:47:16.750 --> 00:47:22.720

Kerry Ressler: If you activate these fear-off cells, you robustly block fear consolidation. And whether you're doing it with optogenetics or chemogenetics, and you robustly enhance extinction of fear, shown in orange here. If you then identify other receptors that are preferentially on these fear-off neurons, one can identify new targets, in this case, neurotensin 2, which has been associated with emotional learning. We showed that neurotensin 2 preferentially expressed in these fear-off neurons. When we take agonists to neurotensin 2 to activate them, we get a robust blockade of fear and enhancement of extinction by activating the neurotensin w subpopulation. And this has recently been replicated, in terms of the importance of neurotensin as mediating positive versus negative valence in the amygdala, by Kay Tye's group.

So, it gives us the promise that if we understand enough about the circuits and the molecular biology of those circuits, we can really start to dissect targeting memories in a valence-specific positive versus negative way for recovery.

So, I'll wrap up by saying, PTSD is important, it is common, but we can understand a lot about it. And I went through some of the neuroscience of fear and threat at the amygdala and hippocampal and cortical level, how the genetics is intersecting with that, and how the sensory systems leading into the amygdala are also critical. And we have to keep that in mind. And that by understanding the plasticity of recovery from fear, that may give us new targets and ability to integrate therapy with medication.

Quick summary, our current medications, pharmacology for PTSD are basically our SSRIs that we use, other medications off-label, often the way we do for general anxiety disorders and PTSD for symptoms. Our best treatments for targeting the underlying memory is exposure therapy, but it doesn't always work that well, and it doesn't often get people to remission. If we can better combine our treatments, we will do better. Take home message number two, our current therapies, talk therapies, really give top-down regulation of amygdala function. Our current medications essentially just decrease symptom intensity. Our future medications may really build on our understanding of the circuit.

And so, I'll end with: PTSD is a tractable set of disorders in which we need to start understanding specific subtypes to give us targeted precision medicine approaches. But that by understanding the circuits and the genetics, I think there's great hope for a precision medicine approach, to both prevent PTSD in the long run, and to treat those who have this disability, disorder. So with that, I will end. I'll thank many funders, particularly the NIH, and I tried to thank everyone as I went through for who did the work. Thank you very much for your attention and for having me here today. I look forward to the discussion.

02:00:13.740 --> 02:00:28.199

James Naifeh: Thank you, Dr. Ressler. An incredible body of research and an excellent presentation. We now have a break until 11.15 a.m. Eastern Daylight Time, which is about 19 minutes from now.

At that time, we will begin our live Question & Answer session with Drs. Manji and Ressler. We hope that everyone will go check out the poster gallery on the conference website, which is filled with submissions from your fellow conference attendees. As a reminder, you may submit questions at any time before or during the Q&A session by using the Q&A feature in the Zoom window. When you do so, please indicate if the question is for a specific speaker or for both speakers. Thank you, we'll see you after the break.

CONFERENCE BREAK

MORNING QUESTION & ANSWER SESSION

Husseini Manji, MD & Kerry Ressler, MD, PhD

Moderator: Lt. Cmdr. Robin Bonomi, MD, PhD

02:19:28.349 --> 02:19:45.359

James Naifeh: Welcome back. For our first Question & Answer panel, we are joined now by Dr. Husseini Manji and Dr. Kerry Ressler. Our moderator for this panel is Lt. Cmdr. Robin Bonomi, who will help us address as many questions as possible during the allotted time.

Lt. Cmdr. Bonomi is a Board Certified Psychiatrist in the United States Navy, and also holds a PhD in biomedical engineering. She is currently a program manager in the Defense Advanced Research Projects Agency, otherwise known as DARPA. She also holds active faculty appointments at Yale University and Uniformed Services University. Dr. Bonomi's research interests include neuroimmune modulation, precision psychiatry, and molecular imaging technologies for brain-based behavioral risk health prediction and prevention. Welcome, Drs. Manji, Ressler, and Bonomi. Dr. Bonomi, you may proceed when you're ready.

02:20:25.840 --> 02:20:31.689

Robin Bonomi: Thank you, Dr. Naifeh. I appreciate the introduction, and I'm really excited to be here and moderate such a terrific discussion between two excellent speakers and so many years of excellent work. So, we'll go ahead and just start off. I'm going to be addressing the questions toward an individual, and in some cases, the questions may be addressed to both Dr. Ressler and Dr. Manji. So, we'll start with Dr. Manji. What is your hope in bringing together other nations in the search for neuropharmacologic treatments?

02:20:57.320 --> 02:22:50.650

Husseini Manji: Great. Thank you, first to the organizers for inviting me to this session, and Dr. Bonomi for sharing it. I do think that we've learned that some of these big problems we can tackle much more collectively. And I think HIV/AIDS previously has been an example where people came together to make a real difference. More recently, [with] dementia, people have

really come together. So, I really do think that mental health is ready for that. Where if we can bring together the power of multiple nations, multiple institutions, together to work on these common problems, we can do things at scale, we can have resources. And I think one of the things that's very important to all of us; we want to try and make sure that our findings are applicable worldwide. We want to help humanity.

So, in some ways, some of the things I'm doing in the UK and France; if we find signals there, we can validate them in the U.S. and see, does it hold up? Does it hold up in different socioeconomic backgrounds, racial, ethnic minorities, if you have comorbid, different medical illnesses, etc.

And just to come back to the dementia… About 12 years ago, former UK Prime Minister David Cameron hosted a G8 summit… so this is the Group of Eight nations summit on dementia. And I'll be honest, a lot of government meetings I've attended are just talk, and nothing happens. This one really had an impact. So, the NIH budget quadrupled, UK, France, etc. And one of the most important things that was formed was something called the Dementia Discovery Fund, and Bill Gates joined it, and the first round was $350 million, second round, $300 million. So, it's a recognition that we can do so much more if we work collectively; and so that's my aspiration, and I'm very confident it's going to happen. Thank you.

02:22:51.150 --> 02:22:51.950

Robin Bonomi: Thank you. For Dr. Ressler, could you elaborate a bit more on the stress and trauma and aggression and family violence risk post-deployment that you alluded to previously?

02:23:05.250 --> 02:24:34.220

Kerry Ressler: Yes, thanks. First of all, thank you, Dr. Bonomi, and I may slip and call you Robin. It's great to see you. Thanks for hosting us today. It's great to see you as well, Dr. Manji, Husseini, and thank you for all you're doing internationally on these parts.

So, I think, whether it's civilian trauma or whether it's military trauma, certainly not in everyone, but we certainly see a subset of people who have a more impulsive-aggressive phenotype when they have PTSD or posttraumatic symptoms. And I think one way of thinking about that is… you can think of posttraumatic stress as the fear system never turning off. And certainly, when one is in battle, or one is in a high-threat situation, one of course should be on [guard], ready; and you

know, that old adage, sometimes, just because you're paranoid doesn't mean that someone's not out to get you.

But I think, where we often see the problem is when people return home in a context that should be safe; and yet they're still on guard, they're still responding in a threat-defensive way. And so, that's one of the areas we've not paid as much attention to. And I think, in both our cycles of risk, people who are most often the aggressors in situations that cause someone else trauma are often people who themselves have been traumatized.

So, I do hope as we look to treat PTSD, we can also look at better ways of treating some of those phenotypes as well. Hope that helps. Thank you.

02:24:35.280 --> 02:24:35.670

Robin Bonomi: Thank you.

02:24:35.670 --> 02:25:29.780

Husseini Manji: If I could just add to Kerry's very eloquent comments, and he's obviously the expert; but I think one of the things he mentioned… I think it's very important, in our society, we do see a lot of interpersonal violence, violence against women, etc. But as Terry mentioned, we often find out that the perpetrators have sometimes been victims themselves. So obviously, it's not to forgive the perpetrators, they've got to be held responsible for the action. But if we're going to break this cycle of violence, and start to prevent things, then let's try and make sure. And again, as we know, unfortunately, in our society, men often don't really acknowledge mental health symptoms, often turns to drugs and alcohol and violence, etc. So, if we can sort of certainly help people who've been victimized, but also try and do a preventative approach by helping the perpetrators. Hopefully, we can start to diminish this.

02:25:30.100 --> 02:25:51.569

Kerry Ressler: Yeah, and just to add one more on that. I think whether it be in jail systems, or probationary systems, or in the military, when someone has committed an act, it's important that they be treated appropriately for justice. But that we're paying attention to treating the

trauma, treating the addiction, and the other components, because we can help prevent ongoing recidivism.

02:25:53.970 --> 02:26:37.590

Robin Bonomi: Thank you both. I think, to kind of build off of that for both of you… There's a question regarding how can we best investigate the neurobiology of PTSD and/or depression, and how do we think about the gap between the phenotypes and the neuroscience, and whether it's clustering the phenotypes in terms of symptoms, or coming at it from a neuroscience level of explanation for certain symptoms and certain circuitry patterns. Could you both comment on your thoughts about whether neuroscience ultimately benefits the understanding, and we should derive that for clustering diagnosis, or whether we should derive more from the symptom cluster side?

02:26:38.410 --> 02:29:34.580

Husseini Manji: Kerry, shall I start? And I know this will sound like a wishy-washy answer, but the answer's both, and I'll explain. So, I think we recognize that our DSM diagnoses, they're basically a checklist. You know, if you look at things like major depressive disorder: depressed mood, anhedonia, sleep too much, sleep too little, eat too much, eat too little, etc. And so, we've recognized that this isn't really biology-based, it's sort of symptom-cluster-based.

But having said that, I think as a field we've done a very good job, a long way to go, of mapping certain illness domains and symptom clusters onto certain neuronal circuits. And those are much more biologically based. So, we can now start to think about… and one good example might be anhedonia, which has been implicated with sort of a reward circuitry. And now we know certain of the molecules that regulate reward pathways, anhedonia symptoms, etc. So, in principle, we can start to identify people who have, for example, prominent anhedonia symptoms, but then use the neurobiology to say, okay, so what? How do we really target the anhedonia circuitry and treat them with the specific modality?

I think one of the important things… and I think we're also at an exciting time with the regulators also sort of are getting this… And I'll be honest with you; I used to be at the NIH for many, many, many years, part of federal government. And so, I interacted a lot with the FDA, who are also our brethren in the regulatory space. And when I first moved to Johnson &

Johnson, I was actually surprised at how much pharmaceutical companies do, because that's what the regulators want, even if they think it's wrong. You know, if the regulators aren't going to approve this, you sort of have to do it. But as I was mentioning, I think there's been a lot of progress, and what we've been able to do recently is work with the regulators to say, look, these, sort of, panoply of symptoms. We're not going to get a single magic bullet that treats everything. If you're willing to consider, with data, about, potentially, an indication, say, for anhedonia, and there's a good treatment that treats anhedonia, then we can treat anhedonia, whether it's a major depression, bipolar disorder, schizophrenia, and so on, and they're receptive to that. Now, of course, they need to see the data.

So, coming back to your question, I think it's going to be bidirectional. I think, again, based on your interest, perhaps we'll come to a question about… in psychiatry, there's a lot of progress being made in trying to identify subtypes of people. Some of them, we may be able to identify by blood-based biomarkers, digital, etc. But some, we might start with the symptom domain and the biology. So, let me turn it over to Kerry.

02:29:34.790 --> 02:31:18.979

Kerry Ressler: I would agree with all of that; and just to put a finer point on a couple of them… I think, of course, the issue is that… not to DSM bash, because it's the best we've got, but, while it's very thick, you could argue there's still only a handful of clusters of diagnoses. There's mood and affective, psychosis, bipolar, etc. And yet we know that there's literally… half the genes in the genome are specific to the brain. And so, there's likely literally thousands of discrete ways the brain can be disrupted to cause these overall homogeneous symptoms that we see.

But how do we get there? And so, certainly, one of those is really using much better tools. I think another metaphor is the cough or the fever; that the brain can only break so many ways that we can kind of be aware of it, and those are the symptoms that we capture and have captured for the last hundred years and cluster together. But if we can use better biotyping, whether it be digital tools, wearable, audio-visual, and then also things like EHR and AI approaches, as well as certainly the full range of biomarkers, the real hope is that that will give us much better biological clustering of these disorders. I think the other way to go, as Husseini alluded to, is sort of known neural circuits; whether it be the anhedonia circuits, the threat circuits, the cognitive circuits, and really say, okay, if we start at this baseline biological truth, what symptoms and what disorders share these disruptions.

And then, finally, I think we haven't quite figured out how to use genetics. We still use genetics in a way that we're predicting the same heterogeneous outcome, and so we're going to get a

heterogeneous predictor. But there's likely ways we can cluster the genetics to really see which genes more likely cluster to specific disorders. So I think there's still room to grow there. Thank you.

02:31:20.860 --> 02:31:41.189

Robin Bonomi: I think that leads actually really nicely into another question that came up, which was: Where do you see the role for whole genetic sequencing and examining rare variants aiding in pharmacologic development, and particularly in understanding depression and bipolar? And I think that would dovetail nicely into that. Thank you.

02:31:42.350 --> 02:35:42.079

Husseini Manji: Terry, shall I start once again? So, I think [it's] a great question, and I think we need to be optimistic, but not oversell things. So, what I mean by that is we are dealing with amongst the most complex disorders known to man. You start with the inheritance of multiple susceptibility genes, probably some protective resilience genes. They interact in some ways with the environment, bring about changes in cells, circuits, behaviors, etc. So, I don't think we're ever going to be at the point where, for example, in oncology, you can do a biopsy and look at the driver mutation, and then target that. Or, closer to neuroscience, Huntington's gene… *the* gene will cause the disease.

So, I think we need to be a little bit more sophisticated in recognizing that our systems are very dynamic. The good news is that they're dynamic, so we can change them. The bad news is that the static measure of sequence variance is a good starting point, but it doesn't tell you the whole picture.

But I think two things. So, as Kerry alluded to, there's more and more work going on [with] this thing called polygenic risk scores. So I think we know that it's not going to be one smoking gun; but if you can combine the number of these genes together, and then look at this thing called the polygenic risk score… I've seen some data recently that compared, for example, schizophrenia to major cardiovascular disease, and the impact of polygenic risk score schizophrenia is much higher than cardiovascular disease. So, we can start to use that. You might start with someone who's got a family loading, and they look at the polygenic risk score, etc.

Because I think, as we know, in almost all fields of medicine, early intervention is likely to have a better outcome. And I think it's particularly true for our major diseases and disorders which, by and large, start in late adolescence and early 20s. And as I'm sure most people are aware, parts of the brain that, for example, regulate executive function are still maturing until about age 25.

So, to me, it's not surprising if you've got this florid illness, bipolar or psychosis, that's occurring during times of brain maturation, you're probably going to have a bad outcome.

So, if we can use some of these genetics and polygenic risk scores, et cetera, to identify potentially at-risk people, it may be that intervening at that point-- and intervening could be psychological intervention, could be [a] much kinder, gentler treatment than a sledgehammer like an antipsychotic at that stage-- we can improve outcome.

The last thing to say is that I think what we found in many diseases and disorders, that even studying what was sometimes called rare variants can be very useful. So, for example, in Alzheimer's; people first started to study the amyloid pathway in people who had this autosomal form of Alzheimer's. But these were families, fortunately very rare, that if you had this gene, you were going to get Alzheimer's dementia and get it early. And then they found that all these genes were related to the amyloid pattern. Then they asked the question: Okay, could the amyloid pathway also be involved in Alzheimer's disease in general, even if you don't have that specific mutation? And the answer turns out to be a resounding yes.

So, just to mention the last thing, related to the question [that] was asked, related to medication development as well. If we can study some of these rare variants, we can understand what pathways they regulate. And it's very likely that those pathways are going to be useful in depression, bipolar, schizophrenia, even if the patients don't have those specific genes. Because the genes are pointing out where things are converging, where we can treat. Let me once again turn it over to my esteemed colleague, Kerry.

02:35:42.380 --> 02:36:52.919

Kerry Ressler: Those were all great examples. Two more things just to add to that… Specifically in this space would be the schema variants in schizophrenia and bipolar, which are a handful of rare variants, but which have causal mutations and look like they carry risk on the order of 20- or 30-fold, as opposed to the common variants, which are often only less than 1%. So, I think there already are, at the Broad and other places, starting to look at targets, targeting some of those pathways. And again, as Husseini said, it may initially start… we could imagine things like

psychosis starting to pull off certain syndromes, 22q11 and some of the large ones, but now maybe some of the smaller ones with these rare variants.

And then having drugs that really are almost like orphan therapies, or rare therapies, but that some of those might have much more relevance as well for the more common. And for example, in our own data that I mentioned, FOXP2. So FOXP2 is both up and downstream of Wnt/beta-catenin, which are all regulated by lithium. Husseini talked a lot about lithium; but again, I think they're pointing us more to the biology of some of the genetic pathways that we can further target for some of the plasticity and emotion regulatory circuits.

02:36:55.150 --> 02:37:35.630

Robin Bonomi: Thank you both. I think, again, continuing in that thread… Where do you see the work going, especially with regard to ketamine? And I think more broader aspects, too, in regard to depression and PTSD, with respect to identifying sex differences in response to treatment and in neuroscience, the genetic or other pathway differences between males and females. I think we're seeing that quite a bit in the substance use studies currently, but it hasn't as much matriculated into the depression and PTSD literature as extensively as the substances currently.

02:37:36.820 --> 02:39:59.519

Husseini Manji: Again, Kerry, if it's okay, I'll start. So, you know, ketamine is something that I had done a lot of basic science work [in] to suggest that some of these plasticity molecules, NMDA and AMPA receptors, could be very relevant to regulating the so-called pathogenesis of depression and the treatment. And when I was at the NIH, there had been a recent publication from Yale that suggested that low-dose IV ketamine had a [antidepressant- unclear] effect. So, at the NIH, we decided to do a more robust study, and we looked at what's sometimes called treatment-resistant depression. The definition of that is if you fail two adequate trials of antidepressants. But as you know, the people who get referred to the NIH are often people for whom nothing else has worked; but these were people who'd failed, on average, six different antidepressants, some had failed electroconvulsive therapy. They've been continuously depressed for three years by the time they came to the study. And giving them either low-dose IV ketamine or placebo, we saw a 70% response within one day with the low-dose IV ketamine,

compared to what you sometimes see in larger studies; for example, the STAR*D, where you see something like a 20% response at eight weeks.

So, this was not slightly better, this was transformationally better. And it was, you needed IV ketamine, an anesthesiologist, etc. So, a little bit after that, I left J&J, and my plan wasn't to develop the ketamine molecule. I thought, okay, let's look at son of ketamine, NR2B, AMPA receptors, etc. And I thought, why not ketamine itself? And I realized that IV and anesthesiologists could be complicated, etc.

So, I thought about an intranasal way of delivering things fast to the brain, and much less invasive. If you've ever taken a nasal decongestant, you know, you deliver a very, very small amount of drug, so you couldn't actually deliver enough ketamine. Then we learned that the S version of ketamine was four times more potent at the NMDA receptor. So we could use S-ketamine, then a whole bunch of studies, eventually. It was the first drug in neuroscience to get FDA Breakthrough designation, and it was basically the first novel mechanism in 60 years. And then we got a second indication for people at imminent risk of suicide.

02:39:59.520 --> 02:42:48.370

Husseini Manji: And I think it's fair to say, because a lot of companies, other companies have talked to me, saying this actually has brought companies back into the field, where they're now recognizing that this could be a tractable condition. Indirectly, it's resulted in the psychedelics sort of boom, if you will. There are now something like 6,000 clinics in the U.S. that are ready to administer Sprovato, esketamine, so when the psychedelics come on board, many of them could be used as well. I think the distinction I'll make is that I've done a lot of work to show that the transient dissociative symptoms you see with esketamine have nothing to do with clinical benefit. You just happen to get them, but the benefit is related to this direct molecular pathway.

We'll see where it lands with psychedelics, and it may depend on different indication. So, I think posttraumatic stress disorder and psychedelic-informed psychotherapy; I think the psychotherapy is going to be part and parcel of it. In depression, I think we don't know yet; sort of whether the mystical hallucinatory experiences are necessary for therapeutic effects, or are they incidental? And if you could remove them and maintain the therapeutic effect, could you have a take-at-home medication, etc. But, you know, people are working on a…

Coming back to one of the most important points you raised, the sex differences. So, I think, we really have to get away from the one-size-fits-all. We recognize men and women are different in biology, physiology… Unfortunately, in our society, women are so much more likely to have been subject to different kinds of stresses, abuse, etc. As Kerry mentioned in his talk, he's thinking

about epigenetic changes, etc. And, you know, there are gonadal steroid changes, estrogen, progesterone, etc.

So, I think it really behooves us, and I'm glad the NIH is sort of now forcing people… You know, it's always easier just to take males of certain age, and often certain demographics, and just study them to reduce heterogeneity, but that doesn't help. You've got to be able to study sex differences, etc., and use that to inform treatment. So, I think we're seeing more and more of that. But unfortunately, I think, you need to push people to do that, because even in rodents; you know, even when I started, and probably when Kerry started… male Sprague Dawley rats… That's what you studied, right? You didn't have to, quote-unquote, worry about the estrous cycle or anything like that. But we were forced to say, no, thou shalt study female rats as well. Thou shalt take into account the estrous cycle, etc. And I think it benefits people, so I think it's very important that we force people to do that.

02:42:50.430 --> 02:42:53.825

Kerry Ressler: Given the time, I don't think I have much to add. That was great, Husseini.

02:42:55.620 --> 02:43:10.539

Robin Bonomi: Thank you. And, in thinking about both talks, could you speak to the role of the antagonism of NMDA receptors with ketamine, and also the effect on PTSD treatments in terms of fear extinction? I think you touched on this quite a bit, Dr. Ressler, in your talk, as well, and just expand upon that a little bit.

02:43:19.640 --> 02:44:43.000

Kerry Ressler: It's a great question, and an astute listener to catch the tweak on the agonism versus the antagonism. And I think it's kind of where a lot of the basic science field is right now. How do things like D-cycloserine or direct partial NMDA agonists compare to ketamine, which we've said is an antagonist, compared to what the psychedelics are doing; if we're saying, at the end of the day, they're all doing plasticity? For the ketamine versus D-cycloserine… So, the critical thing with ketamine is it looks like it doesn't antagonize all of the NMDA receptors the

same way. And, specifically, some of the work from both Yale and Lisa Monteggia and others have suggested that some of the GABAergic neurons, that their glutamatergic receptors are getting blocked more than the pyramidal excitatory neurons in the cortex. And so, it's basically disinhibiting the pyramidal neuron, leading to plasticity in the pyramidal neurons; whereas the D-cycloserine is a direct partial agonist on the NMDA receptors.

And I think there's still a lot to unpack with the psychedelics. How much is the 5-HT2 regulation of plasticity interacting with some of the glutamatergic regulation of plasticity? But it seems that it's all moving with sort of this final common pathway of plasticity, but it may not be the same in all the circuits, it may not be the same at the right timing. So again, kind of back to the point of, it's the timing that matters, along with the location and some of the agonism. All plasticity is not the same.

02:44:43.250 --> 02:46:14.960

Husseini Manji: Yeah, if I could just amplify it- Terry's hit it spot on. So, the data looks very good that, with ketamine or S-ketamine, you sort of block NMDA receptors on these GABAergic interneurons. So, you disinhibit pyramidal neurons, you cause a burst of glutamate release, and then you stimulate AMPA receptors, turn on BDNF, etc. So, as Kerry pointed out, even with NMDA receptors, some of them work, some of them don't work without these nuances.

One of the areas I'm optimistic about… There are these subtypes of NMDA receptors, and there's one subtype called NR2B subtype, that in some of our work and others' work, or at least in animal models, they look like they might be responsible for the antidepressant effect and might have less dissociation. So, I think what we're going to see as a next wave is more subtype-selective, that will hopefully retain efficacy, but maybe have reduced or eliminated some of the side effects. And, you know, there's a long way to go, but I think that's where we're going, to really understand. You may be aware that there's two companies that also have AMPA potentiators, and that's kind of indirectly related to this ketamine story.

And if you're causing a burst of glutamate release and stimulating AMPA receptors, what if you just targeted AMPA receptor directly? And one of the companies, Neurocrine, had some positive Phase 2 data, and they're going into Phase 2. What the other company called [GRIK-unclear]… it's a newer company, they don't have data yet, but I think it's opening up a lot of novel targets.

02:46:17.180 --> 02:46:41.280

Robin Bonomi: Thank you. Could you continue on that, Dr. Manji, a little bit further; and thinking about where the biggest bottlenecks are in translating some of these advances in synaptic plasticity into scalable treatments, and how programs like the UKRI Mental Health Platform can help to navigate or facilitate that transition? And where do we think the biggest holes are in that transition space?

02:46:41.610 --> 02:48:37.080

Husseini Manji: Sure. So, I think that's a very important question; and I think, most of the time, pharmaceutical companies aren't going to actually develop the medicines that make it to people. And academics do fantastic basic science, some translational work, etc. In industry, there's something called the valley of death, because that's where most things fail. So, you may know that, but something like 90-95% of all things that get tried actually fail. So, one of the things we're doing in the UK is we set up this network of about 20 clinical research sites. And, [I've] spoken to Terry, and I've previously spoken to Francis Collins when he was the NIH Director, to form transatlantic tide [unclear], where we have these networks of clinical research sites where we can do what we call de-risking the study. So, if you think an AMPA drug is going to help, first, you start to weight, does it change the biology?

So, with things like magnetoencephalography and other things, you know what an AMPA drug should do. So, you give it to the person; you see, does the circuit change? And if the circuit changes, then you see, okay, do symptoms change? And by doing some of that work, you're sort of de-risking it. As I said, you know, a lot of things will fail. But the things that work, once industry is convinced, they're willing to put hundreds of millions of dollars. But we've got so many exciting targets, and they don't know which ones will work or not work, etc. It's the same thing with… one of the things about your intro to neuroimmune, I think that's going to be a tremendously exciting field.

But it's not going to be every person who walks in off the street. So, you'll have to identify those people who have this immune signature, and then treat them and see, are you changing microglial function in the brain, etc., and then the outcome. So, I think if you can be thoughtful and do it in a stepwise way, we can help patients a lot.

02:48:38.230 --> 02:48:41.810

James Naifeh: Pardon me for interrupting. I think we have time for one more question.

02:48:43.120 --> 02:49:30.080

Robin Bonomi: I was actually going to change gears a little bit, and wrap it up with the last question here. I know there's a number of questions. We have received many more questions than we unfortunately have time to go through today. So, if there [are] specific large areas, topic interests, that individuals in the audience have that they would like to see addressed, you can include that in your post-event conference survey.

But to kind of wrap it up… I think that there's a large portion of the audience who are students and postdocs, and we'd be curious to hear from both of you, your thoughts on mentorship and what's been most impactful for you in relationships with mentors, and what advice you'd give to those students who are in the audience today.

02:49:30.460 --> 02:49:32.420

Husseini Manji: Kerry, please start, and I'll follow.

02:49:32.940 --> 02:50:24.810

Kerry Ressler: Well, mentorship is critical. I think we all have lots of mentors in different ways. My graduate mentor, Linda Buckley, taught me that you can spend as much effort asking an uninteresting question as you can asking an interesting one, so make sure you're focusing on interesting things. I think, we don't have much time, because we could obviously talk hours on this, but I think the critical point is, as a mentor, to help meet people where they are, to find what gives them the most passion, and then help remove barriers and help them to stay focused. I think for so many people in our field, it's the most complicated problem in the universe in some ways. It's hard to stay focused; and so you both have to be able to look at the big picture and important questions, but then try to answer in a focused way, and I wish

everyone the best. Please don't hesitate, anyone, to send me an email if you have questions as well. Thank you.

02:50:25.130 --> 02:51:36.890

Husseini Manji: And I'll extend the same offer to you, and I think Kerry hit the nail on the head. We are in such an exciting time, we're dealing with the most exciting thing there is; but the challenge is you've got to stay focused. Obviously, Kerry and I have been in this field for many, many, many years, so we're doing a lot, but you don't get from 0 to 100 right away. You've got to really focus on something, really master it. And one of the things in my career, and probably true in Kerry's career, it wasn't completely planned out. I tried to do the best I could, whatever I was doing. I thought I was going to the NIH for two years, and then going back to Vancouver, British Columbia. Ended up staying 15. I never thought I was going to move to J&J until they convinced me. I never thought I'd be doing things with the UK government.

So just focus on what you're doing, try and be the best you can at it, and opportunities will arise that you may not have predicted. And if you're well equipped, you know, serendipity favors informed mind, prepared mind, whatever, all those sorts of things. I think this is an amazingly exciting time, and I think there's nothing more rewarding than to be able to work in a field where you can make a difference for humanity, so sincere best wishes and good luck to you all.

02:51:37.760 --> 02:51:38.499

Kerry Ressler: Thank you again.

02:51:38.820 --> 02:51:45.230

Robin Bonomi: Thank you so much. That was a terrific way to end the session, I think, so I really appreciate your comments there. Thank you.

02:51:45.580 --> 02:52:22.320

James Naifeh: Yes, thanks so much. That is, unfortunately, all the time we have for this fantastic Q&A. Thank you so much to Drs. Manji and Ressler for being here today to answer questions. It was so great to learn from you both. And thank you to Lt. Cmdr. Bonomi for doing a great job as a moderator. We will break now for lunch, reconvening at 12.45 p.m. Eastern Daylight Time, which is a little under an hour from now.

We hope everyone will use this as an opportunity to review the poster gallery on the Conference website, which includes a range of submissions from fellow attendees. See you all after the lunch break. Thank you very much.

02:52:23.320 --> 02:52:24.930

Husseini Manji: Take care, everybody. Bye-bye.

02:52:25.960 --> 02:52:26.809

Kerry Ressler: Thank you again.

CONFERENCE BREAK

02:55:14.880 --> 02:55:30.880

James Naifeh: Welcome back. Before we get started with our afternoon speakers, I'm going to turn it over to our Scientific Coordinator, Dr. Joscelyn Fisher, to tell us about this year's poster submissions. Dr. Fisher?

02:55:32.670 --> 02:57:21.950

Joscelyn Fisher: Thanks, Jamie, and hello, everyone. We first want to thank everyone who submitted a poster this year. We had a record number of submissions, and 63 were accepted. This year, we have four poster award winners, two in Pre-Clinical/Translational research, and two in Clinical Research. The Pre-Clinical/Translational Research Poster Contest winners are Alessandra Grillo from the Center for Deployment Psychology at Uniformed Services University, Henry M. Jackson Foundation, and Department of Psychology, UNC Greensboro. The title is "Examining Additive Genetic Variation in the Relationship Between Early Life Stress Exposure and Trait-Level Latent Depressive Symptoms." The second winner is S.B. Raut from University of Tasmania, with a poster title of "Developing Translatable Treatments for PTSD: Invertebrate and Invertebrate Preclinical Models."

The Clinical Research poster contest winners are Tate Poplin from the Department of Psychiatry and Behavioral Neurosciences at Wayne State University. The title of that poster is "Childhood Interpersonal Violence Moderates the Association Between Emergency Department Skin Conductance Response and PTSD Symptom Trajectories." And our fourth winner is Artemisa Zuazo from the Department of Psychiatry, Uniformed Services University of the Health Sciences, and the Behavioral Health National Capital Consortium Child and Adolescent Psychiatry Fellowship, with a poster titled, "Patterns of Family Violence and Co-Occurring Harmful Behaviors in Military Families."

Congratulations to these authors and their co-authors. Please visit the poster gallery on the Conference website to view these posters and all the other excellent submissions that we got. Thanks.

02:57:23.450 --> 02:57:46.799

James Naifeh: Thank you, Dr. Fisher. Yes, congratulations to our poster winners. It's very exciting to have so many attendees share their work with the Brain, Behavior, & Mind community. As a reminder, you can submit questions for our last three speakers at any time using the Q&A feature at the bottom of the Zoom window. Please specify if your question is directed at a specific speaker, or at multiple speakers.

BRIDGET CALLAGHAN, PHD

PRESENTATION

02:57:48.080 --> 02:58:41.440

James Naifeh: To begin the second half of the day, we are fortunate to have a presentation by Dr. Bridget Callaghan. Dr. Callaghan is an Associate Professor of Psychology and the Bernice Wenzel and Wendell Jeffery Term Endowed Chair in Developmental Psychology at the University of California, Los Angeles. Dr. Callaghan's research interests focus on how early experiences influence the development of mental and physical health across the lifespan, and across generations. Her program of research seeks to uncover the mechanisms linking early life experiences to these outcomes, with the ultimate goal of informing better interventions across development. In her Brain and Body Lab at UCLA, Dr. Callaghan and her team answered their questions by examining behavior, neural systems, the microbiome, and physiological measures, such as gastric function, heart rate, and skin conductance.

We'll now begin Dr. Callaghan's presentation, which is titled, “Generational Impacts of Adversity on Mind and Body Health.”

Total Conference Timestamp: 02:58:56.660 --> 03:49:28.609

Within-Segment Timestamps below

00:00:55.380 --> 00:01:09.700

Bridget Callaghan: So, thank you so much for inviting me here today. I'm really excited to present to you all. The title of my talk today is “Intergenerational Impacts of Adversity on Mind and Body Health,” and we'll be looking at pathways that intersect or operate through the brain-gut axis.

So, I think all good talks start with acknowledgements of people who've actually done the work; so I wanted to acknowledge my wonderful students, past and present. So, Fran Querdasi, Naomi Gancz, Dr. Jessica Uy, Paul Savoca, and Genesis Flores. These are the students who've done the bulk of the work that I'll be presenting today, but they represent just a fraction of the work that goes on in the lab as a whole.

So, in the lab, in my Brain and Body Lab at UCLA, we really focus on the most important of our early life experiences, and that involves this critical relationship between a parent and a child. So, we know that when this relationship is secure and strong, it really helps children to navigate almost any challenge that they could face in life. However, we also know that when it is disrupted or ruptured, for example, through abuse, neglect, separation, or chronic stress, it can shape risk across nearly every domain of development. So, we refer to these types of adversities as caregiving-related early life adversities.

Now, caregiving adversities in both the prenatal as well as the postnatal period are among some of the most reliable risk factors for mental health or psychopathology that we know about. So, these adversities account for roughly 30% of adult mental illnesses, and they also increase the risk for a range of physical health problems. Now, the effects of adversity, we know, do not actually stop with the individuals who are directly exposed. There's now strong evidence to suggest that the consequences of early adversity can persist across generations; and we've observed this mostly in the descendants of individuals who've been exposed to famine, war, and genocide.

00:02:55.360 --> 00:04:47.409

Bridget Callaghan: So, for me, these types of statistics raise a really essential question, and that is: How do these experiences, which are occurring within the caregiving relationship, become biologically embedded in ways that shape health, both physical and mental, across generations; so not just the individuals who are exposed, but also their descendants.

So, I think this leaves us with two major priorities for understanding mental illness after these experiences of caregiving adversity. And the first is that we really need to identify mechanisms that can explain the diversity of outcomes that follow adversity exposure. So why some individuals develop anxiety, others depression, others gastrointestinal issues, and others physical health problems, or maybe a mixture of all of those. And then second, we really need to understand mechanisms that can explain the transmission of risk that we see occurring across generations after adversity exposure. So, if we can really identify those mechanisms together, I think we can begin to intervene more effectively in the cycles of adversity that shape health across lifetimes.

So, in terms of some of these transdiagnostic mechanisms that I've mentioned here, one system that I've become particularly interested in across the course of my career is the brain-gut microbiome axis. And the reason I find this access particularly interesting is because this system is associated with both mental and physical health problems across diagnoses. So, depression, anxiety, cardiovascular disease, irritable bowel syndrome, Alzheimer's disease, multiple

sclerosis, you name it, there are so many conditions which seem to have some role for the brain-gut microbiome access. So, it's certainly transdiagnostic, in the sense that it relates to multiple different outcomes.

00:04:47.520 --> 00:06:39.490

Bridget Callaghan: And then, secondly, it also seems to be sensitive to the early caregiving environment. And this is not really that surprising, because the gut microbiome is a developing organ, or a developing system, and its periods of maximal plasticity, where it's showing maximal growth, really overlap with times in life where we're having a lot of input from the caregiving relationship. So, it has this potential to be shaped by these early life experiences that involve caregiving, and thus, maybe, might be related to these generational influences as well.

So today, I'm going to take that generational focus, and I'm going to show you data that spans two generations. And it's all centered on this broader question of how caregiving adversity becomes biologically embedded, particularly at the level of this brain-gut microbiome access to influence health across generations.

So, in the studies that I'm going to show you today, many of them, though not all of them, use samples of youth who have been involved in the foster care system. And this is one of the ways in which we recruit and find individuals who've been exposed to high levels of caregiving adversity early in life.

So, we know that youth in foster care have experienced, at a minimum, some form of maltreatment or neglect. As a result of entering into foster care, they've also been separated from their biological parents, sometimes their sibling and other family members. And we also know that being in foster care is associated with extreme instability, and sometimes, unfortunately, with further abuse. We know, in terms of that instability, that around 40% of youth in foster care will experience two or more placements per year for the entire duration of their time in foster care. So, this really is a highly unstable type of early caregiving arrangement.

00:06:39.830 --> 00:08:29.539

Bridget Callaghan: So, you can see here some data that we've collected from our own lab, showing individuals moving between different types of caregiving arrangements; from their birth family, through kinship care, foster care, guardianship care, and then ultimately into adoptive families. This doesn't even show the instability just within one of these types of arrangements; but hopefully gives you some sort of illustration of how unstable these early life caregiving arrangements are.

So, the talk that I'm going to give to you today- I'm going to split it into three different parts. In Part 1, I'm going to focus on how early caregiving adversity affects the microbiome and the brain-gut access function in ways that are important for mental health. So, we're going to be focusing on one generation who's exposed to adversity for this first part of the talk. In the next part of the talk, I'm going to introduce that generational focus. So, how do these early caregiving experiences affect brain, behavior, and the brain-gut microbiome access in the next generation? So, these are the children of individuals who've been exposed to early childhood adversity. And again, we'll be focusing on the brain and the brain-gut axis here. And then in the final part of the talk, which is just a little mini part of the talk, we'll be looking at how caregiving adversity affects the way that one transitions into parenthood, or more specifically motherhood, and the risk for perinatal depression. And the reason for that is that peripartum depression is one of the most powerful mechanisms through which adversity can be perpetuated across generations. It can influence caregiving, attachment, and early development in the next generation. So, we're really interested in focusing in on the mother here.

Okay, so without further ado, let's dive into the first part of the talk, looking at caregiving adversity impacts on the developing brain-gut microbiome axis.

00:08:30.030 --> 00:10:24.550

Bridget Callaghan: So, the first thing to note about the microbiome is that it is a developing organ. I think we can see that really clearly in these figures here. So, what I'm showing you are three different metrics that are all assessing alpha diversity. That is, a within-individual metric of how rich and evenly distributed the bugs in the gut are.

And so, what you'll see… these are longitudinal data with four time points in each child, and we've got 100 children in this study. You can ignore the different colors for the moment. The most obvious thing that you're seeing in these graphs is that there's tremendous growth in the microbiome from around three months of age to 24 months of age. So, across the first two years of life, we see massive explosion in the diversity of microbes that are present in individuals' guts.

What my graduate student, Genesis Flores, was trying to demonstrate in this study, and I think is shown quite clearly on these graphs, is that these trajectories of early life microbiome development really are related to maternal experiences of distress during pregnancy. So, in the blue line, you'll see, these are children whose mothers reported being highly distressed during their pregnancy. And in the pink line, these are children of mothers who reported much lower levels of stress during their pregnancy. And what's really clear here is that we have different trajectories, where actually the high distressed… or the children from the high-distress

individuals are ending up as higher at the end of these trajectories than the low distress individuals.

So, it's been thought for a while that the best time to look for the impacts of any environmental experience on the microbiome was really early in life, because this is the time in which we see the most drastic changes or development in the microbiome. So, this is a potential period of plasticity during which the environment might have maximal effect on shaping these trajectories.

00:10:24.550 --> 00:12:27.480

Bridget Callaghan: However, emerging evidence really suggests that the microbiome continues to change throughout childhood and adolescence, and may continue to be open to environmental influence during these later years of development. So, to investigate some of these later time points, my graduate student, Naomi Gancz, has been tracking how postnatal adversity in the form of maltreatment and foster care affects the community composition of the microbiome in that childhood to-adolescence transition.

So, what she's seen in this particular study is that there is age-related change in alpha diversity that's moderated by adversity exposure. So, here we have a group of maltreated and foster care-experienced youth. These are called adversity for the moment. And then we've got a comparison group of children who were always with their birth, first, or biological families.

What we can see in the comparison group is that from around two to about 17 years of age, there's really no change in the alpha diversity. So here, looking at a phylogenetic measure of alpha diversity. So, we're seeing stability in the microbiome across this period of time, which is what we would expect for this stage of development. So, we've seen big growth up until around two years of age and then relative stability; so no surprises within the comparison group. But what was really interesting was that adversity group was showing a significant nonlinear decrease in alpha diversity across these ages. And so that was really not expected. It was a very, unusual outcome to actually see the microbiome diversity decreasing in this group over time.

So, this tells us that trajectories of development, or age-related change, because this is a cross-sectional study here, seem to be affected by adversity exposure, and we're seeing that in the previous slide, in the prenatal period, and in this slide, we're seeing it in the postnatal period. So, when these adversities occur, either in the prenatal or postnatal period, we're seeing their impacts on the microbiome in postnatal life.

00:12:28.540 --> 00:14:29.239

Bridget Callaghan: So, in this same study, we also saw nonlinear, age-related change in the microbiome when we were looking at single taxa. So instead of taking these community-based metrics, where we're asking how rich and evenly distributed is this whole community of microbes in the gut, when we're looking at single taxa, we're really just comparing and seeing- are there any taxa that seem to be higher in one group than the other?

And what we found is that there were actually 12 microbes which were associated with age-related change in their relative abundance, and that age-related change in the comparison group was moderated by adversity exposure. So, I'm only showing you three of these 12 for the moment. The reason that I've pitched these three will become obvious soon. But what you can see here, firstly, if we're just focusing on the blue dots in the comparison group. We've got three different microbes here, Clostridium inocuum, a Eubacterium hallii group, and then a butyricimonas, and they all show really different age-related patterns of development.

So, the first thing to note here is, even when we're not considering adversity, the microbiome is not done developing by two years of age. Depending on the metric that we're using to look at the microbiome, whether it's a community-based metric, which does seem to really show maximal development in the first two years of life, or in this case, looking at single taxa, we see extended development throughout the middle childhood and adolescent period.

And in contrast, we see that adversity tends to moderate that; so we're seeing very different patterns of age-related change in the adversity group. So, we're seeing higher levels of this Clostridium inocuum in the younger adversity-exposed youth, we're seeing a U-shaped pattern in the adversity-exposed youth, and on average tends to be higher levels of this Eubacterium hallii group, and then lower levels of this butyricimonas group, on average, in the adversity-exposed group.

So now we can see that these adversities, which are affecting the caregiving relationship, seem to be changing the development of the microbiome at the community level and the individual taxa level from birth through middle childhood and through adolescence.

00:14:29.240 --> 00:16:27.589

Bridget Callaghan: And so now, next comes the pretty obvious question: why should I care? So, you're all sitting there and thinking, hang on, did I sign up to a brain and behavior conference here, and now this lady's talking to me about the microbiome, what's happening here? So, I think the microbiome is interesting in and of itself; but of course, for people who are interested in brain and behavior, and I count myself as one of those, we really are interested in the

microbiome if it's related to other things that we're interested in, like the brain or behavior. So here in this study, we wanted to see whether any of these microbes that showed age-related change, which was moderated by adversity, were associated with outcomes that we care about in terms of mental health. So, we tried to link all of these with internalizing symptoms.

Now, of course, correcting for multiple comparisons, we did find that three of the 12 microbes that were showing the pattern we were interested in, the three that are on the screen now, Eubacterium hallii, the Clostridium inocuum, and butyricimonas, were each associated with internalizing symptoms. We know this microbe is typically pathogenic, and we saw that higher levels of this microbe were associated with higher levels of internalizing symptoms in this study.

Next, this Eubacterium hallii group. We don't have a great idea about the specific species that are in here and their associations with health. We do know that some contain butyrate-producing species, so that could be potentially beneficial for brain health.

00:16:27.590 --> 00:18:26.530

Bridget Callaghan: And we saw that higher levels of Eubacterium hallii were positively associated with internalizing symptoms. And so, we see maybe higher levels on average in the adversity-exposed group here; unsure of exactly how to interpret that. And then the most interesting one we found was this butyricimonas, which contains some butyrate-producing species. This tended to be lower on average in the adversity-exposed group than the comparison group, and it was actually negatively associated with internalizing symptoms. So, in other words, the more of this bug you have, the better off your mental health. So, the lower your internalizing symptoms, like anxiety and depression. So, we thought that this butyricimonas bacteria might potentially be a bacteria that is associated with good mental health.

Now, interestingly, we wanted to look at potential ways in which we might influence the microbiome. Now, lots of people who are interested in influencing the microbiome go straight to probiotics. Probiotics, antibiotics, these are good ways to change the microbiome. But something that is sometimes overlooked is that nutrition, diet… when we change our diet, it's a really good way of influencing the microbiome. So, before we went in and did a dietary intervention, we wanted to first see, are there associations between diet and the microbiome?

And what we found was that that butryricimonas bug, which we tended to see as being negatively related to poor mental health; so, in other words, it tended to be a mental health-promoting, potentially, bacteria. Fiber was positively associated with this bug; so, the more fiber you ate, the more of this potentially good bug that you had in your guts, specifically for the caregiving adversity-exposed group in the orange line here. So, this suggests that these

nutritional interventions, potentially, might be especially salutary for adversity-exposed youth, because we're seeing the association between fiber and these good bugs, specifically for those adversity-exposed youth.

00:18:26.630 --> 00:20:40.279

Bridget Callaghan: And, kind of confirming that, we also found that fiber itself was associated with lower internalizing symptoms in the caregiving adversity group specifically. So, more fiber, lower internalizing symptoms specifically in that group.

Okay. So the gut microbiome is clearly what I'm going to call the darling of the microbiome world. So, I'm sure that you've probably read about the gut microbiome before, maybe in *The New York Times* or some other form of media. Lots of people know about it; there's lots of research on the gut microbiome. However, it is one of many microbial communities across the human body, and it may not be the only important one for our mental health.

So, in the lab, we're really interested in exploring some of these other microbial communities that may play a role in our mental health problems, and that could be associated with early caregiving adversity. And so, the next microbial community that we decided to look at was the oral microbiome. And the oral microbiome we chose because it is the second largest microbial community in the human body. So, what did we find in terms of the oral microbiome? Well, my graduate student, Naomi Gancz, decided to take on this project. And she looked in the literature to see whether there were any prior associations between exposure to caregiving adversity and the oral microbiome community. And she found this one study published in 2021, showing that, indeed, childhood adversity exposure seems to affect the oral microbiome in adults.

So, Naomi wanted to look earlier in development to see whether the same was true in children and adolescents. Naomi also wanted to integrate a focus on some of the other biological systems that we have in our body. And, in particular, she wanted to see whether exposure to cortisol, as sometimes called a stress hormone; obviously, it does many things in the body. But she wanted to see whether cortisol, which we know to be dysregulated in the context of early caregiving adversity, might moderate some of the associations that we see between the oral microbiome community and caregiving adversity exposure.

00:20:40.380 --> 00:22:37.870

Bridget Callaghan: And then, finally, she had this interesting hypothesis that the oral microbiome of adversity-exposed youth may be insensitive to cortisol, because that same association had previously been demonstrated with immune cells. So, in prior studies in

different labs, it's been shown that immune cells actually become less sensitive to the regulatory effects of cortisol after caregiving adversity exposure.

So, in this particular study, Naomi had access to hair cortisol, which indexes tonic exposure to cortisol over the last several months; and she used that as a moderator in models examining the association between chronic adversity exposure early in life and the oral microbiome community. Alright, so what did she find in this study? Well, remarkably, Naomi found essentially the same thing that had been shown with immune cells within the oral microbiome community. So specifically, whereas she saw the oral microbiome community of comparison youth in blue, so alpha diversity here, that within individual metric of how rich and evenly distributed the microbiome is, being regulated by cortisol, so more hair cortisol, lower levels of alpha diversity in these youth. She found that there was no association between cortisol and the oral microbiome community in the context of early caregiving adversity exposure.

Outside of the influence of cortisol, Naomi also found that several taxa were associated with caregiving adversity, including this pathogenic Porphyromonas species, which was higher in the adversity-exposed youth relative to the comparison group in general. And critically, that Porphyromonas species itself was positively associated with children's internalizing symptoms. So, more of this pathogenic microbe, the higher levels of anxiety and depressive symptoms that we saw in these youth. So, this suggests that even microbial communities outside of the gut seem to be affected by caregiving adversity, and these may play some role in the mental health of youth.

00:22:37.880 --> 00:24:27.679

Bridget Callaghan: And the exciting thing about this is that it really opens up even more pathways to potentially influence the microbiome, and thus indirectly have an impact, potentially, on youth's mental health. So even simpler than dietary interventions that we were talking about earlier, the oral microbiome community can be affected by oral health behaviors, like toothbrushing. Now, of course, I'm not suggesting here that our mental health woes are going to be solved by greater flossing and brushing. I wish that were the case, that would be amazing, but we're really thinking about a variety of lifestyle interventions that could be used to improve health generally, and hopefully improve mental health indirectly; and we think that this may be one of them.

So, there really are a multitude of ways in which the microbes in the gut might be linked to children's mental health. However, it is a long leap, right? So, we're talking about these single-celled organisms that are existing in the gut, or maybe in the oral cavity, and then we're making

this link to something that's really complex, like a heterogeneous, non-distinct clinical symptom cluster, like internalizing symptoms, anxiety and depression.

Now, of course, there needs to be an intermediary here, and I think it goes without saying that that intermediary, or at least one of them, is likely to be the brain. So now we have this really challenging problem where we really need to understand more, in developing humans, about the bacterial community in the body, in whatever cavity we're going to look at, and how that is associated with the brain. And we need to do all of this in young kids; we've got to ask them to donate poop samples, and we've got to get their brain scans and have them lie really still in an MRI scanner. So, in other words, this is a really challenging question to address, and I want to show you one way in which we've been working on this particular question.

00:24:27.680 --> 00:26:40.030

Bridget Callaghan: So, in this particular study, we wanted to take a kind of backwards approach. So, we wanted to work backwards from youth's internalizing symptoms to then associate those internalizing symptoms with the brain, and to then try and find microbes that were associated with those internalizing symptom-linked brain patterns that we saw. So, in this study, we had 55 individuals; so again, it's a small sample size, though the methods that we're using here are robust to small sample sizes. The small sample size is reflective of the difficulty with which we have to work with getting these types of data. So, we've got microbiome at two years of age in these youth.

These youth, then, lay in an MRI scanner when they were six years of age, and then we extracted inter- and intra-resting state network connectivity. And then finally, we had youth internalizing symptoms when they were seven and a half years old. So, what we're doing here is this kind of multivariate, data-driven approach. So, we're working, really, in these black boxes of data. So, we're trying to ask what patterns we see in the brain that might maximally predict what's happening, in terms of internalizing symptoms. So, we're going to take a three-step approach here, and I'm going to lay those steps out for you.

So, in Step 1, we're using an approach called multivariate sparse partial least squares regression, for those stats nerds in the audience; and for the rest of you, you can just listen to the rest of this and ignore that regression term. So, what we're doing here is to try and find inter- and intra-resting state network connectivity patterns that predict maximal variance in youth's internalizing symptoms. And we're going to call those internalizing-associated brain networks, or a signature. We're then going to take that brain signature forward and use that as the outcome in Step 2. And now in Step 2, we're using the same approach, and we're asking,

instead, what is the linear combination of microbes that best predicts variance in those internalizing associated brain networks?

00:26:40.230 --> 00:28:37.640

Bridget Callaghan: So, then we're going to get a set of microbes that best predicts variants in brain networks that are tied to internalizing symptoms. And then finally, we're going to take the microbiome networks that we produced in Step 2, the brain networks that we produced in Step 1, and we're going to feed all of that into a mediation framework. So here in the mediation, we're asking, is there an indirect association between the microbiome and youth mental health that operates via the brain?

Okay, so what did we find? We actually found lots of things; I'm just going to summarize and show you the most interesting things today. So, the first thing we found is that there was a very clear set of brain networks that were associated with youth's internalizing symptoms. And these tended to be driven by what I'm going to call the SOFA network, or the SOFA signature. SOFA stands for striatal orbital frontal amygdala. So, if you've done any neuroscience in the emotion space at all, these brain regions will not be surprising to you. We often see the amygdala, striatum, and orbital frontal cortex being associated with mental health problems, with people feeling emotions or expressing emotions; so, it's really not surprising at all. And what we found in this brain signature is that this SOFA network tended to be highly interconnected with a variety of other networks across the brain. So now we have our SOFA network, and we wanted to carry that through to the next step and say, which microbiome patterns predict variance in this SOFA network, or this SOFA signature? And so, this is our SOFA-associated microbiome pattern, and what we found here was really quite interesting and exciting. So, specifically, we found high positive loadings from this bug here, Veillonella, and Intestinibacter. And these are interesting bugs because in prior studies in adults, these have been associated with intestinal inflammation, and have been shown to be higher in depressed adults.

00:28:38.080 --> 00:30:33.770

Bridget Callaghan: And then we found high negative loadings from Fusicatenibacter and Carnobacterium. And again, in prior studies, these bugs have shown interesting association; so they're negatively associated with anxiety and depression in adults. So now we have our brain signature and our microbiome signature. We wanted to test whether there was that indirect association with internalizing symptoms. And we found that, at least for these two signatures, there was. So, this SOFA-associated microbiome pattern when youth were two years of age was indirectly linked to youth internalizing symptoms when they were seven and a half years of age

via their connection with that SOFA signature in the brain, when youth were six years of age. So here, we're really looking at an indirect programming association of the early life microbiome on later internalizing symptoms that seems to operate through the brain here.

This approach is good because it really shows us that we can work backwards from symptoms to try to identify microbes to potentially target in treatment. And so, this is one way in which we can find a set of microbes that might be good candidates to begin to test in a treatment-based framework.

So, I want to summarize Part 1 for you today. What I've shown you so far is that directly experienced childhood caregiving adversity; so when this adversity happens to you yourself, we see that it tends to influence the gut and oral microbiome development of youth, from basically birth, around 3 months of age, through to around 17 years of age, which is the maximal age range at which we've tested. So, we're seeing dynamic patterns of age-related change in the microbiome in the gut and oral cavity that are regulated by early adversity exposure. And then we see that some of these microbiome outcomes are associated with youth mental health. So, this suggests to us that this may be a good system to look at in order to find potential intervention targets, which could, probably in adjunct with other therapies, be helpful in addressing youth's mental health needs.

00:30:34.200 --> 00:32:38.079

Bridget Callaghan: And in order to figure out which microbes to target, our microbiome brain analyses identified several microbes that are linked to symptom-associated brain networks, and we think that these could be potentially good targets for interventions. So that remains to be seen. We need to do those interventions first.

So now that I've spoken to you about the impacts of caregiving adversity that are directly experienced by individuals, I now wanted to move into Part 2 of the talk, switch gears a little, and talk about the generational impacts of adversity on children's behavior, brain, and their microbiome.

So, focusing first on the brain and behavior; in this particular study, which was done by my former postdoc, Dr. Jessica Uy. We had a really great data set that we had access to. It was from a collaborative group called Growing Up in Singapore Towards Healthy Outcomes. So we were able to access data from this group. We had 541 mother-infant dyads, or mother-child dyads, and we had the following data on these dyads. So mums, when they were pregnant with that second generation, reported on their own experiences of childhood trauma; so their own experiences from their own childhood. We then had mums report on their prenatal mental health; so mental health while they were pregnant, their mental health in the postnatal period,

and then we had child emotional health outcomes in those second-generation children when they were seven years of age. And these were both parent proxy-reported; so parent reporting on their child, as well as child self-reported, child reporting on themselves.

And so, what Jess found in this really interesting study was that there was an indirect association between maternal childhood trauma exposure and worse child emotional health at seven years of age that was parent proxy-reported. And this operated through worse maternal prenatal and postnatal mental health in the context of higher levels of maternal childhood trauma.

00:32:38.600 --> 00:34:52.500

Bridget Callaghan: She also found, in terms of child's self-reported emotional health, there was an indirect link between, again, maternal childhood trauma and children's emotional health at seven years of age; but this time it seemed to operate primarily through worsened maternal prenatal mental health. So, this really suggests that there are these generational patterns of adversity that we can detect on children's emotional health outcomes. And what they also highlight is that when mums are exposed to childhood trauma, it seems to influence their mental health, either in the prenatal or postnatal period, in ways that are really important for the second-generation child. So, it's really highlighting here the importance of mothers in transmitting these effects, and potentially the importance of targeting maternal mental health in improving not just the health of the child, but also the health of the mother.

In this same study, just in a much smaller subsample of the same study. This is a smaller subsample because not everyone was targeted for MRI scanning; and then on top of that, we were really aggressive with who we kept into the study based on their movement. Movement is not good for MRI, so we wanted to keep kids who were really, really still in the MRI scanner. So, we now have 89 kids in this particular study, where we have resting-state fMRI data when they're six years of age. So, they're just lying in their MRI scanner with their eyes closed, resting, and we're looking at blood in the brain.

And so, Jess's question here was looking at, again, these exposures; maternal childhood maltreatment, maternal prenatal mental health, and maternal postnatal mental health, and whether we can see influences or associations between any of these types of experiences and children's resting state functional brain connectivity.

And what Jess found in this sub-study was that only maternal postnatal mental health was linked with children's resting state brain connectivity. And so specifically here, we're seeing an amygdala prefrontal cortex resting state connectivity that was more negative in individuals who had mums experiencing high levels of maternal postnatal mental health problems. And then,

critically, this brain pattern we found being associated with worse child emotional health. It was both parent proxy-reported and child self-reporting.

00:34:52.670 --> 00:36:57.330

Bridget Callaghan: So again, highlighting, there do seem to be these intergenerational impacts of adversity on children's emotional health and brain function, and that at least for these behavioral effects, they seem to be mediated through maternal mental health in the prenatal and postnatal period. Or if we're looking at the brain through maternal mental health in the postnatal period, this most proximal relationship to that second generation child. Now, again, kind of linking back to these transdiagnostic mechanisms that I've been talking about for much of the talk today. We're really interested in the gut microbiome, and we were lucky in this study, this Growing Up in Singapore Towards Healthy Outcomes study, that they also had gut microbiome samples from these youth. So, my graduate student at the time, now graduated, Dr. Fran Querdasi, again, wanted to look at these different exposures, maternal childhood maltreatment, maternal prenatal mental health problems, and maternal postnatal mental health problems. But now, switching the outcome, instead of looking at the brain, she wanted to look at the association with children's gastrointestinal microbiome when they were two years of age. So here, the child is the second generation child. And so, we had these data in around 450 youth.

So here I'm summarizing what is a much larger paper that you can read about. It was published in 2023 in *PNAS*. But what Fran is showing here is that each of these different forms of adversity seem to be associated with differentially abundant microbes. So specifically, she found that maternal childhood adversity exposure, so mums who'd experienced adversity when they were children, was associated with higher levels of this bug down here called Clostridium sensu stricto.

Now, this bug is really interesting. It's a butyrate producer. Generally, we tend to think of butyrate as being important for our brain health. But this is actually a group of bugs that may be less efficient in their production of butyrate; so, this may be an indication of less efficient butyrate production. This bug generally tends to have been outcompeted by more efficient butyrate producers in the gut by around two years of age. So, potentially something interesting there in terms of butyrate production.

00:36:57.330 --> 00:38:55.190

Bridget Callaghan: For prenatal adversity exposure in the pink, it was associated with two different bugs within the genus Streptococcus. These are part of the normal microbiome, but several species are pathogenic. And these prenatal adversity exposures were associated with lower levels of Ruminococcus. This is a group of bugs that is associated with immunity, so both anti- and pro-inflammatory; and with dopamine, so some associations with Parkinson's disease here.

And then, finally, for higher levels of postnatal, quote-unquote, adversity, or more accurately stated, maternal mental health problems in the postnatal period, we found that this was associated with lower levels of Parabacteroides, which is a group of bugs that has several probiotics within them. So lower levels of that, and then higher levels of Finegoldia, which is, again, part of the normal microbiome, but can be an opportunistic pathogen.

So based on these data, and in the context of some of our earlier findings, we seem to be seeing a pattern emerging in which butyrate production in the gut is something that tends to be associated or potentially altered by adversity exposure. And we're also seeing here [that] immune function is cropping up as another gut function that might be disturbed, at least in the context of generational adversity.

Now, it's really hard to tell about functions here, because we're really just guessing at functions. The type of sequencing approach that we use for the microbiome here is called 16S rRNA sequencing. It doesn't get us down to a low enough level, or a specific enough level, to really have a good guess at functions. Instead, we're really just looking at taxa and then guessing what those functions are based on the prior literature.

So, what we're doing now in the lab is doing a much more in-depth sequencing approach called shotgun sequencing, and this is going to allow us to say a lot more about the functional potential of the pooled genetic material in the guts of these individuals. So, you can stay tuned for that.

00:38:55.840 --> 00:41:13.690

Bridget Callaghan: So, to summarize Part 2 here: What I've shown you is that generational adversity is associated with children's behavioral health when they're around seven years of age, children's brain amygdala PFC functional connectivity when they were six years of age, and children's microbiome when they were two years of age. And I've also really highlighted in this part of the talk that maternal mental health seems to be a really important influence over which adversity may exert its effect in the next generation, or in the subsequent generation.

And so, really, based on these generational data that we've been getting across this multitude of studies, we've started to focus much more on the mother and the transition to motherhood or parenthood, and how that's influenced by a mum's own earlier childhood adversity exposures, because this is really this critical link or linchpin with these intergenerational effects.

So, I'm going to spend the last couple of slides of the talk today discussing what we're doing, focusing in on the mother; the influences of adversity on the transition to parenthood. So, pregnancy is a really critical period of development, which is also characterized by a heightened risk for depressive symptoms. So, around 12% of women will experience depression during their second or third trimester. Now, critically, this depression risk in pregnancy and the postpartum period is further amplified by pre-existing environmental vulnerabilities, such as exposure to childhood trauma. So, we know that women who experienced childhood trauma are at greater risk for also experiencing depression during their pregnancy or in the postpartum period. Now, focusing on depression in the context of childhood trauma is thus really important for trying to understand these generational or intergenerational impacts of adversity. And this is important not just for the child, because they're going to be the person, the next generation, experiencing this adversity, but it's also very important for the mother, okay? Mothers are humans too, and we don't want mothers to be experiencing high levels of stress and distress when they're transitioning into this really important stage of life.

00:41:14.670 --> 00:43:13.450

Bridget Callaghan: Now, it's been convincingly argued that depression at other stages of the human lifespan arises in part from disordered interoception. Now, interoception is the way that the brain senses, perceives, and models sensory information which is generated from the body. So why do I say that interoception might be associated with depression? Well, we know from several, several studies, many decades of research, that depression involves dysregulation across numerous bodily systems. So, it's not just lower, irritable mood, it's also abnormalities and altered functioning across the brain, the immune, the neuroendocrine system, and a variety of other bodily states.

And so, this really points to a core energetic inefficiency that happens in depression that may actually be critical for producing what we call depression. Now, energy regulation is supported by interoception. This is the way that the brain regulates our energy output. And so, it's not surprising that numerous studies have shown that interoception is actually impaired in depression.

So, we wondered, in this next set of studies, whether interoception may also underlie depression during the perinatal period. Now, depression in the perinatal period and depression

outside of the perinatal period, there's arguments about how similar these are to one another, but those core energetic inefficiencies do translate across the two different depressions at different stages of the lifespan.

So, we really wanted to target interoception here as being really central to that energy regulation. So, when we think about pregnancy, one thing is for certain, and that is that interoception really should change. So again, interoception is that process by which the brain senses and models sensory information from the body. And what's happening during pregnancy is that there's a lot of change in the body.

00:43:13.450 --> 00:45:54.730

Bridget Callaghan: So, we're seeing a massive increase, actually, in metabolic demands, and so that's illustrated in this figure here. This is from a paper that my graduate student, Paul Savoca, and I published in *Neuroscience and Biobehavioral Reviews* in late 2024. So, what we're illustrating here is that across the course of pregnancy, we're seeing a massive increase in metabolic demands that's more or less sustained at a higher level in the postpartum period associated with breastfeeding and caring for a child.

And what we were trying to illustrate from this picture is that we think interoception, particularly under no early life stress conditions, so just under typical conditions, should actually become boosted across pregnancy to catch up or increase in accordance with these metabolic demands, these heightened metabolic demands. Now, it's been shown outside of pregnancy, so for women who are not pregnant and nulliparous, that there is this baseline difference in poor interoception, so lower than average levels of interoception, as a function of early life adversity, or ELS, early life stress.

And so, we hypothesized in this paper that this initial deficit in interoception for early stress-exposed individuals would probably be sustained and possibly even amplified during pregnancy. And that this lower level of interoception, not keeping up with the metabolic demands in this period, would produce an energetic inefficiency that may increase the risk for peripartum depression, specifically for these early adversity-exposed individuals.

And we actually found support for these hypotheses. So, this is a behavioral study where we're looking at self-reported interoception, so belief in one's own interoceptive ability. And we found that early life adversity, or ELA, as measured by the Childhood Trauma Questionnaire, or CTQ, was interacting with pregnancy, status, and to influence interoception levels. So here we have three different forms, or three different subscales, on this interoceptive, sensibility measure, or self-reported interoception measure. Attention regulation refers to the ability to sustain attention to and control attention to bodily sensations. Self-regulation is asking questions about

how an individual regulates their distress by attending to their body. And then noticing is an individual's awareness of their body sensations, regardless of valence. So just how much do you recognize when your tummy is grumbling, when you're hungry, when your heart rate is going up, when you're sweating, etc., regardless of the valence of that, whether that's good or bad.

00:45:55.380 --> 00:47:57.140

Bridget Callaghan: So, what we can see here; the comparison group is in red, the pregnant group is in the blue lines and dots, and in the yellow, we're seeing the areas of significant difference between those two groups, or highlighting where the interaction is significant. And so, we find support for both of our hypotheses, right? So, if we're looking at individuals who have low levels of early life adversity, here and here, we see that the pregnant individuals have more belief in their interoceptive abilities. So there tends to be this potential boost in interoception to keep up with the metabolic demands of pregnancy for low-adversity exposed individuals. But then for individuals who have high early life adversity exposure, so in the right-hand bars of the panel A and C, we're seeing that this actually reverses. So, the pregnant group is doing much worse than the comparison group on their self-reported belief in their interoceptive abilities.

So, this really suggests that interoception may be one mechanism that is associated with brain, body, associated with mental and physical health, that might be affected by pregnancy in a way that could potentially protect against depression, but that this is moderated by adversity exposure. So where we're seeing the kind of reverse of that in individuals who've been exposed to high levels of early life adversity. Now, not surprisingly here, we see that at least two of these measures on that MAIA-2 scale, the attention regulation and self-regulation measures are negatively associated with depression. So, again confirming, as has been seen in numerous studies, that higher levels of interoceptive self-reportability are associated with lower levels of depression.

So, this is self-reported belief in one's own interoceptive ability, but of course there are many other dimensions of interoception that we could look at, and one that we're really interested in is an actual task-based measure of how accurate an individual is at perceiving their own bodily sensations.

00:47:57.610 --> 00:50:05.6400

Bridget Callaghan: And so, in this study, which is a small pilot study, what we did was to bring pregnant individuals into the lab, and to give them what's called this heartbeat detection task.

So, this task assesses whether the mothers could accurately judge whether their hearts were in sync or out of sync with a tone. So it's a signal detection task. So, we're either playing a tone that's in sync with that heartbeat, or playing a tone that's out of sync with their heartbeat. And then, given this is a signal detection task, we're trying to look at sensitivity, and so our sensitivity index here is a non-parametric version of D', it's called A'. And so, we wanted to see whether pregnancy interacted with early life adversity to produce changes on this task in terms of people's accuracy. And so, what we find in a group of pregnant women is that for individuals who are low in trauma, so the blue line here, they tended to see an increase or a boost in interoceptive accuracy across the course of pregnancy. Again, these are cross-sectional data, but we're seeing highest levels of interoceptive accuracy on this task-based measure for individuals who are in their third trimester. So again, supporting that idea that we're seeing this boost in interoception under low early life adversity conditions. It may protect against peripartum depression, and that this is decreased in individuals who have high levels of childhood trauma exposure. So, we're actually seeing no boost or change in interoception levels across pregnancy.

So, to summarize Part 3 and the talk, I've shown you in this section that maternal childhood adversity exposure affected mothers' experience of interoception changes in pregnancy, and this happened in ways that were important for maternal mental health, and specifically depression symptoms during that period of life. And so, this suggests to us that focusing on interoception during pregnancy may be an important way to address these intergenerational patterns of trauma. So we know these patterns exist, we know that being directly exposed to a stressor yourself has an impact on your brain-gut access, we know that having a parent who is exposed to adversity has an impact on your brain-gut access.

00:50:05.460 --> 00:50:24.460

Bridget Callaghan: We think that these generational impacts are operating through the mother and her mental health, and now we've got a potential way in which we can target mental health. And we know that there are several ways in which we can target interoception, from mindfulness-based interventions to interoceptive training techniques, and these might be really helpful for improving maternal mental health in this really critical transition point, the transition to parenthood, which is important for the health of the mother and the whole family.

So, to revisit our priorities for understanding mental illness after adversity, transdiagnostic mechanisms, and importance of generational experiences. We think that focusing on an individual's biology and psychology in ways that integrate the brain and body, so microbiome, interoception measures; and also focusing on mum's health, her mental health, and her adjustment to the metabolic strain of pregnancy and parenting. These approaches together are

going to go a long way in helping us to improve individual well-being after adversity exposure, either in your own generation or in a prior generation.

So, there's obviously much more to be done on this front, and I look forward to sharing that data with you in the future when we're a little more progressed. I'm going to end by saying an enormous thank you again to the lab, the students, postdocs, and staff. So, I highlighted some students whose work I chose to present today, but it doesn't represent all of the wonderful work that students do in the lab, so thank you to all of them. To our collaborators, especially the Growing Up in Singapore Towards Healthy Outcomes team, who has been so generous with sharing a lot of their data with us and allowing us to answer these really interesting questions. And to our funders, including the National Institute of Mental Health and the National Institute of Aging, which are funding most of the current work that we're doing right now. And thank you to all of you; I'm happy to take any questions that you have.

03:49:34.200 --> 03:49:41.089

James Naifeh: What a fascinating start to the second half of the conference. Thank you, Dr. Callaghan.

SHARON DEKEL, PHD

PRESENTATION

03:49:41.460 --> 03:51:42.809

James Naifeh: Our next presenter is Dr. Sharon Dekel. Dr. Dekel is an Associate Professor of Psychology at Harvard Medical School, and the Founding Director of the Postpartum Traumatic Stress Disorders Program in the Department of Psychiatry at Massachusetts General Hospital. She is a leading expert on childbirth-related posttraumatic stress disorder, or CB-PTSD, conducting research that has helped to transform our understanding of maternal mental health and inform new approaches to prevention and care. Dr. Dekel's multidisciplinary work integrates clinical and developmental psychology, psychophysiology, neuroscience, and computational methods to advance early identification and treatment of women at risk for psychopathology following traumatic childbirth. She leads large-scale clinical and translational studies aimed at defining the psychological and biological signatures of CB-PTSD and related maternal-infant bonding impairments. In parallel, she develops innovative methods for screening women at risk and directs clinical trials testing novel early preventive treatment approaches designed to mitigate trauma responses and promote recovery in the postpartum period.

Dr. Dekel was a recipient of Brain and Behavior Research Foundation Young Investigator Awards, and has received numerous awards for scientific and mentoring excellence from MGH and Harvard. Her research has been featured in NPR, NBC News, *The Atlantic*, *Psychology Today*, *Harper's Bazaar*, and *Goop*, among others. Dr. Dekel serves as Chair of the Postpartum Trauma Special Interest Group of the International Society for Traumatic Stress Studies, and as a Board member of the International Marseille Society for Perinatal Mental Health. We will now begin Dr. Dekel's presentation, which is titled, “The Hidden Face of Trauma: What Childbirth Can Teach Us About Stress, Recovery, and Resilience.”

Total Conference Timestamp: 03:51:50.330 --> 04:38:49.899

Within-Segment Timestamps below

00:00:02.380 --> 00:00:12.979

Sharon Dekel: So, thank you so much for inviting me to speak at the Brain, Behavior, and Mind 2026 Conference, and thank you so much for the lovely introduction.

So, in the 19th century, childbirth carried serious risks; and this is an image of a home birth, in which we see a person attempting to give birth as complications unfold, and her family members most likely hoping to assist her.

00:00:34.040 --> 00:01:26.620

Sharon Dekel: Back then, in many Western settings in the 1800s, the rate of maternal morbidity was roughly around 1 out of 200, or 1 out of 100, so definitely a very dangerous entity, childbirth, altogether.

Fast forward, in the 21st century, you do wonder how childbirth is perceived subjectively. We know that perinatal care has drastically increased, and that's, you know, modern medicine. Nevertheless, we remain to know very little about the subjective experience of childbirth, especially as we consider childbirth as a physiologically intense event that often evolves in a very pressured sequence, and entails very drastic biological changes.

00:01:26.880 --> 00:01:46.170

Sharon Dekel: So, let's hear two brief vignettes of participants who took part in our NIH-funded study. One person we studied during the COVID-19 era, and the second person we studied during 2025. And let's hear their very brief stories of their childbirth experience.

00:01:48.300 --> 00:02:01.210

Participant #1: The part that's most upsetting and scary to me is feeling like I was not going to live. I could see my baby from across the room, but…I couldn’t hold her…

00:02:01.530 --> 00:02:04.620

Sharon Dekel: I see…

00:02:04.750 --> 00:02:33.190

Participant #1: And, like, thinking back, it's… like, I didn't get to hold her for, like, 14 hours after she was born. And, like, I was in the ICU a couple days after her birth, so I didn't get to, like, really hold her or have that, like, initial bonding in time.

Sharon Dekel: I see.

Participant #1: But the most, I think, the most traumatic piece is… just the sense of… feeling… like I was dying.

00:02:33.920 --> 00:02:49.300

Participant #2: Yes, I thought I was gonna die during the C-section, and then right, like, post… post-op, I… I was very weak, I felt over-medicated. I just… I thought… I was concerned that I was gonna… die.

00:02:51.040 --> 00:04:03.730

Sharon Dekel: So, zooming out of these N = 2 cases, based on data that we collected from four cohorts that we studied during routine conditions and during unprecedented times, women who delivered at Mass General, since 2023; this is all, as you can see on the right side of my slide, women who gave birth in the peak of COVID-19, so roughly, like, March of 2020 and April, a sample of people who gave birth post-October 7th and resided in Israel, and a small cohort of women who gave birth in an inner hospital in Nigeria.

As you can see in the lower part of the slide, this is, I believe, not surprising to the audience here; for many people, childbirth entailed a high, if not extreme, level of pain. Labor pain is often considered potentially one of the most painful experiences people undergo. The upper part of the slide talks really about your subjective experience with childbirth, and how much you thought you were going to die. And as you can see, a significant portion, although it does vary based on study sample, but a significant portion of women report that they thought they might die in the course of giving birth.

00:04:05.960 --> 00:05:03.589

Sharon Dekel: So, in my lab at Massachusetts General Hospital and Harvard Medical School, we have been attempting to answer a very basic question: Whether childbirth, like war, can precipitate an enduring stress response that eventually would result in a posttraumatic stress disorder. And I think, as we are considering childbirth as a trauma that could lead to PTSD, it's important to, a little bit, reframe back and think about the history of PTSD. So, in World War I, the traumatic stress syndrome was already identified among soldiers; and back then, we referred to this condition as shell shock. And, often, shell shock was understood as an impairment, or some kind of a weakness in the psychological well-being of the person. So, the idea is that the person might have a weak personality.

00:05:03.890 --> 00:06:13.630

Sharon Dekel: It took until the 1980s, in 1980, the DSM-III. Only then did PTSD become a formal disorder in the bible of mental illnesses. And I do believe that this is, in part, due to a skepticism of whether… a causal event, some kind of an external event, could actually really trigger and be the causal reason for a psychopathology. And that might be also the tension as we're thinking about childbirth, and the idea that, really, can childbirth seriously cause a mental illness? And thinking about childbirth in the context of trauma is very timely, because unfortunately, in the US, when we talk about, let's say, positive maternal and physical outcomes, the US is lagging behind other Western countries. And actually, the data suggest that severe maternal morbidity, which entails severe complications in labor and delivery that could put the person's life at risk… These, what we call SMM, are the highest in the US among any other country.

00:06:14.100 --> 00:07:11.150

Sharon Dekel: For, you know, as we talk about the… specifically about the audience who I hope is watching us now, outside the context of the perinatal milieu, it is interesting to think about childbirth as a model of understanding PTSD, and trauma in general. Because, in the context of childbirth, we actually are able to potentially study how was the person's baseline, how was their functioning before they were exposed to trauma, in this case childbirth, and also then study them very closely since the peak of the traumatic exposure all the way to potentially days and months and years, etc. So, we can really identify this kind of trajectory of the precondition, the vulnerability, and as the trajectory of the traumatic stress evolves over time. Which often is potentially not possible in comparison to other forms of trauma.

00:07:13.310 --> 00:08:13:239

Sharon Dekel: So, today we will talk about the focus on childbirth PTSD, which I define as CB-PTSD, focusing on risk factors, on the impact of CB-PTSD, on the biological and psychological manifestations, and on potential treatment outcomes. And we present the data using, ideally, prospective longitudinal designs, and embedding clinical assessments as well as biological assessments, by integrating also lived personal experiences of our participants.

So, at MGH, under NIH funding, we began to study a large cohort of women. These are people who are treated at the MGH Obstetric Outpatient Clinic during pregnancy, and are planning to deliver at MGH, and so far, our cohort includes 2,500 mothers.

00:08:14.430 --> 00:09:34.169

Sharon Dekel: And, among this cohort, we collected data from mothers really in the immediate postpartum, here on average 31 hours after delivery, to better understand what is the prevalence of having an acute stress response to childbirth. An acute stress response to childbirth was defined by a questionnaire, the Peritraumatic Distress Inventory, which really taps into negative appraisal of the trauma and having very negative emotions; that you want experiences either during the event or immediately after. And then you can see at the upper part of my slide, roughly 1 out of 10 women endorse acute stress response at a clinical level.

And in the second part of the slide, the lower part, you can see that the acute stress response is highly correlated, not surprisingly, with the level of physical morbidity; meaning that as a childbirth becomes more medically complicated, in our case, unscheduled Cesareans, then, people report… are more likely to report acute stress distress; and among unscheduled Cesareans, overall, the level of acute stress is around 27%; but in cases of really a lot of physical morbidity, the acute stress even reaches 42%.

00:09:35.990 --> 00:11:01.870

Sharon Dekel: Overall, I do consider the 10% among women, I would say, a pretty representative sample of women who give birth in Massachusetts. Ten percent is, I would say, not a trivial rate, because if you compare this 10% to other conditions that have received a lot of clinical attention, for example, preterm delivery and gestational diabetes, the rate of 10% really falls within the rates of these conditions that are commonly treated and receive a lot of clinical and also research attention.

We further identified that acute stress response could be enduring. And in these two cohorts, we assessed mothers' PTSD symptoms in regard to childbirth using the PTSD Checklist for DSM-5, which is called the PCL-5; potentially the most, I believe, recommended screener for PTSD by the VA. We assess mothers between 2 to 3 months postpartum, and we find that, overall, the prevalence, or the rate of CB-PTSD, is 5 to 20%. Again, this varies based on the medically complicated degree of the childbirth. Under uncomplicated conditions, it's mostly 5%. But when childbirth becomes more medically complicated, the rate is at 20%.

00:11:01.930 --> 00:12:08.599

Sharon Dekel: And more so, in a small cohort, when we did look at the rate of PTSD against diagnostic assessment; so basically, in the small sample, we were able to administer the CAPS, which is really a diagnostic interview of whether you have PTSD by DSM, we find that when people have even more medically complicated deliveries, the rate of PTSD could reach even 33%. And overall, the 20 to 33% of people who have PTSD in the context of medically-complicated delivery largely resembles the prevalence that is reported in conditions of other high-impact traumas. Traumas that involve physical assault as well as personal assault. So clearly, I would say the take-home message is that CB-PTSD, under medically complicated deliveries, to various degrees, of course... this is not only people who have severe maternal morbidity, but CB-PTSD is not a rare condition.

00:12:10.310 --> 00:13:33.640

Sharon Dekel: The symptom profiles of CB-PTSD largely accords with the clusters that we know of in the DSM-5. So, basically, we are talking about these intrusive symptoms that we see in our participants; people really describe the sense of now-ness, as if they are reliving the event during daytime, but also at night, through nightmares. Again, very much aligned with PTSD symptoms by the DSM-5. In the context of childbirth and CB-PTSD, you might imagine how many reminders people often encounter when it comes to the childbirth event, just by going to the postpartum unit for routine checkup, or by having other people, family members, friends, ask them about their childbirth experience.

So, there is a constant reliving of the event. The constant reliving of the event often puts a person in a state of hypervigilance, they feel on guard. This is kind of what we call the cluster of the hyperarousal and the reactivity. And one way of coping with this hyperarousal reactivity would be by avoidance. And a common theme that we see among our study participants is that many people who have CB-PTSD report that they would not consider giving birth again.

00:13:33.820 --> 00:14:17.680

Sharon Dekel: And of course, we also see the negative alterations in cognition and moods. People talk a lot about guilt and shame. They feel that they failed their baby, that their body failed them. Unfortunately, CB-PTSD symptoms, as you can see on the right side, for some people, the symptoms can be enduring; and based on our data, we followed people with assessments all the way out across the first postpartum year. We do find that the rates of PTSD symptoms, or CB-PTSD symptoms, at 3 months postpartum highly correlate with the levels of CB-PTSD symptom severity one year after childbirth. So, let's hear from our study participant what it means to actually have these intrusive symptoms of childbirth.

00:14:17.830 --> 00:15:39.959

Study Participant #4: There are moments where, you know, if I think about it, if I live in that moment, it feels like I'm there again. It feels like I can see the fluorescent lights, I can feel how cold it was, I can feel how uncomfortable the bed was, and it feels like I'm back there.

Sharon Dekel: So, clearly, this is a very vivid representation of, this sense of, the kind of vivid memory of childbirth versus childbirth eventually becoming an event that happened in the past. The person constantly is reliving the experience, and this is a very daunting and debilitating experience. A critical question that we attempted to answer is, basically, what are we actually observing when people report PTSD symptoms? So, we see that PTSD, I mentioned CB-PTSD, is not that uncommon. It actually could occur, as we said, in one out of five people who have medically-complicated deliveries; but nevertheless, how much is this condition related to childbirth, or are we actually seeing people who might have CB-PTSD, but their condition or their PTSD syndrome already began before childbirth. You know, as we know, people who have PTSD, when they are confronted with a subsequent trauma, they're likely to also experience PTSD in regard to a subsequent trauma.

00:15:40.050 --> 00:16:52.129

Sharon Dekel: So, based on our data, as you can see here on the left side of my slide, roughly one out of five mothers who actually endorse CB-PTSD based on the PCL-5 cut-off score of 32 and above. If you assess their PTSD symptoms in regard to another trauma, which is not a childbirth, their PCL score is actually very high. In this case, you see 52. So, for these people, we could argue the CB-PTSD is potentially a reactivation of a prior unresolved PTSD syndrome.

However, the take-home message is on the right part of my slide. As you can see, 81% of mothers, so roughly the vast majority of women who have CB-PTSD, their PCL score in regard to a prior trauma is actually a score of 11, as you can see in green. So that means that basically for these people, they did not endorse PTSD in regard to a trauma. And their CB-PTSD could be coined as a new onset of a new psychopathology altogether. Meaning that without undergoing childbirth, they would not have a mental illness in the form of PTSD.

00:16:54.750 --> 00:17:59.029

Sharon Dekel: Currently, PTSD in DSM-5 does not have a postpartum-specified onset. And this, in part, might lead to the fact that, in the clinical field, at least the vast majority of people that we are studying at MGH often don't even know that they're actually experiencing CB-PTSD. It really goes under the radar of many clinicians. What makes this condition become even more visible is that the symptoms of childbirth PTSD are highly correlated with other known conditions in the postpartum, and this is mainly postpartum depression. There's a lot of interest and a lot of research into postpartum depression, and we know postpartum depression these days is actually the most common condition, most common complication of childbirth. And basically, our data using network analysis shows that the symptoms of PTSD, here in green, are strongly related to some symptoms of depression, OCD, anxiety, and somatization, here depicted in blue.

00:17:59.710 --> 00:19:27.509

Sharon Dekel: So, even if we argue that, indeed, mothers seem to have a new onset of, say, PTSD altogether, a new PTSD onset, it's still somewhat unclear whether this PTSD is actually a sub-syndrome of depression, maybe, actually integral with postpartum depression. So, how much are mothers really experiencing a separate, fear-based disorder that really is classified by PTSD remains somewhat unknown.

So, to address this, I believe, important clinical, pressing issue, we have complemented, in addition to diagnostic assessments and self-report data, which we know even diagnostic assessments are actually coming from what people are reporting to us, we are also including biological assessments in our study, to better understand, or to better offer validation for CB-PTSD. Is that really indeed a condition that would qualify for PTSD; how much is that resembling general PTSD, and how much is actually different from postpartum depression? And the way we're doing it is that we are inviting our participants to the lab, and in the lab, we're hoping to provoke the stress syndrome; and when we are provoking their stress response, we are assessing physiological and neural markers using fMRI.

00:19:27.630 --> 00:20:28.140

Sharon Dekel: And we're using two complementary paradigms. The first is a script-driven imagery, which has been studied, if you'll go on PubMed, many, many, papers use a script-driven imagery to actually validate, initially, PTSD following the Vietnam War and, later on, validating PTSD in other, potentially trauma survivors. So, we kind of adopted a script-driven imagery in which, basically, participants, in this case postpartum mothers, they would hear a recording of their childbirth narrative; and then we ask them to vividly imagine, as much as possible, the childbirth… their childbirth experience. And we are measuring physiological reactivity as well as neural reactivity during this imagery phase. And additionally, we also employed the Hariri task, which is a very common method in which the person is exposed to distressing faces, and this is a common method to basically evoke amygdala activity.

00:20:30.070 --> 00:21:49.689

Sharon Dekel: So, we find that using the Hariri task, amygdala activity is heightened among people who have CB-PTSD. And basically, as you can see here on the left side with the red circle, the higher the amygdala activity on the left side, the higher is the PTSD or CB-PTSD symptom severity.

As importantly, if you can see the gray circle, the amygdala activity was not significantly correlated with PTSD in regard to another trauma. That actually offers validation that, indeed, the amygdala activity is a signal of being exposed to a traumatic event that happened in childbirth, and the alteration related to CB-PTSD symptoms are specific to a childbirth experience, rather to other forms of trauma. And altogether, the data suggest that, like general PTSD, so clearly so much research to show that one of the signatures of general PTSD is kind of heightened or alteration in the amygdala. Here, we find the same thing for CB-PTSD, suggesting a lot of alterations in potentially threat detection, and the threat detection might lead to what we see on the surface as hyperarousal.

00:21:51.620 --> 00:23:07.789

Sharon Dekel: What we also find is when we examine how much the person's amygdala activity relates to how they actually parent their child; and in this task, we observed 5-minute free mother-infant interactions, and we measure what is called the mother-infant bonding. So, the mother-infant bonding is basically derived from these daily positive interactions, and the mother-infant bonding, we know, is a very critical output to how people eventually develop secure and insecure attachments. We find that the amygdala reactivity is positively correlated

with maternal intrusiveness. So, the higher the amygdala levels are, the higher the impairment in the mother-infant bonding in the form of intrusiveness. We find a similar pattern when we look at physiological data. This is data we looked at in the context of descriptive imagery, so as mothers are hearing or imagining their recent childbirth experience and focusing on the most traumatic aspects of childbirth, we see that, this is mothers who have CB-PTSD here in the green.

00:23:07.790 --> 00:24:30.160

Sharon Dekel: The CB-PTSD group has heightened skin conductance and heart rate as they are listening to the story of their childbirth, as they're imagining it, in comparison to people who don't have CB-PTSD, this is a gray. And again, autonomic reactivity is potentially the biomarker of general PTSD, so we're finding, again, similar alterations on the physiological system for people who have CB-PTSD, compared to those who have general PTSD. As you can see, I also have this dotted line with a soldier; and basically, at least in our study, although the sample is small, the autonomic reactivity of these people who have CB-PTSD is actually higher than autonomic reactivity reported in other studies in which most of the samples were Vietnam vets. So, the data could suggest that CB-PTSD is a very extreme form of PTSD in general, in which there are really extremely high levels of impairment on the kind of autonomic system. And again, in parentheses, you can see that the physiological activity does not relate to a stressor that is in regard to another form of trauma. Again, offering specificity to the childbirth event as a causal trigger of these physiological alterations.

00:24:31.420 --> 00:26:01.340

Sharon Dekel: And once again, when we look at whether these physiological alterations are indeed correlated with how mothers are actually taking care of their babies. Again, employing these behavioral observational methods of observing this free play between mothers and their infants, we are finding that the more people have heightened skin conductance and heart rate, we see this is correlated with higher maternal intrusiveness, and also altogether negative dyad. So, really, a lot of tension between the mother and her infant, and this is done usually in our study around 2 to 3 months postpartum. So really in the early postpartum, we see how the alterations of CB-PTSD not only are impacting mothers' functioning, but could be directly impacting how the mother is actually able or not able to successfully parent a child.

Using whole brain analysis, and again, using the descriptive imagery, we find that as mothers are imagining their childbirth experience, there is heightened activation in the insula, which again relates to the threat response and the salience network. And this activation, as you can see here in the red circle, is correlated again with the CB-PTSD symptoms. And again, insula is another area in the brain that we know is often altered as a signature of general PTSD.

00:26:01.370 --> 00:28:10.410

Sharon Dekel: What we further find is, I think, really, really interesting, is when mothers are also listening to the cry of their infants, and we are measuring their neural reactivity through the cry of the infant, the same area in their brain, which is the insula, is actually very likely to be active. So, basically, you could conclude that the imagery of childbirth for these mothers who have PTSD very much resembles the cry of their infant, or even vice versa. The cry of the infant actually resembles, potentially, a traumatic cue. So, the way we're thinking about this is basically first defining CB-PTSD as potentially a cross-generational disorder. And the idea is, under what we defined as the MAM model, which is the Maternal Alarm Model, is that potentially the infant is closely tied to the traumatic childbirth experience.

Therefore, the infant can trigger the traumatic memory, and eventually the stress response. And when the stress response is triggered, this is likely to be very difficult for the person to provide what we call optimal care to the infant, and be able to successfully identify the cues from the infant and respond to them properly. And there is a lot of data to show that when the bonding is impaired, that also increases the risk of child development problems.

So overall, we find in our larger studies that women who have CB-PTSD are more likely to report bonding impairments, and more so, as you can see in the lower part of my slide on the right side, we find that PTSD, as measured in the early months postpartum, here around 2 months postpartum, leads to maternal-infant bonding impairment that is measured here at 3 months postpartum, and these bonding impairments subsequently lead to potential problems in infant development. In our study, we find this relates to communication and social-emotional functioning.

00:28:11.210 --> 00:28:54.969

Sharon Dekel: So, definitely kind of giving us a lot of empirical data to support that CB-PTSD is overall like general PTSD, but in many ways, I could consider it as a disorder in the dyad. There are a lot of direct implications of how the pathology could be indirectly transmitted to the child via impairment in the maternal-infant bonding, and in turn, in the ability of the child to

successfully meet important milestones already in the first year of life. So, let's hear from our study participant about what it means to have the baby become a trigger of a traumatic childbirth experience.

00:28:55.200 --> 00:29:33.880

Study Participant #5: And then every now and then, it's… it's like I'm looking at him, and it's almost for a brief flash, I see right when he was handed to me after the C-section less than half a minute before… I started feeling faint again, and almost blacking out, and then… and then hearing that I was hemorrhaging, you know, and I… I don't want to associate those memories with him, and I'm glad that they are very infrequent events, but… but when they do happen, it is… it's so visceral, and I… I… again, it catches me completely off guard.

00:29:36.370 --> 00:30:29.129

Sharon Dekel: So, this really calls for early on detecting people at risk, and at a minimum, making sure that we screen people who already have the pathology, to make sure they receive appropriate services. So, really, the first step would be screening to reduce the enduring chance of having symptoms over the course of the first year postpartum, to promote recovery, and to maybe even allow opportunities for psychological growth.

Currently, in hospitals in the US, to the best of my knowledge, and also globally, there is no routine screening for PTSD or CB-PTSD, even among women who have medically-complicated deliveries. So, really, people are just not screened; and therefore, this remains, again, as I would argue, a very invisible disorder.

00:30:29.200 --> 00:31:45.149

Sharon Dekel: We do have screening for depression, so the EPDS, Edinburgh Postnatal Depression Scale, is routinely performed in most hospitals in the US to screen for postpartum depression, which is very important and great. The problem is that the EPDS doesn't really assess many of the PTSD symptoms; so hyperarousal, avoidance, intrusiveness, it's not really the best questionnaire to detect PTSD. So, what can be done to improve screening for maternal CB-PTSD? And we have shown that a simple self-report questionnaire, in this case the PCL-5, which is, again, as I mentioned, the recommended measure to eventually have a provisional diagnosis of PTSD before more thorough evaluations are possible. The PCL is commonly performed in many other trauma settings, and we found that the PCL for the postpartum women can also

perform very well. So basically, our findings show that if you take the PCL and you compare it against the CAPS, which is a diagnostic assessment, overall, there is a high level of accuracy in the diagnosis.

00:31:45.150 --> 00:33:14.189

Sharon Dekel: And overall, in order to identify women who have clinically meaningful CB-PTSD symptoms, we would suggest a cut-off score of 32 on the PCL, so anybody who has 32 and higher on this simple questionnaire. And if we want to improve sensitivity; let's say we're thinking about initial screening in the clinic to make sure we're not missing anybody who might develop PTSD, then a better cutoff score would be 28.

Now, the PCL-5 is given usually, ideally, at least based on the formal way that the questionnaire's instructions are, it's usually supposed to be given one month following the trauma. And why is that? Because, indeed, PTSD by the DSM can be diagnosed, actually, within one month after the traumatic exposure.

We want to hopefully move into the realm of prevention, and the question is, how can we, early on, detect who is likely to have CB-PTSD, even before screening makes sense to implement. So, a basic way to think about risk factors that would eventually allow us to develop a screening model would be using the diathesis-stress model. So based on this model, we're thinking about the person's vulnerability; so how is the person functioning, and what is their psychological baseline before the trauma exposure?

00:33:14.090 --> 00:34:11.099

Sharon Dekel: And then we take into account the level of exposure. And we take into account the level of exposure in the case of child with PTSD; we've been very much interested in what I call the objective stressor, or the magnitude of the objective stressor. It's basically what actually happened in labor and delivery. How much were there unplanned interventions?

And of course, to what degree did this person go [into] OB complications? At the same time, we're also interested in subjective experiences according to the DSM-IV. Basically, to what extent did the person appraise the event as a trauma, and what was their initial emotional response? And in general, based on the diathesis-stress model, the PTSD constellation is a combination of your premorbid risk factors and stressors, or what we call peri-traumatic factors that entail or take place around the time of the, in this case, childbirth.

00:34:11.429 --> 00:35:39.079

Sharon Dekel: And using machine learning models, we really wanted to identify the most important risk factors for CB-PTSD. And again, CB-PTSD, in general, is a heterogeneous disorder and, therefore, we're likely to find many risk factors. And what we identify, if you look at the middle part of my slide, in terms of the objective stressors, or the birth stressors, we're finding that CB-PTSD symptom severity is predicted by more complications in labor, delivery, having an unscheduled Cesarean, higher level of pain in labor and pain in delivery, and also by the time when the childbirth event actually took place.

Then, if you look at the right side, we're also taking into account in our model what you call the infant stressors. And I consider the infant stressors as actually already amplifying a stress response that is unfolding. So, maybe without these stressors, there's a better chance to recover, and the stressors amplify your likelihood to develop PTSD. And these infant stressors include less breastfeeding, less skin-to-skin, or no skin-to-skin, no breastfeeding, and, most importantly, infant complications that were measured here by the infant going to the NICU. So, in many ways, the idea is that people are actually having a double level of trauma. They have the complications, and then there's medical complications in the infant, and separation from the infant, and potentially risk for the life of the infant.

00:35:39.080 --> 00:37:17.319

Sharon Dekel: And this kind of double trauma definitely increases your risk of having CB-PTSD. Of course, as you can see on the left side, we're also identifying what we call vulnerability factors, factors in the person or the person's life history that would increase the risk for CB-PTSD; and these vulnerability factors likely resemble general PTSD, which means history of mental illness, history of trauma exposure besides the recent childbirth, and a history of OB complications.

What is really, I would say, the most notable finding in our analysis is, you can see here, as indicated in a red circle, the subjective stressor, or the magnitude of subjective stressor, which is basically how much do you perceive the event as threatening to your life and how much you felt emotionally overwhelmed; that seems to be the most important predictor of who is likely to develop PTSD or not. And of course, you know, the objective magnitude of a trauma often correlates with a subjective event, correct? So, if you have more complications, you're likely to perceive the trauma as more stressful; but it's not always 100% of a correlation, and we do see some people who have, let's say, less severe complications. Nevertheless, appraise the trauma as very upsetting to them, and vice versa. So, really, it seems that the subjective level of

exposure, how much you appraise the trauma as upsetting in a very critical degree, is a strong risk factor for developing PTSD.

00:37:19.240 --> 00:38:29.739

Sharon Dekel: So, if this is the case, we were very interested in understanding- can we develop a screening tool to detect PTSD, CB-PTSD, by actually focusing on the subjective level of exposure? And the way we were thinking about it was, basically, let's have mothers write a brief narrative, open-ended narrative, of their childbirth experience. And the thought was that this narrative would basically depict their subjective appraisal of the event, and how much they were emotionally upset by the event. So, in this study, we were able to assess more than 1,000 women, and we asked them to provide a narrative that has a minimum of 30 words. On average, actually, mothers provided 145 words.

And then we used machine learning models. So, basically, we took this textual information. The textual information was converted into numerical information presented by vectors. These are kind of meaningful numbers coming from the text. And, basically, we fueled a machine learning model with these features.

00:38:30.040 --> 00:39:43.749

Sharon Dekel: And we find that, overall, among those who have CB-PTSD, if we just look at their narrative and the words that they use in the narrative, and we use AI to basically understand what these patterns mean, vis-a-vis their psychopathology, we're able to accurately identify as much as 85% of those who actually had the pathology. So that looked very, very promising.

And more recently, under NIH funding, we were able to find that, in addition to the birth story, if you also are able to have some objective marker of the trauma, which would be, again, in the form of medically-complicated information about the childbirth it could be available in medical records- in addition to asking very specific questions about specific emotions, this very low-cost and brief way of assessing level of acute stress and risk for CB-PTSD that could potentially be done at the person's bedside, this model using AI could actually offer quite promising sensitivity. As you can see here, 90%, so again, the vast majority who had CB-PTSD were able to be identified based on this textual information.

00:39:44.080 --> 00:40:55.240

Sharon Dekel: And, as you see, specificity is 95%, meaning that the chances of a person being detected as having PTSD, if they didn't, was very, very low. So, our false positive cases were very, very low, and we're hoping under NIH funding to continue and develop this AI tool eventually to see its ability to actually perform in real time in the clinic at the person's bedside.

So, early prevention is very important for any psychopathology. It's especially important for CB-PTSD because CB-PTSD offers an optimal opportunity for prevention.

And this is because, in general, when people are exposed to trauma, we don't really know when the trauma will happen. If the trauma occurs, we don't know for how long the trauma will continue. We often don't have access to survivors. Here, in the case of CB-PTSD in general, childbirth is a time-defined event. People, for the most part, are actually in the hospital, and especially those who have a medically-complicated delivery, they're actually staying in the hospital for a couple of days.

00:40:55.550 --> 00:42:02.819

Sharon Dekel: So, this really means that we could screen them early, and also potentially intervene early in-house, even before people actually go home and are discharged, and potentially offer, maybe, some level of prevention. Now, prevention might be possible, because as we're thinking about PTSD in general, there is data to suggest, you know, in accord with the golden hours, that really what happens in the immediate phase, post-trauma exposure, or even as the event unfolds, there are these crucial biological processes that relate to fear learning and memory consolidation, and these biological processes might be implicated in the pathophysiology of PTSD.

So, the idea is that if we can, early on, identify people who are likely to have CB-PTSD, and offer them intervention at bedside, potentially, we could avert the stress response. And in turn, also, therefore, avert the PTSD's trajectory and reduce the occurrence of CB-PTSD.

00:42:03.060 --> 00:44:23.970

Sharon Dekel: As importantly, the immediate postpartum is also considered a sensitive time for bonding. So, as we are reducing the stress response with interventions, potentially we can boost maternal bonding to really optimize the successful mother-infant dyad outcomes.

So, there is a lot of opportunity. The research is a little bit, still behind. We performed a meta-analysis in 2024. I don't think so much has changed since then, only maybe a few studies; and

overall, looking at what we call secondary prevention for CB-PTSD, basically interventions, RCTs, randomized control trials that have been tested in the hours, days, and weeks following childbirth, before the one-month mark, before PTSD can be officially diagnosed, altogether is very, very, very few studies.

What we do know is that educational materials, for example; if you have a person who had a medically complicated delivery, and they are experiencing some degree of distress, if you give them a brochure and you tell them how PTSD would look like, if they would develop it eventually, this information doesn't really help. We also identify, based on the meta-analysis and the existing studies, the psychological debriefing given to people at risk for CB-PTSD, again, doesn't seem to be so helpful. What does seem to be helpful, but again, the studies are small, so we can't really conclude clear-cut conclusions.

Nevertheless, with what we currently do have, it seems that trauma-focused therapies that focus on the reprocessing of the childbirth experience in different ways; this is through narrative writing, through EMDR, or different versions of cognitive behavioral, there does seem to be quite promise to suggest that this early trauma-focused therapy could be beneficial. And, currently under NIH funding, we are testing, indeed, whether expressive writing, briefly short writing for three consecutive days about your childbirth experience in people who had complicated deliveries and report acute stress symptoms, whether the expressive writing intervention, again, very low cost, very easy, we do it remotely, whether this intervention could eventually reduce or decrease the chances of having PTSD.

00:44:24.150 --> 00:45:56.060

Sharon Dekel: And we, additionally, based on our meta-analysis study, find the psychological counseling that are performed usually by midwives, again, at bedsides, in which people, kind of… it's more of an open-ended, kind of one-on-one dialogue with a patient to really process emotions and kind of make more sense of their childbirth experience. Psychological counseling also seems, potentially could be helpful in buffering the stress response and reducing the likelihood of having PTSD symptoms that remain over the course of the first postpartum year.

Some evidence might suggest that blocking the trauma memory consolidation- there has been some work on using Tetris game, that people really, in the first hours after childbirth, they play the Tetris game to kind of, you know, basically break the memory consolidation of the trauma; that seems to be maybe also promising, as well as mother-infant-focused interventions.

But overall, again, my slide basically calls for much more research. And, of course, antidepressants, which are often prescribed for people who have postpartum depression, sometimes also for people who have PTSD. Antidepressants, we know, cannot really help in

preventing PTSD of any kind of form, and also for CB-PTSD. So, definitely, we are hoping to, with more science and more funding, to identify novel targets for biological intervention in the form of psychopharmacological options for these mothers.

00:45:57.410 --> 00:46:07.130

Sharon Dekel: Overall, I want to thank my lab members who have been working very hard to provide education and inform the public, and NIH, and the perinatal providers, and the scientific audience about what it means to have traumatic delivery and develop PTSD.

And, of course, I want to thank my collaborators at MGH. I'm really very, very grateful for all the support from the MGH OB department, as well as my other collaborators within psychiatry and neurology, collaborators with whom I collaborate globally, in Nigeria and Israel. And, of course, this research could not have been done without the generous support of the NIH and Harvard and MGH, and the Brain & Behavior, and as well as other private foundations, and the really generous help of participants who were very open to sharing their experiences and participate in the various assessments that we have been performing over the past decade. Thank you so much.

04:38:53.990 --> 04:39:32.399

James Naifeh: Thank you, Dr. Dekel, for sharing your incredible work that has shed much-needed light on the topic of childbirth trauma. We now have a break until 2.45 p.m. Eastern Daylight Time, which is just over 15 minutes from now. At that time, we'll begin the last presentation of the day, followed by our Q&A. Please remember, you can submit questions at any time using Zoom's Q&A feature at the bottom of the window. And please specify to whom you are addressing your question. Also, here's your last chance to visit our poster gallery to learn more about the incredible work being done by your fellow attendees. We'll see you after the break.

CONFERENCE BREAK

BRUCE D. PERRY, MD, PHD

PRESENTATION

04:54:58.540 --> 04:58:21.600

James Naifeh: Welcome back. Our final presenter today is Dr. Bruce Perry. Dr. Perry is the Principal of the Neurosequential Network and an Adjunct Professor at La Trobe University. His work on the impact of abuse, neglect, and trauma on the developing brain has informed clinical practice, programs, and policy. Over the last 30 years, Dr. Perry has been an active teacher, clinician, and researcher in children's mental health and the neurosciences, holding a variety of academic positions, including at the University of Chicago School of Medicine, the Baylor College of Medicine, during which time he was Vice Chairman for Research in Baylor's Department of Psychiatry, and also Chief of Psychiatry for Texas Children's Hospital. And from 2009 to 2024 at the Feinberg School of Medicine at Northwestern University in Chicago.

Dr. Perry co-authored several popular books, including *The Boy Who Was Raised as a Dog*, a bestseller based on his work with maltreated children, and *Born for Love: Why Empathy is Essential and Endangered*. His most recent book, *What Happened to You? Conversations on Trauma, Resilience, and Healing*, which he co-authored with Oprah Winfrey, has been translated into 26 languages and spent over 100 weeks on *The New York Times* bestseller list, after reaching number one on the list in April 2021.

Dr. Perry has conducted both basic neuroscience and clinical research. His clinical research and practice focus on the complex impact of developmental adversity. His work on the positive and resilience-building effects of healthy relational connections has been instrumental in describing how childhood experiences, both negative and positive, change the biology of the brain, and thereby the health of the child. Dr. Perry's clinical work has been focused on integrating emerging principles of developmental neuroscience into clinical practice. This work has resulted in the development of innovative clinical practices and programs. These include the Neurosequential Model, a developmentally sensitive, neurobiology-informed approach to clinical work, education, caregiving, and sport. Community and government agencies have consulted with Dr. Perry following many of the most high-profile disasters, mass shootings, and other traumatic incidents involving children.

Dr. Perry has published over 500 journal articles, book chapters, and scientific proceedings, and is the recipient of numerous professional awards and honors. In 2024, he was the recipient of the National Alliance on Mental Illness, or NAMI, Scientific Research Award, and the NAMI Exemplary Psychiatrist Award. He has presented about child maltreatment, children's mental health, neurodevelopment, and youth violence in a variety of venues, including to policymakers,

such as at the White House Summit on Violence and the U.S. House Committee on Education. Dr. Perry and his work have been featured in a wide range of media, including 60 Minutes, National Public Radio, The Today Show, and The Oprah Winfrey Show, among many others. We will now begin Dr. Perry's presentation, which is titled, “Application of a Neurodevelopmental Framework in Clinical Practice: The Neurosequential Model of Therapeutics.

Total Conference Timestamp: 04:58:30.630 --> 05:47:58.039

Within-Segment Timestamps below

00:00:04.260 --> 00:01:32.879

Bruce Perry: My name is Bruce Perry, and I'm very happy to be here. I appreciate the opportunity to share some of our work. I, like many of you, have been working with individuals and families that have been impacted by all kinds of adversity over their lives, and part of what I have been doing with the work group that I am part of is trying to figure out ways to better understand how people are impacted by experiences, both good and bad. And today, I'm going to share with you a little bit about the progress in our thinking in developing and implementing a model for approaching clinical work; that is attempting to integrate some of the learnings from developmental psychology and from the neurosciences in ways that help us do our work in a more effective way.

And I just want to make sure that you appreciate that I'm presenting at a point in time where we have made a lot of progress, but we still have a lot of progress yet to make; and hopefully this snapshot will give you some sense of the way we're thinking about this, and maybe helpful for the way you think about your work.

00:01:33.190 --> 00:03:27.359

Bruce Perry: As all physicians, I'm very slide-dependent, so I'm going to go ahead and start showing my slides, and go from there. So… as you probably know from the title of the presentation, I'm going to talk about what we call the Neural Sequential Model of Therapeutics, NMT. And I think the easiest way to kind of understand what that is, is to get an appreciation of the evolution of this approach. And it really all started, for me, when I was a neuroscience undergraduate in college.

And this, of course, is a picture of the brain. And as an undergraduate, one of the things I was looking at, as part of a bigger research team, was the development of the stress response systems in the brains of rats, predominantly. The idea was, of course, that we would learn things that might be relevant or helpful to human beings; but it was fundamentally neuroscience research, looking at core regulatory networks in the brain, how they developed and how their organization was influenced by early developmental experiences. And I think everybody in our field knows what the locus coeruleus is. This is this nucleus down here in the lower part of the brain. It's a norepinephrine-containing nucleus. It has, basically, a wide distribution in the brain,

and plays a major role in all kinds of functions, including mediating and modulating responses to various stressors.

00:03:27.910 --> 00:05:36.509

Bruce Perry: And so, as I studied that, I learned a lot and focused a lot on the human brain. And one of the things that I learned, and I think most of you know, is that the brain is pretty frickin' complicated. And so, I, both as an undergraduate and then as a graduate student in neuropharmacology, I was looking at all of the complex component parts of a neuron. So, and the reason I'm going to talk about this, is that part of our challenge when we do clinical work is that we have to essentially try to do effective translation of a huge catalog of complex content in ways that might ultimately be useful for the clinical work that we do. And so, I learned a ton about the brain… about neurons, and I focused on synaptogenesis, and what happens in the release of certain neurotransmitter substances, and what happens with the reuptake, and how there are genetic differences in the expression of proteins that are intrasynaptic, that play a major role in neurotransmission. And what I realized, and what I was very well aware of, was that the brain is incredibly complex.

Now, this is not my work, this is other people's work. And it's just illustrating the number of intracellular proteins that have to do with just synaptic functioning. And here's some more recent stuff that, you know, images, beautiful, beautiful images, elegant work, that illustrates, again, the complexity of the human brain. And I learned a lot about that. Learned a lot about studying the neurobiology of how neurons differentiate, how they migrate, synaptogenesis, and all of the incredibly complex phenomena that have to do with the development of the human brain.

00:05:37.150 --> 00:07:29.289

Bruce Perry: Just to kind of give you a tiny snapshot of this complexity. If you just start to look at the component bits, just the component parts, of neurons and neural networks and intracellular functioning in neurons, and then add in the dynamic activity, you essentially get to the point where you realize that the complexity of the brain is well beyond the capacity of any human being to actually grasp.

Now, that doesn't mean that there are not things or principles or concepts that each of us can learn; but the reality is, in order for us to essentially make sense out of all of this, we have to use models. And everybody uses models. And just to be clear. See this picture? This is a model. This is not really the brain. The brain is not transparent. The brain doesn't have colored

components that show you this stuff. This is a model. The question is, is it helpful? And I would answer that, in some ways, this model, even though it is not the truth, it captures some things that are true. It's helpful. You can teach people about, for example, the transmission of information from the eye into the lateral geniculate over to the visual cortex, and you can use that to teach people about vision.

And so, is this true? No, this is a model, this is a drawing. Is this really true? No, this is a drawing. Even this elegant, elegant, beautiful piece of work, this is a reconstructed model.

00:07:30.070 --> 00:09:25.639

Bruce Perry: And the point I want to make is that in order to capture these complexities, we have to use simplified versions of these concepts. And the dilemma of that is that when you use a model, you will necessarily create things and summarize things that are not completely true. They're not completely accurate. And so, what I want to tell you… this is probably not what anybody really wants to hear; but from this point on, as I talk to you about the Neurosequential Model, everything I tell you is essentially not true in some way.

The question that we've been asking ourselves is: Is the model that we've developed, is it helpful? And that's what I'm going to talk about. Is this model helpful in understanding individuals and providing effective therapeutic suggestions and educational supports and enrichment experiences that are going to help this person get on a healthy developmental trajectory and heal from past developmental experiences. So… A couple of things about selecting a model. I'm going to just, you know… I think a lot of you have probably seen something like this. This is a model. This is sort of a heuristic; it's a teaching device to teach people, help people understand some of the stuff about the brain. And I would argue that for communicating to a parent about the brain, this might not be that helpful. Actually, even for organizing your own thinking about what's going on in the brain of somebody. I don't know that this is that helpful.

00:09:26.080 --> 00:11:25.370

Bruce Perry: Now, it's not that this is bad. It's just you can tell that this is developed by a space shuttle guidance system engineer. Looks like an engineering diagram. So, I'm going show you something that's just… you guys are probably not going to feel all that comfortable with it, but the reality is, this is the model that we've settled on. And the reason we settled on this is that, when I was a neuroscience… you know, doing my research in neuroscience, at the same time that I was doing my residency in psychiatry and child psychiatry, I found myself, time and again,

drawing an upside-down triangle to try to explain to somebody why I thought that their issues with relationships, and their difficulties with concentration and focusing, and the difficulties with sleep, and their essential physiological instability, that these were not four different problems.

I would talk to them about the fact that, in the lower part of your brain, we have these really important neural networks that originate down here; there's norepinephrine, dopamine, serotonin, and collectively, these neural networks reach every part of the brain, and they go out into the body through the autonomic nervous system, and they influence the neuroendocrine systems, and all of the systems that influence your heart, your lung, your gut, your skin. And these systems collectively play a major role in keeping you in balance. They're involved in helping you regulate hunger and satiety, and sleep, you know, wakefulness and sleep. They help you focus attention, they help you respond to external threats.

00:11:25.600 --> 00:13:55.369

Bruce Perry: And the elegant design of this is that all of the feedback from the inside of your body, and all of the input from the external sensory apparatus you have go to these lower parts of the brain initially, and tell you what's going on. And so, these systems help your brain monitor and respond to everything that's going on inside you and everything that's going on outside you. And I kept using this diagram and saying, listen, this is why I think the bad things that happen to you, these stressful things, these traumatic experiences, because of what we know about neuroplasticity, they changed the activity, the set point of some of these systems, and it influenced not just sleep, but also appetite, and the way you form relationships, and the ease with which you can learn to read, etc., etc., etc. So, you don't have four different disorders, you've got a regulatory issue that is going to have multiple areas of impact throughout your brain and body.

And of course, all of you, hopefully, those of you who are thinking about the ACE studies, our understanding… that if these core regulatory networks are impacted by adversity… And again, this is a whole narrative that's sort of not part of this presentation, but… you've all learned about this, that X patterns of activity, of activating these systems that are unpredictable and extreme and prolonged and uncontrollable will lead to changes in these systems so that there is an alteration in their activity and reactivity, which then impacts end organs. And the end organs can be anything in the periphery that is influenced by these core regulatory systems. Your neuroimmune system will be altered, your skin will be different, the way you digest will be different, your regulation of your heart and your lungs will be different; and you will be

changing risk for the development of problems in every system that is essentially impacted and either mediated or modulated by these core regulatory networks.

00:13:56.580 --> 00:15:50.320

Bruce Perry: So, if you disrupt core regulatory network development in utero, you're going to have a cascade of increased risk in all these different domains. If you have primary attachment disruptions, which play a major role in organizing those stress response systems, you're going to have increased risk for these global health problems. And if you have experiences of sensitization, which could come from lots of different things, including chaos, unpredictability, overt threat, what we would consider classic capital T trauma, that will alter the reactivity of these stress response systems, and then lead to, again, a cascade of risk. And this is basically…on a very, if you will, 10,000-foot flyover, these are the mechanisms by which the ACE epidemiological studies are the result of, right? You will predictably find all of those problems that the ACE studies say you're at risk for, because you've had developmental adversities.

Now, this is one of the most important and, I would say, enduring observations of a huge body of research that's been around for 50 years, more or less, that reinforces what I've just talked about. That when you activate the stress response networks, that means norepinephrine, dopamine, serotonin, in any way, you can do this with an external drug, you can do this with any variety of stressor. When there's unpredictability, and it's extreme, and there's no controllability, and it's prolonged, these systems become sensitized.

00:15:50.560 --> 00:17:42.640

Bruce Perry: And what sensitization basically means is you change your stress reactivity curve from being proportional to external challenge. And where there would be a proportionally appropriate internal activation to a sensitized reaction. So, rather than having an active alert response to a daily challenge, you have a fear response to a daily challenge. And, again, those of you who've worked with children who have come from backgrounds of abuse and neglect and chaos and threat and trauma, you know that they have all kinds of overreactions to relatively minor challenges.

Transitions, tests, you know, somebody saying no. And I, again, I could go on and on about this, but the bottom line is, part of what we were able to do, and part of what we have used this primary heuristic for, is to help teach people, including our colleagues, a little bit about some of the neurobiology of trauma, neglect, stress, and so forth.

Now… This is pretty simple. There's a couple key things here about this heuristic that we've emphasized. And again, the reason that we've called this the Neurosequential Model, is… The neural part first; I've been talking about it a little bit, but… I remember sitting as a resident in front of a young child who was one of the first, if you will, patients I ever had in child mental health.

00:17:43.810 --> 00:19:56.419

Bruce Perry: And he had been referred to me because he was struggling in school, didn't do well with his peers, had attentional problems, was impulsive, was aggressive, wandered the house at night, couldn't settle down, had all kinds of classic symptoms of being what we would call a sensitized stress response system.

Now, of course, he got labeled as ADHD because, as many of you who have a lot of experience with trauma know, our field has had kind of a… it's been a struggle for our field to really understand and incorporate trauma, and developmental trauma, particularly, into our conventional DSM framework. And I think that, in part, this is one of the things that is motivating some of the efforts to push for changes within the DSM… is that it's not capturing certain things very well. And trauma, and developmental trauma in particular, are very confusing for the DSM currently. And so, what'll happen is, kids that have early developmental experiences will end up meeting criteria for all kinds of stuff. This, of course, is not very clinically useful.

And so, when I first started training, this is the kind of thing that I would see. I would see that individuals who had early developmental trauma characterized by attachment problems, and multiple placements, and family issues, and exposure to community violence, and all kinds of things, they would be viewed in a very odd… I mean, from my perspective, a very odd way. These kids confused traditional frameworks. They end up with incredibly inappropriate polypharmacy as a way to treat them. And they end up with multiple placements, and they get bounced around the system, and passed on, and misunderstood.

00:19:56.810 --> 00:21:59.739

Bruce Perry: And part of what I started to do is think about… I had been studying in animal models the impact of the nature and the timing of stressors on how the brain developed. And what I saw, and what many other people were seeing, was that early developmental stressors could have profound and enduring impact on the neuroendocrine system in animals. And it was different. If the pattern of a stress was a certain thing, the animals actually, as I showed you

earlier, could develop a form of resilience. If it was unpredictable and uncontrollable to the animal, they would develop incredible sensitivity, even to the point where many of them would have tiny little stress-activated seizures.

So, there were very different patterns of experience that happened that could result in very different organization in the central nervous system. And… all the way back in 1998, I took a group of four, basically, 11-year-old kids who all had exactly the same score on a conventional trauma inventory about traumatic experiences. Traumatic experience exposure was exactly the same. But if you look at this pattern of developmental experience, this is age… And this is basically severity, of the negative or adverse experience, and this is basically sexual, domestic violence, physical abuse, emotional abuse, and other. And you can see all four of these kids had different patterns of early developmental experience.

00:21:50.860 --> 00:24:05.849

Bruce Perry: And they had very different patterns of, if you will, phenotypic expression of their symptoms. They all had problems, but they were all different. And the problem was, using our DSM labeling and the metrics that we had at the time, these were all considered equivalent individuals. They were put in the same bucket. And I recognized that that was just not very helpful. And so, I just started to get a little bit more courageous about thinking this through. Part of what I thought about was… I had just come out of the, you know, when I went into psychiatry, I'd just come out of the cardiac ICU. And I had seen lots of different folks, and all kinds of different problems, and I just sat down and said, alright. The heart's got two billion cells. Most of them are similar. There's a few subsystems, but there's not that many functions that the heart mediates. You know, lub dub, lub dub… And I don't mean to offend any cardiologists out there, but, you know, it's kind of… you're pumping blood.

And there's other stuff that's important too, but if you compare that to the brain, the brain has 86 billion unique neurons. They're all unique, they're all different. Twice as many, probably, maybe not, glial cells, but they also have many functional roles in the central nervous system. There are hundreds of major neural networks that mediate thousands of functions and subfunctions. Yet, if you go into a public mental health clinic and look at all of the DSM labels, you've got… eight or nine. And most kids have multiple of them. In other words, we're completely inadequate in describing what's going on with these kids and finding ways to study them effectively.

And so, again, this is the kind of stuff that we were seeing. We were seeing different… and just so you know, this graph right here on the left-hand side of the slide.

00:24:06.830 --> 00:26:11.489

Bruce Perry: This is from our Neurosequential Model of Therapeutics web-based metric. It's a simpler version of that very detailed developmental experience graph I showed you. And again, one of the things I showed you, you know, what I'm looking at here is adversity, right? And kinds of adversity. What I recognized early on is that developmental risk is not just a fact related to adversity, it's related to the counterbalance… the balance between adversity and relational buffering, protective buffering. And so, if you assess and measure both adversities and relational connectedness at the same time, you get an estimate of developmental risk.

And so, this is part of our web-based tool that I'll talk about in a minute. But what I want to show you here, really, was the dilemma that I was facing, and I think we all were facing, when I started to go through and look at the developmental histories of these kids. This, for example, is a six-year-old who had lots of developmental adversity early, and then ended up in a pretty healthy environment. But still, at the time that he was evaluated at age six, even long after getting out of that environment, he met criteria for these issues. And, when we did spec scanning, had areas of, if you will, abnormal functioning.

And again, I don't want to go into this in great detail but, to simplify this, anything that is not gray is at least one standard deviation different from a large population of over 150,000 cases of children who are neurotypical. And so, if it's not gray, it's abnormal.

00:26:11.730 --> 00:27:38.640

Bruce Perry: So, I just want you to kind of look at this, get a gestalt of… there's a lot of stuff here that's either underactive or overactive. Now here's a completely different child. Thirteen-year-old, same thing, early developmental risk; and at age 13, met criteria for all of these things. And this is what his spec scan looked like. Kind of the same, but different.

And this is another 13-year-old. Different pattern of experience, a little bit more prolonged, pretty adverse, but same DSM labels. Different looking brain. Now, I'll talk about these in a minute, but the point that I wanted to make here is that every one of these kids had the same DSM label, but had very different phenotypic presentation, very different neurodevelopmental presentation, when you look at various brain-related biomarkers. And we've done this with… we've done over 5,000 comparisons of these spec scans, with the Neurosequential Model of Therapeutics heuristic map that I'm going to teach you about.

00:27:39.240 --> 00:29:15.070

Bruce Perry: So, here's kind of the dilemma with this; and again, I want to be really clear. I do know that function in the brain is not localized to a region. I do know that. That's actually a big part of the work I did when I was doing my neuroscience research.

However, what I can tell you is, that there is a hierarchy of organization in the brain. And that if you have some information about… if you know something, a little bit, about a person's appetite, and about their sleep, and about their capacity for attention and arousal, that will tell you something about how well-organized the networks in the diencephalon are. And so, even though CNS function; it's really an oversimplification to think about a brain region as being responsible for a function. You can do the opposite. The function can tell you about the organization of a region of the brain. Let me say that again. And all of you probably have had this experience, or known someone. If somebody has a stroke, and they lose the capacity for speech and language, that loss of speech and language tells you something about the organization of the cortex.

00:29:16.420 --> 00:30:59.590

Bruce Perry: That doesn't mean that speech and language are only a product of that area of the brain. Speech and language are a product of multiple interrelated networks that span multiple regions. The reason I'm making this sort of fine-tuned distinction is that we actually, in the development of our metric, the NMT metric, tried to essentially figure out a way to make a reconstruction of somebody's organization of their brain by looking at various functional capabilities that you could measure pretty easily.

And so… the NMT metric that helps us make decisions about how to select and sequence therapeutic interventions is essentially put together by looking at how certain functions are… Are they age-appropriate? Are they developmentally appropriate? And then using those functions to create a reconstruction of how an individual… how their central nervous system appears to be organized. And let me illustrate this so it makes a little bit more sense. Let me give you a few examples.

00:30:59.760 --> 00:32:58.260

Bruce Perry: So, if you do conventional IQ testing, that gives you some information about cortical organization. If you do the trauma symptom checklist, [that] gives you some information about diencephalic and limbic, and some cortical capabilities. So, you get a little bit of a snapshot about how different parts of the brain are working. If you do a speech and language

evaluation, you get some snapshots about how these cortical areas, and even some of the brainstem and diencephalic areas involved in speech and language are working. And so forth. And so, we developed a semi-structured interview process that allows us to create and look at how well-organized somebody's central nervous system is. Now, the scoring… just let me take one second here to describe the scoring.

The scoring of this is based upon comparison to a healthy, fully functional adult brain. So, a newborn has a brainstem that is moderately organized compared to an adult brainstem, and a cortex that is pretty undeveloped compared to an adult, right? We don't have speech and language. And as you get older, your brain organizes and becomes more adult-like in functioning from the bottom up, and this is the typical organization of a two-year-old. Brainstem's pretty similar to adult brainstem functioning. Cortex, you know, diencephalic functioning is emerging, corticolimbic functioning is getting more adult-like, the precursor capabilities of full mature functioning are emerging; and if you do this all the way up through adult life, you get these typical maps.

00:32:59.220 --> 00:35:04.719

Bruce Perry: The place where this model starts to be helpful is when you actually compare it to… oh, this is our early childhood map. When you start to compare it to an individual who has a fully organized, age-typical central nervous system. And this part of what you all probably have seen, and what we see all the time, is children who have histories of developmental trauma end up with developmental lags. They have certain systems that appear to be disorganized, they have other systems that appear to be undeveloped. And the Neurosequential Model; the fundamental primary organizing principle of our clinical approach is that we want to meet children where they are developmentally.

And so, let's go back to this. You can see this is an age-typical 6-7-year-old, and this is the client that we were talking about over here, who had this early developmental adversity, and the resulting, if you will, abnormal disorganization and organization of key systems in their brain. And you guys can't read this, but basically, everything over here that's red is consistent with sensitized core regulatory networks.

Hypervigilance, sleep problems, inability to modulate their reactivity. These tell us that there's sort of attachment-related problems. And so, rather than putting this 6- to 7-year-old into a conventional therapeutic approach that would be appropriate for them developmentally, we recognize that this is a kid who really is not going to be able to benefit from cognitive-dominant treatment.

00:35:06.020 --> 00:37:13.520

Bruce Perry: These lower systems need to be organized and better functioning before we create the expectation that they can do more conventional relational and cognitive therapeutic work. Hence the sequential part. And we use these metrics, we use these maps, to help us essentially create the beginning of an effective treatment plan to select and sequence activities and interventions that will plausibly result in meaningful change in the networks that appear to be abnormally organized and abnormally functioning.

Let me just show you a few of these. This is a 9-year-old client who had profound and severe developmental neglect and attachment problems and, unfortunately, went from place to place to place to place; all of these places essentially viewing him as, when he was six, they had expectations that he would act like he was six. But because he had the developmental capabilities of a two- or three-year-old, he was continually failing, and continually unable to meet the adult expectations that he act his age. And many of the programs that these kids get put into use a predominantly behavioral program, where there's points and levels, and there's punishments. And the truth is, those approaches do not work with kids who are developmentally organized this way, and kids who have a sensitized stress response. And, obviously, I don't have time to go into that in great detail, but the bottom line is, this is a kid who is going to require tremendous somatosensory activities that would be more typical of the developmental experience of an 18-month-old than a 9-year-old.

00:37:13.890 --> 00:39:14.470

Bruce Perry: And so, this team… here's kind of the heartbreaking part of this. And I just want you to hear me clearly. I am not saying that cognitive-behavioral stuff doesn't work. I'm saying that it works great when you have the cognitive capacity to take advantage of that intervention model.

This is a sequenced intervention that started with a very heavy somatosensory… therapeutic massage, music and movement, all kinds of, it's kind of an occupational therapy diet-guided day. And there were minimal cognitive expectations on this child. He was not put into an educational environment where he would clearly fail. Over time, he became more mature, more regulated, and more capable of benefiting from both parallel and then ultimately dyadic relational activities. This is more play therapy-related stuff. There is also lots of somatosensory work that happened here, and then ultimately, when he got to this point, this child was able to do traditional cognitive-behavioral work. Now, the somatosensory work continued, the relational work continued; that cognitive work was layered on top of it.

And what we saw was lots of progress. And again, back to the point I was trying to make earlier that I forgot to make, was that this child had been, prior to coming into this setting, had been in a… it's a good place, but they were using and were only getting funded to do evidence-based interventions. And so, they were trying to do TFCBT with this 9-year-old who was profoundly developmentally delayed.

00:39:14.810 --> 00:40:52.669

Bruce Perry: And all they did was have session after session after session after session while they chased the kid around the room. He didn't make any progress. Didn't change at all. In fact, probably got worse in many regards, because he got bigger, and his tantrumming became more aggressive and scary, et cetera, et cetera. Now, we literally have hundreds of cases like this. And this approach, and I haven't completely presented this in an ideal way, but this approach has attempted to help clinicians create a structured understanding of the developmental history of a child by measuring, in a systematic way, using a web-based tool, both adversity and the timing of the adversity; but also, very importantly, positive relational buffers, and the counterbalancing experiences, and their timing, and the nature of those experiences, along with current functioning.

The current functioning is essentially simply organized in a way that allows us to create this brain map. And then we look at the current relational milieu, which is very important in determining whether or not we're going to be able to provide the density of therapeutic experience that is required.

00:40:52.790 --> 00:42:49.190

Bruce Perry: Now, we have a version of this that's for children less than six, and we have a version of this that we use across the full life cycle. This is an exam… just so you get a sense of what the report looks like after you do this. This is from our conventional metric. This is the developmental history. A little bit of a chart here. This shows when there was the highest developmental risk, and then what happened as they were taken out of that adverse environment. This is a really important part, very simple tool. It's current relational health, but it's the best predictor of how well somebody is going to do in any kind of treatment. And if somebody is below this little red threshold, it doesn't matter if they get the best therapist on the planet, they make minimal progress. If they get high up over here, the truth is, most of what you need to do is a little bit of psychoeducation and support for the people in that individual's, what we call, therapeutic web.

So, this is part of the report. There's a different page to the report that illustrates some of this information. This is a normal development of really what is essentially executive functioning. And these little things show you this is where the client is, so you can look at how they're tracking with executive functioning. And then there are essentially guideposts; not specific prescriptive recommendations, but guideposts to how to select and sequence therapeutic work. And this is an example of sort of a filled-out NMT-guided treatment plan.

00:42:50.180 --> 00:45:12.189

Bruce Perry: The thing that we do is that we start really with a therapeutic web, you know; the school, the community, after-school programs, mentors. And then we do treatment planning for that, and then we telescope, where we start to look at the family. And we try to identify and provide supports and interventions that will help them help the child, and then we get to the individual child. And we create a treatment plan that is developmentally-guided. And so, it's very common for a child, for example, at one point in their treatment process, to have a somatosensory-dominant set of activities, and then over time, to have a relationally-dominant set of activities, and then, as I said before, you add in the cognitive content.

Now, this is a relatively young therapeutic approach, but it definitely is not on the shelf. We now have… and this is actually an old slide, but we now have almost 200,000 cases in our web-based dataset that has children from all over the world who have had similar developmental assessment and current brain mapping, so that we're able to start asking and answering some very interesting questions.

The process of learning the core content, the principles that underlie this approach, and then learning how to use the online metric and do the treatment planning, it takes a lot of time. And so, we have a certification process that's manualized, that is web-based, that has a very…kind of robust process to track fidelity and adherence to the training process.

00:45:12.390 --> 00:47:19.659

Bruce Perry: And over time, we've ended up with clinicians and programs; and this, again, this is an old slide, but we have programs that are using this model in education, in conventional therapeutic settings, all over the world. And we have had a number of excellent outcome studies that have been published using this approach. Again, any of you who've ever done clinical outcome studies, you know it takes a long time to set them up and to get the outcomes, but we've been very pleasantly surprised at how effective these interventions have been,

particularly with individuals where there's significant developmental trauma, and they've been, if you will, a challenge to our systems.

And I'll show kind of an example here. We have, over the years, developed partnerships with residential and/or hospital programs all over the world, and this is from 10 of those sites, where we tracked restraints and critical incidents events as a function of introduction of the Neurosequential Model into their programs. And we've seen, in all of these programs, significant reduction and maintained reduction in restraints and critical incidents. And this is over a 10-year period where the data have been collected using this model. So, it has been effective, and it has been effective in a sustained way. And if you monetize that, if you just look at the impact of just the decrease in restraints alone at these sites, it's a multimillion-dollar savings.

00:47:20.000 --> 00:47:26.930

Bruce Perry: So, again, we're very optimistic about the potential to use this framework with challenging individuals, particularly if they have a challenging developmental history where there are attachment- and trauma-related symptoms. But we've also used this very successfully with individuals who have a variety of neurodevelopmental problems.

I know that there will be probably a number of questions, and I'm looking forward to talking with everybody about… answering anything that I can. And, hopefully… you all will have some good feedback for me about areas that we need to continue to expand and continue to improve. The positive thing about this approach so far, for me, has been that this is not just an evidence-based approach, it's an evidence-generating approach. So, every single one of these assessments, it's a semi-structured assessment, where people are trained to do this approach, and the data goes into a core dataset, where we can then use that to make significant… to analyze and ask and answer lots of interesting and important questions about the timing of adversity and the outcomes that are associated with that.

And we obviously have a long way to go, but we now have the N number that will allow us to ask and answer some very, very good questions related to how early developmental adversity and how positive, healthy relationships play a role in the developmental trajectory. And, over the years, I hope that we'll have more to share with you guys. So, I think I'll stop there, and I'm looking forward to the Q&A.

05:48:03.190 --> 05:48:10.170

James Naifeh: Well, thank you, Dr. Perry, for highlighting the clinical utility of your Neurosequential Model.

AFTERNOON QUESTION & ANSWER SESSION

Bridget Callaghan, PhD, Sharon Dekel, PhD, & Bruce D. Perry, MD, PhD

Moderator: Maj. Louis N. Lachman, MD

05:48:13.190 --> 05:49:12.900

James Naifeh: For our second and final Question & Answer panel, we are joined by Drs. Bridget Callaghan, Sharon Dekel, and Bruce Perry. Our moderator for this panel is Maj. Louis Lachman.

Dr. Lachman is a Board Certified general and child and adolescent psychiatrist in the United States Air Force. He is an Assistant Professor of Psychiatry at the Uniformed Services University, and currently serves as the USU Psychiatry Clerkship Director, and as a Scientist in the Center for the Study of Traumatic Stress. Dr. Lachman, you may proceed with asking questions from attendees when ready.

05:49:13.800 --> 05:49:37.679

Louis Lachman: Thank you so much. And panelists, thank you again for your wonderful presentations, and also for taking these questions. Beyond grateful for your contributions to the field and your time today.

So, first question going to Dr. Callaghan. What method, or what methods, if any, were used to control for non-adversity-related factors such as diet, environmental exposures, breastfeeding versus bottle feeding, etc.?

05:49:40.200 --> 05:51:12.109

Bridget Callaghan: Thank you so much, Dr. Lachman, and thanks for that great question. So, we tend to control for things in a variety of ways. So, things like breastfeeding, C-section, or mode of birth; these are things that we control for if we have that information. And I'm saying if we have that information, because sometimes with the communities that we study, so children who've been adopted from foster care, it's not always possible to get that information in the detail, or at all in the detail that we would like, or at all. So, we control for that when we have it. And usually, we don't see that those covariates are usually significant, but they're usually not

kind of overriding the effects of adversity otherwise. Diet is a different one. So diet, we always collect dietary information. Diet is a very challenging thing to collect; so, once you start collecting diet, you gain a real appreciation for nutritionists and other people who work in that field. It is a very, very challenging thing to collect. So, we do collect it, and we do sometimes control for it; but actually what we tend to do now more than anything is not control for it, and instead test it as a mediator or moderator of the outcomes that we're interested in.

So, one of the things that I presented was our fiber findings. This is one example of the way in which diet seems to act as a moderator of some of the impacts of adversity that we're seeing, or some of the associations with adversity that we're seeing.

05:51:14.040 --> 05:51:33.619

Louis Lachman: Thank you, ma'am. Really, really insightful. Second question going to Dr. Dekel. This is from Dr. Cozza. Are there any suggestions for preparing women who might be at risk of a complicated pregnancy or delivery to decrease the risk for childbirth-related PTSD? Do we know of any protective factors at this point, or anything like that?

05:51:34.300 --> 05:53:53.780

Sharon Dekel: That's a great question. So, who would have, eventually, a medically complicated delivery? We call it in OB care, high-risk pregnancies. Not all of these women eventually will have childbirth PTSD. And in fact, high-risk pregnancies are often medically monitored; so, their chances of having a more medically complicated delivery often is actually lower than anticipated. That's all part of the prevention of physical… or improving physical outcomes of women.

In an ideal model, we would know *a priori*, before people give birth, who are really the people who are at the highest risk for having PTSD of childbirth. Currently, I think, based on the kind of existing scientific knowledge that is still somewhat lacking, we do have risk factors, which would be women who have a history of trauma, especially women who have prior medically complicated delivery and experiencing some degree of PTSD unresolved symptoms and enter pregnancy the second time.

And, of course, people who have a history of sexual assault, we find it as an important, unfortunate predictor of perceiving childbirth as more potentially stressful, especially in this

context of the kind of prior traumatization. So, we could identify a high-risk group who might have risk for developing PTSD and intervene in what we call primary prevention. That would be during pregnancy, potentially, through different psychological interventions, to discuss the forthcoming delivery in these people who might be at risk for medically complicated delivery and PTSD. Based on our data, what we find is, often, people during pregnancy, regardless of the level of objective complications that they are experiencing during pregnancy, are already experiencing some degree of anxiety about the forthcoming delivery. And even, we have assessments during pregnancy of what we call PTSD in regard to the forthcoming delivery; so actually assessing PTSD symptoms before the trauma even occurred. And we are finding that people's degree of these [what] we call PTSD-like symptoms do seem to add some information to the overall prediction model. So, ideally, we want to, again, offer some level of support to these high-risk mothers.

05:53:53.920 --> 05:54:57.930

Sharon Dekel: I think what is really, I would say, quote-unquote, unique about the child with PTSD is that we can actually provide a lot of trauma-informed care in labor delivery. So as the traumatic event is unfolding, we actually have the medical staff; and the more we educate the medical staff within the trauma-informed care lens, then we could potentially reduce the chances of having an emotional response to an event that objectively is medically complicated.

Because again, potentially, we won't be able to amend medically complications in labor and delivery, but potentially we can amend the emotional response of mothers. And lastly, of course, as I showed in my slide, we need to really optimize this, what we call secondary prevention. So, people who had medically complicated deliveries and we know are now at risk for developing PTSD, how can we, early on, when they're still in the hospital and closely monitored for their physical health, how can we make sure that we're also monitoring them at least in the same way for their psychological health, to really reduce the odds of having PTSD.

05:54:58.900 --> 05:55:12.570

Louis Lachman: Thank you. And follow-up question to all of that: Is there a timeframe that you have found that is most helpful to start some of these interventions, especially with these higher-risk pregnancies, or is earlier better, or is there a specific window?

05:55:13.710 --> 05:56:33.369

Sharon Dekel: Seems like, again, there's what I would believe is likely to happen, and what we're actually seeing. There's very few what we call secondary preventions that have been done in the first day. So, within, let's say, an interval within 24 to 72 hours postpartum. And these overall studies, more like trauma-focused intervention seems to be helpful. Again, these studies don't really have any kind of objective marker of whether PTSD really improved or what's prevented besides self-reporting. So, the samples are often small. So, I think definitely we need much more research. But I think the take-home message is that, again, versus [with] other forms of trauma, potentially we could even intervene earlier than 24 hours postpartum. We could even intervene, really, as a person is delivering, or in [those]first hours postpartum, because people are in the hospital. So, any kind of intervention within what we call the golden hours, which is often considered within six hours post-trauma exposure might be really the ideal time to intervene as early as possible to really buffer this stress response on a physiological level, to kind of really buffer the memory consolidation. But definitely this warrants more research to come.

05:56:36.490 --> 05:56:46.939

Louis Lachman: Absolutely, and thank you. Dr. Perry, this question is for you. How is trauma transmitted across generations biologically and psychologically?

05:56:48.800 --> 05:56:51.100

Bruce Perry: Sure.

05:56:51.100 --> 05:56:51.980

Louis Lachman: Easy question, right?

05:56:51.980 --> 05:58:28.590

Bruce Perry: Let me write a dissertation for you. So… First of all, it is transmitted. We know that. But there are multiple mechanisms; and I think it's really important that that we're aware of it. And I think, one of the most common ways that we transmit the residue of a traumatic experience, particularly if it involves sort of cultural trauma or a major traumatic event, is through learning. If we teach people about those people who did something to our people. And so, we transmit it in what we teach, we transmit it in our statues, we transmit it in our holidays, we transmit it in the creation of a VA system that institutionalizes healing following war. And then we transmit it within the family; so there'll be familial things that will be passed on.

I remember one of the first experiences I had with that was when I was working with a Vietnam veteran, who had pretty bad PTSD. But he was sort of an identifier, so he wore his uniform all the time, went to Vet groups, and that was part of his identity. And his child started to develop trauma-related symptoms that were cue-specific to the cues that his father had. And I've heard many, many, many people who've worked in the VA system [who] have seen similar kinds of intrafamilial passage of trauma-related behaviors and reactivity.

05:58:27.350 --> 05:59:25.750

Bruce Perry: And then I do think that there's a lot of evidence to show that there are epigenetic elements that are part of the transmission of experience. And the degree to which it's the specific experience or the global experience is still sort of being examined. But I think that that's important, again, to recognize; that we have, from our social-cultural mechanisms, to our family mechanisms, to individual mechanisms, and how those are translated into physiology, all the way down to the transmission through epigenetic means. I think that that can really impact, in a sense, carry the echo of a trauma. And again, obviously, you could take any one of those elements and write several books. So it's a big area.

05:59:27.040 --> 05:59:35.760

Louis Lachman: Absolutely, and I think speaks to the scale of the problem. We have both, like you said, epigenetic all the way through macro-societal level stressors and compounding factors that impact us as human beings, and how we process our day-to-day life and experiences. So, appreciate you trying to condense all that into… not a dissertation, but a quick introduction.

05:59:52.330 --> 05:59:53.990

Bruce Perry: Feebly condensed.

05:59:53.990 --> 05:59:56.739

Louis Lachman: No, I appreciate it.

05:59:56.980 --> 06:00:14.009

Louis Lachman: Dr. Callaghan, [a] question for you. Does breastfeeding link to passing on microbiome traits from mother to child? And if so, then would that potentially change the recommendation for breastfeeding for mothers who have a history of mental health impacts from adverse experiences?

06:00:14.930 --> 06:02:10.249

Bridget Callaghan: Thanks… these are really fantastic questions. So, I think breast milk is a very, very interesting area when it comes to the microbiome; and even just in and of itself, breast milk is a very interesting area. So, we don't actually study breast milk in the lab ourselves, but something that a lot of people are doing right now is looking at fats in breast milk and thinking about how those fats may actually nourish certain microbial members. And then there's also a lot of research looking at the transmission of microbes via the act of breastfeeding. And usually this is through the skin surface as the infant is nursing and can consume microbes from the mother that way.

I don't think it's going to change the recommendations for breastfeeding in mothers, because of course the microbiome is one piece of a much larger puzzle that's going on. And so… other things that we know about breastfeeding… this is a really important way to promote mother-infant bonding, and I would presume that the effect size for mother-infant bonding that's promoted through breastfeeding is likely to be a lot larger than any kind of microbial transmission. I could be wrong there, but that would be my hypothesis. So, I think it's certainly an area that is extremely interesting, and one that we should look into, but I don't think

anything that we find in that space is going to actually change the recommendations for breastfeeding itself. Maybe it changes certain things around breastfeeding. I could imagine in the future some, I don't know, probiotic interventions or something along that line that might help support this act. But the act of breastfeeding itself is serving a much wider purpose than simply nourishing the child, or even less than that, simply nourishing the microbes that are in the child's gut.

06:02:11.020 --> 06:02:30.300

Louis Lachman: Absolutely, and also with the immunologic benefits of it, too. I mean, like you said, very big effect size, and part of why it's recommended for those who can do it, so thank you, ma'am.

Dr. Dekel, how has your research looked at marginalized women and low-income demographics?

06:02:31.890 --> 06:04:38.849

Sharon Dekel: This is such an important question. I just want to add to the discussion on breastfeeding and bonding. Data does suggest that definitely breastfeeding relates to bonding, but actually this idea of developing this emotional bond is above and beyond breastfeeding. So, the take-home message is you could be a great mom, regardless of what kind of breastfeeding you are practicing.

To your question. So, in the U.S., underrepresented minority groups demonstrate a higher level of severe maternal morbidity, which would be a marker of medically complicated delivery. Based on our studies, when we did this matched control design in which we compared mental health outcomes, focusing specifically on acute stress response to childbirth and PTSD between underrepresented groups in our study, defined as Black and Hispanic women versus non-Hispanic white, and we control for these demographic backgrounds through this matched control design, as well as OB complications. So, regardless of the level of OB complications that a person might experience, and regardless of their demographic background, people in the underrepresented group scored higher on the acute stress, as well as PTSD. So, again, you do wonder about…

In my slide, I talked a lot about the psychological experience of childbirth, and potentially different people as they are giving birth in the U.S, mostly in the hospital; then the event could be perceived differently, regardless of the objective complications. And, as we're talking about trauma-informed care and supporting women during pregnancy in the immediate postpartum and during the postpartum. Ideally, we want to identify especially people who are at the highest risk, which would include those who would be affiliated with more underrepresented ethnic and racial groups in our society.

06:04:40.750 --> 06:05:19.220

Louis Lachman: Thank you, and crucially important, like you pointed out. We really want to understand who's at greatest risk, and making sure that we help all people. So thank you.

Dr. Perry, a question for you. Given your comments on how type and timing of childhood adversity often differentially impacts behavioral outcomes, do you have any thoughts on the emerging dimensional model of childhood adversity? I.e, if more specific analysis that takes into account maltreatment type might be able to help us disentangle issues with DSM classifications, etc.?

06:05:21.750 --> 06:08:38.660

Bruce Perry: Well, I have a lot of thoughts about that. The NMT actually is a dimensional measure of developmental history. We look at the timing and the nature of adversity at multiple time periods during development; very different than a conventional ACE retrospective score or a PACE retrospective score. And so, I have to say, I saw a few other questions about the DSM. I think, one of the challenges that the DSM has had for a long time is that it has not been very developmentally-informed. And it really has not paid much attention to what are clearly crucial factors in etiology. So, I think that in the revisions that are coming, if into the matrix they begin to filter in developmental factors, that will be really positive.

We actually, essentially, created the NMT process and the assessment process because using DSM to cluster people to study neurobiology really didn't help us distinguish adequately the populations that we wanted to study. So, we went in a different direction and are very descriptive in the way we create our assessment matrix. And then we use that to try to figure out… is it the event? Is it the duration of the event? Is it the pattern of the event? Is it the timing

of the event? And what we're finding so far is that if you do anything to activate the stress response system in a way that is unpredictable, extreme, or prolonged, that will result in sensitization, that then has a cascade of effects that are functional. And the specific functional effects will be very different depending upon many factors, including whether or not there are post-event buffers, whether there are pre-event vulnerabilities, and so forth. And again, it gets extremely complex.

The one thing I can say, and this is why I think the work that both Sharon and Bridget are doing is so important. It turns out that the major factor is the timing of the event. So, we found that the first two months after birth were better predictors. The developmental risk at that time were better predictors for outcomes in adolescents and adults than any other factor. And I'm just editing a paper right now where we've backed up, and we're finding that the intrauterine development of risk is even a better predictor. Which, again, if you understand how the brain develops, that's when most brain development happens in utero. And so, if that's the time when that process is disrupted, you're likely to have more long-term downstream risk. And so, I hope that the people that are involved in the new DSM actually start to look at the pre- and perinatal period with a lot more intensity.

06:08:40.310 --> 06:09:11.560

Louis Lachman: Absolutely. Because, like you pointed out, development starts way before we are born. So, to kind of ignore that part or give it lesser context of any kind of model seems to be doing a little bit of injustice there, so thank you.

Dr. Callaghan, next question for you. Other than fiber, are there any other nutritional or supporting strategies to improve the microbiome diversity or specific bacteria related to mental health?

06:09:13.120 --> 06:11:31.049

Bridget Callaghan: So, I think it's probably best to think about diet as it relates to the microbiome from a whole foods perspective. Because, this is what we're actually eating. So, I think the best recommendation for dietary support of the microbiome are leafy greens. So, the more leafy greens you eat, the many different substrates that are in there that the microbes really love to eat. So, a lot of what we're eating in leafy greens actually goes towards supporting

microbial health directly. Beyond that, having foods that are fermented can be really helpful if you can tolerate those. And so, different cultures have a variety of different fermented foods that have been in the diet for a very long period of time. So whether it's sauerkraut or what have you, these can be very supportive for our gut health. And then beyond that, steering clear of things that we know are not very good for either us or our guts, or things that are really high in processed sugar, for example. So, I think the recommendations for dietary health stand both for the health of the individual, us, the host, as well as the microbes that live inside of us.

We could go further and talk about specific probiotics and whatnot. I think that for the majority of the population who are eating a healthy diet, those are likely to be unnecessary in most circumstances. Once you've got a healthy diet going, if you're feeling like you've got good gut health, then it's likely that that is. So, this is a community that's been living around inside of us for our entire existence, and so it has a pretty good way of regulating its own health and existence there. I will say that paying attention to what is coming out of us is also a very helpful way of understanding our gut health. So, paying attention to your stools, their consistency, and their ease of pooping is actually a really good indication into your gut health. So, if things are not going right there, then that could be a suggestion of things to pay attention to in the future.

06:11:32.560 --> 06:12:01.209

Louis Lachman: Thank you. And it sounds like we hear with diet very often, consistency and intentionality, very important to optimize that microbiome and just overall health. So thank you.

Dr. Dekel, question for you, ma'am. We know that effective pain management can help reduce the risk of PTSD in patients with severe injuries or pain. In what ways can pain and other complications be proactively managed to reduce risk?

06:12:01.910 --> 06:13:53.290

Sharon Dekel: That's a great question. I think we have to step back; and the idea is that, n the context of labor and delivery, usually we're talking about labor pain, which is part of the inherent process of giving birth. And also, people who are in the course of giving birth have a lot of opinions about how much they want to manage their pain or not. And there is a lot of promotion of what we call natural birth, which would mean minimal interventions; which would include also minimal intervention to manage pain. To me, based on our studies and studies out

there by other groups…Currently, the way we're thinking about managing pain is in a way that focuses, again, on these objective birth outcomes. So, usually in labor and delivery, this is really the focus on improving the birth outcomes, less so about what would that mean if we have data to suggest, and there is data to suggest this, that as levels of pain become very, very high, that might be another factor that would increase the risk of CB-PTSD, as well as postpartum depression. So, this what we call risk ratio, kind of risk-benefit ratio in medicine, in perinatal care, doesn't yet really, I think, approach it in a more holistic way, which would also take into account the mental health outcomes of experiencing pain. And I think once this is more acknowledged, then there will be subsequent better ways to think about how to manage pain, Because in our data, we're finding that it's not so much, whether the person received an [epidural- unclear] on time or not, which might be an objective proxy about how much pain, objectively, this person was experiencing.

06:13:53.290 --> 06:14:06.889

Sharon Dekel: But a lot has to do in terms of PTSD, which would be the perception of pain. So how much you felt the pain was intolerable for you subjectively. So, if that's the case, and that relates to PTSD, then we can think more about mindfulness approaches, of other approaches that people could even practice. People who might be very sensitive and have a lot of perceptions about what it means to have extreme levels of brain already during pregnancy. But I think, again, for that, we would need to first acknowledge the implications of medically complicated delivery, as well as potentially [unclear] level of pain that are subjectively perceived as such, and the implications of maternal mental health.

06:14:36.960 --> 06:14:53.989

James Naifeh: Hi, I'm going to break in really quick and say that we've got about five minutes left in our 30-minute Q&A. So I think that probably gives us time for one more question per speaker; so I will let Maj. Lachman decide which question he's going to ask.

06:14:55.340 --> 06:15:08.720

Louis Lachman: Appreciate you, sir. So, with that being said, Dr. Perry, question for you, sir. What are your thoughts on TMS, specifically related to those who have a sensitized stress response?

06:15:09.970 --> 06:17:22.090

Bruce Perry: Basically, I don't have the expertise to make a comment on it. I do think, however, that there's a lot of promising work in that area. And it's like a lot of things in the neurosciences. The complexity is stunning. But the promise of that kind of intervention is also pretty exciting.

But currently, there's no evidence that you can change a sensitized stress response system through TMS. My argument about that is that there are lots of other non-invasive ways that are much more natural and culturally embedded that can alter the sensitized stress response, and that's kind of the way we're preferring to go with our work. And we think maybe in another five years we'll be able to give you some information on it.

But we think that humanity has had trauma, tragedy, disaster, war, pain. PTSD stuff before there was even the label PTSD. And we've survived. And one of the major mechanisms that we have allowed ourselves, basically where we've buffered and then ultimately healed from traumatic experiences, is by using deeply embedded cultural mechanisms, such as dance. You know, pattern-repetitive rhythmic things. Dance, poetry, storytelling, communal ceremony, ritual, routine, the things that we actually really need to figure out how to recapture in the modern world, so that we can become a more resilient set of cultures. And, again, that's not to diss TMS. I just think that these other, more naturally flowing, more pervasively available experiences throughout the week are more likely to have the neurobiological dosing and spacing required to make meaningful change in the brain. So, I'll stop there.

06:17:23.870 --> 06:17:51.749

Louis Lachman: No, very helpful, and I think paints the picture of the importance of practicality in interventions, and not just what's the newest and shiniest thing, especially for our patients. What's feasibly implementable is a very, very important aspect in what we should be considering when treating our patients, so thank you.

Dr. Callaghan, last question for you, ma'am. What are some of the treatment options being explored for gut microbiome changes?

06:17:53.560 --> 06:20:09.609

Bridget Callaghan: This is a very interesting space. There are many treatments that are being explored currently, and the evidence for them is variable. It depends on exactly what's being treated. So, one that people are getting very excited about is called fecal microbiome transplants, or FMT. This is kind of how it sounds. So, you might take a pill that includes fecal matter from someone who's healthier than you, who maybe has some sort of profile that's different than yours, and you can consume that. And the idea is that those bugs that are in that fecal matter would then help to colonize your gastrointestinal tract, and could produce certain outcomes that might be of interest to you.

So, this has been explored much less within the realm of psychological health, though these sorts of treatments are considered curative for things like Clostridium difficile and infections of that nature. There have been studies showing that those types of treatments, when applied to something like Clostridium difficile, while they cure that, there might be some unintended consequences to psychological health; and so those types of things are being explored. This is also being explored in terms of body composition and weight loss management.

So, I think those are all very interesting and exciting, but it's extremely early days with those at this point in time. The other ones are obvious; so those are prebiotics and probiotics. So, prebiotics being things that feed the microbiota, probiotics being bugs that have a beneficial effect on the host. And again, I would say these are very early days. And they're unlikely to be a magic bullet. So, echoing what Dr. Perry said here, not to diss those treatments either, but I think they're going to be part of a much larger lifestyle intervention to support a broader sense of health for individuals. So, do I see a future where we could implement probiotics and prebiotics to support people's mental health? Absolutely. But I don't think that those will be stand-alone treatments. I think they'll be embedded in a much larger kind of lifestyle intervention or model.

06:20:11.090 --> 06:20:24.060

Louis Lachman: Thank you, ma'am.

And Dr. Dekel, last question for you. Is there a difference in the rate at which mothers develop childbirth-related PTSD when you look at the level of social support post-birth?

06:20:25.850 --> 06:22:17.630

Sharon Dekel: So, the data that does exist basically shows that social support, as it is often the case in what I call the general PTSD, PTSD outside the context of the postpartum, definitely could be a buffer, or could be a protective factor to some extent. But again, as we were seeing that the level of medically complicated deliveries is really peaking high, and people are already developing these early acute stress symptoms, the social support, again, could reduce the chances or the severity of the PTSD. But potentially as a standalone intervention for people already developing these acute stress responses in the first hours after delivery, that might be insufficient.

So, the take-home message would be that social support is great at any time point. As we're talking about pregnancy, people who might be at risk for PTSD, who have a lot of anxiety about the forthcoming delivery, I would believe that, at home, but also social support within your larger community is almost a must. And definitely after medically complicated delivery especially, we're finding that people who have childbirth PTSD is often the case of general PTSD. They are experiencing a lot of guilt and shame, that basically their body failed them, and they basically maybe failed their babies as well. So, the idea of actually sharing their experience and healing through disclosure is often very limited.

So, this idea of having a social support system that could encourage the self-disclosure experiencing, and another way to basically expose yourself to the childbirth event and potentially develop a more benign recollection of what happened could be very, very healing. But again, for people who are already experiencing the symptoms, social support alone would require an add-on treatment. But definitely important.

06:22:19.490 --> 06:22:28.809

James Naifeh: Well, I wish we had time for more questions. We are grateful to Drs. Callaghan, Dekel, and Perry for being here to share your expertise. And thank you to our moderator, Maj. Lachman. Now I'm going to turn it back over to Dr. Cozza for some closing comments. Dr. Cozza?

CLOSING REMARKS

06:24:17.280 --> 06:27:10.430

Stephen Cozza: Thank you so much, Jamie. Just an incredible day, outstanding. As we bring our Conference to a close, I want to communicate our deep gratitude to many folks. First, to our featured speakers, Drs. Manji, Ressler, Callaghan, Dekel, and Perry. Thank you for the transformational work that you do and your contributions to science, your excellent presentations today, and your participation in today's panel discussions. This has just been an outstanding day addressing multiple areas of trauma-focused basic science and clinical care; exactly what we were hoping for, and you certainly delivered. So, thank you so, so much. I also want to thank our panel moderators, Dr. Robin Bonomi and Dr. Louis Lachman, for facilitating such engaging discussions with our speakers.

I would be remiss if I didn't extend my sincere thanks to the people who really made this day possible. First, I want to thank the entire Brain, Behavior, & Mind Planning Committee. An event of this scale and technical complexity requires seamless planning, coordination, and execution by many members of our Center's professional team. A special thanks to our dedicated organizers, Dr. Jamie Naifeh, Dr. Holly Mash, and Dr. Rachel Shor, for your leadership in coordinating this event. Thanks also to Dr. Joscelyn Fisher for your work in managing and bringing our virtual poster session to life today. And my gratitude also goes to our administrative support team, Allie, Luke, and Hanna, who played key roles in this Conference and do that every year. Also, thanks to our colleagues in the Center for Deployment Psychology at USU, who provided technical support that was required to broadcast this virtual conference today.

And then lastly, thank you, all of our participants who are here today for your time, attention, participation, and commitment to advancing the field of traumatic stress. We hope to see you again for our Center's future educational events. As a reminder, there is a Brain, Behavior & Mind lecture that will take place in the fall that will feature a single distinguished speaker focusing on a specific topic related to traumatic exposure. And this spring event will recur next spring, and you all will be getting further information regarding those upcoming events at the

email address you used to register for today's conference. So, again, wonderful day. Thank you for all of the effort, participation, and excellent presentations, and I will turn it back to you, Jamie. Thanks so much.

06:27:10.500 --> 06:28:05.140

James Naifeh: Thank you, Dr. Cozza. And I just want to echo your thank you's to everyone and to the audience for sharing your thoughts and questions and emojis. You helped make the Conference a lot of fun today. A recording of this event will be publicly available on the Brain, Behavior & Mind website once the video's been transcribed. Registrants will be notified by email when that video is available.

Just want to go back to Dr. Cozza's mention of the Brain, Behavior, & Mind 2026 Fall Lecture. This year's distinguished speaker is Dr. Richard Davidson, the renowned mindfulness researcher from the University of Wisconsin-Madison. Registration for that event is not yet open. That event will take place on September 23rd. Please keep an eye out for those announcements in your inbox. Take care, and we'll see you next time. Bye.