CENTER FOR THE STUDY OF TRAUMATIC STRESS
DEPARTMENT OF PSYCHIATRY
UNIFORMED SERVICES UNIVERSITY OF
THE HEALTH SCIENCES

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BRAIN, BEHAVIOR, & MIND
2025 SPRING CONFERENCE

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TUESDAY, APRIL 22, 2025

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This transcript was produced from audio provided by Uniformed Services University of the Health Sciences.

P-R-O-C-E-E-D-I-N-G-S

DR. NAIFEH: Good morning, good afternoon, or good evening, depending on where you are. Welcome to the Brain, Behavior, & Mind 2025 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, and the USU Brain and Behavior Hub.

My name is Jamie Naifeh, and I am a member of the Center for the Study of Traumatic Stress and the Department of Psychiatry at USU. This is our first Conference under the name Brain, Behavior, & Mind. Those of you who have attended this event in the past knew it as the Amygdala, Stress, & PTSD Conference. We changed the name to more accurately reflect the breadth of research that we feel is relevant to understanding how events in our lives, and the stress resulting from them, can alter and injure brain function and how we can prevent, treat,

and recover from these injuries. So, stress injury mitigation has always been the goal of this Conference and remains the goal of all Brain, Behavior, & Mind events.

I'd like to take a minute to share some Conference-related information. You can find today's agenda on the Brain, Behavior, & Mind website. You can also find the downloadable Conference program on the website. We'll post that link in the chat.

This morning, we will have two presentations and a Question-and-Answer panel with our first two speakers. This afternoon, we'll have three more presentations, and then a second Q&A panel with those speakers. There will be breaks in the morning and the afternoon, as well as a break for lunch. During breaks, we encourage you to visit our online poster gallery with submissions from fellow conference attendees, including the winner of our poster contest. You can find the winning and Honorable Mention posters as well as the links to the other submissions on the “Posters” page of the

Conference website.

Please use the Q&A function at the bottom of the Zoom window to submit questions to our speakers at any point prior to or during their Question-and-Answer panel. You can submit those at any time as long as the panel has not ended. When submitting questions, please note if your question is for a specific speaker or for all of the speakers in the panel.

Continuing Education credits are available for physicians, psychologists, and social workers for this event. We'll 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 2025 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 Defense.

With that said, we would like to start by

sharing a message from COL Vincent Capaldi, Chair of the USU Department of Psychiatry.

COL CAPALDI: Good morning. Distinguished guests, colleagues, and friends, as the Chair of the Department of Psychiatry here at USU, it is my great honor and privilege to welcome all of you to the Brain, Behavior, & Mind Spring Conference. Today's event is a testament to our shared commitment to advancing the frontiers of neuroscience and mental health. We are delighted to have you join us for what promises to be a day full of insightful discussions and meaningful connections. This Conference is part of the Brain, Behavior, & Mind series, a global forum that brings together distinguished scientists, clinicians, and leaders from across neuroscience, psychiatry, psychology, and public health. Each event in this series explores new insights into health and illness, by bridging knowledge from genes to communities, from the research bench to bedside care. In doing so, we advance science and clinical practices needed to support our military service members, their

families, and communities at large as they face complex and stressful challenges.

In short, this Conference exemplifies the vital connection between cutting-edge research and real world clinical impact, which is of paramount importance to both the Department of Defense and our broader healthcare communities at large. We have an exceptionally robust agenda for you today, featuring a wide range of timely and important topics. Over the course of the day, we'll hear about advances in precision psychiatry, exploring new prospects for advancing risk and resilience in mental health. We'll delve into the brain and body connection in stress and depression, shedding light on how physiologic circuits influence psychological well-being. Later, we'll examine the neuroscience of parenting and perinatal mental health, a crucial area for understanding family wellness and early life development. Our program also includes innovative approaches to care, such as single-session interventions, that can bridge gaps in mental health treatment, and

even a discussion on the implementation challenges of MDMA-assisted therapy in healthcare systems.

This breadth of topics from fundamental science to novel therapies reflects the multidimensional nature of our field, and the holistic approach that we must take to improve mental health outcomes. Each topic of our agenda will be presented by world-renowned experts in their domain. We are privileged to host speakers from around the world who are at the forefront of research in clinical practice.

Our distinguished presenters include: Dr. Jordan Smoller of Harvard Medical School, a leader in psychiatric genetics and precision medicine; Dr. Scott Russo of Mount Sinai, known for his groundbreaking work on the neurobiology of stress and depression; Dr. Jodi Pawluski, from the University of Rennes in France, an expert on maternal mental health and the developing brain; Dr. Jessica Schleider of Northwestern University, a pioneer in brief,

single-session mental health interventions; and Dr. Paula Schnurr, Executive Director of the National Center for PTSD, whose work has greatly advanced our understanding of trauma and its treatment.

We are truly grateful to have such an eminent lineup of speakers with us. Their participation is a clear indicator of the Conference's caliber, and I want to thank each and every one of them for taking time to share their expertise with our community today.

The Conference of this scale and quality does not happen by accident. I'd like to thank -- to take a moment to thank and recognize the impact of our planning committee, especially the Co-Chairs, Dr. Jamie Naifeh and Dr. Holly Mash, for their extensive work in organizing this event. Dr. Naifeh and Dr. Mash had devoted countless hours to crafting today's program and coordinating logistics through leadership, along with the efforts of the entire planning committee, have been instrumental in bringing this Conference to life.

On behalf of everyone here, thank you. Thank you for your dedication and hard work in ensuring that today's forum is both enriching and seamless. Please join me in giving them a virtual round of applause. I'm not sure if your applause buttons are working in this forum, but if they are, please press the button now.

This year's Conference also marks an important moment of transition for our community. As many of you know, the Center for the Study of Traumatic Stress, CSTS, which sponsors the Brain, Behavior, & Mind series, is undergoing a leadership change. After a long and distinguished tenure, Dr. Bob Ursano is stepping down as director of CSTS. Dr. Ursano has been the heart and soul of the Center since he founded it in 1987, and his impact on the field of psychiatry cannot be overstated. He served as a Chair of our Department of Psychiatry for 25 years, mentoring countless clinicians and researchers, and he has guided CSTS to international prominence through his vision and dedication.

Dr. Ursano's scholarly contributions are prolific, with over 500 publications and numerous books to his name, and his leadership has fundamentally shaped how we understand and respond to psychological trauma, both in the military and beyond. From pioneering research on disaster psychiatry to co-founding the National PTSD Brain Bank, his accomplishments have paved the way for breakthroughs that save lives and have improved care. We owe Dr. Ursano a tremendous debt of gratitude for his decades of service, his unparalleled expertise, and the legacy he leaves us.

Bob, if I may be able to speak to you virtually, directly for a moment, thank you for your mentorship, your vision, your steadfast leadership, all that you've provided to me as the Chair here, and also to our Department, CSTS, and the entire field at large. Your impact will be felt for decades to come.

At the same time, we are very fortunate to have a highly capable leader here at USU as a successor, stepping into the role as Acting CSTS

Director. It's my privilege to welcome Dr. Stephen Cozza, Steve, as the new Acting Director for the Center for the Study of Traumatic Stress. Dr. Cozza is exceptionally qualified to lead CSTS in its next chapter. He's a retired U.S. Army Colonel with 25 years of experience, and he has long served as the Associate Director of CSTS' Child and Family Program. In addition, he is Professor of Psychiatry and Pediatrics at USU. Well-known for his expertise in trauma psychiatry, Dr. Cozza has dedicated his career to understanding and mitigating the impact of trauma on service members, veterans, and their families. Many of you are familiar with his work on the needs of military children and families. His contributions have been invaluable to expanding our knowledge of how deployments, injuries, and loss affect the loved ones of those who serve, of those who stand in harm's way. We are confident that under Steve's leadership, CSTS will continue to thrive and remain at the forefront of traumatic stress research and education.

Steve, thanks for stepping into this role. Thank you for your willingness. We look forward to your guidance and for the new ideas and energy that you'll be bringing as acting director.

In closing, I want to once again thank you all for being here today, virtually here today for your commitment to learning and collaboration. The Brain, Behavior, & Mind Conference embodies the spirit of unity in scientific and clinical pursuit, a spirit that is evident in this virtual room.

As we come here together, advancing our understanding of the brain and behavior, I encourage you to actively engage with the speakers, put your questions into the chat, voice your questions throughout the day, share your perspectives, consider how the knowledge that you gain here can be translated into better practices and policies within all of our organizations. Thank you for your attention and participation. It's now my privilege to officially open the Conference. I wish you all

a very stimulating and productive day ahead, and look forward to the discussions and discoveries that will emerge from our time together. Welcome, and enjoy the Conference. Thank you.

DR. NAIFEH: Well, thank you, COL Capaldi, for a wonderful introduction to this event.

Next, a few words from Dr. Robert Ursano, the Founding Director of the Center for the Study of Traumatic Stress. Dr. Ursano?

DR. URSANO: Thank you, Jamie. Let me first thank Dr. Capaldi, then, for the kind words. Much appreciated. And I also want to echo welcoming Steve Cozza as the Acting Director of CSTS. We are so pleased that he agreed to take on the Directorship of the Center. He will be outstanding.

To get now to the conference, I want to thank Jamie and Holly, Rachel, and the entire committee for what is really an outstanding meeting. The change in the name reflects preparing for the next decades as we move forward. In fact, this Conference has gone on for over two decades, 20 years, beginning in

2004, really, the child at that time of Luke Johnson, who was a basic science researcher working in Amygdala, now in Australia, and perhaps signed in today.

The Conference, as Vin pointed out, has always been focused on bringing together basic scientists, clinical scientists, epidemiologists, and care providers. It is a challenging Conference, and it's meant to be. We hope you'll visit a different world, not just the world that you're familiar with, but one that, it's a bit like visiting the moon or Mars or Venus, because you'll only understand part of what's being said, but the opportunity to broaden your concepts and to learn from areas in which you don't know. As we all know, learning a new language is often accomplished best by visiting that particular world, that particular country, and that's what the Conference provides the opportunity for.

The new name reflects the breadth which has always underlined what was the Amygdala Conference: the brain, the behavior, and mind.

It is in those three realms that we struggle to learn and that we operate in order to help our patients and the world and, in particular, our soldiers, sailors, airmen, and marines. Through research, which, always remember, is basically observation, different tools of observation based on the area of research, but observation. Through observation, we learn from our patients, from our friends, and from those that teach us from the bench as well as from the community.

I've often said that the way I made it through medical school was the 3-by-5 card method, and I encourage you choose your 3-by-5 card, I kept in my pocket close to a pen or several pens. And my rule was when I heard a word three times that I didn't know, I wrote it down. That was that night's homework. And it literally was learning a language. It was through the words that one begins to learn the way in which different people look at, understand, and strive to help those that we care for.

To a different perspective, but one that's very close to what we have been talking about, highlighted perhaps by -- I think it was two years ago, when our Dean, Dr. Eric Elster, founded Hubs within the university, which are truly neighborhoods, and our Hub, which I had the honor to lead for the first year, was the Brain and Behavior Hub.

Secondly, the name Brain, Behavior, & Mind is one that we had used many years ago as a series of awards given from the Center for the Study of Traumatic Stress, including distinguished scientists, such as Myron Hofer and James Barrett and Tom Uhde; all, again, reflecting the realms in which we operate. The focus of our work is the impact of stress on the brain. And it's worth remembering that, at least as a metaphor in terms of the way in which stress creates injury to the brain. And what we strive to do is to find moderators of that pathway, in order to assist in the care of our soldiers, sailors, airmen, marines, and their families.

If we remember and think about the brain being subject to the stress injury, just as might be a muscle or a bone, that we're in the familiar realm of event-related disorders, in general, our focus is on when an event happens in the world, how that changes our brain and, therefore, our behavior. Studying event-related disorders, which now has a home in the DSM under stress-related disorders, is really the realm of military medicine, looking at extreme environments and their impact on our brain and behavior.

That is our focus here in the Conference, and I look forward to our speakers leading us forward. There is a neurobiologic example of that, called the kindling model. Again, as a euphemism helpful to remember; if you, in fact, place an electrical probe on the cortex, you'll get a seizure on the brain. If you do that multiple times, you'll continue to get seizures. After some point in time, it becomes autonomous. You no longer need to, in fact, place the probe. Many of our disorders, and

particularly those that are stress-related, can be seen under that model. They begin as event-related and can transition to being self-sustaining. Those models lead us forward as we listen to the speakers today.

I look forward to joining you in learning from those that are talking today. And I thank you, all, for attending. Back to you, Jamie.

DR. NAIFEH: Thank you, Dr. Ursano, for framing this event so eloquently.

Our first speaker today is Dr. Jordan Smoller. Dr. Smoller is the Jerrold F. Rosenbaum Endowed Chair in Psychiatry and Professor of Psychiatry at Harvard Medical School, as well as Professor in the Department of Epidemiology at the Harvard T.H. Chan School of Public Health. He is a psychiatrist, epidemiologist, and geneticist, whose research has focused on understanding the genetic environmental determinants of psychiatric disorders across the lifespan and using big data to advance precision mental health, including improved methods to reduce risk and enhance

resilience.

Dr. Smoller holds several other positions, including Associate Chief for Research in the Massachusetts General Hospital Department of Psychiatry, Director of the Center for Precision Psychiatry, Director of the Psychiatric and Neurodevelopmental Genetics Unit in MGH's Center for Genomic Medicine, and Co-Director of the Center for Suicide Research and Prevention at MGH and Harvard. He has played a leading role in national and international efforts to advance precision medicine. He is an author of more than 600 scientific publications and also the author of the book *The Other Side of Normal*.

We will now begin Dr. Smoller's presentation, which is titled, “Precision Psychiatry: Prospects for Addressing Risk and Resilience.”

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PRECISION PSYCHIATRY: PROSPECTS FOR ADDRESSING RISK AND RESILIENCE

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DR. JORDAN W. SMOLLER

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P-R-O-C-E-E-D-I-N-G-S

DR. SMOLLER: Well, thank you so much. It's really great to be part of this event. And I'm going to talk a little bit about precision psychiatry and what it may offer us in terms of addressing risk, resilience, and a number of unmet needs in the area of mental health. And I'll just start out with my disclosures, just so that you can take note of that.

And also start with something that I think is probably well known to many people in this audience, which is that psychiatric disorders are enormously impactful. They carry tremendous burden. In fact, they are the leading cause of years lived with disability. And there are tremendous unmet needs that we face. So, we have limited tools to reduce risk — to identify who might be at risk and to try to intervene or prevent the onset of many of the complications that we worry about. These are conditions that can be not only impactful in terms of morbidity, but mortality. As many people may know, those with severe mental illness have on average a 10- to 25-year shortened life expectancy. And

suicide is the second leading cause of death among young people in our country.

We have treatments that are effective for many people, but not good enough for many as well. And, in fact, most of the approved medications that we have, almost all of them are based on biological insights that really date back decades. So, we have a formidable task ahead of us to try to address some of these unmet needs.

And what I want to talk about today is the framework of precision medicine and how that may apply here. Precision medicine is defined, at least here from the Precision Medicine Initiative Working Group report a few years back, a good definition, I think: "An approach to disease, treatment, and prevention that seeks to maximize effectiveness by taking into account individual variability in genes, environment, and lifestyle." And I think the key thing there is individual variability. The heterogeneity that we know so well in our field of mental health is actually the focus of precision medicine.

When we think about opportunities for bringing precision medicine to psychiatry, there

are many important ones. One is clarifying how we make our diagnoses: What are the diagnostic boundaries? And what is the underlying etiology of many of the conditions that we are concerned with? How do we better identify individuals at risk for targeted prevention or intervention strategies? How do we match patients to treatments that will be most likely to benefit them and reduce trial and error prescribing, let's say, or even in terms of psychotherapy. And can we use some of the insights that we gain to develop novel treatments to target some of the underlying causes of illness, to develop more effective, more specific kinds of treatment? And so, I'm going to walk us through a few examples of that, and I'll be drawing on the work that my colleagues and I have done as well as others in the field.

So, let's talk first about this issue of clarifying the really diagnostic structure of mental illness. And this is something that I think we face clinically every day, right? One of the areas that we've seen tremendous growth in is the genetic research on psychiatric disorders. And what you're looking at here is a graph that

shows the number of genetic risk variants that have now been pretty convincingly identified for a range of psychiatric disorders. And you can see that until about 2008, there was almost nothing that people really could agree on that was associated at a DNA-level with psychiatric illness. That has now just been on an upward curve ever since, in part due to the availability of large-scale, genome-wide studies.

You can see, in the table on the right-hand side, the number of risk loci that have been really very strongly statistically significantly associated with a range of these conditions. We've known that they are heritable, that the DSM-defined conditions of things like anorexia or bipolar disorder or PTSD or depression have substantial heritability. That is, we know that genetic variation contributes to these conditions as we define them.

And so, that's all good, but we also know that how we define these conditions is a little bit of a moving target. And if you look at the evolution of the DSM, for example, from the first edition to the fifth edition 12 years ago, I guess, you can see this rising number of

diagnostic labels in the manual, which really reflects a process of lumping and splitting that we've been undergoing to try to better capture the landscape and boundaries among various mental health conditions. And it's a moving target. Even if you just look at three groups of disorders and look at how they've evolved over that span from, say, DSM-III to DSM-5, sort of the modern era, you see this, I think very well illustrated, and I'll show you on the next slide.

So, looking at what we might think of as pervasive developmental disorders, like autism, as one group, mood disorders, anxiety disorders. And what you see along the bottom is the timeline of DSM. And as this goes forward, you see conditions that are dropping out, some of them are coming in, and a reorganization of the diagnostic categories. When we get to DSM-5, something happens that rarely happens. And that is, instead of just splitting, we see lumping there in terms of autism spectrum disorder, but a continued sort of reshuffling of these other conditions. And, in fact, some now moving out from the anxiety disorder category into their own category, and certainly relevant here, trauma and

stress-related disorders.

So, it's a little bit of a moving target. We know that the DSM categories, while heritable, are not necessarily capturing an underlying, you know, biological or, even more broadly speaking, ideological set of conditions. And one of the things that we've been able to do now using large-scale genomic studies is to ask these kinds of questions at the level of DNA. So, through work by the Cross-Disorder Work Group of the Psychiatric Genomics Consortium, a very large, collaborative effort, we've been able to put together genomic data for multiple disorders and ask the question: How distinct are they? Or how much of their genetic basis do they share?

The answer, in a nutshell, is there is a great deal of overlap at a genetic level among conditions that clinically we think of as rather distinct. And, for example, in a study recently, you can see the genetic correlation matrix. That's that square with some of the darker blue squares — the darker the blue the greater the correlation at a genetic level between conditions. So, you can see, for example, PTSD on the Y-axis there. If you scroll

your — you know, your eyes over to MDD, those are very strongly genetically correlated.

And to the right of that are results using something called genomic structural equation modeling, which basically is a fancy way of saying, "Let's take all these genetic data and look at how these conditions go together." Not just pairwise, but are there some underlying latent genomic factors that explain most of this correlation structure among disorders? And you can see in that path diagram that, in this study, there were four latent factors — four genomic factors that seem to underlie the genetic basis of, in this case, 11 different disorders. One group we refer to as the compulsive disorders type: anorexia, OCD, Tourette's. And then there's one that's heavily loaded on schizophrenia and bipolar disorder. Internalizing disorder is another factor, and neurodevelopmental disorders.

We can also look at a DNA level at what are these specific variations and genes that seem to have these effects that cross our diagnostic boundaries? And, for example, loci that have these pleiotropic or boundary-crossing effects

seem to turn on — these genes seem to turn on their expression particularly strongly in the second trimester of fetal development, and then they stay relatively highly expressed relative to other genes. That's what you're looking at at the bottom there, the brain developmental expression trajectory. So, we're learning something about this.

And, actually just recently, we've been able to expand this work in the Cross-Disorder Group, now looking at 14 different psychiatric conditions. And these studies are large. You can see 1.6 million cases and 5.5 million controls with genomic data. And we see this factor structure again. We've now added a fifth factor, which comprises substance use disorders — so cannabis use, alcohol use, nicotine and opioid use disorders. The internalizing disorders are still there — PTSD, MDD, anxiety. They all cluster together at a genetic level. And so, we're beginning to get a sense of this underlying structure, a little bit more precision there.

Why does that matter? Well, one thing is it could inform how we diagnose disease. Certainly, it is a fascinating look at some of the

underlying biology. But it also might have implications for treatment. So, for example, building on this factor structure, we looked at the genes that were associated with these various factors and looked at their gene expression profiles, and then mapped those two mechanisms of action of drugs. And through that process, we were able to identify 39 potentially repurposable drugs that were predicted to treat psychiatric disorders that were identified through this factor structure. So, for example, L-type calcium channel blockers for the schizophrenia, bipolar disorders factor. That's actually a result that emerged as a potential opportunity several years ago. We're seeing more evidence of this now. But there's certainly others that we could think of.

Let's move on to another topic for precision psychiatry: Risk stratification. We're not that good at knowing who is at risk for various conditions ahead of time, and that makes it difficult often to target preventive strategies. One of the tools we have here is this burgeoning area of machine learning and artificial intelligence, coupled with the big data that are

now available. And, you know, we've been living in an AI world for quite some time. You know, for a long time, companies like Amazon and Netflix and Google have used AI kinds of methods to determine what we would like to see in our feed or what we would like to buy based on, you know, what data they have. So, basically, what they're doing is collecting vast amounts of data about people's behavior and then using that to build models to predict their future behavior. And that is essentially what we can do and would like to do, but in the healthcare setting. And I want to give you a couple of examples of how that kind of thing can work.

First of all, where do we get the data? One of the big data sources and opportunities that we have is electronic health records. And of course, as you know, any time these days that you have an encounter with a health system or a provider, various aspects of that encounter are documented in the electronic health record. It's a vast and ever-growing resource of real-world health data, and it's very high-dimensional. It is large. So, for example, at our health system, Mass General Brigham, our EHR has, you know, more

than three and a half billion rows of data. The data come in a couple of different forms, essentially. One is what we would call structured data. So, these are variables where there are predefined values, like a diagnostic code or a prescription.

And then there is the much larger corpus of text that, you know, emanates from clinicians writing notes or radiology reports or all those kinds of things, and now we can leverage that as well through the process of natural language processing, to essentially convert those text values into analyzable data values. So, this is a tremendously valuable potential resource.

One question that comes up is, well, but how good are those data? We all know that the electronic health record is not designed for research primarily. It's designed for billing. It's designed for tracking care. And, several years ago, we wanted to know the answer to that question. How good are these data for things like diagnosing a psychiatric disorder? And we looked at this in the context of a very large study that we were doing on the genetics of bipolar disorder, and we wanted to rapidly accrue

cases and controls for bipolar disorder.

So, we went to our health system, EHR database, and we built models or algorithms that we trained to diagnose bipolar disorder or that somebody was a control, unaffected. And then we wanted to know how would this compare to the standard — the gold standard in-person psychiatrist, structured SCID interview. And so, what we did was we had the algorithm identify people who it thought had bipolar disorder, people who it thought were controls. We also invited in people who had in their record a diagnosis of depression or schizophrenia. And we invited these people in for a diagnostic interview by a blinded psychiatrist who was blinded to what their diagnosis might be, who then administered the SCID.

And what you're looking at here is, this is a study of maybe nearly 200 people. Our first algorithm, which was based on natural language processing, plus the structured notes had a positive predictive value of 86 percent, meaning 86 percent of the time when the algorithm diagnosed bipolar disorder, a blinded clinician doing the, you know, multi-hour SCID interview

came to the same conclusion. We had a few other diagnostic algorithms. They all did quite well, especially when you consider the inter-rater reliability that we often see, just between psychiatrists. The match of the algorithm to the interview for controls was 1.0 or 100 percent.

We also — because we could then collect genomic data on using this algorithm — we compared the genetic components of our EHR cohort, which ultimately had about 3,300 cases, about 4,000 controls, to traditionally diagnosed large-scale genomic studies of bipolar disorder. Bottom line was, they were very highly genetically correlated with the standard traditionally diagnosed cases. And so that really gave us some confidence that these kinds of data are very scalable and also can be very accurate.

So, we have subsequently used those in a variety of studies, and in fact used this algorithm for bipolar disorder in a study through our PsycheMERGE consortium, which is a large consortium of health systems with bio-banks that we established several years ago. Could we predict the onset of bipolar disorder among those

who were unaffected? As you may know, the average delay in diagnosis from the time somebody develops symptoms to getting an accurate diagnosis can be six to 10 years, and the longer that goes on, data show, the worse the outcome in terms of prognosis and severity and frequency of suicide attempts.

So, through this consortium, we put together data from our system, Mass General Brigham, Vanderbilt, and Geisinger, and we did this kind of thing of developing algorithms to see, could we predict the diagnosis of bipolar disorder? And I won't spend too much time on this, but essentially, we used that validated definition. We had each of these sites train a model, and then we validated those models at the other two sites. And what you're seeing, in the bottom table, there is effectively a combination of these models. The area under the receiver operating curve, which is that first column, which you like to see as a measure of sort of accuracy in terms of the model discriminating cases from non-cases, you like to see that, you know, 0.75 or higher. It's consistently higher here. The relative risks, that is, if you were

classified as high risk, let's say in the top one percent of risk by the algorithm, you had about a — depending on the site — 12 and a half to 19-fold increased risk of later being diagnosed with bipolar disorder.

We've also extended this to look at bipolar disorder in youth. And again, I won't go through all the details here, but this was trying to say, now, could we do this for early onset or earlier onset bipolar disorder? And in a recent paper that just came out, we found that we were. In this case, we trained models looking at the data in three different sorts of cohorts. One is the general, kind of, child and adolescent population in our health system — about 300,000 — and then a sub-cohort of individuals who had already been seen in mental healthcare or who had already had a mood disorder or ADHD diagnosis, where the differential diagnosis can be tricky. And suffice it to say, the performance was good across all of those. Those in the top 20 percent of predicted risk by our algorithms accounted for about 60 to 80 percent of cases of bipolar disorder within the next two years.

So, these are some examples, but I want to

actually focus on one other example where we've taken this even further, and that is in addressing the problem of suicide which, as I mentioned, is the second leading cause of death among young people, and the rates have been pretty steadily increasing over the last two decades. Now the use of electronic health records and health settings, we think, is a real opportunity, largely because most people who attempt or die by suicide are seen by a healthcare provider in the preceding month, even. However, a minority of people who die by suicide disclose their suicidality to healthcare professionals. They're often not even seen by healthcare professionals, if they come to the ED. They often don't have a documented psychiatric disorder and, you know, systematic reviews have shown that the clinical risk factors that we use are often not very predictive.

And so, a number of years ago, we wondered whether these kinds of approaches that I've been talking about could help us do better in identifying those at highest risk. So, on the left, you see our initial study where we used data for 1.7 million patients, and developed and

validated risk prediction algorithms for suicide attempts or death. And the AUC, which actually got cut off here, was about 0.77. It detected 45 percent of all suicide attempts or deaths, with 90 percent specificity on average, about two to three years in advance.

So, encouraged by that, on the right, we said, could we see this kind of performance in other health systems? And we collaborated with our colleagues at five other healthcare systems. Now, 3.7 million patients did the same thing and, effectively, their performance was the same. We also conducted, on the bottom there, a detailed economic analysis asking the question, how accurate would risk prediction models like this have to be for them to be cost-effective to actually use? And the answer was that our algorithms — and now others that have been developed — do exceed those thresholds. They would be cost-effective if paired with evidence-based interventions or preventive strategies in actual clinical care.

We went on to prospectively test the value of these algorithms, and this was a study with Matt Nock and Ron Kessler and others, where we

were looking prospectively at more than 1,800 patients who presented to our psychiatric ED with psychiatric problems. And we asked clinicians, "What do you think is the probability that this patient will make a suicide attempt in the next month or the next six months?" And then we compared that to what our algorithm and a brief self-report measure that we also had folks administer — how that performed. And, in essence, the discriminative accuracy of the clinician prediction was not very good and was certainly exceeded by our EHR algorithm, which you could see there, especially when paired with this brief point-of-care self-report measure.

But, if you look at the bottom part of that table, I think that's the striking finding. So, if you were identified as being in the top decile of risk, the top 10 percent of predicted risk by the algorithm with the self-report, 40 percent of those patients went on to make a suicide attempt in the next month, and nearly 60 percent in the next six months. So, we think those are actionable numbers, and we actually went on to build a clinical decision support tool that could be integrated into the electronic health record

at the point of care to provide clinicians with this kind of risk-stratified information, to help them develop a safety plan and to help them consider what the options would be for this particular patient at a given risk level, always with the clinician's ultimate judgment and decision making as the, you know, the final arbiter there. But we are now in the process — we've just launched a large-scale, randomized trial of patients in the emergency department — 4,000 — half of them being randomized so that their clinicians would receive this kind of risk information in the EHR, half without, and we're going to see, in this kind of setting, does this actually make a difference in terms of suicide attempts over the next one to six months?

Another question that comes up is, let's say you find somebody is at high risk. What should you do? And if you think about it, when somebody comes, let's say to an emergency department, and they are either voicing suicidal ideation or have made a recent suicide attempt, one option that we, of course, always consider is psychiatric hospitalization. But is that the right choice for everybody? And one of the things that this

kind of precision psychiatry approach can lead to is the development of what we would call precision treatment rules. That is, can we use data to help us decide, for a given person, what is the most likely beneficial outcome?

So, in this study, again led by Ron Kessler, Eric Ross, and others, they took data for all VA patients with a psychiatric or substance use disorder who presented to the ED or urgent care with suicidal ideation or a suicide attempt, and they asked, for example, over the next year, what was the probability that somebody would make a suicide attempt if they were hospitalized at that ED visit, or if they weren't? And on the right side, you can see, for the entire sample, if they were hospitalized, 12 percent of those who were hospitalized made a suicide attempt in the next year. However, 12 percent of those who were not hospitalized made a suicide attempt in the next year. So that didn't seem to alter the course there.

If you just looked at people who had suicidal ideation without recent attempt, again, it didn't seem to matter overall whether you hospitalized or didn't hospitalize people, in

terms of next-year suicide attempt. If you looked at the people who had just made a suicide attempt in the past two to seven days, also really no significant difference. But if you looked at people who had just made a suicide attempt in the last day, rather, it actually did make a difference, and hospitalization was statistically significantly beneficial in that case. And so, they used this information to address a couple of things.

First of all, overall hospitalization reduced suicide attempt risk in about 28 percent of patients, but it actually increased risk in about 24 percent. So, a model was trained to predict the conditional average treatment effect. What that means is, if based on the data available, this person was expected to benefit from hospitalization, as we had just showed, you would hospitalize them. If they were expected to actually have an increased risk of suicide attempt with hospitalization, you would avoid it. Otherwise, defer to clinician judgment. And simply applying that rule would have prevented 16 percent of suicide attempts and about 13 percent of hospitalizations. So, this is really an area

we and others are very interested in, and another way to think about using data-driven precision psychiatry approaches.

Let's move on to prevention a little bit more, and this concept of resilience. Let me give you an example here about: What do we know about prevention, and how do we think about it?

So, imagine depression, for example. What can we tell people about how to prevent the onset of depression? If you look at the strongest risk factors, you might say, well, don't have affected relatives, because there is clearly a strong familial risk. Don't have significant childhood adversity, because that's a big risk. And maybe don't use drugs.

These are not the most actionable kinds of messages, but there are a couple of things that have been implicated as potentially having a resilience-enhancing or protective effect. And the question is, can we provide and use data-driven approaches to evaluate the degree to which that's true?

One of them is physical activity. And we can use genetic data in a sort of clever way to ask the question about, "What is the causal

relationship of physical activity to preventing risk of depression?" This is work led by Karmel Choi, as are a number of studies I'm going to show you here, in which we took data from the very large UK Biobank sample, in which people had measurements of their physical activity by accelerometer, so actually objective measurements, and also measurements of who developed depression over the next five years from baseline versus who didn't.

And we could ask, using this approach called Mendelian randomization, which is a way of kind of mimicking a randomized trial by taking advantage of the fact that we, to an effectively random degree, inherit risk variants that either increase our exposure to some phenomenon, in this case, physical activity, let's say, or decrease it. So, if you have genetic variants that are strongly associated with some exposure of interest, you can use them as what we would call instrumental variables to effectively assign people to different conditions, and then look at the outcome. And that allows you, like a randomized trial, to get a picture of the causal effect.

So, when we did this, we found, in fact, that there was evidence of a causal effect of increased physical activity on reduced risk of depression — of incident depression. About 26 percent reduced odds for every standard deviation increase in average accelerations. Roughly, that translates to replacing, say, 15 minutes of sitting per day with 15 minutes of running. It's not large amounts of activity.

We also, in a subsequent study, looked at, well, what if you were at high genetic risk of depression? Would this still have benefit? And first of all, in our large Biobank here, we found that, again, the more physical activity you had, the lower your risk of incident depression. But if you look on the right, you're seeing, if you divide people into high polygenic — we'll say more about that — or genetic risk of depression versus low, whether you were at low, intermediate, or high genetic risk, physical activity was protective against developing depression, in a fairly comparable way.

We've seen a somewhat similar situation with another factor that we think of as a resilience factor in depression and other stress-related

disorders, and that is social connection. And this is a study in collaboration with a number of people, including Bob Ursano, Murray Stein, again, led by Karmel Choi, in the Army STARRS cohort, in which in one component of that study, we had data for active duty service members before and after deployment, to combat in Afghanistan, in this case. And we could look at who developed depression upon return from deployment. And we were particularly interested in this idea of social connection, which was operationalized as the concept of unit cohesion, which will be familiar to those in the military, or veterans, as this sort of sense of how cohesive socially, or, you know, connected you are to your unit. How much do you feel supported by your commanding officers, et cetera?

So, what we were able to do was calculate a genetic risk score for each individual, and you could see on the right side there, in the blue graph, the higher your genetic risk of depression, the more likely you were to develop depression after returning from combat. The higher your unit cohesion, the lower risk you had of developing depression. And, interestingly,

even regardless of your genetic risk on the left, or your exposure to deployment stress, this unit cohesion had a protective effect that reduced the risk below baseline of developing depression.

And so that's really, I think, encouraging evidence, which we've extended elsewhere as well. This was an even larger study, looking at 105 potential modifiable factors — lifestyle and behavioral factors — that might be associated with reduced risk of depression. This, again, in the UK Biobank. What we saw, you're looking here at a graph where on the Y axis, you have this: the $-\log_{10}(p)$. So that's just a measure of how statistically significant the results are. Everything above the dashed lines in this graph is statistically significant, and you can see the different categories of interventions or behaviors at the bottom.

The thing that was significantly positive as having a protective effect was frequency of confiding in others. Also, significantly protective appeared to be exercise. We already had physical activity, gym, and sports, and other kinds of social connection, as you'll see.

We then did this process of applying

Mendelian randomization, you'll remember, which tries to get at to what extent are these likely to be causal effects. And once again, frequency of confiding in others. Frequency of visits with family and friends. Exercise. These things seem to have a causally protective effect.

We've also seen in other settings, social support, by the way, having this kind of effect. These are data that we had from the All of Us Research Program during the early part of the COVID pandemic, and looking at to what extent people had social support in those periods. This was a study of nearly 70,000 individuals in the study. The bottom line was, social support had a pretty potent protective effect on the risk of developing clinically significant depressive symptoms. And if you had multiple sorts of forms of social support, emotional, tangible, or positive social interaction types of support, that was associated with 85 percent lower odds of developing depression. So, these are actionable kinds of things we can get by using real world data.

What about identifying biomarkers of risk? Here, I'll come back to something that we

mentioned previously, which is the idea of using genetic information as a potential biomarker. And many of you may have heard of the concept of a polygenic score. So, when we do these large-scale genetic studies, we often find variants, as I showed you earlier, that might be associated with a condition. Let's say it's depression or schizophrenia. But these are variants or DNA variations that by themselves have a tiny effect. However, when you add them up, they can have a more substantial effect.

And so, for any individual, if you've already done a large scale, let's say, genetic study of depression, you can now know, to what extent do any of those variables, or variants, rather — and let's say there are a million variants in that genome scan that were done — are associated with an effect size. And now if you take somebody who was not in that study, you can look at how many of the alleles or variants they have at each of those variations, so SNPs, or single nucleotide polymorphisms, and each of us would carry zero, one, or two copies of any variant at one of those. You can multiply them by the effect of that variant in your prior

study, and then you do that for all, let's say, million, add them up into one score, and you've got what we call a polygenic score, which is usually normally distributed, and can be applied to anybody for whom you have genomic data as a kind of index of their genetic vulnerability, at least for what we think of as common variations in the genome.

And there are a few things to know about this. One is, they're very robust, in the sense that those genetic scores have been repeatedly associated with conditions that we're concerned with. However, they're not diagnostic tests. So, these are data on schizophrenia, let's say. So, if you were in the top 10 percent of a polygenic score for schizophrenia, compared to people in the bottom 10 percent, that's about 16-fold increased odds of having the disorder. If you took the top one percent compared to everybody else, it's about a 5.6-fold increased risk.

But look at the distributions on the right there. The cases and the controls are very overlapping. So, we think of this as a risk factor like we might think of other risk factors

that we use in medicine. Not a diagnostic test, but a kind of biomarker of risk. And in studies that we've done in real world health data, for example, through the PsycheMERGE consortium, we've found that, for example, a schizophrenia polygenic risk score does in fact have a very strong association to schizophrenia risk in healthcare systems. But again, it's, you know, not diagnostic. So, a little more than a two-fold increased risk, if you're in the top 10 percent, compared to everybody else.

The other thing you can do is look at what else is it associated with, in the health phenome or all of the conditions that we have in the electronic health record? And that's what you're looking at on the right. So, you can see diagnostic categories listed by their systems in the body: mental, behavioral, respiratory, digestive, et cetera.

We find that, for example, a schizophrenia polygenic risk score is associated with certainly a lot of mental health conditions, but also some things that we might not have expected. Viral hepatitis C, obesity, urinary tract issues, et cetera. So, this opens up other areas of

connecting biomarkers of psychiatric risk to other health conditions.

And here's another example of that. This, again, led by my colleagues Lea Davis and PsycheMERGE. Now, we took a polygenic score for depression, and used the laboratory data that are available in the electronic health record. So, we have hundreds of labs that are drawn in routine care, and we can think of those as biological assays, with the appropriate, you know, caveats about why they were drawn.

But, in the interest of time, I'll just summarize that if you do that, and you take a polygenic score for depression, and you look at, what laboratory values is it associated with? The one that is very strongly associated is white blood cell count with a p-value of, like, 10^{-10}. And we then tried to replicate this among multiple healthcare systems, Mount Sinai, the Million Veteran Program, Mass General Brigham, Vanderbilt. The results were really very consistent, even if you control for depression diagnosis or anxiety diagnosis. So, it obviously resonates with the notion that people are very interested in how inflammation or immune

activation might be related to these kinds of stress-related disorders. But it gives you a flavor of how you might, somewhat creatively, I think, use the data that we have to look for biomarkers that might be valuable.

What about treatment? We know that currently our treatment approaches are typically a kind of one-size-fits-all, trial and error proposition. People, for example, with medication may get started on a treatment that may not work. Eight weeks later, we decide didn't work. We should add something, we should switch something. Meanwhile, people are spending weeks with inadequately treated depression, psychosis, et cetera. On average, the effect of an antidepressant, based on clinical trials, is pretty modest. So, in meta-analyses, the mean drug advantage versus placebo is actually less than two points on the Hamilton-D Depression Scale, which is not really even clinically meaningful. But we know that's not the whole story, because we know that some people do very well and have clear apparent benefit, and others don't benefit at all. So, this heterogeneity is an important factor that we need to take account

of.

One thing that we've done to try to address this is apply the kind of methods that I talked about before, using artificial intelligence with very large-scale, real-world health data. In this case, research led by Yi-han Sheu and our Center, looked at EHR data for more than 17,000 patients who were started on an antidepressant of one of the first-line classes of medicine: SSRI, SNRI, bupropion, mirtazapine. We had 38 years of longitudinal data. We had natural language processing of notes, and we evaluated a number of machine learning and AI models.

And, just to remind you, right now, if I'm seeing a patient with, say, depression and I look at the research studies, STAR*D or others, about what's likely to work, these various classes, the prior probability is that they're about the same, right? About 50 percent of people will respond to one of these, but I don't know which one. When we applied our approach, it correctly predicted the response for 74 percent of patients. And these are actually data for two real patients from the dataset, Tom A. and Megan B. You can see that Tom was predicted to have a

very strong response to or a very likely benefit from an SSRI. Megan not so much, 28 percent.

But you really want to know, well, if it's not that good for something, you know, if you're predicted response to an SSRI, for example, is not very high — what else might you respond to? That's sort of the clinically relevant question. And the nice thing about these models is that they can predict responses to different antidepressants. So, in this case, Tom was predicted to respond well to any of these medicines, although SSRIs were the best. For Megan, actually, mirtazapine was predicted to be the best choice. So, you can see how this kind of information could inform better decision-making.

Okay, lastly, I want to touch on the notion of using genome and other data to inform the development of novel therapeutics. We know, as I said before, that many of the drugs that we use, almost all of them, are really based on biology that's, you know, from the 1950s, '60s, '70s. But what's become clear from a number of studies, is that if you have drug mechanisms that have genetic support as the target of the drug that

has been implicated in genetic studies as convincingly associated with the phenotype illness condition that you're interested in, that confers about a 2.5-fold increased likelihood of succeeding of bringing that drug through to launch, basically. And it doesn't even really matter how common that variant is or what effect size it has on the phenotype, it's pointing to a pathway. There are drugs that we commonly use that now have genetically supported targets, although none of them were found through genetic information, and I've listed a few of them here.

The opportunity is, what if we started with what we're finding genetically, to try to identify and develop drugs that would be more likely to succeed through this pipeline of drug development? And in these genetic studies, we're seeing not only hundreds of loci, but they are beginning to coalesce into themes of genes and pathways that affect certain systems. Certain functions. So immune inflammatory is a big one. Neurodevelopment. Chromatin remodeling — sort of epigenetic regulation. Synapse structure and function. Glycosylation. So, we're beginning to get these clues that could fuel some novel

directions. And I want to give you the example from this last glycosylation example. So, this is work led by Robbie Mealer, who used to be with us, now at UNC, who began to study a variant that in genetic studies of schizophrenia was one of the most strongly associated with schizophrenia, and it is a coding variant, meaning the variation in this gene actually affects the protein translation.

And it turned out to be a missense variant in this gene called SLC39A8 — probably not one that was on the tip of your tongue — but it's relatively common for something that actually affects the protein structure. That variation is relatively common. That's interesting, because that gene is a manganese transporter. Manganese is a co-factor for a whole slew of enzymes and other intermediates involved in the process of glycosylation, which of course is adding sugar polymers to proteins, for example, on cell surfaces or to lipids. And that's critical in cell adhesion and brain development. Now, it turns out that Robbie was able to, through our Biobank, profile the cells of patients who carried this variation in this gene and

identified that they had lower levels of serum manganese.

They also, when you use mass spectrometry to profile their cells in terms of their glycosylation profiles, they have less developed glycosylation profiles than others. If you knock in this risk allele for schizophrenia into mice, you can see altered cortical protein glycosylation in specific regional patterns. And it turns out that many of the genes, now in retrospect, that have been linked to or associated strongly with schizophrenia, are targets of glycosylation. And that's led to this notion that glycobiology, something that I don't think we talked much about in med school or in the last, I don't know, 20 years in terms of schizophrenia, might be a pathway relevant to the development of this disorder, which I think illustrates how you can get these new clues about causal biology from genetic studies. It also suggests there might be a therapeutic opportunity.

And, in fact, Robbie and colleagues have shown that if you supplement people who have effectively knockouts of this gene — there are

congenital disorders of glycosylation that are due to loss of function, knockouts of this gene — you can partially reverse the impaired glycosylation that you see on their cells. And now, in work that he's pursuing in, you know, knockout mice and in cellular models, like IPS models, can we think of modifying this, either through manganese supplementation, for example, or through intermediates in these glycosylation pathways, that might provide a novel therapeutic approach.

All right. So that was a lot. But just to summarize, I hope that I've given you a sense that there are some new tools and resources that are finally beginning to enable us to apply precision medicine to psychiatry, by leveraging all these different types of individual differences. And, of course, precision medicine has had tremendous success in the areas of oncology, and cardiology, and actually infectious disease, and rare disease.

We have lots of gaps in how we diagnose, treat, and prevent mental health conditions. And our model here at Mass General is, you know, an emphasis on driving innovation to implementation

— really following those leads that could lead to some real change in ultimately clinical practice. I'm very excited about the opportunities, but it's a complex field that's going to need to leverage and integrate all of the developments that we're now seeing in AI, and genomics, and epidemiology, in clinical psychiatry and, importantly, in implementation science, to bring these kinds of advances to the future of mental health care. So, I'm going to stop there and I will look forward to having an opportunity to answer some questions a little bit later. Thank you so much.

(Whereupon, the above-entitled matter went off the record.)

DR. NAIFEH: Thank you, Dr. Smoller. What a great way to start things off today.

Our next speaker is Dr. Scott Russo. Dr. Russo is a neurobiologist and Professor in the Nash Family Department of Neuroscience at the Icahn School of Medicine at Mount Sinai and the Friedman Brain Institute, where he directs the Center for Effective Neuroscience. His research focuses on understanding the neural and immunological basis of neuropsychiatric disorders. He has been listed as a highly cited researcher in the field of neuroscience by Clarivate Analytics since 2015.

We will now begin Dr. Russo's presentation, which is titled, "Neuroimmune Mechanisms of Stress and Depression."

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NEUROIMMUNE MECHANISMS OF STRESS AND DEPRESSION

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DR. SCOTT J. RUSSO

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P-R-O-C-E-E-D-I-N-G-S

DR. RUSSO: Thank you very much. I'm really pleased to be delivering this virtual presentation. Today, I'm going to talk to you about our research looking into neuroimmune mechanisms that regulate stress responses and the relevance to those stress responses in the expression of depression.

So, I think all of us probably who've studied the brain are very familiar with this particular setup where we've got a nerve cell that sends out an axon to neighboring cells and other circuits. It may interact with glial cells, like astrocytes and oligodendrocytes. And this forms, really, the basis, the neural basis, for complex behavior. And it's also the circuits that we think go awry in neuropsychiatric conditions like depression. But I think a lot of us don't think about the broader picture here, that these cells don't just exist in isolation. They have rich interactions with systemic compartments, so peripheral organ systems, and

they do so via both direct and indirect interactions at the neurovascular unit.

And so, what I'm showing on the right side of this cartoon schematic is a blood vessel where the wall of the blood vessel is actually wrapped by astrocytes, which can sense information from circulation. Circulation and the specific types of signals can be brought directly to the neurovascular unit through immune cells, shown here in white. And that these mechanisms may, in fact, be both important for the expression of complex behavior as well as symptoms associated with neuropsychiatric diseases, like depression.

And so, we became very interested in this potential interaction, these brain-body interactions, if you will, for several reasons. First and foremost, I think, is that when you consider depression, it's not just a unitary construct. It's often comorbid, not just with other psychiatric illnesses, but with a whole host of peripheral organ system diseases. For example, cancer. This relationship is actually

bidirectional, whereby if you have depression and you develop cancer, your response to treatments is blunted, and the likelihood survival rate, for example, is diminished. Cardiovascular disease. Patients with depression have an increased risk for developing cardiovascular diseases. But both of these relationships also go in the opposite direction. In other words, if you have cancer, you may also be more likely to develop depression. Similar data exists for all of these other illnesses.

Now, what's common amongst these illnesses might not be clear at the onset, but all of these illnesses have some component of immune system dysregulation. And in fact, if you look at worldwide prevalence rates for patients that suffer from some of these illnesses, you can see that their likelihood of developing depression is far greater than the general public, from diabetes all the way to asthmatic patients, with prevalence rates rising up towards nearly 20 percent.

And because these illnesses all have shared underlying disturbances within the immune system as a particular risk factor, we and others have really hypothesized that it might be these shared immune-related mechanisms generated in the periphery that might be impinging upon the brain to affect stress susceptibility and, ultimately, the expression of depression.

So, a few years ago, Kenny Chan, a postdoc in my lab, put together this analysis based on the literature to look at the types of immune signals, mostly cytokines and chemokines, which have been studied broadly to date. But to look at the overlap between depression and anxiety with several common inflammatory illnesses, both in human subjects as well as in animal models of those particular diseases. And what you can see, of course, is that there's a lot of shared dysregulation, first of all, within these models, between mouse and human, but also across the various illnesses, from several pro-inflammatory cytokines that are up-regulated in depression

that are also found in these other conditions.

And so, this has really allowed us to hypothesize that it might be that these systemic factors are not just unrelated biomarkers of the illness, but actually causal changes that occur that put us at risk for these central diseases like depression. So, this is where we came into the field, and I think this is where our contributions started. We first asked, what are the cellular mechanisms underlying the inflammatory subtype of depression? And the reason we asked that question is that, to date, most of the studies had been focused on looking at protein analytes in circulation. For example, like I mentioned earlier, several pro-inflammatory cytokines and chemokines. But it was really unclear which cells were producing these inflammatory molecules, and maybe even more importantly, which organ compartment were they coming from.

The second question that we asked was, if these immune signals are originating in the

periphery and impacting the brain to control symptoms in depression, how do these immune cells actually access the central nervous system? And what are the mechanisms by which they can directly control neuronal function? Which again, as I mentioned, is really the final common substrate of these illnesses.

So, many years ago, we established a collaboration with Dr. James Murrough. He leads our Depression and Anxiety Center here at Mount Sinai. This project was led by a former postdoc, Flurin Cathomas, who's now back in Switzerland and is a group leader with his own research program. And what we did was, we started to form a biomarker repository based on patients that were coming through the Depression and Anxiety Center for either treatment or other study designs. So, for each patient that comes in, we first get a complete blood count with differential, which allows us to analyze all the different leukocyte subtypes, or many of the different leukocyte subtypes, in blood in

patients with major depressive disorder. And we found that the most common enduring change in these patients is myelopoiesis.

And what myelopoiesis is, it's an increase in the production and release of myeloid cells into the bloodstream. Myeloid cells include not just monocytes, shown here in the left-hand panel, but also neutrophils. And we see significant elevations in a subset of these patients across both. You can see it's not everybody. Some estimates from epidemiology studies have suggested that the immune dysregulation shown here represents about, you know, 25 to 30 percent of the overall population. We don't see broad changes in other blood cell types. But what we do see is strong correlations with markers of stress.

So, what I'm showing here is the correlation between monocyte level or content with a marker of traumatic stress experience. This is based on data that we accumulated from the Childhood Trauma questionnaire, which is a screen that

allows us to quantitate the type and number and intensity of traumas. that one may have experienced early during development, and it's normed for late adolescence. You can see a strong positive correlation between these two factors. We also see similar correlations with other stress scales. For example, the Perceived Stress Scale, where we simply ask a patient whether or not they feel stressed, and those show similar correlations with myelopoiesis.

Another feature of these patients is that the monocytes are also more reactive to stimuli. So, we can take peripheral blood mononuclear cells, which contain monocytes, and we can put them into a culture dish and use an agonist. In this case, we use lipopolysaccharide, which binds to a receptor on the monocyte itself, stimulating its activity, which is associated with an increased release of pro-inflammatory factors like interleukins. And we find that depression patients, their monocytes are much more responsive or reactive to this LPS stimulation.

In addition, several years ago, a postdoc in my lab was very interested in the blood-brain barrier. This is the area that I mentioned earlier, which contains the neurovascular unit. And we hypothesized back then that in order for these immune signals or cells to interact with the brain, there must be some type of change at the blood-brain barrier. There must be some type of measurable interaction between these systemic immune factors and the blood-brain barrier. So, she collaborated with several of our clinical collaborators, first in Montreal, Gustavo Turecki, and second in Texas, with Carol Tamminga, who run psychiatric brain banks. We obtained nucleus accumbens tissue from patients with a diagnosis of major depression at the time of death. And what she found was that the endothelial cell-specific tight junction claudin-5, which is critical for blood-brain barrier health and forming the initial layer of the barrier that prevents things from our bloodstream to enter the brain, she found that there was

evidence, molecular evidence, for a decrease in the expression of these tight junctions.

Functionally, what that would mean is that the barrier of a patient with depression might in fact be more open to peripheral factors perfusing in. I hope you notice that we split these cohorts based on antidepressant treatments, but I should caution you, most of these cases were suicide cases, and the fact that they were on antidepressants is based simply on toxicology screens at the time of death. So, we don't know if these medications were being taken as approved. We don't know if they were effective. And we don't know what types of antidepressants were being used. It's just a broad category. In fact, when we do more controlled studies in rodent stress models, where we control the dosing and we measure treatment outcomes, mice that are exposed to the antidepressant imipramine, that respond positively from a behavioral perspective to that regimen, do in fact show evidence of blood-brain barrier normalization. So, it might

be that even our standard antidepressant toolbox can play some role in promoting blood-brain barrier health and preventing neurovascular damage.

A few years back, actually last year, this group published a study that indicated there may, in fact, also be functional increases in permeability in line with our molecular data here. The way that they did this was to use gadolinium with contrast MRI. So, this is a procedure in which you can inject systemically a tracer, gadolinium, that you can then detect in the brain by a magnetic resonance imaging. So, you do an MRI before and after the injection of gadolinium and you measure the change in fluorescence as that contrast agent perfuses into the brain as a direct measure of blood-brain barrier permeability. And, while not a huge difference between groups, there was a significant increase in a subset of patients in the striatum when we compared MDD to healthy control patients. So, this was evidence, for

example, that there is in fact functional blood-brain barrier damage.

We did a similar study with James' group. This was led by Sara Costi and Flurin Cathomas. It's just been submitted, so this is not published yet. We took a subset of patients, 40, with major depressive disorder, and compared their responses to 25 healthy controls. These are the variables that we measured in our data sets. We measured, for example, region-specific and whole-brain permeability, several immune factors, such as metalloproteinases, immune cells themselves, and we correlated these with different clinical features, for example, perceived stress, the Childhood Trauma Questionnaire, et cetera. We built a network using pairwise correlations just to see the relationship between many of these factors. The green lines represent positive correlations and the red lines represent negative correlations. The thickness of those lines represents the strength of those correlations.

And we, interestingly, found that there was a strong correlation really with childhood trauma, as our earlier data suggested as well. And really, the immunological disruptions and the blood-brain barrier changes that we observe are largely tied to increased frequency of psychological and physical trauma. And what I can show you -- I can show you the breakdown of those specific data. The CTQ collects data not just on total trauma, but also the specific types. So physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse, we correlated those features with blood-brain barrier permeability, and we found that, in large part, the physical abuse and the emotional abuse correlated most strongly with these changes in blood-brain barrier permeability.

We also correlated leukocyte subtypes with these various brain permeability measures, and what you can see is that monocytes, in particular, seem to be correlated with much of the brain-wide changes in blood-brain barrier

permeability that we observe. No correlations with lymphocytes or other blood cell types. A slight correlation with neutrophils under certain circumstances.

So, this really led us to this -- our hypothesis. This is really our working model. So, we believe that in the case of depression, and maybe anxiety, chronic stress is leading to myelopoiesis. This is an increase in the production of monocytes and neutrophils. Those monocytes and possibly neutrophils then traffic to brain neurovascular spaces. We think this is actually an active process that we're still studying, but we think it might be due to increases in chemokine receptor expression within these myeloid cells.

Once at the blood-brain barrier, we think that they actively dock at the endothelium through the binding of junctional adhesion molecules, and when there's damage to the blood-brain barrier in those regions, we also see perfusion of myeloid-derived factors, possibly

interleukins, or other factors that those cells are producing. Once inside the brain, those factors potentially could have diverse roles on all of the cellular phenotypes locally -- localized within those regions, and that might ultimately impair or alter neurotransmission and change behavior.

It's also possible that these cells themselves can traverse through the damaged vessels, get into the brain parenchyma, and cause their effects more locally. But I'll show you some data where we think that we've now ruled that possibility out.

Okay. So, digging into this, it's really difficult to model psychiatric illness in mice, or rats, or even non-human primates, for example. So, I don't want to make any claims about modeling depression in mice, or PTSD in mice. But what I do want to say is that our physiology, between mouse and human, is fairly well-preserved at some levels. And I think modeling the body's physiological response to trauma maybe is a bit

more valid, in terms of trying to understand how humans cope with and respond to trauma.

We've been using this trauma model, it's a social defeat stress model, for many years to study the negative impacts of psychosocial stress on brain and behavior. And just to briefly describe the protocol and how we employ it, we select large, aggressive, outbred mice as residents. We then expose C57BL/6 inbred mice, which are more docile, a bit more subordinate, to these larger, aggressive mice for five minutes a day, over a 10-day period. Each day, they experience this five-minute physical altercation, and 24 hours of a psychological sensory period in which they're housed next to the aggressor.

At the end of this 10 days, the animals exhibit a broad range of physiological and behavioral changes. One of the more prominent changes that we've characterized over the years is social avoidance. We use social avoidance really as a rapid screen to determine mice that are considered to be susceptible, and mice that

are considered to be resilient; meaning that they've somehow adapted and not succumbed to the stress at a behavioral or physiological level. And what the test includes is a simple measure of interaction with a CD-1 aggressor mouse in a cage. We measure how much time they spend interacting. The resilient mice interact just like control mice, as if they've never been stressed out, and the susceptible mice avoid that social target at all costs.

Now, there's been some criticism of this model over the years, particularly with respect to what this metric of social avoidance means. There's a few problems with the model, in my opinion. First, is that we've got this wire mesh barrier, and so it's unclear how barriers impact naturalistic social behavior. And one question has always been, are they resilient? Maybe they just learned safety signals more quickly. They maybe learn that the CD-1 mouse can't actually physically attack them anymore, because they're behind this barrier, which is possible.

Other criticisms have been, maybe the resilient mice are just dumb, and they don't remember that they've been attacked by this other animal.

And thirdly, what are we really measuring? Are we really measuring social behavior? And what aspects of social behavior are we measuring? One might interpret this type of avoidance as social fear, for example, rather than an uninterest or disinterest in engaging in social interaction, which is a little bit more indicative of some of our major depressive disorder patient cohorts.

So, we've kind of modified this strategy a bit. I'll just show you real quick a few videos. We also, in addition to measuring interaction with a CD-1 mouse, we also measure interaction with juvenile, non-aggressive, same sex, C57 mice in their home cage.

Okay. So, when you look at those types of interactions, you can see a resilient mouse is quite interested in this juvenile social target.

They're found to be rewarding under control conditions. He's very interested. He's exploratory. He's, you know, engaging the social target.

Contrast that with a susceptible mouse. You can see, once the juvenile is placed into their cage, it's actually the juvenile that approaches the susceptible mouse, and they withdraw from those social encounters quite dramatically over time, and they end up exhibiting strong social avoidance of this juvenile social target.

And so really, the way that we're conceptualizing the social defeat model at this point is that it's probably leading to some type of generalized fear of sorts, whereby all social targets now become somewhat aversive to the susceptible mouse because of those earlier negative social experiences that they've had. And so, this is really the model that we use going forward.

To test what mechanisms, the first question I brought up was, what are the cellular

mechanisms that might be driving this? To do this, we used a new -- at the time, it was a relatively new method, called mass cytometry. It uses antibodies bound to heavy metals, and allows you to really deeply phenotype at the single cell level the types of immune cells in circulation in mice following social defeat stress. You can see all the different broad categories of immune cell subtypes that we see here on the right, and you can see their expression profiles shown in these t-SNE plots.

So, I'll show you the data that we think is interesting to begin with. So, first and foremost, much like humans, we find this interaction between stress and myelopoiesis. So, stressed mice, whether they're susceptible or resilient, exhibit more inflammatory monocytes and neutrophils. No differences, though, between susceptible and resilient mice. They also exhibit inhibited, stress-inhibited, adaptive immune responses. This is showing several B-cell subtypes involved in these processes. And you

can again see a general stress effect, but no differences between susceptible and resilient mice.

Now, if you do the same protocol, but you first isolate whole brains from mice following social stress, and perform mass cytometry, you can also look at immune cell subtypes in a similar way. First and foremost, I want to point out the fact that there's far fewer immune cell subtypes in brain, and that's largely because not all cell types can enter the brain parenchyma readily; and also the largest population of immune cell subtypes, of course, is the microglia, or the resonant macrophage.

Of the cell types of interest, though, what we do find is that myeloid cells can enter the brain parenchyma, or at least they are found in these whole brain preparations. Whether they're in the brain parenchyma or sitting in the vessel is another story. And I'll show you some data in a few minutes.

But when we did this now, there was a bit

more of an encouraging split between susceptibility and resilience, where we really found that the monocytes were more enriched in the susceptible brain, but not as much in the resilient brain. While encouraging, there still statistically is no meaningful difference between susceptible and resilient mice, and one of the weaknesses or limitations of this method is that we had to use whole brains in order to obtain enough cells for us to quantify their expression within the brain.

And so, we wanted to get a more specific and topographically accurate map of myeloid cell expression in the brain. And so, for that, we turn to brain clearing, and whole brain mapping of monocyte trafficking. You can see here, this is an iDISCO+ brain clearing preparation. You can see the brains are quite translucent. We used a CCR2-positive red fluorescent protein expressing mouse, which labels peripheral myeloid cells and allows us to track them. And when you look throughout the three-dimensional structure

of the brain, each small red dot, once we zoom in, is going to be one of these RFP-positive monocytes.

So, you can see there's actually quite a few of them in this brain preparation. We still don't know from these images where exactly they are, but we can at least measure differences or changes across the different brain regions. And the resolution does seem to be better than what we were getting with CyTOF, for example.

So, here's one interesting finding. We were able to replicate our whole brain CyTOF data, pretty similar. In fact, it does look like there's a very strong increase in CCR2-positive monocytes in the brain of susceptible mice, but not in resilient. And this measure correlates with the expression of social avoidance behavior.

But what was also interesting was that we started to see some region specificity in these responses. So, first of all, the NAC seems to be an area where a lot of these cells are trafficking to, at least in susceptible mice, but

not much in resilient. In the prefrontal cortex, we don't really see any evidence of either stress causing increased trafficking, or of differences between susceptible and resilient mice.

And so, this region specificity is interesting for several reasons, but I think most importantly was that our previous study had shown that areas across the brain that become more permeable in the mouse brain following social defeat are also region-specific, and they tend to overlay with these myeloid trafficking profiles.

So, for example, if you look at the middle column, these are susceptible mice. The more yellowish to black colors means more blood-brain barrier permeability using gadolinium MRI. And you can see several regions, like the accumbens and hippocampus, show increased blood-brain barrier permeability, but not the prefrontal cortex. And these are also the two regions that differ in their monocyte accumulation.

And while we don't know this for certain, we've hypothesized and are testing whether or not

myeloid-derived factors are in fact producing proteins that can cause the blood-brain barrier damage in the first place, which might explain why certain regions are more vulnerable than others, i.e., those regions that accumulate myeloid cells.

But where are these cells? I've alluded to this a few times throughout. They're not in the brain parenchyma and they're not in the perivascular space. So, let me orient you to these images. We took brain slices from the nucleus accumbens of mice where we see significant myeloid cell accumulation and significant blood-brain barrier damage. We stained for endothelial cells using the marker CD31. We stained for RFP using the RFP mouse line that we have. And then we stained for the astrocytic endfeet using aquaporin-4.

So, the inner layer, which is a bit purplish, is the blood vessel itself. It's the luminal side of the blood vessel here. And you can see all of the RFP containing cells are

localized within that three-dimensional structure, suggesting they're actually on the luminal side of the blood vessel rather than on the parenchymal side.

We also looked at the perivascular space, which is the space between the astrocytic endfeet shown here, and the CD31 positive endothelial cells. And we found no evidence of these RFP positive monocytes within these perivascular spaces, as well as no evidence of them getting into the brain parenchyma. And you can see the clear quantification shown here. So, this is really why we think, in fact, that these cells are adhering to the inner lining of the blood vessel and possibly secreting factors locally, which then can enter the brain parenchyma to control neural function.

But before we get to that, we wanted to understand what these brain trafficking monocytes were possibly expressing that might explain their role in regulating brain and behavior. So, for this, we performed a monocyte-specific single-

cell RNA sequencing study where we first isolated monocytes and then performed single-cell sequencing on those sorted monocytes. We found four unique clusters based upon their transcriptional profiles, and you can see that shown in these heat maps to the left here.

You can also see how those four clusters are expressed across control susceptible and resilient mice. And you can see that there are some clusters, for example, like cluster two that seem to be reduced in both susceptible and resilient mice relative to controls, others which might be increased or enriched, and still others, which are uniquely regulated in susceptible mice. For example, this cluster is zero here. And so, this is the cluster that we focused on for the remainder of our studies.

We performed a gene ontology analysis of cluster zero. And these are some of the top terms that came up when we did that analysis. Some of these were not surprising. Oxidation reduction processes are well-established

mechanisms involved in responses to inflammation, and so we weren't too surprised to see some of these. But we were actually quite surprised and intrigued by terms such as extracellular space and extracellular matrix. Prominent among these is MMP-8, which you can see here to the right. This is a matrix metalloproteinase that's uniquely expressed in peripheral myeloid cells. And you can see that it seems to be enriched in susceptible mice compared to their controls.

I'd like to pull back to the clinical relevance for one second before I show you evidence to test causality related to MMP-8. When we measured MMP-8 in our patient cohort, we did see a subset of patients that had elevated MMP-8. This is at the protein level, and you can see this right here. Levels of MMP-8 correlated with measures of stress. I'm showing you data here from the CTQ.

But I also want to point out that three additional studies, two large-scale studies using RNA sequencing of blood cells and a more recent

study looking at protein expression, has confirmed that there are significant elevations in MMP-8 in patients with major depressive disorder. Those studies didn't correlate them with more sophisticated clinical outcomes like trauma and stress, but they do suggest that MMP-8 is a bona fide target within major depressive disorder.

So, what does MMP-8 do? And I think as a neuroscientist, I understand what metalloproteinases do, in large part based upon their role in regulating synaptic plasticity via the extracellular matrix. But MMP-8 is not actually produced in the brain. And there was really no literature on MMP-8. What there was literature on was MMP-8's role in cardiovascular disease. And so, I'd like to use this example, because it helped to ground me and help me to understand how this particular factor might, in fact, regulate the brain's ECM.

So, under conditions of cardiovascular disease, or when plaques form in blood vessels,

the plaque itself is organized in a very specific way. These dense lipid cores in the middle here are usually stabilized by a fibrous cap. And so, under kind of steady state conditions, we probably all have some level of plaque in there. They're largely stable because the fibrous cap prevents this lipid core from bursting out, floating through circulation, and causing a cardiovascular event. The fibrous cap is made up of collagen, and MMP-8 is a collagenase, meaning that it can break down collagen.

So, under chronic stressful states, what we think happens is that monocytes traffic to the fibrous cap. They express metalloproteinase, is like MMP-8 that might actually degrade the collagen, destabilizing the plaque and allowing for that lipid core to rupture and travel to other parts of the body and cause cardiovascular events. And, in fact, this is what it looks like happens in chronic stress conditions using our mouse stress model.

This is work done with Ed Fisher and Ozlem

Tufanli at NYU. We put our stress-susceptible and -resilient mice on a high-fat diet, and we simply looked at plaque composition. And what you can see actually is the mice that have -- the susceptible mice actually have more of these macrophages, which are derived from monocytes, that are located within the plaque, which is consistent with the model that I just proposed.

This paper is in submission. I'm not going to go through the details and what we did here because I want to focus my time. But I just thought I'd introduce this topic as a way to potentially think about MMP-8's action in brain. Given the fact that it is a peptidase and can break down collagen and collagen-like markers, it's possible that MMP-8 in the central nervous system might be able to reorganize the brain's extracellular matrix, altering synaptic plasticity and changing behavior via that circuit adaptation.

So, the question is, since we have increases in blood MMP-8 in our depressed patients, what

does it look like under stress-susceptible conditions? We measured MMP-8 in circulation and in brain, and you can see a strong increase in both compartments in the susceptible mice relative to both control and resilient mice to determine whether MMP-8 was actually capable of entering the brain parenchyma; because, remember, we know the cells aren't getting in there. But if the factors that the cells are producing can get in, that may explain how they can impact the function.

And so, to do this, we use a strategy where we label with biotin recombinant MMP-8 protein, and then we inject this into circulation of mice following social defeat stress. We flush the system out using PBS, and then we generate brain slices. And by immunohistochemistry, we can then identify that biotin-tagged recombinant MMP-8 throughout the brain and determine whether or not it was entering the brain parenchyma.

And so, when we do this, you can see that quite a bit of MMP-8 that's tagged with biotin

can enter the brain parenchyma of susceptible mice. The red here is a blood vessel, and you can see these green dots is the MMP-8 biotin. You can see it localized well outside of the blood vessels and throughout the brain parenchyma.

And this was exciting, because -- and this really does highlight the possibility that the myeloid cell producing MMP-8 is likely interfacing indirectly, but the products of those myeloid cells are interacting directly.

Now, I've alluded to this a few times throughout the talk, but ultimately, what we know about MMPs in plasticity is that they're capable of opening up windows of plasticity by degrading some of the proteins that make up the extracellular matrix. That means that the spaces between cells open up, and that is a necessary restructuring event for new synapses to either form or existing synapses to enlarge and strengthen. And so MMP-9, for example, has been shown to cause an increase in excitatory synaptic

transmission, because it can increase dendritic spines on neurons and it can also increase the size and strength of those synaptic contacts.

We did, in fact, look at the extracellular space in our mice. This is in the nucleus accumbens again. And we used electron microscopy to measure spaces between these brain cells. And you can see that it does, in fact, increase in susceptible mice. This increase is really nicely correlated with MMP-8. And we were surprised, because it was such a small cohort, but we do, in fact, see a nice correlation between MMP-8 levels and extracellular space, suggesting that it may actually be causally linked to changes in extracellular space.

Moreover, we directly measured one of the components of the extracellular matrix, which is aggrecan. And you can see that there's a loss of aggrecan protein consistent with ECM breakdown by MMP-8.

To pull this one step back, the reason why we were initially interested in this is that our

past research showed synaptic profiles consistent with the events that I just described. So, these are nucleus accumbens medium spiny neurons, and you can see we've shown over several years, in several different manuscripts, that there's an increase in the number of dendritic spines that form on these medium spiny neurons in this brain region where there's extracellular matrix remodeling.

So, we wanted to test this, and in order to test this, we generated MMP-8 knockout mice, but we didn't want to use germline deletion developmental knockouts. We wanted to bypass that and we wanted to ensure that we restricted MMP-8 knockout to the immune cell compartments. Probably overkill, because MMP-8 is really only produced by myeloid cells. But for those reasons, we chose to generate bone marrow chimeric animals. This is where we can isolate hematopoietic stem cells from an MMP-8 knockout mouse, and we can graph them into an otherwise healthy wild-type mouse. And we can shift their

immune systems from a wild-type immune system to an immune system that lacks MMP-8. And when we do this, and put mice through chronic stress, we can prevent stress-induced changes in synaptic transmission.

This is a slice electrophysiology study where we measured spontaneous excitatory postsynaptic currents. You can see we corroborated our previously published data and we show that MMP-8 knockout chimeras do not exhibit this effect. It also prevented extracellular space changes that we've identified by electron microscopy.

And last, but not least, we were able to normalize social behavior. I'm showing you data from the juvenile social interaction test. You can see that MMP-8 knockout mice show a strong increase in interaction with the juvenile, similar to unstressed control mice. And so, this tells us that systemic peripherally derived MMP-8 is necessary for both synaptic adaptations as well as stress-related social avoidance behavior.

And with that, I'm just going to leave you with our method, our mechanism. So, what I've shown you is that chronic stress in mice and people is associated with myelopoiesis. And in particular, it's associated with an increase in the circulating levels of monocytes and neutrophils. Monocytes at least, we know, can then actively transport up to these brain neurovascular spaces, where they can attach directly to the luminal side or the lining of the blood vessel. We think it's through an active mechanism. We have not yet tested it causally, though.

When areas of the brain that are damaged receive these monocytes, they can secrete factors like MMP-8 that can get into the brain parenchyma, they can restructure extracellular matrix proteins in the brain, and they can change neural activity by adding new synapses onto their dendrites. And this then leads to social avoidance and related stress phenotypes.

So, with that, I'm going to just thank the

people in my lab that did the work and our collaborators. A big thank you to Flurin Cathomas and Kenny Chan. They really led this and other work on the neuroimmune mechanisms of stress in the lab. I'd also like to give a really big shout out to Georgia Hodes, Caroline Menard, and Maddie Pfau, previous postdocs and students in the lab that really started this entire research program of studying systemic immunity and its role in regulating stress responses. And then our wonderful collaborators, Miriam Merad, who leads our Immune Institute here, to James Murrough, and many others. And last, but not least, I would be remiss if I didn't thank the funding agencies that were critical for this work, including NAMH, NHLBI, and the Leon Levy Foundation. And of course, I'd like to thank you for your attention and I'm happy to answer any questions.

(Whereupon, the above-entitled matter went off the record.)

CENTER FOR THE STUDY OF TRAUMATIC STRESS
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BRAIN, BEHAVIOR, & MIND
2025 SPRING CONFERENCE

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MORNING QUESTION AND ANSWER PERIOD
DR. SMOLLER & DR. RUSSO
+ + + + +

TUESDAY,
APRIL 22, 2025

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This transcript was produced from audio provided by Uniformed Services University of the Health Sciences.

P-R-O-C-E-E-D-I-N-G-S

DR. NAIFEH: For our first question and Answer panel, we are joined now by Dr. Jordan Smoller and Dr. Scott Russo. Welcome. Our moderator for this panel is Commander Christina La Croix, who will help us address as many questions as possible during the allotted time.

Dr. La Croix is a Commander in the U.S. Navy and Assistant Professor in both the Department of Psychiatry and Department of Physical Medicine and Rehabilitation at the Uniformed Services University. She is a board-certified psychiatrist, physiatrist, and also subspecialty-certified in brain injury medicine.

Welcome, Drs. Smoller, Russo, and La Croix.

Commander La Croix, you may proceed with asking the questions from attendees when you're ready.

COMMANDER LA CROIX: Thank you so much for that very generous introduction.

Our first question is for Dr. Smoller. The question person asked, "Where's the opportunity for the next breakthrough in precision

psychiatry? So for example, what percentage of hospitals have databases similar to yours and what percent could develop precision tools for their communities?"

DR. SMOLLER: Thanks for the question and good to be able to talk with you all. Well, as I talked about in the presentation, precision psychiatry is sort of a broad concept, but I think you're referring specifically to this idea of leveraging big data, electronic health records, for example.

Electronic health records are themselves pretty ubiquitous. And so it is certainly possible for many health systems to do the kind of work, and many health systems are doing this kind of work. The obstacles have to do with, you know, having maybe some computational or informatics expertise to extract the relevant data, which many, at least larger health systems do have.

Also developing algorithms, and if you're not developing algorithms, let's say yourself, there are now methods in which we can develop

them at, say, one site and use things like federated learning that allow us to kind of calibrate or tailor the algorithms to another site, making them, you know, much more generalizable.

So I think that one of the things that's exciting about that kind of work is the fact that it is so accessible, that it does so directly connect with clinical care. But it has a lot of challenges to overcome, including some of the computational challenges, concerns about, how do we ensure that algorithm bias, for example, is not built into some of these kinds of predictive algorithms or clinical decision support tools and a variety of other things.

But I think it really is a near-term possibility. We've been particularly drawn to things like suicide as an outcome because of, obviously, its incredible impact, but also because some kind of improvement in what we're doing, could have a major impact, similarly for treatment matching as well.

COMMANDER LA CROIX: And have you or your

team identified the top variables that each hospital should strive to collect electronically?

DR. SMOLLER: That's a really good question. So one of the things that we can do when we build these models is identify what are the most influential features. And what we see is that it really depends on the outcome that you're predicting. It depends, to some degree, on the kind of modeling approach you're using. And the further caveat is that something might be highly predictive and yet not causally involved, right? Because what you're doing is maximizing the predictive validity, but it might be that the thing that pops up top on the list is correlated with an actual causal factor. So one area that we and others are very interested in is causal machine learning or causal AI.

But again, I think, in terms of the beauty of electronic health records, is that they are essentially the same kinds of data across all systems. And so that allows us to, relatively speaking, ensure that everybody has the same

data. The key, then, becomes building the model for which outcome you're interested in and optimizing it for your system or learning from other systems. So the answer briefly is, there isn't one specific set of variables in these models that we've seen emerge, it's really sort of use case-dependent.

COMMANDER LA CROIX: Thank you so much. My next question is for Dr. Russo. Dr. Russo, could you say more about the nucleus accumbens and its relationship to psychiatric illness, most particularly in depression and PTSD?

DR. RUSSO: Thank you, Commander La Croix. It's really a pleasure to be here. You know, the accumbens is generally thought to be one of the primary centers in the brain that allows us to experience things as being rewarding. So there are links, really, to symptoms of depression and PTSD, including kind of general malaise and anhedonia seems to be really broadly linked to this output region. The mesolimbic dopamine system, which is the nucleus accumbens.

COMMANDER LA CROIX: Thank you so much. So,

turning back to Dr. Smoller, what can you say about variations in folate processing or function and psychiatric risk?

DR. SMOLLER: Well, a number of people have been very interested in folate and the metabolism of single carbon metabolism. There are genetic variations that folks have looked at that are related to those biological processes. There's been a lot of interest in, for example, MTHFR variation which, I would say, like many other sort of candidate genes with respect to psychiatric and behavioral outcomes, has had some interesting evidence supporting it, but I would say it's pretty mixed at this point.

We have seen, in some studies, some evidence for involvement in pharmacogenomic or sometimes related to psychosis outcomes of genes in that sort of whole pathway. But I can't say that I've seen strong evidence, at least personally, linking folate metabolism to outcomes at a sort of population or clinical level. And you know, that's something that is not surprising, in a sense, because we think of all of these things

at a genetic level are highly polygenic and highly complex.

COMMANDER LA CROIX: Thank you. So turning back to Dr. Russo, we have this question. Does disruption of the blood brain barrier lead to microglial activation?

DR. RUSSO: It certainly can. And I think it depends on the region of brain that's being studied. There's been a lot of interest in microglia. It's always been thought that they kind of represent a monolith of cells that are largely supportive. But, don't all kind of have the same features or functions, and recent data largely coming from cell type-specific RNA sequencing studies has moved beyond this idea that they are a single monolith, and that they have very unique and distinct functions across the lifespan, but also across discrete brain regions.

So I think, in large part, it's going to really depend upon the type of microglia, the state that microglia is in and which signals from the periphery are actually entering the

brain parenchyma through those damaged vessels to activate or incite those microglia. So certainly, we believe that there's going to be some unique differences. And, just as a brief example, in controlled rodent studies, we find evidence that frontal cortical microglia may have or exhibit a more inflammatory transcriptome profile, whereas in striatum, we just don't see quite the same degree of evidence in our models.

COMMANDER LA CROIX: Thank you. So for Dr. Smoller, could you please comment on the demographic composition of the participants who were studied? The questioner had the comment that, generally, Europeans are the focus of research, with models, then utilized in non-white communities and then considered evidence-based.

DR. SMOLLER: Well, one question would be there, are you talking about the genomic studies or, say, the EHR studies? In genomic studies, which I did touch on there, absolutely there has been a kind of Eurocentric bias in terms of

ancestry. Still, although that problem has been pointed out, now, for over a decade, more than 90 percent of the genomic data that are available worldwide are from people of predominantly European ancestry, which we know is a limitation, because some of the findings and, for example, polygenic score performance and all these kinds of things don't necessarily generalize very easily.

There's a lot of effort now to develop trans-ancestry, for example, polygenic scores, which is the approach that we typically now take. In the genetic data that I showed, about sort of cross-disorder function, those were largely from -- because of the size of the samples and the data that were available. Although we did more recently do some work with the available non-European ancestry samples, to show that some of the findings were concordant. But unfortunately, it's still vastly underpowered.

In terms of the health system kinds of data or biobank data in our health system, there is

variation in demographics across the whole health system. We have, I think, as I mentioned, about six and a half to seven million patients in the Mass General Brigham system. In the PsycheMERGE network that I mentioned, which now has data for about 29 million individuals, it is very diverse and we are actually looking very intentionally at to what extent some of these algorithms or findings that are developed generalize across demographic groups.

One resource that I hope people become more familiar with, is the All of Us research program, which is a nationwide cohort study, now enrolled more than 800,000 individuals and is very diverse along many axes. And so we are increasingly using those kinds of data as well. So we are limited to what is out there, unfortunately, but at least on the EHR side, that has typically been pretty diverse.

COMMANDER LA CROIX: Thank you. So for Dr. Russo, did the mice without MMP exhibit any behavioral anomalies along with the normalization of their social response?

DR. RUSSO: Hmm. That's a good question. You know, we haven't noted any general abnormalities in their behavior. We've done quite a bit of characterization across the broad array of behavioral phenotypes. There don't seem to be baseline deficits, broadly speaking, in motor activity, learning and memory, anxiety, or exploratory-based behavior.

It really does seem to be -- and I don't want to say that it's specific to these social outcomes, but it does seem to be relevant to stress-induced changes in behavior. So which is important, if you think about drug development and drug discovery -- we want to target things that don't have broad side effect profiles. And I think MMP as an antagonist might represent one of those classes.

COMMANDER LA CROIX: Thank you. So for Dr. Smoller, in your opinion, how helpful do the clinicians find the recommendations for high-risk individuals based on the electronic health record? Do you think they're utilizing the tools or they're finding them burdensome?

DR. SMOLLER: Yeah, that's a good question. I mean, one concern we always have is not adding to the onslaught of alerts and administrative work and all kinds of things that sometimes can be overwhelming in clinical practice, which is why we've done a quite a few focus groups to try to tailor these kinds of tools to what clinicians might find most useful.

We are in the process now of doing this 4,000 person randomized trial, controlled trial of delivering this information. And so, we'll have a pretty large sense of feedback from clinicians and patients about obstacles, barriers, and so on.

We did do a sort of quality improvement program in the emergency room, delivering this kind of risk information, although it was, at that point, largely based on the brief survey that we use along with the EHR risk score. 86 percent of the clinicians said that they felt it was useful and helpful to them. Some of them felt that it was actually helpful in sort of clarifying next steps or even in speaking with

insurance companies to buttress clinical decisions and so on.

But I think that is something we have to pay a lot of attention to because, obviously, if people find this either confusing or not useful, it's not going to do any good. We've tried to really contextualize the information, make it visually quite understandable, and so far we've gotten pretty good feedback, but we're going to have much more data at some point soon.

COMMANDER LA CROIX: Thank you. So, Dr. Russo, your proposed mechanism is elegant and presumably important in many diseases, as you show for cardiovascular disease. Are you thinking about any other non-brain disorders that you're thinking about this mechanism for?

DR. RUSSO: It's a really good question, and the short answer is yes. I mean, our general entry point into this field came from years of epidemiology showing these links between many of what we consider systemic or organic illnesses, like cardiovascular disease, irritable bowel, and many others, with depression and related

psychiatric diseases.

So the initial thought really was that they shared an underlying biology, being disruptions in the immune system, and you could kind of envision a system or a situation in which stress is causing the release of these inflammatory monocytes from bone marrow stores into circulation. There's no really good reason why they should only go to the brain. They can hone to any organ system, and if they can infiltrate that organ system, they can impact it. So beyond cardiovascular diseases, we're thinking irritable bowel is one. We've got some good data on it. Asthma, which is highly, highly comorbid with depression, could be another one where we're seeing immune cells potentially infiltrating respiratory tissue, creating local inflammation, and causing exacerbation of those illnesses.

COMMANDER LA CROIX: Thank you. I think this will be important to study many different diseases, so thank you.

So for Dr. Smoller, do any of the factors

that you talked about that mitigate depression risk also apply to PTSD or anxiety disorders?

DR. SMOLLER: We think so, yes. In particular, two of the ones that I highlighted, which really have just, I think, a super convincing degree of convergent evidence, that is physical activity, social connection, do seem to also, in other studies -- appear to be protective for anxiety and PTSD, or potentially for the mitigation of symptoms. So those seem to be the ones that we see over and over. I'm trying to think if there are others that -- along the lines of what we've found. I think those are probably the two which have the broadest evidence for sort of what we would think of as internalizing disorders.

COMMANDER LA CROIX: Thank you. So Dr. Russo, since depression is more common in women, does MMP8 have any sex relationship?

DR. RUSSO: It's a really good question. There's nothing sex-specific that we can find at face value. So in our human cohorts, there doesn't seem to be a sex or gender difference in

our mice. We see similar MMP8 profiles in both stressed males and stressed females.

In general, though, what I would say is that any of these mechanisms that we've defined in the periphery, particularly those from bone marrow-derived immune cells, seem to be somewhat more severe in females. The direction of change is similar, but it might be heightened, it might be exaggerated in women and in female mice, which might explain why, for example, at least in this particular subset of depression, there might be an increased risk for women in general.

COMMANDER LA CROIX: Thank you. So, Dr. Smoller, I have a somewhat long question, so please bear with me, but the questioner commented that VA's predictive and analytics suicide prevention model was operationalized by proactively reaching out to those at highest risk with a phone message, asking if their health needs are being met, as opposed to saying that they're at increased risk of suicide. And this message was actually welcomed by many of the veterans, many of whom had not yet been

actively thinking seriously about self-harm. So the questioner's understanding is that that operated far upstream, such that hospitalization was not usually required to address risk, and this intervention could be done by social workers, nurse clinical specialists, and/or peer support specialists, rather than the more limited pool of psychiatrists.

Have you considered such low intensity, far upstream interventions?

DR. SMOLLER: Yeah. That's a great question, and I think we're talking about the REACH VET, program, and I think a couple of points about that. One of them is couching it as a more supportive outreach, rather than necessarily specific to the apparent suicide risk, can be helpful and certainly make it easier for people to accept that kind of outreach. This also bears on a huge issue, which is workforce shortage. And we know that there are some evidence-based interventions. One of them is this kind of intervention of caring outreach, or sometimes called caring

contacts. A lot of the time, though, these things are not actually practiced in the real world to the degree that they might be. And part of that has to do with the constraints on health systems, the costs, the limited workforce. And so, expanding the pool of folks who can do this, I think, is a really important opportunity.

And one of the things that we've done now over the past few years is to develop a new intervention, which we call an enhanced outreach intervention. This is through a partnership with Samaritans of Boston. Samaritans is the organization that, for example, answers the 988 number in our region. And we reasoned that these are folks who have tremendous experience with supporting people in crisis situations; and so, we now have this kind of hybrid intervention in which we partner with them. This has not been deployed yet, but it's going to be the subject of a randomized controlled trial that we're very soon to launch for individuals who may be at elevated risk, based on our

algorithmic evidence of highlighting folks at high risk.

And then, effectively, people who come through the ED, we know that the period after discharge from an acute care setting like that is a particularly high-risk period, especially in the first one to three months. And so, this intervention involves pairing folks with, effectively, a coach who can support them and help us to deliver the kinds of outreach interventions that you mentioned, as well as other things like safety planning interventions, problem solving, encouraging people to stay in treatment, and so on.

So I think that is a really crucial opportunity. We'll get some randomized controlled trial evidence of this new version of it that we're hoping to deploy. But I think expanding the pool of providers or peer professionals who can deliver this is going to be crucial, because the reality is we don't have enough folks who are psychiatrists, psychologists, to be doing all of that outreach.

COMMANDER LA CROIX: Thank you. So, Dr. Russo, since we've heard a lot about exercise this morning, are there any effects of exercise on MMP8?

DR. RUSSO: Oh, that's a great question. I don't know, is the short answer. I'd love to do work in that space. My prediction would be that exercise will train our immune system or immune cells to operate appropriately, and that should, in fact, lead to a reduction in stress or depression-associated monocytosis and MMP8. But that is just really a prediction based on some of the exercise physiology literature.

COMMANDER LA CROIX: Thank you. And so, for a follow-up question, I have one for Dr. Smoller, which is relevant to me as a military member.

Is the protective benefit of exercise -- would it be present in groups that were compelled to exercise?

DR. SMOLLER: Good question. I don't think I know the answer to that specifically about -- except to say that what we've seen and others

have reported is that we see benefits across the spectrum of levels of physical activity. So people often say that even relatively mild degrees of physical activity can be helpful. And it is probably a sort of inverted U-shape, in which obviously excessive physical activity for many people might carry risks of injury and so on. Whether compelling people to exercise or the kind of training that our active duty military personnel undergo adds some benefit or detracts in some way, I actually don't know that I've seen evidence one way or the other on that.

COMMANDER LA CROIX: Thank you. So, Dr. Russo, we have a questioner who would like you to speculate on any clinical implications for some of your findings. Please feel free to share.

DR. RUSSO: So, I mean, the obvious one would be to harness therapeutics to target MMP8, and that's definitely something that we're actively pursuing. The limitation is that there are no drugs available, so we're actually working with some chemists and structural

biologists to generate our own. We'll see what comes out of that. Part of the reason for the kind of paucity of these compounds is that, historically, targeting MMPs or metalloproteinases in general has been challenging. There's been a lot of toxicity that's been identified, and so a lot of those early trials that were done for other things like cancer were kind of halted.

But I think it brings up kind of a more important philosophical question, and if you are of the opinion that we should be blocking the immune system as a treatment for depression, I'm not sure the answer to that. In fact, somebody in the comments, I think, kind of alluded to this, but our immune system's there for a reason, and one of the side effects might be -- is that it alters our mood, but it's active for a given reason. If we cut it out, if we ablate it, if we get rid of it, we're going to probably cause damage to other organ system function or other things that the immune system is necessary for.

So my opinion is that, if we could harness strategies, whether they be therapeutic or behavioral, to train the immune system, rather than to shut it off or turn it on, we want it to work properly and in kind of the sweet spot or the middle zone. And a good example of this is exercise. There's been a lot of discussion now about exercise and the benefit of exercise, but you know what exercise does acutely? It causes monocytosis and an increase in pro-inflammatory cytokines in your body. Over chronic periods, though, it trains your immune system to respond kind of appropriately when it needs to, and I think that's what we need to harness in a pill. Nobody has done that, to my knowledge, at this point. We've just used strategies where we shut it off completely and prevent it from elevating during stress.

COMMANDER LA CROIX: Thank you very much. I totally agree. Shutting down the immune system universally is not a good idea. So I do think we have one more question we have time for, and to -- everyone's given such great questions,

it's hard to decide what to ask, but I think we might want to ask one to Dr. Smoller, because there's some concern about what protections might need to be in place to prevent discrimination based on genetic risk factors, while we can allow people to use that information to best prevent, identify, and treat disorders.

So, for myself and the military, right, should the military be using these data to determine if an individual should be even allowed into the service, or what role they could play there?

DR. SMOLLER: Very important issue about the risks of risk information. When it comes to the genetic information specifically, so far what we've seen is that genetic predictors are not that useful, actually, in clinical practice. So I don't know of a case in the kinds of realms that we're talking about where you would use a genetic risk score, for example, in any kind of determinative way.

And so, I think the answer I would say is,

yeah, I don't see the risk-benefit ratio of that kind of thing as favoring its use at this point, at least individually. There is some reason to think that you could use genetic information to augment other risk factors. I think I may have showed a slide where we looked at our suicide risk prediction algorithm and added a polygenic risk score for psychiatric illness or suicide. It really didn't help.

Now, you could ask the question about, well, what about just the algorithm itself, just the clinical data? And there, that is an issue, as I mentioned before, where there are now a number of tools we can use to interrogate the fairness of our algorithms, to the degree to which we think there might be bias in them. And we've recently done that actually with the suicide risk algorithm, and have found pretty reassuring results, doesn't perform differently, at least across the major demographic groups. But it's something that we always need to be thinking about and vigilant about, because typically we are training these algorithms on real world

data, and real world practice often has implicit or explicit kinds of biases built into it.

COMMANDER LA CROIX: Thank you so much. And I just want to say -- I know we're going to have to say we're out of time. I just want to say, thank you, gentlemen. This is very helpful to me personally. And I really appreciate you sharing your knowledge and your wisdom with us and ways to move forward.

DR. SMOLLER: Thanks so much.

DR. NAIFEH: That is unfortunately all the time we have for questions this session. I'm sorry that we weren't able to get to all the other great questions that were sitting there waiting to be asked. Thank you so much to Drs. Smoller and Russo. It was wonderful to have you join us and share your expertise, and thank you to our moderator, Commander La Croix.

We will now break for lunch, reconvening at 12:45 p.m. Eastern Daylight Time, which is just under an hour from now. We hope everyone will use that time as an opportunity to go review the poster gallery on the conference website, which

includes a range of research submissions from attendees. Thank you. And we will see you after the lunch break.

DR. NAIFEH: To begin the second half of the day, we are excited to share with you a presentation by Dr. Jodi Pawluski. Dr. Pawluski is a neuroscientist and affiliated researcher with the University of Rennes. Her research has focused on understanding how the brain changes with motherhood and the impact that stress can have on this process.

She also investigates the role of perinatal depression and its treatment on neurobehavioral outcomes in mothers and offspring. In 2020, Dr. Pawluski started a podcast called, "Mommy Brain Revisited," which focuses on bringing current research on the parental brain to the general public. In 2022, she authored *Mommy Brain: Discover the Amazing Power of the Maternal Brain*, the first book on the parental brain by a neuroscientist who researches this topic.

We will now begin Dr. Pawluski's presentation, which is titled, "The Neuroscience of Parenting and Perinatal Mental Health."

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DR. JODI PAWLUSKI

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P-R-O-C-E-E-D-I-N-G-S

DR. PAWLUSKI: Hi, everyone. It's a pleasure to be here and it's a real pleasure to be part of this conference, the Brain, Behavior, and Mind Spring Conference, and I'm here to talk to you a little bit about how the brain changes with parenting and perinatal mental health.

So, over the next few minutes, I really want to delve into some key concepts or key discoveries of the science recently of how the human brain is changing across pregnancy and the postpartum period, and what we know of these changes in relation to perinatal mental illness, with a focus on postpartum depression. It's a lot to cover in a few minutes, but I want to really cover those key concepts.

And I would encourage you also to refer to any of the citations that I provide, as well as I'll be providing episodes to my podcast, *Mommy Brain Revisited*, where you can really hear from the neuroscientists who do some of the research

that I'm talking about, although I obviously do some. Much of my research is in this area as well.

So, I'm going to just jump right in. I want to talk about motherhood and really what happens to the brain in mothers across pregnancy and the postpartum period, and in this regard, I'm going to be talking about primarily gestational mothers.

I'm going to be talking a bit about fathers, because I think it's really important that we acknowledge, of course, that fathers, and non-birthing parents, and adoptive parents have a very important role in parenting, as well as many changes in their brains, and then I'll touch on a little bit about brain changes associated with perinatal mental illness.

And, as I'm getting started, I really want to just point out a note on language, because I know our language is really quickly evolving and, you know, over the past few years, there's been

a kind of move to talk about parents and not so much mother and father.

But I'm going to be using the terms mother, father, birthing parent, parent, non-birthing parent, but primarily mother and father, primarily because the research to date has been done on individuals who identify as mothers and fathers.

But also, I think it's really important that we acknowledge that there isn't gender neutrality currently with regard to parenting roles, and so the role of a mother is quite different than the role of a father, and I think we still need to continue to do research on these separate roles.

Now, my research has really been interested in how the brain changes across pregnancy and the postpartum period in the mother, how this is involved in maternal caregiving, as well as memory and mental health, and the role of hormones in these changes — kind of this intersection between the brain, behavior, and

hormones.

And I do research in this area. I've written extensively about this, but today I'm going to give you kind of an overview of some of the key changes we know about the brain across these phases in a woman's life and in the human research, because I also do some research in animal models.

And one of the main reasons I do what I do, and I share the science, and provide options for other neuroscientists to share the science with regard to how the brain changes with parenthood and perinatal mental health, is because it's important that we know.

And I think Emma Jane Unsworth really summed this up nicely. She wrote this book, *After the Storm*. It's a memoir about her experience with postnatal depression, and she calls it the utter weirdness of new motherhood.

But what she posted after releasing her book on Instagram is she said, "Huge changes happen in

your head. Maybe if I'd known there was a 'normal' mental sea-change coming, I wouldn't have been so blindsided, and it might not have tipped over into PND. Maybe."

And I think, for me as a scientist in this area and also as a parent who parented after I had, you know, learned a lot about these changes with regard to the brain in a mother, I have been really struck by this desire to know and how important it is to know what's going on.

And this is why I think it's really important to provide access to the information, and so that we can have a proper understanding of these changes, because perhaps it will help someone during this transition to parenthood and, like Emma says, maybe if she had known, she would have been healthier.

And, of course, I think the parental brain and the maternal brain is something we all should be very excited about, and fascinated with, and spend time studying.

I might be biased, but I think we can't forget, as this graphic shows — and this is actually an ad from Anne Klein, who designs clothes, and I found it in a magazine that was left in the pocket of the chair in front of me when I was on an Atlantic flight and didn't have any other source of entertainment.

So, I had this magazine and I saw this ad, and I thought, oh, my goodness, this is so true and we don't think about it. And she says here in the ad, every human being is born out of the body of a woman and, in fact, that's quite profound to think about.

And so, often, we don't think of the fascinating and important role of the female body, but more than that, we're not spending time understanding how this affects a woman.

And, you know, if you think of motherhood or parenthood, we know that 80 percent of human females will give birth. They might not all parent, but they will have the experience of

pregnancy, that motherhood or this stage of life we're calling matrescence, akin to kind of adolescence, another developmental stage.

And this term was coined in the '70s, but has been used more and more the past decade or so. We know that motherhood has a profound impact on a woman's life, not just biologically and neurobiologically, but also psychologically and in terms of her role in society.

And we often forget about this. This is a huge transition in life for many. And we know that 80 percent of mothers will talk about feeling like just their brain isn't working as it should, and this is something that we haven't spent enough time understanding.

But, over the past few years, more research and more talk has been taking place in understanding what's happening to the brain of mothers and this kind of idea of “mom brain” or “mommy brain.”

We know that this is a period in a woman's

life when more females and women are admitted to psychiatric institutions than any other time in life, the postpartum period, and we know that one in five will struggle with a mental illness. So, this is one in five mothers and about one in ten fathers, and so it's a time of vulnerability.

And we know, as I'm going to talk to you about, that the brain changes in structure and function during pregnancy, and the postpartum period, in fact, in all parents and not just in those that have been pregnant. Of course, you'll see there are some differences, as can be expected.

Now, I really started my research looking at the idea of "mommy brain" or memory in motherhood. And this is perhaps one of my favorite memes. It's, "I used to have functioning brain cells, but I traded them in for children."

And so, often when we think of the brain and motherhood, we're thinking of a deficit or

the brain not functioning as it should. This has been around for a few decades, if not longer — this kind of idea of brain dysfunction when we have children.

Now, if you pause and actually look at this woman who has perhaps twins in this cartoon — healthy twins. They seem functional and growing. You know, I think we can say she's probably doing a pretty good job in keeping them alive, and that's all her brain. Her brain is actually functioning, but often we just don't acknowledge the role of our brain in caregiving, and I think that's something that needs to shift a bit more. So, do we actually trade in our brain cells for children?

And in fact, this is kind of where I did my PhD research now a couple decades ago in rodent models, where I was interested in looking at how changes in the brain, the neurogenesis or the production of new neurons in the hippocampus, an area of the brain important for memory and stress

regulation, may or may not be related to changes in memory in these mother rats, and the hormones involved potentially in this relationship.

And to sum up four years of research in a sentence, I will tell you that first-time mother rats, they don't actually trade in their neurons for their kids. What we see is that they produce fewer new neurons in the hippocampus, but they also have enhanced learning and memory. So, it's a fine-tuning. I like to talk about this as a fine-tuning of the maternal brain.

And interestingly, in humans — although we need much more research in this area of motherhood and memory and brain plasticity — we're seeing that there are enhancements in memory with motherhood — surprise, surprise — also as well as some slight deficits, such as in working memory and verbal memory.

And so, you know, I think we need to really think about these changes in the brain that occur across pregnancy and motherhood as adaptive, as

important, as healthy, and perhaps change our narrative about motherhood and the brain kind of not going together and becoming a dysfunction, so I'm happy to talk more about that.

But, let's delve into those brain changes, because over the past probably five, eight years, we've been seeing more and more research coming out talking about how the brain is changing in human mothers across pregnancy and the postpartum period, and it's been quite fascinating to see this interest in the research and really to see what's happening with regard to the brain during this time in adult life.

So, we're going to talk about structure and function. I just want to highlight here what exactly this is, just to give some clarification to those out there.

So, when we're looking at the brain of humans, we don't have the same kind of techniques or capacity to deep dive into molecular changes like we do with animal models; but often we're

looking at structure, which is gray matter volumes.

So, this is looking at size, volumes, and other structural characteristics of the brain, and this is from brain images, and this gray matter is made up of cells like neurons and glial cells.

And then, other research also looks at function, which is another important aspect when we're considering plasticity of the brain and particularly with regard to parenthood, and function is looking at changes in blood flow or aspects of blood flow — oxygenation — or it can be with regard to looking at activity in terms of what we would call "brain waves," and that's with an electroencephalogram, an EEG machine.

So, I'm going to be talking about both what we know about structures, some key points, and points of clarification, because they're often misconstrued when you see these things on social media, for example, the interpretation of the

data, and then also function, because the two are very important.

So, when talking about structure, we're going to start with structure, because this has gotten a lot of press lately. People are like, "Oh, the brain shrinks across pregnancy. Oh, my gosh. This is crazy. This is why I'm forgetting all the time." Which I will say right now is not true, but I'm going to give you a little story about what happens to the brain across pregnancy.

So, in 2002, this was the first study that really showed that, in terms of structure — brain size — there is a decrease in the size of the brain across pregnancy, with this kind of increase in the postpartum period back to what seems like, you know, preconception size.

This was a very small cohort of individuals in this study. So, you can see this nice decrease. I'm going to get my laser pointer here.

So, this is across pregnancy, the time of pregnancy, and this is postpartum, and this is

percent change, and this is the volume. So, they're looking at the size of the ventricles here as well as the whole brain volume.

And so, what they saw was an increase in the size of the ventricles, and a decrease in the overall size of the brain across pregnancy, and then it seemed to come back.

This is, you know, quite interesting to think about, because we often are thinking that the adult brain doesn't change so much, and here they're showing that there's about a four percent change in size.

Now, that was in 2002, and really it wasn't until 2017 when there was really a deep dive into the structural brain changes. I'm just going to get rid of my pointer here and change the page, okay.

So, this is the study in 2017, headed by Elseline Hoekzema, Susana Carmona, and Oscar Vilarroya, and this one really showed us in more detail what's going on in the brain across

pregnancy.

So, they looked at — they took pictures of brains prior to becoming pregnant and then in the early postpartum period, and then were able to look at the structural changes across pregnancy in the mothers' brains compared to adult females who had never mothered.

And what they found is that there are specific brain areas that decrease in size across pregnancy. So, in this image, you can see this is first-time mothers, and they looked at mode of conception, so this is natural conception or fertility treatment. There's no difference between these groups.

But, you can see there's a number of different brain areas highlighted in yellow and orange where there are decreases; whereas in the women that never were pregnant and didn't have any children, there were no differences across this time period of about nine, ten months.

So, what they found is that there's about a

one percent decrease in gray matter volume in many brain areas that are important for social behaviors or theory of mind, the ability to understand the needs of others. This is really important for parenting.

So, the brain seems to be decreasing in size in these areas that are important for this, which again feels a bit counterintuitive, but we talk about this as less can be more and it's a fine-tuning.

What's also important and really fascinating to think about is that this finding was very consistent. So, the majority of birthing parents, the majority of these women that went through pregnancy had the same brain changes.

And, in fact, they developed an algorithm where they could take the images of the females' brains and they could predict with this algorithm whether or not the woman had been pregnant, and so these changes in the brain are really

consistent.

This is probably one of the most highly consistent changes I've been told in adulthood when it comes to the human brain and the impact of an experience on it. It's very consistent.

They also showed in this study that these brain changes were not related to the mode of conception, the mode of birth, the levels of stress, the sleep quality, or any memory changes, and they had given different questionnaires to look at this.

So, this is really showing that across pregnancy, there's a decrease of about one percent in certain areas of the brain that are really important for social behaviors or understanding the needs of others.

So, what does this actually mean, then? Well, luckily, they also investigated that aspect, and what they found is that this reduction in size of these brain areas during pregnancy is associated with stronger feelings of

mother-infant bonding.

So, it was associated with increased sensitivity of the mothers towards their infants in the early postpartum, as well as a decrease in any hostility measures toward the infants. They did these different investigations.

So, this is, essentially this idea, again, is this fine-tuning. So, this decrease in brain size is associated with an increase and stronger feelings of sensitivity toward the infant, so this is a good thing and it's an adaptive and healthy thing.

So, this is also really fascinating if you think about it from a brain plasticity perspective, because it's showing that the brain is changing to a high degree during adulthood, and in a short period of time of just, you know, a few months.

Now, does this one percent actually mean anything? Do these brain changes, is this like a big deal or not a big deal? I just said it was

a big deal because it is a big deal, but I am going to prove to you here why it's a big deal, or put it in perspective.

So, this was a great study out of Susana Carmona's group where they, in fact, compared mothers, so these first-time mothers, and they're highlighted in blue, and they're looking at structural brain changes here, such as cortical thickness and surface area.

So, they were comparing their mothers with adolescent females, because we all agree that adolescence is a time when there is so much change happening in the years of adolescence. The brain is changing, social relationships are changing, all sorts of things are changing. So, they compared adolescent girls with first-time mothers and then with adult females who were not parents, and they looked at different structural characteristics of their brains from these brain images.

And you can see really clearly here in the

red and the blue dots, and that's the adolescent females and the blue ones are the mothers, how similar the changes in their brain structure are on all the measures they looked at compared to the adult female.

So, you know, for me, this gives us a better understanding of what this means, these structural brain changes, how important they are, because they're akin to what's being seen in adolescence, which is actually years of life, in fact, and we're seeing this within a few months.

So, these brain changes in structure are really fascinating. They're important for caregiving. They're on the level of what we see with adolescence, and I think we need to keep that in mind when we're thinking of the transition to parenthood; that, you know, not just the body is changing, but the brain is changing too.

Now, take it one step further. This is really a dynamic period of brain plasticity,

because there's been other research showing that, in the early postpartum period, so if you look at between months four and six, for example, that there's actually an increase in the structure of certain brain areas, in the frontal areas, and that this increase in brain structure is associated in a positive way with parenting, parental self-efficacy score — so how well a parent feels about their capacity to parent.

And so, you can see if we're going to draw this out, there's this kind of decrease, and we know now from recent studies in January as well as in November, or September, I believe, there was another study that came out where there's a decrease in many areas of the brain across pregnancy.

And the decrease seems to be at its highest, I guess, the greatest decrease is in late pregnancy, and then a slight increase in the postpartum period, and then there seems to be a bit of a decrease that continues up to six years

postpartum in certain brain areas.

So, it's a really dynamic period, and here is a nice figure, kind of — and this is a review — summarizing this dynamic structural plasticity, where there's this decrease across pregnancy, a bit of an increase in the postpartum months, and then a continued decrease.

And it really speaks to the fact that the brains of gestational mothers have a high degree of structural plasticity, and that these changes are healthy, adaptive, and they're related to positive feelings of parenting.

So, this is that idea of less can be more. I often talk about these structural changes as thinking about them as dynamite comes in small packages. You know, just because something is smaller doesn't mean it can't be impactful, and important, and function well, and I'll talk about function in a minute as well.

So, let's talk about function. So, these functional brain imaging studies are often done

by presenting a parent and non-parent with a picture of a child, listening to a baby cry, for example, video of a child. There are different ways of doing this, but looking at how the brain is responding to an infant's cue, essentially.

And what's generally been shown is that a parent will have increased activity in many brain areas in response to an infant cue compared to a non-parent. This is for mothers as well as fathers.

And, in addition to that, often a parent will have increased activity in the different areas of the brain important for parenting in response to their own infant versus an unfamiliar infant. So, there's a lot of activity in certain brain areas in response to infant cues, particularly in parents.

And this research has really been going on probably for the past two decades or more, looking at these functional brain changes, these changes in brain activity, primarily focused on

mothers, with some research in fathers as well.

But what's been summarized here, and I think this is quite nicely summarized in this review of Ruth Feldman from 2015, is you can see that there's a number of different brain areas that are involved in parenting. These are brain areas we use every day, whether or not we're parents, for different abilities to function in our environment; but these are, you know, brain areas that seem to come together to coordinate parental caregiving, and they become more active in response to an infant in parents than in non-parents.

And so, she characterized two main areas that are really important as the amygdala and the hypothalamus, and these are hubs of the parental brain caregiving neural network or the parental caregiving neural network; and then these other areas that are important for other aspects of behavior and understanding, so motivation and reward circuitry. So, we want to be motivated to

care for our infants and find them rewarding, at least most of the time.

Empathy is really important, right? Understanding the needs of others, you know, perceiving action, understanding what's going on, understanding the mental state of others, an ability to self-regulate, make decisions, organize tasks, and other aspects that are dependent often on the prefrontal cortex to some degree, but, of course, not one brain area is important for one function.

So, you can see parenting kind of brings together a number of different neural circuits, we could say, different brain areas. They have to work together to coordinate how to parent. You have to learn to parent, of course, so the hippocampus is also involved. Learn to parent, learn to respond to that infant, and essentially keep that infant alive.

So, I think we have to always think about this when we're seeing those studies coming out

with regard to structure like the brain shrinking or what have you; and if we look at function, it's actually becoming more active in many brain areas; and so, this again reiterates that theme of efficiency. Less can be more. Dynamite comes in small packages. There's a lot going on in the brain of a parent, as many of you probably know.

It's also important to point out that research is showing that this increased brain activity in response to infant cues is linking to stronger bonding and heightened sensitivity towards an infant. That's important.

And what's also really interesting to think about is that the maternal brain at rest, so in the absence of an infant cue, actually seems to be functioning in a different way, or the activity level is different than when compared to a woman who has never been a parent.

This is fairly recent research. We're not sure exactly what this means, but again, it's adding to this narrative of this dynamic period

of plasticity in the brain. We see changes in structure, changes in function, and even changes in the function when the brain is at rest.

And, of course, the question often becomes why? Why are these changes happening? There recently has been some research showing that estradiol is a key hormone that's important for the structural changes. With regard to those functional changes, we know that oxytocin plays a role, dopamine plays a role, cortisol can play a role.

I put a picture up here of a schematic of the hypothalamic, pituitary, adrenal, and gonadal axes, and this is a schematic in pregnancy. And, you know, we often think hormones are the driving force, but, in fact, when it comes to pregnancy, we still don't know. We don't have all of the answers to what's going on with regard to these hormonal systems or neurotransmitter systems in the brain and how they change across pregnancy and even the postpartum period; but indeed,

hormones, of course, are an important piece to the puzzle when we're trying to understand these structural and functional brain changes with motherhood, and with fatherhood as well to some degree.

So, let's talk about fathers and let's talk about what we know about their brains and how they change in structure and function, and this, again, is recent human research. It's, again, really, I think, fascinating research to see and to really compare to the experience of pregnancy in those gestational mothers.

I also want to point out that there has been a little bit of research looking at particularly brain activity or function in adoptive parents, and what seems to be the theme, and I would suspect we're going to see similar changes in all non-birthing parents, but as a function of experience with the child.

So, your brain does change whether or not you give birth to your child, but it changes often

in terms of or as a result of experience parenting, and I'll get to this a bit more in a moment. So, let's talk about structure and function in dads.

Now, we'll start with structure, and this is work out of Darby Saxbe's lab, and she talked about in this piece in the conversation and based on her recent research that a father's brain essentially shrinks too; not to the same degree as what is seen across pregnancy in a mother, but there's research showing that in some brain areas, not as many as what is seen in a mother, there is again about a one-percent decrease in brain volume, in these gray matter volumes.

And she talks about her recent study here where they showed that greater volume loss happened in fathers who spent more time with their infants at three months postpartum, took more pleasure in interacting with their infants, and experienced less parenting stress.

So, this is a little bit more of an

experience dependent change in structure. Now, their finding also showed that these structural brain changes, this decrease in volume in different brain areas in fathers, was linked to more sleep problems in fathers, as well as more mental health struggles.

And so, this is really an interesting, you know, piece to the puzzle of what's going on in a dad's brain, and I think what's really important is that we're seeing that, yes, there's a decrease in the structure of a dad's brain.

Again, this is related to experience and this importance of interaction with the child, and this is, you know, perhaps a fine-tuning we might say as well; but in fathers, it also seems to be linked with other things, such as sleep problems and mental health struggles, and I would be curious to see where the research leads us on this one.

And again, in fathers, when we look at functional brain changes, we know that fathers

essentially have everything in their brain they need to parent; and again, we see very similar changes in function and activity as we see in mothers in those brain areas that are important for parenting — this global human parental caregiving neural network.

Now, I want to highlight one study that I think — and I always bring this one up because it's really important, because it's not just about looking at mothers versus fathers, but it's actually taking into account who is the primary carer; and this is that piece of experience that's really important and I think we often forget this.

We often think that mom might know best. She's just wired this way, but in fact, we forget that parenting is really, you know, it's not necessarily instinctual. There's a drive to learn and to be motivated to care for your child, but you have to actually rapidly learn how to do that, and that takes time and experience, motivation,

and different factors are involved there.

So, this study is an important one, because it speaks to how experience can really shape the brain of a parent. So, what they did in this study is they had primary caregiver mothers, compared them with primary caregiver fathers, and then they had fathers that were not primary caregivers also involved.

And they were looking just at the function of the brain — and this is about two years postpartum. They had them look at a video of their own child and then they were looking at the activity in the amygdala, for example, as well as other brain areas.

And what was really interesting is that they saw — and I'm going to point it out here. So, the pink is the mothers that were primary caregivers, this green is the fathers who were primary caregivers, and then you have — they called them secondary caregiver fathers, the other caregiver fathers.

What you can see in the amygdala is that both the mothers and fathers, their amygdala responded as it should, right, and was really activated when they saw a picture of their infant or a video of their infant, and it activated to the same degree. And these were in the primary caregivers.

So, this speaks to the importance of experience, of course, and the need for experience and interaction with the child to have this brain plasticity and to essentially, as I've said, learn how to parent. But I also want to point out a different area of the brain that is perhaps not primarily linked to this parental brain network, that there is a sex difference.

You know, this could be for many reasons. One could be because of biology, perhaps because of socialization. But you can see here that fathers are more similar in the activation of the superior temporal sulcus compared to the mothers.

And again, in this main hub of the parental

brain, in the amygdala, you can see quite a difference if you've been the primary caregiver or not, and it's not dependent on whether or not you've given birth. So, primary parents have similar amygdala activation, and experience parenting is really key in shaping the parental brain.

I also want to leave you with one other point that I found particular interesting, and this is work from Pascal Vrticka's lab at the University of Essex, but he has found that in fathers, their belief in the importance of their involvement in child rearing plays a role in the brain-to-brain synchrony between father and child.

I think this is really another fascinating piece of the puzzle when it comes to parenting, brain function, and brain plasticity — in fathers, there's this element of belief in the importance of their role.

Now, Pascal hasn't asked mothers about

their belief of their importance in their role and how that might be related to the brain. I did ask that question of him because I think we often assume — and mothers often have a belief — that their role is quite important, but I think this is also another interesting piece to the puzzle, and perhaps a piece that we should think of in terms of how society can interact with biology or neurobiology and how that can impact behavior.

So, that's a little bit about dads to think about. So, we have that moms and dads both have changes to the brain with regard to structure and function. The functional brain changes seem to be more similar between mothers and fathers and are based on experience as well as other things, such as belief system in fathers.

The structural brain changes are more significant and pronounced with pregnancy itself, which perhaps isn't surprising given all of the physiological changes occurring across

pregnancy; but these structural brain changes are adaptive, important, normal, and healthy, and are related to sensitivity toward the child, and I think this is really important.

And this is from a chapter we wrote and I think it's an important thing to remember — that the parental brain is primarily built through caring for offspring. This involves mismatch reparation, and involves making mistakes and learning from them, and it's not unique to birthing parents, and it also overlaps with brain areas we use in other social relationships.

So, that being said, I mean, we know that parenting is quite transformative. For many individuals, it's a happy time. It's also a really difficult time, and for some, it's more difficult than it is joyous.

And, you know, it was recently that the Surgeon General in the United States said something with regard to how stressful parenting is, and I think that this is important to keep in

mind, because I feel that we are often burdening parents or there's too much mental load, particularly for mothers, and this isn't healthy for the brain, of course, and for anyone.

So, you know, we do see that there's huge changes in our brains during pregnancy and the postpartum period, and we often are thinking about, well, is this a time of vulnerability or risk for perinatal mental illness because of the brain changes?

And sometimes I like to think about this: well, the brain will do just fine if we give it the space to do what it needs to do, and perhaps it's not that there's a vulnerability because of the biological changes, but the vulnerability is there because there's not the social support and the community that's needed.

This, again, is something for further discussion, but I think it's important to remember that against this backdrop of huge biological change and neurobiological change, we

often aren't providing the supports necessary for brain health.

Of course, you know, perinatal mental illness is occurring at a high rate. This is a stress-related disorder, or these are often stress-related disorders, and we could do better and need to do better, I think, in terms of preventing illnesses in pregnancy and the postpartum period.

So, let's just talk a little bit about the brain and perinatal mental illness. And as I mentioned in the beginning, I'm going to be focusing on postpartum depression, but I do want to point out that perinatal mental illness, as I said previously, occurs in about one in five mothers and about one in ten fathers. There's a number of different illnesses, in fact. I'll be talking about perinatal depression or postpartum depression.

We know there's high levels of anxiety and different anxiety disorders happening during this

time; postpartum psychosis is incredibly debilitating and requires immediate attention and occurs in one in 1,000 individuals postpartum.

We see that there's also, you know, there can be other mental illnesses that show up during this time as well, because there's a lot of different factors that are playing a role here; but, the impact or perhaps the changes physiologically, combined with the lack of support, previous life experiences, and different factors can really increase the risk of mental illness.

What's perhaps even more shocking is that suicide is the leading cause of death in pregnancy and the postpartum period, and this is in a number of countries studied to date, and this is actually quite sad to think about and shocking that it's suicide that is the leading cause of death for mothers.

And, of course, treatment is needed, different forms of treatment. I think we need to

develop better treatments. We need to have better interventions, preventions, options, support, and what have you for parents during pregnancy and the postpartum period, and I've done a lot of research looking at different types of interventions — antidepressant medication use, for example — and how important it is, among other things.

So, we have much to do, but let's just go through and talk really briefly about some of the brain changes. Now, we wrote this review in 2017 on the neurobiology of postpartum anxiety and depression, really looking at what happens in the human brain with these illnesses.

And, in fact, one of the most surprising things from this review was how little research there was on this topic at the time. It's increased a bit in the past, what, five, almost ten years, but at the time, if you think that 80 percent of women will be pregnant, that 20 percent of those women will struggle with

anxiety, or depression, or another mental illness, and there were only maybe 20, 25 studies looking at the brains of humans struggling with postpartum anxiety or depression, and actually I'll say there were zero specifically looking at postpartum anxiety and the brain.

This should be quite upsetting to think about. These are disorders that, of course, impact the mother, but also impact her child and the family, and so we really need to do better and spend more time looking at these mental illnesses and what's going on in the brain.

So, I'm going to just go through a couple of factors to highlight when we're thinking about the neurobiology of perinatal mental illness. These are things that we covered in our review that really spoke to us and just reminded us about how we need to treat this time in life a bit different when we're thinking of brain health.

So, the first thing is that similar brain areas are involved in depression during the

postpartum period and depression at other times in life. We've kind of highlighted this here. The postpartum is in the pinks and then we have depressive disorder and anxiety, highlighting some key brain areas — of course, not all of them — in the green and yellow.

So, you can see there are some similar brain areas involved here, but what was really interesting is that the brain areas are responding a little bit differently, and so this came about when we did this review.

We saw this, but in some areas, there's an increase in activity with postpartum depression when there's a decrease in activity with major depression, but no one at the time — we published this paper in 2017 — had actually compared a woman with postpartum depression with a woman with major depressive disorder — so a non-mother with major depressive disorder.

And, in fact, I think, to date, there's only been one study that's done this — done this

comparison to really get at the differences in neurobiology, and I'm going to talk about that study right here just to give you an idea. And this is specifically looking at the amygdala, looking at the response to own infants, so this isn't applicable to those individuals with major depressive disorder. So, what's important to look at here is the unfamiliar infant cue and then you have scenery, and they're looking at how the amygdala is responding.

So, you can see that the mother with postpartum depression, and this is a non-mother without postpartum, or a mother without postpartum depression, so these are the mother groups, and then these are the non-mother groups, one with major depression and a group without depression.

So, what you can see here is that the amygdala is really activated in a mom with postpartum depression, and this is a common finding that the amygdala becomes extra activated

often with postpartum depression; but what's interesting is this is quite a bit different than not only the mother without postpartum depression, but also compared to the individual with major depression.

And I think this is important. Maybe it's not a surprise, but it's important to point out that even though these are similar brain areas that are important in these illnesses, that the way they're being activated can be quite different in pregnancy and the postpartum period, in part because there's also that infant involved and there's also been all of those physiological changes involved across pregnancy and the postpartum period. So, similar areas, but different function involved.

And also, we know that many of those areas involved or associated with postpartum depression are also important for parenting; and so, again, this also speaks to the need to consider the neurobiology of perinatal mental illnesses as

being unique, because there is this activation of the brain or the parental brain circuitry.

Also, there is this, you know, because there is this relationship with the child that has arrived during this time, however that relationship may be, because often we know it can be quite a struggle for moms to feel connected with their child or they feel quite anxious about their child's health when they're struggling with a mental illness.

So, one thing that's really important when we're thinking about the brain and perinatal mental illness is that, you know, perinatal mental illness should be treated as having a distinct neurobiology, or at least a uniqueness to the neurobiology, and I think this would really help us to move forward when we're thinking of preventions, interventions, and treatments for mental illness during pregnancy and the postpartum period.

But, ultimately, as I've mentioned

previously, I think we need to give the parental brain the space to develop, and so then the question that really comes to mind for me is how can we unburden the maternal, or the parental, or the paternal mind? How can we unburden the mind so that it can do what it's supposed to do, and that is to learn how to parent?

And I think we have a way to go with that, but I hope with greater understanding about the brain changes, the healthy normal brain changes across pregnancy and the postpartum period, will motivate us to actually focus on brain health in this time in an adult's life.

So, thank you. That's it for me, and I look forward to discussing further with you.

(End of recording.)

DR. NAIFEH: Some fascinating research to start off the second half of the conference. Thank you, Dr. Pawluski.

Our next presenter is Dr. Jessica Schleider. Dr. Schleider is an Associate Professor of Medical Social Sciences, Pediatrics, and Psychology at Northwestern University. She's the Founding Director of the Lab for Scalable Mental Health and also serves as Director of Digital Services at Northwestern Center for Behavioral Intervention Technologies. Dr. Schleider's professional mission is to build, test, and disseminate scalable evidence-based mental health solutions that bridge previously unfillable gaps in mental health ecosystems, with a focus on single-session interventions for underserved youth.

She has created or co-created seven open access single-session mental health programs, which have reached 70,000 people to date. Based on these programs, Dr. Schleider and her colleagues wrote a self-help book called, *The Growth Mindset Workbook for Teens*. She also co-

edited the *Oxford Guide to Brief and Low-Intensity Interventions for Children and Young People*, and wrote the book, *LITTLE TREATMENTS, BIG EFFECTS*, on how single-session interventions can transform mental health. She was previously chosen as one of Forbes' 30 under 30 in healthcare.

We will now begin Dr. Schleider's presentation, which is titled, "Leveraging Single-Session Interventions to Bridge Gaps in Mental Health."

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SCALING SINGLE-SESSION INTERVENTIONS TO BRIDGE GAPS IN MENTAL HEALTH ECOSYSTEMS

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DR. JESSICA L. SCHLEIDER

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This transcript was produced from audio provided by Uniformed Services University of the Health Sciences.

P-R-O-C-E-E-D-I-N-G-S

DR. SCHLEIDER: Thank you so much for the kind invitation to present some of our lab's recent work. We have a lot to get through, so I'm going to dive right in. And hopefully the discussion that follows this will be a lively one, because I'd love to discuss how this work may apply in the realm of treating and reducing traumatic stress symptoms.

So, it's likely that I'm preaching to the choir when I say that our mental health care system is not quite cutting it in terms of meeting the needs of folks who need mental health support. And I believe that meaningful transformation of the mental health care system that we have today is going to require reckoning with three sobering realities. The first is that about 80 percent of youth and approximately 50 percent of adults with mental health needs don't access any form of mental health care, let alone mental health care that is based on evidence.

The second reality is that supports that do exist are often structurally incompatible with how folks actually want to engage with care. By that I mean, most interventions are designed for face-to-face delivery in brick-and-mortar settings on a once weekly basis. Where when we talk to youth in our qualitative research, we find that young people want support that adheres to when they're actually experiencing problems and is accessible on their own terms, when and where they want it, and where they can choose whether and how to engage in that support. So digital supports come up a lot in terms of what youth actually want. And also, briefer supports and more flexible supports.

The third reality, which I think is possibly the most important one for this talk is that, despite decades of excellent research, identifying effective psychotherapies for a wide variety of problems — these therapies last on average 12 to 16 sessions, sometimes longer. If we look at national insurance reimbursement data

and examine how often people actually show up to mental health care appointments once they begin, once they get in the door at all, the most common number of sessions that people actually experience is one. And that's actually true of both face-to-face traditional psychotherapy services and informal mental health care services, like in primary care. And also, for interactions with digital mental health tools. Even those that are designed for multiple interactions, folks generally log on once, and then aren't going to come back, due to a variety of logistical and personal barriers.

Often, a solution that's proposed for this really huge problem is to expand the mental health workforce in the United States. And, of course, that's going to be one part of the larger solution. But the shortage of mental health care providers in the U.S. today is simply too extreme to fix the need-to-access gap just by expanding our workforce. This is a map from hrsa.gov. You can create your own SAD [shortage area

designations] map anytime you want to that shows the federally designated mental health care provided shortage areas in the United States in dark blue and medium blue. It's not an error that the whole map is dark and medium blue. That's just the state of the situation that we're facing. And I think this really reinforces the need to think creatively about how else beyond workforce expansion we can democratize access to care.

And that's where I'm hopeful our lab can come in. I direct the Lab for Scalable Mental Health here at Northwestern. We started up in 2018, and we've been hard at work towards our mission to design, test, and disseminate brief barrier-free interventions to reduce mental health problems at scale. Now, the interventions that I'm going to discuss during this talk aren't specific to PTSD or traumatic stress. However, given the prevalence of exposure to traumatic events, both big T and little T traumas, I'll mention the percentages of our various samples

that have been exposed to trauma, but it's very high. So, the interventions I'm going to discuss today have all shown acceptability and clinical utility in populations experiencing or with exposure to trauma. Just to contextualize that, even though the primary outcomes we generally look at are things like depression, anxiety.

So, I want to start off by sharing a little bit about the primary mode of investigation that we use to fulfill our mission to create brief barrier-free interventions. And that's by studying the shortest possible kind of intervention: a single-session intervention. And I know these have actually quite a mixed history in the traumatic stress treatment world, with Critical Incident Stress Debriefing being a particularly well-known example of an iatrogenic intervention that's delivered in one go. I'm going to explain a little bit why Critical Incident Stress Debriefing would actually not be considered an SSI under this definition. So, the way I understand SSIs and the way the field

defines them are specific structured programs that intentionally involve one visitor encounter with a clinic, a provider, or a program. That intentionality is key, because there is a shared understanding that we're going to make the most of this moment. And that change is possible within one single encounter. And there's an understanding that we're going to make the most of this particular encounter, whether or not there are future ones. So, showing up for an initial intake and not being able to return due to logistical considerations wouldn't be considered an SSI because that initial intake wasn't meant to be one session.

Importantly, single-session interventions are not a one and done as a rule intervention. They certainly can be accessed once, but they can also be accessed many times, whereby each individual experience stands alone and holds promise to individually impact clinical change. So, it's a one-at-a-time approach to support, not a one-and-done approach. These can

be self-guided or person-facilitated. I say human-facilitated as a broad term, because many SSIs that are evidence-based are deliverable by lay providers. And they can be accessed either within or outside of formal healthcare settings, making them particularly ripe for scalability. But in all cases, SSIs draw the often false assumption that clients can and will return for another session while instilling the belief that change is possible at any moment for any human, creating a context of competence, whereby people can build on strengths that they already have to take steps in a positive direction.

Now, going back to Critical Incident Stress Debriefing, for me, that would not be considered an SSI, because, as it's traditionally been delivered in the trials that have been reported, it was sort of required that folks exposed to a traumatic event immediately relive the trauma that they experienced — rehash it in ways that they may or may not feel comfortable with. An SSI is always an opt-in form of support, and it's

always a strength-based form of support. So, both the techniques and the requirement to engage are very, very counter to the single-session model as it's been studied in the literature. Happy to discuss this more in the context of what might be helpful for folks experiencing traumatic stress.

Fortunately, the single-session approach isn't just a nice idea. There's actually decades of research and hundreds of randomized controlled trials suggesting that these interventions can be helpful for a wide variety of problems in both youth and adults. We just published in the *Annual Review of Clinical Psychology* the most comprehensive review of SSIs to date. It was an umbrella review that included and summarized the results of 24 systematic reviews of single-session interventions. And that included 415 unique clinical trials and over 50,000 participants across these trials. And what we found is that, overall, SSI clinical benefits emerged in 20 of the 24 systematic reviews that

we included both for mental health-related outcomes, like anxiety, depression, and stress, and for service use outcomes. As in, SSIs can not only be used to reduce symptoms directly, but they can also be used to increase motivation to engage in further services when such services are actually available.

When directly compared to multi-session therapies, single-session interventions are looking pretty good. The effect sizes are not all that far off if you look at them directly, head-to-head. And four of the systematic reviews or meta-analyses in this study directly compared the impact of single- and multi-session psychotherapy interventions to each other. In only one of those four meta-analyses did multi-session therapies outperform single-session. They were either tied or single-sessions outperformed multi-session in the other meta-analyses.

So, 12 of these 24 systematic reviews included a meta-analytic component. And the

outcomes you can see here. Across the board we're seeing overall positive effects across a wide variety of outcomes. You'll see that traumatic stress is not one of the outcomes that's listed here. That's, I think, largely because of the legacy that Critical Incident Stress Debriefing has left. I believe folks have been hesitant to engage in this kind of approach with folks experiencing trauma as a primary problem. I'd love to discuss ways to move forward, because I do think there are highly relevant models that could be adapted to be more trauma-informed that could really benefit this population and improve access to support.

I want to emphasize — and this is really key — that nothing that I'm about to share in this talk suggests that single-session interventions can or should replace any other forms of mental health care that we already have in our system. Of course not. What I do think is that the current supports we have are clearly not enough. They're not meeting the population-

level needs. They're never going to do that because they weren't built to. They were built to serve people who actually make it into the healthcare system, not those who never get their foot in the door. So, SSIs, I believe, can bridge these otherwise unfillable gaps that we have in the system today and change and revise our system into one that actually is a population model of mental health support for all.

Now, we've been studying single sessions in our lab for a long, long time. Our main focus is on digital, self-guided single-session interventions for adolescents, but we also have provider-delivered interventions for all ages — so adolescents, adults, and younger kids. SSIs for parents of kids experiencing anxiety and a variety of other programs. But overall, over the past seven years, our lab's evidence-based single-session interventions have served more than 70,000 people through various community partnerships, including non-profit and for-profit partnerships, along with our randomized control

trials that we conduct in-house. All of our interventions are built with co-design for folks they're designed to serve. So, we want to make sure we're building things that people will actually want and use and benefit from. So, we really leverage lived experience and preferences in design of our end users when creating these programs.

And, as a result of this and as a result of the dissemination channels that we use — for instance, waiving parental permission requirements for adolescents to access these online single-session modules that we've created — most folks who access our interventions identify as sexual and gender minority youth or racial or ethnic minority youth. And that's something we're very proud of, and it's quite opposite to the trend of access in other kinds of more traditional mental health care services. All our SSIs are accessible as needed with or without parental involvement.

These are a few logos of some of the single

sessions that we've developed and tested in multiple randomized controlled trials with follow-ups that span from immediate post-intervention to nine months later. So, we're not just saying that single sessions can impact change right away. Those effects can actually last across multiple months.

I'm not going to go into each intervention, but in short, they each teach a concrete skill or way of thinking that is emblematic of something that's taught in a longer-term form of evidence-based treatment. By focusing on one skill, they enhance the opportunity to retain the information and to promote success and competence and a feeling of self-efficacy at the end of each module. They each take between 10 and 20 minutes to complete, except for the single-session consultation that's a solution-focused brief intervention delivered by a human on the right there. And that's an intervention that can just fit into a regular therapy session format. We made it originally for folks stuck on waiting

lists for treatment to prevent deterioration in that context. I'll talk about that in a little bit.

So, what they all have in common is that each SSI targets modifiable short-term beliefs or behavior, whereby short-term improvements in things like perceived control, autonomy, hope, and self-efficacy can spur upward spirals of meaningful change in our RCTs between three to nine months post-intervention compared to active controls.

In terms of a generalizable theory for how SSIs work, and this seems to apply per our active ingredient studies that we've been doing recently. Regardless of SSI content, we believe that each SSI through the lens of self-determination theory, which is a well-known social psychological theory of behavior change, helps instill a sense of autonomy, a sense of competence, and a sense of relatedness as in not feeling alone, feeling supported by somebody else out there. And we believe that by fulfilling to

a certain degree — to some degree, each of these basic human needs that all of us have in order to spark behavioral change — we're able to trigger subsequent changes in things like hopelessness and motivation and, in turn, spur better mental health outcomes and service uptake for folks who have access to other supports.

And now, I want to overview a few of the different kinds of research that we do by highlighting a couple of trials that we've conducted, so that you can get a sense of the focus of our work and the breadth. This first trial that I'm going to share about was the largest randomized controlled trial of single-session interventions to date. It focused on adolescent depression during the COVID-19 pandemic, when many youth were actually losing access to the few supports they did have, mostly because schools went on lockdown and they no longer had access to IEPs or 504 plans that provided them with care. So, we wanted to really put our single-session interventions to the test

during this context in which, theoretically, digital self-guided SSIs could be the most useful. So, in an NIH-funded randomized controlled trial, which included 2,452 adolescents across all 50 U.S. states, 80 percent of whom were LGBTQ+ and 50 percent of whom were racially or ethnically minoritized youth, because, I believe, of the parental consent waiver that we secured to do the study. We, by the way, recruited all of these teens through Instagram. So, they found the interventions on social media platforms, which is the number one place that teens look for mental health information and support in the first place.

In this trial, this three-arm trial, we tested whether two previously tested online, self-guided, digital single-session interventions — one teaching growth mindset, specifically the idea that depression is malleable rather than fixed, and one teaching behavioral activation, the idea that what you do can shape how you feel and by making an action plan, you can help

yourself get unstuck from negative mood spirals — could either of these interventions, compared to an active control, reduce depression, anxiety, traumatic stress symptoms related to the COVID pandemic and restrictive eating?

Here are some screenshots showing what our active SSIs look like. These are components or design features that are present regardless of the content of our digital single-session interventions. But the specific words and skills that we focus on are different across each intervention. But all of our digital SSIs include a component of psychoeducation of some kind.

Here, you can see brain science-focused. So, we teach in this intervention, the growth mindset intervention, that because of how brains work, because of our ability for change and neuroplasticity — we have a brief brain lesson, a brain science lesson there — all of us are capable of change. We're built for change. Depression isn't an inherent part of our

personality or something we're stuck with forever. It's something that, through practice coping in different ways, we can actually rewire our responses to stress and setbacks to forge new pathways forward for coping and experience depression to a less degree.

We include peer testimonials, which we've sourced from actual teens with lived experience of depression, sharing how they use the skill targeted in the particular SSI to cope with stressful events. Each SSI includes an action plan, where people make a very concrete step-by-step plan that's personalized to them to take one small but meaningful step towards using the new skill and coping more effectively in their daily life.

And in all of our SSIs, we have a component of sharing advice. This is because of the well-known idea that helping others helps yourself, and teens in particular are motivated by pro-social opportunities to support others with their own lived experience. So, we ask teens to give

advice to a hypothetical peer about coping with depression using the skill they just learned and also their own lived experience of depression. And we give teens the option, if they want to, to share exactly what they're finding or to share their advice with other teens publicly on our project, YES, Youth Empowerment and Support Advice Center, which is an online resource for other teens, which I'll talk about later on. But we do this because it's with an opportunity for users to internalize the main message of the intervention, and also for them to feel some agency in being able to help folks in the similar experiences as them.

Now, what do we compare our active SSIs to? In this and other trials, the most likely and realistic, or face valid, ecologically valid, control condition would actually be nothing. That's the most likely thing that teens are going to access without an SSI like this when scrolling Instagram. But nothing is not a particularly scientifically compelling comparison condition,

so we created a placebo SSI to be able to control for non-specific aspects of going through a positively valenced, self-guided online activity that's length-matched — so also about 15 minutes in length.

The Sharing Feelings placebo SSI aims to teach people to normalize and encourage sharing your feelings with others. It's designed to resemble advice that people often receive when they're having a tough time, often something that would be stressed in supportive psychotherapy and it's face valid. So, youth don't successfully guess above chance whether this is the active intervention that we're testing or whether it's the control.

There's no mention of malleability of personal traits and there's no action plan in the Sharing Feelings project. And there's no advice-giving embedded. But there are the same number of interactivity points, such as writing exercises, to match it on that feature.

So, what do we find in this trial? Well, we

looked both at immediate post-intervention outcomes of the interventions compared to the control and three-month follow-up, with depression as our primary outcome of interest. The reason we look at immediate effects of these interventions is because we found in some of our other work that proximal improvements in mechanisms of change, like hopelessness and perceived agency, can actually predict the magnitude of longer-term changes in things like depression and anxiety months later. So, we want to see that initial signal of movement because it's a promising indicator that the intervention could have longer-term effects.

What we found is that both the ABC Project, the behavioral activation intervention, and Project Personality, the growth mindset intervention, resulted in a significant reduction in hopelessness compared to the placebo control and a significant increase in perceived agency compared to the placebo control at immediate post. So, good signs so far.

At three-month follow-up, we were pleased to see that both interventions significantly outperform the placebo control in reducing depression symptom severity at three-month follow-up. That effect size, 0.18, is in the small range. However, I want to highlight that the placebo control is not inert. The within-group effect size on depression symptoms for folks who complete the sharing feelings project is about 0.3, whereas for the active interventions, it's closer to 0.6. So, I just want to highlight that this is outperforming a not-inert condition. So, we're particularly excited to see this sustained effect.

We also found that Project Personality, but not the ABC Project — perhaps because it was more specific to depression — did also result in reductions in anxiety symptoms and COVID-related trauma symptoms. I want to highlight that the vast majority of youth in our sample had a history of adverse childhood experiences and about 20 percent were experiencing food or

housing insecurity at the time of the trial, unfortunately. So traumatic stress was not uncommon at all in this sample. And the presence of traumatic stressors did not moderate outcomes across the board. So, we were really pleased to see that it's equitably serving folks in different life circumstances.

To our surprise, both interventions also outperformed the placebo on restrictive eating behaviors and reducing those over three months. That's not something that the interventions discussed or targeted. It was a surprise secondary effect. It has since actually spurred a whole new line of research on body image and eating disorder-focused SSIs. I won't have time to talk about that today, but if you're interested, please feel free to reach out. I'm very excited about what we're finding so far.

I also want to highlight that because of the significant diversity in the socio-demographics represented in our sample, we were able to do an equity analysis so we could look at whether

acceptability or effectiveness differed by race, ethnicity, gender, or sexual orientation. And they did not. We were really excited to see this, primarily because one, most interventions that are developed for psychological problems are developed and tested on relatively privileged samples, higher income, white populations. And so, saying they're evidence-based doesn't mean they're evidence-based for all people necessarily. So, we were able to look at whether these interventions were actually equitably serving folks, and they were, which was very promising in terms of the dissemination pathways forward.

Okay. So, what I just shared with you are overall on average results for a large clinical trial of SSIs for teen depression, but overall effects, as all of us know, don't necessarily reflect whether an SSI will work or any intervention will work for the person sitting in front of you, for the person receiving an intervention online. So, we've been searching

for consistent moderators of what impacts SSI response. But really, all I have for you at this point, despite our attempts with tens of thousands of participants included in these studies overall are a list of things that don't moderate SSI response with any consistency or at all.

One of those factors is the severity of baseline symptoms. This was a really big surprise to me personally, because I sort of went into this work expecting that folks with lower level symptoms or mild symptoms might benefit more from a low-level, low intensity intervention like this. But that's not the case. And, in fact, what we see instead is that folks with higher levels of symptoms and greater acuity in those symptoms are more likely to use an SSI when it's offered to them, because they're in immediate distress. It's generally difficult to get folks who are feeling generally okay to engage in a service. So, the moderating effect we see here is in uptake, not an outcome.

Presence of self-injurious thoughts and behaviors also don't moderate the impact, which goes to that severity piece. Again, we actually have a self-guided safety planning SSI that we offer everyone in our trials who endorses non-zero suicidal or self-injurious behaviors. And happy to share the literature on self-guided safety planning tools, which result in a safety plan, just like you would in a face-to-face session.

History of adverse childhood experiences does not seem to moderate outcomes of SSIs for depression, nor does receipt of concurrent treatment, which may speak to the variability of what treatment actually is in the real world. So instead of looking at baseline characteristics that might predict favorable response to SSIs, we've shifted a bit to working with groups who tend to gravitate towards SSIs and working directly with those individuals and those end users to figure out how can we better tailor our single sessions to the needs that you are

experiencing qualitatively?

One example of this work has been a co-design effort with LGBTQ+ teens, because they represent an enormous and surprisingly big portion of folks who end up accessing our interventions when we put them available online. And so, we were able to get a grant from The Upswing Fund for Adolescent Mental Health to do some of this co-design work to learn from teens: how can we better adapt our depression-focused SSIs to meet your needs?

And what we learned in those focus groups was really interesting. We learned that, in general, sexual and gender minority teens liked the behavioral activation of the growth mindset SSIs — our other ones on self-compassion and other topics, they thought they were generally good, but what they repeatedly noted was that we don't talk in these interventions at all about the larger structural influences that may be impacting their mental health. Notably, these days, the policy landscape and legal

discrimination that's happening, particularly against trans youth, and how stressful that is and how that contributes to their mental wellness or lack thereof.

So, we took this feedback and ran with it and we decided that rather than trying to integrate those things into behavioral activation interventions, we would just create a different intervention that really did this topic justice. And that's how Project RISE was born. Project RISE is an SSI that teaches about minority stress theory and why holding a minoritized identity, like sexual or gender minority identity and other intersectionally minoritized identities, can simply create a different kind and quality of stress that's not fair — you shouldn't have to deal with this extra layer of stress and this shouldn't have to be something that you learn to navigate in your life — but there are ways of coping, and Project RISE helps people make an action plan for finding hope and empowerment and strength and community and support even in a

world that's not always fair.

And we built this intervention, which is now freely available on our lab website. We did an RCT of 538 sexual and gender minority youth, ages 13 to 16. Again, recruited via Instagram, again with a waiver of parental consent, because it would be very unethical to ask teens to out themselves to their parents in order to take part in an online activity like this. And we found that Project RISE significantly improved hopelessness, self-hate, and internalized stigma, versus an information-only control. And that internalized stigma effect lasted two weeks later. So, we're now thinking about ways to integrate Project RISE with other interventions, such as the safety planning intervention. We have a grant to integrate both of those things to better serve the needs of the LGBTQ+ community, who are often kept out systematically of other resources.

Another line of work that we have beyond these self-guided single-session interventions

for adolescents is a body of work studying a solution-focused brief therapy single-session program, designed for delivery by providers to individuals on waitlists for treatment. Why waitlists? Because waitlists are a ubiquitous problem. It's incredibly discouraging and disempowering to finally reach out for some kind of support and be told, "Great job reaching out. Now hold that thought for six to eight months, we're not sure when we can find you a provider with an opening." And waitlists actually cause harm relative to not seeking treatment at all.

So, what we wanted to do with the single-session consultation was create an easy to deliver, easy to learn intervention that could be deployed sustainably to folks on waiting lists for treatment to prevent deterioration and maybe even increase motivation and reduce symptoms while folks are still waiting for care. The single-session consultation, the research question was, can this brief solution-focused therapy SSI reduce hopelessness, increase agency,

and keep symptoms from getting worse for folks on waitlists? The intervention is extremely simple and structured.

When I was creating this intervention originally, I wanted it to be deliverable by a highly motivated college student, maybe to peers, like on a residence hall. So, it's built for both professional therapists, licensed folks, and unlicensed folks to be able to deliver it. And to date, we've trained more than 500 providers, the majority of which are unlicensed, to fidelity in delivering this intervention.

The provider training is brief itself. It's first a 90-minute didactic, followed by a fidelity-checking, live-practice session of the SSC with one of our team members, and the SSC itself is designed to last from 30 to 60 minutes. And the goal of this intervention is to help people get one small but meaningful step closer to a goal that matters to them.

So, it's a problem-agnostic intervention. It can meet people wherever they are, help them

identify a corner of a problem that is meaningful to them and that would make a difference in their life if it were addressed, and make a concrete set of steps to be able to address it a little bit more.

Not to address it completely, but to start, get on the pathway, take one step forward to addressing it. So, it's designed to make people leave feeling empowered and efficacious to better cope with a problem in their lives with a concrete tool to do so.

Just to illustrate how simple this intervention is, this is it. If you complete this action plan with a patient in a session, you've done it. So, this document serves as not just the action plan for the patient or the client to take with them when the session ends, but also a fidelity-monitoring tool, because we have a codebook where you can code each fill-in-the-blank slot there for whether it was delivered correctly.

And it's also something you can upload as

part of a clinical note to document exactly what happened during the session. So, we want to make it as easy as possible, not just to deliver, but to sustainably implement and monitor for fidelity.

We've done several different trials on the SSC. All of them have been open trials to date. There's a large body of literature, including RCT, suggesting the effectiveness of solution-focused brief therapy. So, these really illustrate the utility of the SSC on its own.

In one study looking at folks on outpatient waitlists for the SSC — both adolescents and adults — when the SSC was offered via teletherapy, folks who received it — which were 80 percent of folks who were offered it — showed an 85 percent chance of significant decline in hopelessness and 80 percent chance of showing increases in readiness for change once they did get to the top of the waitlist. And reductions in anxiety and depression across two weeks, which, of course, is the opposite of what we

often see on waitlists, which is an increase in symptoms, because people are discouraged and hurt by not being able to be seen right away.

So, we have quite a bit more literature on the SSC. We recently trained a cohort of peer providers in Uganda to deliver the SSC and found real success in being able to reduce clinically-significant depression for folks waiting for lay-provider-delivered services. But for the sake of time, I want to get to a third sort of arm of our research program, which is single-session interventions designed for parents.

Of course, I believe that empowering adolescents to on-ramp onto digital self-guided supports like these is extremely important, but when we think about preventing problems among younger children, they're not going to be able to advocate for themselves if they're four or five years old. Their parents are really the advocates we need to mobilize and reach in order to leverage the impact that SSIs can have for this population for prevention.

So, Project Empower is a parent-directed, single-session, digital intervention that lasts 20 to 30 minutes. It's based on an evidence-based treatment called the SPACE program, which came out of the Yale Child Study Center, created by Eli Lebowitz and Wendy Silverman.

The SPACE program is a treatment for child anxiety disorders that only involves interactions with parents. It teaches parents to accommodate their children's anxiety less and support their engagement in brave behaviors more. And just by focusing on those parenting skills, the SPACE program has actually been shown to be non-inferior to child-directed exposure therapy in treating anxiety disorders in children.

However, the SPACE program is very long, it involves many group sessions, and it takes a really long time to train providers to do it. So, we wanted to see if we could take some of the core messages in the SPACE program and distill them down to a single-session activity that could have a similar impact.

To date, we've done two RCTs on Project Empower. The first RCT was a mechanism target engagement trial, essentially. We wanted to see if Project Empower, when delivered to parents, could reduce the accommodation that they engage in, in their child's anxiety or avoidance behaviors, and if it could improve their ability to tolerate distress in their children, because that's a common reason why they accommodate in the first place.

Study 2, because study 1 was successful in targeting the mechanisms, looked at whether Project Empower could actually reduce anxiety symptoms when delivered to their parents over a month. The first trial with 301 parents experiencing high anxiety symptoms — because we know anxiety runs in families — showed that Project Empower, relative to an information-only control, significantly reduced parent accommodation of child anxiety, which was very exciting. That was our primary target, with an effect of 0.61, and also significantly improved

parent-distress tolerance, with an effect size of 0.43 across two weeks.

This was really promising and led to our second trial, which focused on parents experiencing financial insecurity. Why? Because financial insecurity is an enormous driver of why many parents are unable to access traditional mental health services. So, it's particularly important that folks in this demographic, in this population, experiencing this kind of stressor, are going to be able to benefit from this program.

In this study, we found that in over four weeks, Project Empower, again, significantly reduced parental accommodation of child anxiety, and significantly actually improved child anxiety symptoms with an effect size of Cohen's d of 1.36 over four weeks compared to an information-only control. That's a really large effect size for any psychotherapy, let alone one that's a self-guided program with no clinician, that lasts 20 to 30 minutes.

We're now really thrilled to be partnering with the Florida Institute of Child Welfare, which is affiliated with Florida State University, to be adapting Project Empower with and for parents and guardians of foster children, to infuse more trauma-informed elements into this intervention. Because often, foster parents are in a position where they have to support their children experiencing anxiety that's trauma-related rather than sort of a traditional anxiety-disorder related.

We're learning so much from working with these families and are really excited for what we're producing, which is a version of Project Empower that really is enhanced with components that help identify whether an avoidance instinct is due to traumatic stress responses versus a fear-based avoidance response purely, and guides parents in empathizing and encouraging their kid to cope positively, depending on what the source of their anxiety is.

So, one piece that we've encountered,

particularly when delivering things like the single-session consultation, our provider-delivered program, is that the insurance system, the sort of healthcare ecosystem in the United States right now, is not actually built to accommodate a single-session approach.

By that, I mean in order to bill through Medicaid for a single-session intervention, you'd first have to do an assessment, an intake assessment. Unfortunately, doing an assessment means you're spending your first encounter with somebody on diagnosis alone, which means you lost your opportunity for many people, who won't be able to come back due to various barriers, to actually deliver an SSI.

So, we've been working with stakeholders at the state level, and networks of Medicaid-funded clinics, particularly in Pennsylvania, to identify and test the feasibility of pathways to Medicaid reimbursement for single-session interventions. In Pennsylvania in particular, we were able to, in collaboration with Community

Care Behavioral Health network of Medicaid-funded providers, secure a new code to be able to reimburse for a single-session intervention offered to folks on waiting lists.

This was really exciting to us, and we're in the process of doing our pilot trial, testing whether offering Medicaid-supported folks a single-session intervention while they're waiting for treatment can actually result in better outcomes overall for the system, reduce burden on the system by increasing the speed at which folks recover once they do access care. And pending good results, that code will be able to be permanent in Pennsylvania and, hopefully from there, other states as well.

So, I've gone over a few different ways that we've studied digital single-session interventions for adolescents, human-delivered interventions for folks on waiting lists, and digital SSIs for parents to prevent youth mental health problems from emerging.

At this point, our lab is — rather than

conducting more clinical trials to just test effectiveness, we believe it's really time for us to move into implementation. And because of the strength of the evidence, we've pivoted quite a bit to figuring out what strategies are most effective at scaling up SSIs and making them sustainable components of our mental health care ecosystem at large.

We're trying a lot of different things. I won't have time to discuss all of them today, but the results so far are helping us understand where and how SSIs can bridge gaps in care, and what barriers might get in the way on this pathway.

So, I want to take you on a short journey of the evolution of our first effort and longest-standing effort to disseminate single-session interventions digitally to adolescents, called Project YES. Project YES stands for Youth Empowerment and Support.

This is a website, SchleiderLab.org/yes, that anybody can access and use any of our

digital SSIs listed there at any time, freely, anonymously, and at their own pace. Folks can come back and do multiple SSIs, they can do one multiple times to create a new action plan each time, and they can take the SSIs in multiple languages, which we've been able to offer thanks to partnerships with folks who are very generous with their time across the globe.

You know, in retrospect, I now understand that making things free on its own is not a wonderful dissemination strategy sustainably, but it was our way of making sure that the results that were coming from our trials actually reach the folks they were designed to serve.

How Project YES works is, folks can choose one of the activities, one of the single-session supports listed there. They can, if they want to, give us pre- and post- data on what they think on proximal mechanisms, like hopelessness and agency, and qualitative feedback for us to use to improve the programs.

And we ask teens to share, if they want to,

their best advice for others in coping. And if the teens give us permission, we post that advice on the Project YES Advice Center for other adolescents to benefit from if they use Project YES in the future. So, they know and they can see how they're contributing to a resource that's useful to folks in their position and their community.

We've disseminated Project YES across multiple channels in multiple contexts and settings, and that includes disseminating through social media platforms, partnering with local governments to disseminate, and in schools in San Antonio, Texas, working with youth shelters in Syria and Lebanon to offer these to war-exposed youth, and offering the SSIs through primary care. And we found promise in all of these. The interventions, when folks access them, are showing the same effects that we see in our clinical trials.

However, we realized in doing this work that, you know, we're not computer engineers,

we're not graphic designers. We're going to need to partner with agencies with a more sustainable pathway to scaling and reaching youth when and where needs arise in order to actually make this go as a force for youth mental health.

And so, we've pivoted in the past year and a half, our lab, to focusing all of our projects to partner with at least one non-academic organization, whether that's nonprofit, for-profit, local government, state government — some kind of larger organization with an existing pathway to reach many people and offer SSIs sustainably, so that way we are recognizing the fact that we, our lab, are never going to have the full expertise and capacity to be the primary disseminators, implementers, of these interventions. These other agencies are already positioned to be the implementers, and we need to be working with them from the very start to embed the SSIs that we know work into their delivery systems and platforms in order to reach youth sustainably.

One example of a partnership I'm particularly proud of is our work with a nonprofit called Koko. Koko is a digital mental health nonprofit that contracts with large, web-based platforms like Instagram, Tumblr, Pinterest, and WhatsApp to embed crisis-detection-and-support capacities into those platforms, such that when users search for terms like suicide, or depression, or therapy, they're automatically flagged and offered resources that can help them in that moment.

Several years ago, we decided - me and the CEO of Koko, Rob Morris, decided that the SSIs that our lab has been testing would be perfect things to offer in this circumstance. So, we decided to embed the single-session interventions into Koko's platform to offer SSIs as just-in-time supports to people seeking mental health information on large online platforms.

We were then able to test our SSIs in this context when it was delivered in this way. Our first test was within Tumblr, a large social

media platform that tens of millions of people still use every week, and we wanted to see whether our depression-focused and self-harm-focused SSIs could be useful in this context.

So, to embed our SSIs into Koko, we actually had to reduce them in length even further, because nobody is going to do a 15- to 25-minute program online, if they're just scrolling social media — if they're not getting paid for it as part of a clinical trial. So, they had to be shorter in order for people to do them in this context. And simply by offering our SSIs after adapting them as just-in-time supports on Tumblr, 6,179 adolescents accessed and completed them within one year. And because we'd already conducted many randomized control trials, including these same interventions, we could benchmark the immediate effects of the interventions in Tumblr against those that we had seen in larger clinical trials with longer-term follow up. And we saw that hopelessness reduced at least as much in the Tumblr-based SSIs as in

our RCTs. But completion rates were much higher through Tumblr with the five-minute versions as they had been in Project YES, with the 15-minute versions — not surprising because these were much shorter and easier to complete. So, we were really happy to see that we could retain similar impact at least in the short term while reducing the length substantially. We've also worked with Koko to leverage SSIs, not just to reduce hopelessness and depression directly, but to increase uptake of crisis resources. Often, when folks are offered resources on social media platforms, if they type suicide into the search bar, they'll get a list of hotlines to call. Unfortunately, most people who see these hotlines don't actually use them. They're not sure what they are. They don't feel personalized to them. They worry about what will happen if they do use them.

So, we wanted to create a one-minute single-session intervention to increase uptake of crisis resources when they're offered in this kind of

setting based on search terms. And that one-minute SSI that we built with Koko's interface simply offered a one-line testimonial from a peer saying how using one of these hotlines or resources had helped them before, some stats normalizing how common suicidal thoughts and behaviors are, and a choice of three different kinds of crisis resources to use, some of which were hotlines and others were self-guided supports. And just by offering this intervention, this one-minute program right before offering crisis resources, we were able to see a doubling in uptake of crisis resources after they were provided in social media platforms. This was an RCT of 355 young people who were flagged as being high risk for suicide on social media. Compared to the crisis response as usual where 38 percent of users uptook a crisis resource, after our one-minute SSI, we saw that 78 percent of users used a crisis resource within ten minutes. This is now Koko's standard protocol for encouraging folks to use crisis

resources when they're in acute distress.

I'm really excited, because at this stage we're now expanding our partnership with Koko to create a better and bigger version of Project YES that can meet, a lot more flexibly, different communities' needs. We're aiming to deliver just-in-time digital SSIs to youth with on our mental health supports just like we are in the studies I just presented. But we also want to leverage Koko's tech powers to help bridge the gap between these online SSIs and actual community-based support that young people may have access to. So, this web-based platform, which we are still calling Project YES, will have a suite of evidence-based SSIs packaged within it, and they can flexibly accommodate and be offered to youth with different types of difficulties. And the platform will also include not just a crisis detection protocol to escalate support for youth experiencing suicidal thoughts or behaviors, but also the opportunity for youth to get off of the platform and connect with local

resources, like at their school or their primary care provider or in their community, using geolocation technology that allows them to de-anonymize themselves and actually reach out for support. To give you a sense of what this platform is going to look like, it's going to be a free digital suite of evidence-based SSIs for teens.

It's going to be an easy to use digital tool to seamlessly integrate within different settings. So, you can use it to check in with adolescents, to connect them to local resources, share science-backed self-help supports. And they're all designed to boost mood, reduce hopelessness. and build coping skills. This platform can be accessed either through a QR code or through Koko's platform, which is embedded in large online platforms and social media. It'll be offered to users who are flagged as potentially being able to benefit. They'll go right to Project YES. There's no login. It's an anonymous platform if folks want it to be, and

it's accessible either on web or mobile. Onboarding takes seconds. Users quickly understand exactly what to expect with no login requirements. It's not an app you have to download. It's a web app that you can just use immediately.

We can embed questionnaires pre- and post-SSI so we can track progress and impact. People can select from a list of SSIs or they can take a couple of different screeners to identify SSIs that might be particularly useful for them in that moment. They're guided through six- to eight-minute versions of SSIs, all of which end with an action plan for youth to screenshot and keep. If a youth, at any point, inputs information into the free text boxes on this platform that indicates they're at high risk of suicide, a crisis protocol is triggered immediately using Koko's existing technology, and they're given on-demand resources that are local and national as well as access to a self-guided safety planning intervention that we've validated

separately.

And we have capacity to follow up with youth who agree to be contacted by us in the future so that we can check whether they're using their action plans, whether they followed through with their crisis resource plan, et cetera. And right now, we're working on a multiphase project with multiple states, including Montana, South Carolina, and Georgia, to not only implement and culturally adapt this platform to different communities and their resource options, but also to create a dissemination toolkit to help this stick in different community settings, and to conduct hybrid effect as implementation trials to evaluate its impact over time when deployed to an entire county or state. We're very excited, we're working with lots of different partners for this very wide-scale effort. And I hope to have results to share with you soon on many of the phases.

Last thing I'll talk about and then I'll wrap up for today. I want to highlight that

alongside the importance of creating interventions that are scalable and easy to access, it's also important to understand that no matter how scalable we make an intervention, it won't matter if there are structural barriers, legal barriers, policy-level barriers, to actually deploying those interventions to folks who are positioned to benefit. And I want to focus on one particular kind of roadblock that we've experienced in many of our studies, which is state laws around parental consent requirements for youth to participate in mental health care. When we interview youth, and we've interviewed hundreds of youth at this point from our clinical trials on SSIs online for depression, and we asked them, what has gotten in the way when you've tried to seek out mental health support and haven't been able to get it? Between 32 and 42 percent of those adolescents say their parents were the primary barrier to accessing treatment.

That's not necessarily because parents are

saying no when their kids ask for treatment. But kids fear that their parents will respond in an invalidating manner — that they won't take their problems seriously, or that they haven't taken their problems seriously, or some teens don't want to burden their parents with an extra worry about their mental health because they see them struggling on so many other fronts in life already. So, parents aren't at fault for this necessarily. It's just that the reality of the state that we're in is that often youth cannot go to the adults in their homes to ask for support. And about a third of the states in the U.S. do not allow adolescents to seek out mental health care of any kind without active parental consent, so that leaves many kids in a really tough spot. Our qualitative research has shown this repeatedly, but we wanted to see if we could quantify it in a different way at a different level. So, we conducted a legal mapping study, testing whether parent consent laws are related to youth access to care among adolescents with a

recent history of depression, because depression is often an internal problem that isn't necessarily visible to parents. So, there's often a huge discrepancy between parents' likelihood of referring their youth to intervention versus youth experiencing actual problems with depression.

We use data from the SAMHSA National Survey on Drug Use and Health looking at state levels of adolescent treatment access among adolescents meeting criteria for clinical depression in the past year. And we mapped all of the laws and policies in each state as to whether adolescents could access care independently or not. And what we found was that treatment use among adolescents with past-year depression was significantly lower in states that did mandate caregiver consent for professional mental health services. Specifically, in states that do allow for independent minor consent, 46 percent of teens who had experienced depression in the past year were able to access treatment in the past year as

well. However, in states that require parental consent, that figure was only 37 percent. I want to highlight that 46 percent is still really low. We should be aiming much higher than 46. But the fact that a law can be associated with such a large difference, such a noticeable difference in access, points to some barriers that may be really high priority in terms of dismantling to increase access to support.

Okay. I'm going to skip teens' testimonials. I'll leave them up here so you can pause it if you want. But this is what teens have to say about the laws. They're really thoughtful when we interview them about these consent laws across the nation. And lastly, if you're interested in this topic, our lab here at Northwestern in Chicago medical campus is really excited to be hosting the Fifth International Single-Session Therapy Symposium, the first time this event will be held in the U.S. It's previously been held in Canada, Australia, and New Zealand, and Italy, where SST is already

quite common and popular, but you can attend either virtually or in person if you want to learn more. There are several talks focused on trauma explicitly and traumatic stress. So, I hope to see some of you there either virtually or in person. And thank you so much for your attention. I truly appreciate it. Please feel free to follow up with me if you have any questions or want to talk about any of this further; I'm more than happy to.

(Whereupon, the above-entitled matter went off the record.)

DR. NAIFEH: Our final presenter today is Dr. Paula Schnurr. Dr. Schnurr is a psychologist and the Executive Director of the National Center for PTSD in the Department of Veterans Affairs Office of Mental Health. She previously served as the Center's Deputy Executive Director, beginning in 1989 as one of the Center's co-founders. She is a Professor of Psychiatry at the Geisel School of Medicine at Dartmouth and is Editor-in-Chief of the *Clinician's Trauma Update-Online*. Dr. Schnurr is a past President of the International Society for Traumatic Stress Studies and former Editor-in-Chief of the *Journal of Traumatic Stress*. She's a fellow of the American Psychological Association. Her research focuses on PTSD treatment and on risk and resilience factors associated with the long-term physical and mental health outcomes of traumatic exposure.

We will now begin with Dr. Schnurr's presentation titled, "Psychotherapy for PTSD: Where We Are and Where We Need to Go."

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2025 SPRING CONFERENCE

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PSYCHOTHERAPY FOR PTSD:
WHERE WE ARE AND WHERE WE NEED TO GO

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PAULA P. SCHNURR, Ph.D.

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This transcript was produced from audio provided by Uniformed Services University of the Health Sciences.

P-R-O-C-E-E-D-I-N-G-S

DR. SCHNURR: Thank you. I'm so pleased to be here with you today to talk about psychotherapy for PTSD, where we are, and where we need to go. There are four parts of the talk. First, I want to talk about PTSD clinical practice recommendations -- because I work in the VA, I'll focus on the VA/DoD Clinical Practice Guideline and then spend a little bit of time talking about psychotherapy versus medication and recommendations around that. Then I will move into talking about comparative effectiveness research and illustrate this with a study that I and colleagues did, comparing cognitive processing therapy and prolonged exposure. And lastly, I will end by talking about what we need to be doing to enhance treatment outcome in PTSD, and especially focusing on psychedelic drugs as a strategy.

Just to review, when we talk about PTSD, the diagnostic criteria require that a person be exposed to a traumatic event in which they experienced, witnessed, or were confronted by death or serious injury to self or others. There

are four symptom clusters in PTSD: intrusion, avoidance, negative changes in cognition and mood, and hyperarousal. And most people have these symptoms after a traumatic event.

So, we don't diagnose PTSD until the symptoms last at least a month and they cause clinically significant distress or impairment in functioning. It's important to remember that a person can have these symptoms without meeting the criteria for diagnosis. So, we're only diagnosing a disorder when the symptoms are severe and have a significant impact on a person.

There are a number of Clinical Practice Guidelines for PTSD. American Psychological Association, which is updating their current Guideline, the Australian Guidelines for the Treatment of Acute Stress Disorder and PTSD, the International Society for Traumatic Stress Studies has a Guideline, which they will be updating soon. In the U.K., the National Institute for Health and Clinical Excellence has a Guideline. And then VA and the Department of Defense in the U.S. have a Guideline that we'll focus on today.

So, we developed Clinical Practice

Guidelines for a variety of disorders that affect military populations in VA and DoD. This is overseen by the VA/DoD Evidence-Based Practice Work Group. We use an international best practice for developing guidelines known as GRADE. I'll explain a bit about that in a minute. And I think it's important to remember, when we think about guidelines, is what they're supposed to do, which is to provide information and assist decision-making. They're not intended to define a standard of care.

So, GRADE is a framework for developing and presenting evidence summaries, and it provides a systematic approach to make clinical practice recommendations. There are five types of recommendations in the GRADE framework: "Strong for," which means we recommend this offering, this is the strongest evidence; "Weak for," we suggest offering this option; "Weak against," we suggest not offering this option; and "Strong against," we recommend against offering this option. "Insufficient" is used when there is lack of evidence or the evidence does not permit a definitive conclusion.

So, in the VA/DoD guideline, the

strongly recommended psychotherapies are: Cognitive Processing Therapy, EMDR (Eye Movement Desensitization and Reprocessing), and Prolonged Exposure. There are a number of clinical trials, RCTs, in veterans and non-veterans demonstrating the effectiveness of these treatments. They've been found superior to waitlist, but also to active and quite rigorous controls.

They're not only effective -- these three treatments are not only effective, but they also have very durable effects. One study demonstrated this in a sample of female sexual assault survivors. They were followed up about six years after they were originally treated with Cognitive Processing Therapy or Prolonged Exposure. And at that point, an average of six years later, 80 percent no longer had PTSD. And on the right of this slide, you can see the severity scores on the CAPS, this is the CAPS for DSM-IV, starting out at a very severe level in the high 70s and six years later in the low 20s. Twenty on this version of the CAPS was the standard for remission. So very pronounced and very durable effects.

The VA/DoD Guideline also recommends or

suggests several other therapies for PTSD: Written Exposure Therapy, Present-Centered Therapy, and a type of cognitive therapy developed by Anke Ehlers. There are a number of studies in veterans and non-veterans, again, superior to waitlists and active controls and for Written Exposure Therapy, which is called WET. There are also several studies showing that WET is non-inferior to Prolonged Exposure or Cognitive Processing. The Guideline also has a Weak recommendation for Mindfulness-Based Stress Reduction, which offers an alternative to psychotherapy as a strategy.

When you turn to medications, the recommendations are mixed and the options are fewer. There is a strong recommendation for sertraline, venlafaxine, and paroxetine, a weak recommendation for prazosin for nightmares. And that's essentially what the evidence suggests is effective for treating PTSD or nightmares in people who have PTSD. The Guideline strongly recommends against benzodiazepines and cannabis. And this is for lack of demonstrated efficacy and known harms. There is Weak against recommendations for risperidone, ketamine, and

prazosin for overall PTSD.

And, on ketamine, it is a recommended treatment in the Guideline for depression. So, it may be indicated for treating depression in people who have PTSD, but it is not recommended for treating PTSD itself. There is insufficient evidence for a lot of other treatments, fluoxetine, other SSRIs, other antidepressants, MDMA-assisted psychotherapy, which I'll talk about later, psychedelic treatments in general, topiramate, quetiapine, olanzapine, and combination treatments as well.

In addition to recommending or suggesting these specific treatments, the VA/DoD Guideline recommends psychotherapy over medication as a first-line approach. The meta-analyses show superiority of psychotherapy over medication. There are few head-to-head comparisons. And, admittedly, some of them don't find a difference between medication and psychotherapy. But overall, when you look at the body of evidence, psychotherapy has larger effects.

They're larger when psychotherapy is compared to a waitlist. And, of course, you might think, well, that's a weaker control than

placebo, and you'd be right in thinking that. But the psychotherapy effects are also larger to medication effects when compared to active control and non-specific active treatments. And these are controls that are equal to or stronger than placebo control.

And, as I mentioned earlier, the effects of psychotherapy can be very durable. And, typically, what we see with medication is that when people stop medication, they don't maintain the gains they have. And so, this combination of efficacy and durability is why we recommend psychotherapy first.

So, we have a number of other treatments as well as these active treatments. And we really don't know how many of them compare to one another. There is a great need for what is called comparative effectiveness research to try to understand, do effective treatments work better, or is a given treatment that hasn't yet been established, is it comparable to an established treatment?

In a study that I published with colleagues a few years ago, we compared Prolonged Exposure and Cognitive Processing Therapy, because they're

highly effective. They're widely used in VA and DoD, but there is only one comparative effectiveness study that did not show a difference between the two treatments in female sexual assault survivors.

This was an important study for us to do in VA because we're implementing these treatments. We have a national training initiative that has trained over 10,000, I think now over 11,000, therapists. And so, we have a situation where we have two effective treatments. We don't know how they compare to each other. And so, this study was needed to inform choice overall about which treatment works or which treatment works for which patients.

So, in the study, we found that both treatments reduced PTSD symptoms from before to after a treatment with large effects, but PE was more effective than CPT. However, the effect was statistically significant but not clinically significant. Our predetermined threshold for clinical significance was an effect size of 0.25, and the effect size was very small, 0.17.

On the right of this slide, you can see the trajectory of symptom change from baseline

through six-month follow-up. And from pre- to post-treatment, both treatments had meaningful effects that were maintained over time. However, what I just showed you was the primary outcome, PTSD severity. When we looked at other indicators of clinical response, we saw a different picture, in which PE outperformed CPT meaningfully.

We defined response as a 10-point decrease on the CAPS-5, loss of diagnosis as response plus not meeting symptom criteria, and also having a severity score less than 25 on the CAPS-5. And then, remission as a CAPS less than 12, which is equivalent to the less than 20 we had established for the CAPS-4.

And what we found is that PE was more effective than CPT overall. 35 percent more likely -- greater likelihood of response in PE, 46 percent greater likelihood of loss of diagnosis, and 63 percent greater likelihood of remission. And what you can see on the right of this slide are simply the percentages of people who achieved each of these outcomes.

So, it looks really pretty good. Over 70 percent of people in PE and 60 percent of people

in CPT had a response. But then when you look at more substantial indicators of response, you can see that the majority of people are still not responding. So even in PE, which was the better treatment, only 40 percent lost their diagnosis, according to the symptom criteria that we established, and with [CPT], only 20 percent remitted. So, this is good, but it means there's room for improvement. And I'd like to now turn to talking about that question in more detail.

The upshot of where we are in PTSD treatment research is really a glass half full and a glass half empty. In terms of the empty, there's few effective medications for PTSD. In terms of the full, we have select trauma-focused psychotherapies that are effective, and they're more effective than medications. And most people respond, but the half full part is that many people have persistent symptoms.

You've probably seen articles like those depicted on this slide questioning the effectiveness and acceptability of these evidence-based psychotherapies for PTSD. For example, many with military-related PTSD do poorly in treatment with first-line

psychotherapies. That's not really true if you look at the evidence. And so, I encourage you to be thinking about the fact that the treatments that work work, but there's still room for improvement.

It's also important to look at what we see in PTSD in the context of treatment response in other mental disorders. I was part of a group led by Kim Kuypers in the Netherlands to recently publish a paper looking at the response to psychotherapy for PTSD and other mental disorders in a large international sample. And what you're seeing on the slide, it's busy, is the response rate in control and psychotherapy conditions, and those are then mapped out graphically in the middle of the slide.

And then, on the right-hand side, the relative risk of achieving response, which was defined as a 50 percent decrease in symptoms. This is very often used in depression research and other disorders. And, essentially, if you look at PTSD, which is the third from the bottom, you can see that the response of 38 percent is comparable to the response in many other disorders. Depression has the highest, which in

psychotherapy is a 42 percent response rate. And then, if you look at the relative risk on the right-hand side, you can also see that PTSD is comparable to the response that we see in depression, panic, phobia, et cetera. OCD has a larger responsiveness in these analyses, but that's really because the response to control is especially low in OCD. So, the takeaway here is that there's room for improvement in treatment outcome in all mental disorders. PTSD is not unique in this respect.

PTSD is also not unique in terms of the rate of dropout that we see. This slide depicts the results of a meta-analysis published now almost 10 years ago looking at dropout before treatment and during treatment in randomized trials. And in PTSD, 8 percent dropout before treatment, and then 27 percent dropped out during treatment. That doesn't look very good. But then if you look at depression, 22 percent before treatment and 36 percent during treatment. So, the takeaway from this slide and the prior slide, again, is that we have room to improve in enhancing the efficacy and the acceptability of treatment for mental health disorders.

So, where we need to go with this body of evidence is that we need in PTSD to identify more effective medications and to enhance the effectiveness of both medications and psychotherapy. There's a number of strategies that we can use to do this. One is matching or tailoring. Using, for example, biomarkers to predict whether a person might be more responsive to medication or psychotherapy or PE versus CPT. Personalized Advantage Index is simply a quantitative method of determining the advantage, how many points a person would additionally improve if they had their ideal treatment versus another treatment. People have also worked on flexibly tailoring protocols, both in terms of the amount of treatment, the number of sessions, as well as what's emphasized, depending upon the particulars of a given case but within the framework of that treatment.

Another strategy to enhance treatment outcome is changing the format. Intensive protocols have been growing lately. And what I mean by an intensive protocol is, rather than the standard weekly therapy that people have, doing it multiple times per week, even every day. So,

the shortest intensive protocols may be as short as a week. Usually they are two to three weeks. And what we see with these protocols so far is that you get much greater completion. So, in VA, a recent study found that over 80 percent of people completed a course of evidence-based therapy, and that's -- in clinical practice, that's usually less than 50 percent. But what we're not seeing yet is that there's clear signal that treatment outcome improves, but theoretically it should if people have a greater dose of treatment.

Another approach to enhancing treatment outcome is empowerment strategies, such as shared decision-making and measurement-based care. These have been shown for other mental disorders and other conditions in general to enhance treatment outcome. In PTSD, this evidence is still emerging, but generalizing, from the existing evidence, we can also get better outcomes by engaging in shared decision-making with patients and using measurement-based care to determine possible tweaks to a protocol, depending on how a person responds.

And then, lastly, there are psychotherapy

enhancers, such as MDMA, which I will talk about, cannabidiol, CBD, ketamine, TMS. All of these have been tested as ways to enhance PTSD treatment outcome and all appear to have promise.

So now I want to talk about psychedelic drugs. What I mean when I talk about psychedelics, first of all, classic psychedelics include a drug such as psilocybin and LSD, and these mainly interact with the 5-HT2A receptors, which are targets for the neurotransmitter serotonin. The effects of these drugs may bring on vivid visions or sensations, hallucinations, alter a person's sense of self, and promote feelings of insight or connection. Dissociative drugs include things such as ketamine and PCP, and these block the action of NMDA receptors, which are part of the brain's system for transporting glutamate. And while the dissociative drugs can alter perception, they're not like the classic psychedelics. Typically, they make people feel more disconnected from their body and their environment. And then, lastly, drugs such as MDMA, ibogaine, salvia work on a variety of brain functions to cause psychedelic or dissociative effects. Cannabis

can have psychedelic effects on some people, but it's not classified as a psychedelic.

The social and legal context in the U.S. for psychedelic drugs has been quite active over the past decade. But right now, cannabis and hallucinogenic drugs are classified as Schedule I by the U.S. Drug Enforcement Administration. That's the DEA. And it means they have no currently accepted medical use and a high potential for abuse. So, Schedule I drugs can be used in carefully regulated research and cannot be used clinically without a regulated exception. Schedule II drugs are those that have benefit, but also a high potential of abuse or dependence, such as oxycodone and fentanyl, Ritalin. And then Schedule III drugs have benefit and a low potential for abuse or dependence, such as ketamine. And I'm aware that there is increasing interest in the abuse potential of ketamine, but it is relatively lower, at least at the present time, than we see for the Schedule II drugs that I mentioned.

Now, also in the U.S., the Food and Drug Administration granted breakthrough therapy designations for MDMA for PTSD in 2017, and for

psilocybin in treatment-resistant depression in 2018, and then major depressive disorder in 2019. Pending a successful completion of clinical trials, then companies can request approval for a drug for a given disorder, which can then lead the DEA to reschedule the drug for clinical use. Many states -- that's the federal landscape -- but many states have passed legislation legalizing or decriminalizing cannabis or allowing it for selected medical use that is not evidence-based. In fact, PTSD is a common indication for medical marijuana. And I just want to make a note that DEA and DoD providers must follow federal guidelines and cannot prescribe marijuana, even in states where it's legal, at least at the present time.

Now, Colorado and Oregon have legalized, regulated use of psilocybin with guides. This is not the psychotherapy that is accompanying psilocybin in the trials that are ongoing. It is just a guide to promote safety during the psilocybin experience. Another thing that has happened in the U.S. is that Congress has shown sustained interest in promoting psychedelic research and treatment for veterans. And various

charities also exist to support veterans traveling outside of the U.S. to receive psychedelic therapy.

Now, in August 2024, the FDA denied an application from a company known as Lykos, formerly MAPS, for a PTSD indication, and it requested another Phase III trial. There were issues raised, including binding, safety, inclusion/exclusion criteria, the type of psychotherapy it was used with. And similar rulings in 2026 and beyond should be happening for psilocybin, to support applications for treatment-resistant depression, or depression. Usona is the company for major depression, and Compass is the company for treatment-resistant depression.

So, I'm going to focus now on MDMA, because it is the most well-studied of the psychedelics for treating PTSD. MDMA is a triple reuptake inhibitor that produces antianxiety and pro-social effects through the release of a variety of transmitters, such as serotonin, norepinephrine, and dopamine. It's not a classic psychedelic, and it's rather called an entactogen or an empathogen. It also increases the release

of oxytocin and prolactin, which are hormones associated with trust and bonding. And on top of all this, it also affects the hormones that influence the HPA axis and the stress response.

At the brain level, it decreases left amygdala activity. That's a brain region that's associated with fear and trauma. And I want to say that, from this slide forward, some of the content is coming from colleagues, Leslie Morland, Barbara Rothbaum, and Jessica Maples-Keller, and Jennifer Mitchell.

So, looking at the Lykos protocol for MDMA-assisted psychotherapy, the MDMA is taken during three eight-hour sessions, scheduled three to five weeks apart, using a two-person therapy team. The therapy includes 12 non-drug sessions of psychotherapy, 90 minutes each, and these are used for preparation and integration. And the idea is that MDMA is a catalyst to promote empathy, introspection, and emotional processing.

The therapeutic approach is grounded in the recognition that each person has intrinsic wisdom and ability to heal. So, although the process is trauma-informed, it's really participant-driven. Wherever the patient goes, the therapist

follows. The idea is that healing occurs over time, as the experiences of the trauma and the medication sessions are integrated with the help of trained therapists.

So, this slide is a graphic depiction of the MDMA protocol from Lykos: three preparatory sessions, an MDMA session, followed by three integration sessions, and then the cycle repeated two more times. So, each MDMA session is six to eight hours, usually eight, and psychotherapy is 90 for the 12 sessions, 90 minutes.

So, if you do the math and look at how many clinical hours are needed to treat a single patient with this protocol, it's 84 patient care hours. That's a lot of hours in many systems. In fact, doing a standard PE or CPT protocol, you could treat almost five PE patients or seven CPT patients. So, this is a protocol that can have very significant impact on resources within a system, and could actually affect access for other patients, given the amount of resources needed to treat a single patient.

Well, let me show you, the data looked promising. There were substantial effects in both of the two trials that Lykos submitted for

the FDA indication. This is the graph of the primary outcome, which is the CAPS-5 severity score. And you can see, there's actually meaningful improvement even in the placebo group, but much larger effects in the MDMA group. So, this looked very promising, and if you only looked at these data, you might have a hard time understanding why the application was denied.

But there were several factors, most notably functional unblinding. So, the studies were blinded, randomized, placebo-controlled trials with blinded assessors. Functional unblinding means that unblinding happened despite the design. And in Study 1, blinding was not formally assessed, but it was anecdotally reported that 84 percent of placebo and 96 percent of the MDMA groups correctly guessed their assignment. Blinding was formally assessed in the second study, which found 75 percent of placebo and 94 percent of MDMA groups correctly guessed their assignment.

So, the upshot of this is that blinding was not preserved in either trial, and that's a problem when you have such high expectancy about a treatment. It's a problem anyway, because you

don't have the protections of blinding, but for a treatment that is novel, where there's a lot of what's been called hype and hope in this -- in the case of psychedelics, it undermines the interpretation of the kind of positive effects you see here.

So that was one of the key concerns raised by the FDA about these Phase 3 trials. In addition, and I think compounding the unblinding, was high expectancy among participants, many of whom had prior MDMA use. There were also concerns about inadequate safety monitoring during and after the trials. And, in fact, the trials had very limited follow-up. 18 weeks from the initial prep session, which was usually not long after the last session. In contrast, most psychotherapy studies would follow people not only within a week or two after treatment, but also three months later and six months later.

And then, the FDA was concerned that the psychotherapy was not an evidence-based treatment. It's really a rather flexible protocol, and although there's a training manual and a training procedure, there have been concerns raised about the flexibility, or what is

perceived as the lack of structure in the protocol.

So, future research in this area needs to use active placebo, such as low-dose MDMA, stimulants, other drugs, excluding people with prior use, more complete safety monitoring, as well as long-term follow-up, and then pairing the MDMA with evidence-based therapy. One idea of pairing MDMA with therapies that exploit the mechanisms of each, such as fear processing in both MDMA and PE, for synergy.

And, in fact, Barbara Rothbaum and Jessica Maples-Keller evolved a protocol to do this. It's called the Emory MDMA-PE protocol. I'm using this right now in a study led by Leslie Morland at the San Diego VA as part of our Women's Health Sciences division in the National Center for PTSD, and this is a very different protocol than the Lykos protocol. It's much briefer. There's only one medication session, and during that medication session, there are two imaginal exposures, and then PE is delivered in a compressed schedule at Emory. It's daily treatment, and in an intensive outpatient format for two weeks.

In our trial, which is being conducted in a VA setting, outpatient, we are randomizing 10 veterans to standard or low-dose MDMA with outpatient PE delivered over a three-week period. But this is still a much shorter duration and many fewer hours of therapy than the standard protocol. So, if this is successful, this could present a more efficient alternative for MDMA-assisted psychotherapy. But right now, our primary goal is assessing feasibility and safety, given concerns about potential anxiogenic effects of low-dose MDMA. So far, and we're early into the trial, and we're blinded to patient condition, we believe we're successful in the patients that we've seen so far in demonstrating feasibility.

So, that's the landscape now on MDMA and what I think is a very promising direction, to not only address the FDA concerns, but also move the field forward.

So, where are we going in psychotherapy research for PTSD? Efforts are underway to enhance outcome by using a variety of strategies, combining treatments within and across modalities. Psychedelic-assisted psychotherapy

is one such very promising combination. In this work, there's an important need to study military populations, because there have been few participants in the current trials of MDMA who are veterans, and I think essentially none in any of the psilocybin work that's been going on for depression. And then none of the participants in these trials are active duty.

So, what we need to be doing, as we look at where we are and try to move the needle in this research with psychedelics, is use more rigorous placebo control, evidence-based psychotherapy, and enhanced safety monitoring, to determine whether MDMA-assisted psychotherapy or any other psychedelic psychotherapy combinations are more effective than what we currently offer our patients.

So that's all I have for today. Thank you very much for listening.

(Whereupon, the above-entitled matter went off the record.)

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AFTERNOON QUESTION AND ANSWER PERIOD
DR. PAWULUSKI, DR. SCHLEIDER, & DR. SCHNURR

CONCLUDING COMMENTS
+ + + + +

TUESDAY,
APRIL 22, 2025

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This transcript was produced from audio provided by Uniformed Services University of the Health Sciences.

DR. NAIFEH: Thank you very much, Dr. Schnurr, for helping us understand the state of PTSD treatment research, including the challenges of MDMA-assisted therapy and other psychedelic therapies.

Before we move on to our second Q&A panel, we'd like to take a moment to acknowledge our poster submissions. I hope everyone has had a chance to go check out the poster gallery on the Conference website. Thank you to all of those who submitted their research. The winner of this year's poster contest is Biggs and colleagues, "Speculating about PTSD symptom cluster circuits and sleep disturbance circuits: New questions." Honorable mention goes to Hanif and colleagues, "Slower heart rate during fear extinction in people with head injury is associated with worse future post-traumatic stress disorder," and also to Raboy and colleagues, "Augmented reality 3MDR therapy for the treatment of PTSD and comorbid moral injury: A case study abstract." Congratulations to all.

And now, for our second and final Q&A panel, we are joined by Dr. Jodi Pawluski, Dr. Jessica Schleider, and Dr. Paula Schnurr. Our moderator for this panel is Commander Eric Serpico. Dr. Serpico is a Commander in the U.S. Navy, a psychiatrist, and an Assistant Professor in the Department of Psychiatry at USU.

Commander Serpico, you may proceed with asking questions from attendees whenever ready.

COMMANDER SERPICO: Thank you so much. And we have so many great questions for our wonderful presenters that I'm just going to dive in so that we can maximize our time together.

So our first question we have is for Dr. Pawluski. Are there differences in brain changes in women with PTSD versus without PTSD with depression versus without depression?

DR. PAWLUSKI: Yeah. So these are great questions. And so, in terms of PTSD typically often in the perinatal world, we're talking about childbirth-related PTSD. And I know that there hasn't been any published research to date on this with regards to how it affects the brain

in a mother postpartum. Work is ongoing, so there's some great labs looking into this.

But there have been, to my knowledge, two papers that have looked at mothers who have had PTSD not related to childbirth and looking at functional changes in brain activity, and shown that there are some slight differences there. And these are small papers and we need some more replication. Unfortunately, this has been an area not really well-focused on when talking about the neuroscience of motherhood or parenthood in general and that connection with PTSD.

We see a lot more research done on depression, right? Postpartum depression, and actually not very much research done on anxiety. And I'm speaking about research in terms of looking at brain changes in parents in relation to struggling also with a mental illness. So, depression, we're seeing a lot of more research out, showing that, indeed, different brain areas function differently in a mother who has depression compared to an individual who has

depression at other times in life, or compared to a mother who doesn't have depression. For example, the amygdala's one -- recent research has shown that there's really this increase in function in the amygdala in a mother with depression when she's viewing a picture of a child, for example, whereas a woman who has depression but who's not a mother doesn't have that same increase in the amygdala when she's viewing a picture of a child.

So what it -- for me, what's really important to take away when we're talking about mental illness in the perinatal period or in mothers in particular, is that often we have similar brain -- it seems I'm going to say, we need more research, but what we're starting to see is there's similar brain areas involved that you would see involved in other times in life. But the way they're functioning can be different and how they're getting cued, like what's triggering their functionality, is a bit different. Because, of course, your brain at this time is, kind of, geared towards parenthood

and you do have a child, which is quite different than struggling with the mental illness at other times. So we need much more research in these areas for sure, to really figure out what's going on and how to better prevent, I think, the impact of these mental illnesses on parents and individuals in general.

COMMANDER SERPICO: Thank you so much. Our next question is for Dr. Schleider. Have there been any clinical comparisons made between telehealth versions of an SSI versus in-person SSI programs?

DR. SCHLEIDER: Yes. Great question. And hello, nice to see everyone's Zoom screens. So direct comparisons -- my preface for this question is direct comparisons tend not to be what I focus on, primarily because digital interventions and in-person interventions are really reaching very different audiences much of the time, in particular digital self-guided single session interventions. Those are primarily reaching folks who don't get their foot in the door in any mental healthcare system

or any system of care. Whereas anything delivered by a provider is more likely to be delivered to somebody who has already interfaced with some kind of system of care and has that foot in the door.

So I don't typically encourage direct comparisons, because the catchment areas or the samples that they're likely to reach are quite different in terms of treatment seeking, motivation for change, and things like this. However, with our single session consultation, which is our provider-delivered single session intervention, it's modeled after solution-focused brief therapy; we have conducted RC clinical trials, both of delivering that intervention over telehealth and in person face-to-face.

Although those weren't two arms of the same trial, we can benchmark the effects against one another across the trials, because the outcome of batteries were identical. And we do not find any differences in that intervention, the single session consultation, delivered via telehealth

or in person. What we do find is that rates of uptake of the SSC are much higher closer to 75 percent than 50 percent when they're offered to folks on waiting lists via telehealth versus having folks come in. So the outcomes are not different, but the access is. Hopefully that addresses the question you were asking.

COMMANDER SERPICO: Thank you so much. Our next question goes to Dr. Schnurr. What is your read on the growing evidence against any long-term pharmacological interventions across health and mental health due to irreversible organ damage that is caused by such exposure to medications. How will this impact your past, current, and forthcoming initiatives' R&D.

DR. SCHNURR: So I am -- my focus primarily is on psychotherapy and I am not an expert on the topic of this question, but I do follow the conversation. And it's my sense that there's some significant debate about the long-term impact on organ systems and the like. I myself study psychotherapy, because in the case of PTSD, as I've tried to argue, I think it's a

more effective treatment and it's also more durable because it's intended to be curative.

And so, the way I think about the medications we currently have for PTSD, is they address the symptoms and they bring the symptoms down, but they don't cure the inherent problem. Now, I'm not saying, like, PTSD is an infection and we need an antibiotic to cure it. But the kind of model that we have in psychotherapy for PTSD is we have at least theoretical frameworks and we have some science behind the thinking of why a given treatment works, what the mechanism is, and how that addresses what is causing and maintaining the PTSD.

So to -- and I realize I'm not answering your question because, as I said, I'm not the expert in this area, but why I think psychotherapy is such a promising strategy and why I think we need to improve it for whatever we're treating is because the psychotherapies right now aren't curative for these disorders, and seeing the great need that we have not only in PTSD and not only in VA, but in all disorders

at a global level, I'm putting my money right now on psychotherapy, where I'm encouraging all the people who know how to develop drugs and test drugs to do that, because there's room, in my view, for both of those.

COMMANDER SERPICO: Thank you so much. And just by gracing us with an answer, you are answering our questions. So thank you. This next question is actually very fun, because it's for all speakers. So we can go in order as we just did. But what would you say as we, as global health and mental health professionals, organizations can do to ensure that there are drastic decreases within health and mental health service, in accessibility, exclusionary practices, and/or therapeutic and/or medication inequity accordingly?

DR. PAWLUSKI: Did you want me to go first?

COMMANDER SERPICO: I was going to say Doctor --

DR. PAWLUSKI: Everyone else gets more time to think about this one?

COMMANDER SERPICO: Is that okay? Yeah.

DR. PAWLUSKI: I mean, jump in if someone has a more immediate answer. This is a huge, huge, huge question. And it also, for me, I think it depends on where you're located, right? Different countries have different access to care, for example. I'm thinking mental health itself has a lot of stigma, mental illness, right? So I think we do need to change that. For me, when I talk about and I think about mothers and parents in particular, but mothers specifically, those who identify as mothers, there needs to be a cultural shift as to what that role is and what it means. And because, often, what we're seeing is just the pressure of trying to be the perfect mother, trying to fulfill all the roles, the literal cognitive, emotional labor, and physical labor that goes into expectations of mothers and the role of a mother. It is just overwhelming. And I think, in this regard, there needs to be some sort of shift.

I think that would be somewhere where I'd love to see a lot of change is realizing that

parenting is meant to be done by many people. That a mother, although incredibly valuable, is not essential. It's not just her that's shaping her child's development. And so I think that that narrative needs to shift in general.

But, of course, we need access to care. We need affordable care. We need care that works. We need, you know, to be asked about how we're doing more regularly. We need to not assume that mothers are happy in this context. You can't tell. Moms who are super depressed will have a smile on their face. So you know, we need better ways of assessing, but also better ways of preventing, not just with maternal mental illness. But I think, in general, but motherhood is a special -- for me, it has its own challenges that need to be addressed on a broader social and cultural level.

COMMANDER SERPICO: Thank you, Dr. Pawluski. Dr. Schleider, did you have a response to this question?

DR. SCHLEIDER: I'll try to keep it brief. I have many thoughts. So we're starting from a

place of, you know, our current healthcare system was never built for access. That was never the optimization point. It's grandfathered in from a really long history of incarceration-focused intervention, as in asylums and out-of-sight out-of-mind, sort of locking folks with mental illness away from the rest of society.

There started to be a reintegration of folks in the 60s with differences in sort of more psychotherapy-focused approaches to mental health treatment, but even then the resources were not scaled up appropriately to match the shift in the model of care delivery and never really have been sufficient. And so what we're stuck with is a system that was never built for scale, never built with population mental health in mind, and kind of has exclusionary practices built into the very framework of what is available and how.

So we're not starting from a great point through the lens of accessibility. So, what I do think really needs to happen and your

questions included: What should we do? There are many "we's," many different intersecting groups of "we's" that I could talk about with respect to this question, but I'll talk about what researchers and clinical psychology leaders and psychiatry leaders might be able to do to make a dent in this.

One, think more broadly about what care can be. Where it can live, who can provide it, how it can be delivered. And where people are looking for actual health [care] often isn't in brick and mortar clinics. It's online, or their peer networks. So, thinking more creatively about how can the practices that we're expert in, and the knowledge that we have as a field, be democratized and scaled out in more creative ways and shapes and sizes. That I think will inherently increase access to at least a minimum, a minimally helpful dose of some kind of evidence-based support.

Beyond that, I mean, the solutions are going to be multilevel and structural. Of course, there needs to be more funding for more

professional clinicians, and easier access to care when folks first reach out for it. But those solutions are going to require really long timeframes and shifts in the legal and policy landscape of the country, and of other countries. So thinking about what can we do in the interim for the people who are suffering now, and how can we expand our concepts of where and how treatment and support can be delivered, is probably the most critical thing that we're going to need to do.

And in engaging with that work, one necessary facet of it is going to be interfacing with folks who have access to large swaths of the population from other sectors outside of healthcare. So thinking, you know, the technology sector. They have huge reach to large portions of the population. How can we as psychologists, and psychiatrists, and leaders in this space partner with them to get proactive evidence-based messaging out that can be helpful in increasing support, access, or just awareness that support is out there. So yeah, I would say

thinking creatively about how to help people outside of our own training sometimes, and cross-sector partnership, and embracing what we can all do jointly and collaboratively to change the landscape.

COMMANDER SERPICO: Thank you, Dr. Schleider. And Dr. Schnurr?

DR. SCHNURR: Sure. Thank you. And Dr. Pawluski, I do feel for you, because as you were talking, and then Dr. Schleider was talking, I was making myself some notes. And I think, Dr. Schleider, you were mentioning technology just as my phone rang, and so, yeah, phones are part of the solution, but there's more than that.

I think that this is a fabulous question. It's actually a great focus for a conference, to really think from different perspectives, because it has to be a multidisciplinary, multimodal approach. What we're talking about is healthcare, and we don't even have good access to healthcare globally, or even nationally. So some of it has to be that it's not on us in mental health alone to address this

problem.

I think, Dr. Schleider, you were mentioning what I think about as points of access, and who the providers are. We need to think much more about non-traditional providers. And especially when we're outside of first-world countries, where there might be a few psychiatrists in the whole country, and even nurses are scarce. And so thinking about chaplains, teachers, people who can deliver interventions that are tailored to their scope of practice and the setting is important.

I mentioned technology, and I think that it is a wonderful solution. Certainly our National Center for PTSD has been very involved in technological treatment strategies for PTSD, but sometimes the solutions are very simple. I remember hearing a talk about issues on this in India, and they were talking about telehealth. And essentially, the approach to telehealth that they were presenting is putting a nurse on a scooter, and having the nurse drive village to village. Now, that's not our definition of

telehealth, but it is a way to deliver intervention.

And lastly, I want to say that I think often I and we as a field go to simplifying interventions that we might study in our RCTs when we think about scale and going especially to low resource, low literacy environments. And it turns out that you can actually bring Cognitive Behavioral Therapy for PTSD into those kind of environments if they're culturally adapted. There's a fabulous study that was led by Judy Bass at Hopkins, where they did Cognitive Processing Therapy in the Democratic Republic of Congo, randomizing villages to receive CPT or more usual care support for domestic violence for women in those villages that had experienced domestic violence.

And the interventionists, I think, on average had about an 11th grade education, and the majority of the patients were not literate. And so they had to retool -- because if you've done Cognitive Processing Therapy, you have worksheets, no less. So they had to come up

with strategies that would enable people who couldn't write to use alternative means to work out the cognitions. And some of it, I think, involved dance, storytelling, things of that sort that fit with the culture, but also fit with the actual abilities of the participants. Now, this is hard work. There's only a few studies out there right now like this, but I think they show us what's possible.

And if you had asked me before this study was done, could you do it? I would've said, probably not. And now I would say, why not?

Because it's been shown that there's a whole different way of thinking about translating what works here in the U.S. or in first-world countries around the globe.

COMMANDER SERPICO: Thank you so much, Dr. Schnurr.

Our next question will go for Dr. Pawluski. Do you know if these pregnancy- and postpartum-associated brain alterations follow a different pattern in people with postpartum psychosis?

DR. PAWLUSKI: Yeah. This is another great

question. There's a really great team of Paola -- Dr. Paola Dazzan in London, who does a lot of this research on postpartum psychosis, which is really, really challenging research to do when you're looking at the neurobiology. And their research in terms of the patterns across pregnancy and postpartum, they haven't shown any pregnancy changes that would be related to the postpartum in terms of brain imaging. Their research has been specific to the postpartum period, and it's the only research I know of that's done neuroscience research on postpartum psychosis.

But what they are seeing is definitely there's those overlapping -- as I mentioned with the first question, there's similar brain areas that are involved in psychosis at other times in life, are involved in psychosis in the postpartum period. But what's interesting about their research, again, there seem to be some differences in terms of how those brain areas are responding to different cues in the postpartum period as compared to other times in

life.

So, we don't have a way -- I would love to have a way to, let's say, predict. You know, these are the brain changes that are happening in pregnancy, and that will really increase your risk in postpartum psychosis. We're not quite there yet. There's been a little bit of research looking at pregnancy brain changes and how they might relate to how you feel about your child, or how you interact with your child in the postpartum period. But we're not quite there yet, research-wise, to really use it as a way to predict postpartum psychosis in particular.

But, of course, we do know other ways and risk factors that are important to be aware of, that are important in potentially preventing postpartum psychosis. And one of the biggest ones is when the sleep shifts in the postpartum period. When she's not sleeping. That's a huge one. And we know sleep is really important for our mental health at any time in life. So yeah, we still have much work to do, but this is

definitely a disorder that does need immediate attention and a medical intervention quite rapidly. And in many cases, people end up being healthy in the end after treatment, right? So I think that's very promising. But it needs to be investigated further. Definitely.

COMMANDER SERPICO: Thank you so much. For Dr. Schleider. Given the history of CISD, I'm curious if you have any thoughts about current trends in hospital settings, such as Code Lavender and Stress First Aid, for staff involved in traumatic events in medical units?

DR. SCHLEIDER: Yeah. Absolutely. And I'm glad this question came up. And I absolutely think that when thinking through what is the best way to respond to traumatic stress and in settings where that's part of the job or continuously happening, the history of CISD should be taken into account more than it is in informing best practices.

And so, there is quite an array of techniques that stemmed from the (inaudible) intervention literature that could be leveraged

for this purpose, to divert attention away from forced re-traumatization or forced recounting of everything terrible that just was experienced, and towards identifying resources to cope in more generalized ways with stress and how to foster a sense of being able to seek help when that help -- when an individual is ready to seek that help.

And there are a variety of evidence-based protocols out there that have been shown to reduce general distress in the moment, and increase receptivity to seeking more care. We've actually, through a HRSA grant, been able to deliver single-session consultations to frontline healthcare providers during the COVID-19 pandemic and during lockdown, and found that they were highly acceptable and effective among frontline healthcare workers who were dealing with rapidly changing and incredibly stressful hospital-based contexts every day.

So, I think there are practices that could be leveraged that have already been evaluated in other contexts that could be used to inform how

to mitigate unintended consequences as much as possible. I just wish there was more crosstalk between folks who study traumatic stress and PTSD-based prevention and response, and other psychotherapy researchers who don't necessarily focus on that, but who might have knowledge of techniques or supports that are highly scalable and could be integrated into those kinds of settings. And I'm happy to talk to anyone who's interested in going in that direction. I have a whole bunch of ideas from our lab's work and other teams work that might be helpful.

COMMANDER SERPICO: Thank you. For Dr. Schnurr. Can you elaborate on using acupuncture, non-invasive brain stimulation for PTSD or other mental health disorders?

DR. SCHNURR: So, the use of acupuncture, we looked at very carefully when we did the VA/DoD Guideline in 2023, and there's promising evidence there, but it did not appear conclusive at the time. There's since been a study, a large, well-done study suggesting benefit. And I would anticipate that that study will

certainly lead to further conversation and possible consideration for some kind of recommendation going forward.

I think the new American Psychological Association PTSD Guideline, I don't believe they looked at practice -- complementary and integrated practices, like acupuncture. So I don't know that that will show up anytime soon, but I think that there is some promise. Non-invasive brain stimulation involves a variety of techniques, and probably the best evidence we have is for TMS. When we looked at it for the Guideline, the data are inconsistent; they appear somewhat favorable, but part of the issue that my colleagues who do this work have helped me understand is that there's so many parameters that you can be considering, right or left, and what frequency. And then there's a lot of now new research, trying to make more efficient protocols, because TMS is a rather a lengthy protocol.

And so, I think there's active work underway. VA has a large study focused on

depression, but with a substantial number of people with PTSD that should help us in going forward. And in terms of going back to the idea of practices that are considered complementary and integrative, even if we don't have the evidence, they may be very helpful, in my view, for promoting wellness and enhancing recovery.

And we often use the term recovery when applied to people with serious mental illness, but I think we need to [missing word] our minds about this, and really think about recovery as a goal for everyone. And living a recovery life, becoming well, isn't just about decreasing your symptoms, it's really returning to life, and feeling engaged, and feeling healthy. And so, many, many practices that are not in a Guideline may still be useful when a person is being treated with -- well, hopefully with a Guideline-recommended treatment. But when a person is being treated with a standard therapy, there is a role for these other interventions to really get the person fully recovered.

COMMANDER SERPICO: Thank you so much. Our

next question is for Dr. Pawluski. You mentioned multiple macroscopic changes in a mother's brain. What microscopic changes are the causes of these macroscopic changes? Fluid volume shifts, increased number of cells, decreased number of cells, gain/loss of intracellular space, et cetera?

DR. PAWLUSKI: This is a great question. I mean, I typically work in animal models, so this is what we do, is we're looking at receptor distribution, various aspects of neuroendocrinology, neurotransmitter changes. And there's a whole book summarizing this research to date, so it's a huge field. But what we're seeing, in fact, is there are a lot of different changes.

And for me, I work more often looking at neuroplasticity at a cellular level, so looking at neurogenesis, and we recently did a review where we were looking at, what do we know about these cell changes across pregnancy, from animal models to what we see in humans? So, in humans, as I talked about, there's these structural

changes that seem to be this kind of decrease or this fine-tuning of the brain. And what's interesting, and I mentioned this briefly in my talk, is that I also showed when looking at neurogenesis in the hippocampus, there's a decrease in neurogenesis as well. There's a decrease in microglia. We've seen this in animal models across pregnancy in the postpartum period.

So there seems to be this shift. I mean, I talk about it as fine-tuning. Essentially, the brain becoming a bit more efficient. That's on a cellular level but, of course, there's other things driving this, right? So we see changes in neurotransmitter communication, neuroendocrine function. I mean, there's so much going on. There's not just one thing that's changing. It's the whole system is being modified and geared to care for the child. So it's really multi-level changes that we still are discovering. And when it comes to the human brain, of course, we don't have the techniques to delve into it, but because of the

similarities in systems and brain areas, we are getting a picture.

But it is quite complex, and we're often just studying one area. Some of us just study -- I love glucocorticoids, for example. But they don't work alone, and they interact with many different systems, and they just don't work in one brain area. So, it is really is a complex system. That's why I think the parental brain is quite so fascinating, is because it is so complex and there's so many changes happening.

But, in terms of these structural changes, I like to think of it -- there seems to be this fine-tuning, essentially. And I think that that's very exciting to see, especially during adulthood. And we have more questions than answers, perhaps, but I think it really is fascinating to see these changes and uncover more about what's going on.

So I don't know if I answered the question, but I'm happy if there's a more specific question or to refer to other literature to cover this in more detail.

COMMANDER SERPICO: You did. Thank you so much.

DR. PAWLUSKI: Thank you.

COMMANDER SERPICO: For Dr. Schleider, you talked about safety planning and crisis intervention. Can you comment on any other interventions focused on suicidal ideation and important focus in the Department of Defense?

DR. SCHLEIDER: Absolutely. So, the safety planning single-session intervention that we've put together is probably the most directly targeted to suicidal ideation in particular. However, we've also tested a couple of other interventions in randomized controlled trials that have shown promise. One of them is actually a crisis resource uptake intervention. And what this is, is we actually partnered with our nonprofit partner, Koko, to develop a one-minute single session intervention to offer structured support to increase the likelihood that somebody will be motivated and able to reach out for immediate crisis support or help when needs are detected.

We tested this in the context of deployment via social media platforms, monitoring what people were typing into search bars. So, if they type something into a search bar that indicated they were having suicidal ideation, they would receive this sort of one-minute direct message-based intervention that would increase their odds of reaching out for help.

And what we found was that with this one-minute intervention, versus just offering crisis hotlines and text lines, the rate of uptake of crisis services boosted from 38 percent to 78 percent within ten minutes. So we were really excited to see that we're not just able to target suicidal ideation directly in certain safety planning interventions, but we're also able to move the needle a bit on willingness to seek out support when those kinds of thoughts and difficulties arise.

We also have tested, in a randomized controlled trial, an intervention for non-suicidal self-injury, which is a separate issue, but often related and often co-occurring with

suicidal ideation in general. And that intervention basically teaches the concept that one can separate out their urges from their actions and helps people make an action plan for doing just that when thoughts of self-harm arise. And we found that does significantly reduce intentions to self-harm and increase capability of coping with self-harm-related thoughts.

So, there are several promising directions in this space, but a lot more needs to be done, especially targeting suicidal ideation in particular, which is often not the target of suicide-focused interventions. It's often reducing suicides, the behaviors. But the ideation can be a really important earlier target as well. So, I think there's a lot of room for growth in this space, but we have some promising need.

COMMANDER SERPICO: Thank you. Dr. Schnurr, do you worry about symptoms persisting due to veteran concerns for the status of their benefits?

DR. SCHNURR: This is not the best question to ask someone when there's only a few minutes left in a meeting, because there's a lot to say.

COMMANDER SERPICO: Yes.

DR. SCHNURR: But, yes, because I hear about it. Anyone who works with veterans has talked about cases where people have actually explicitly expressed concerns about how they might be reporting symptom improvement with a concern about how it would affect a disability pension. In the clinical trials that we do, where people are assured the research data are confidential and they are not released to a clinical record, we really don't see this as creating a kind of bias in which people aren't reporting their improvement.

The data from our electronic medical record suggests some evidence that people who are receiving disability compensation may appear less likely to respond to treatment. It's hard to interpret that, because disability compensation is supposed to compensate people based on the seriousness of their illness and

its impact on their functioning.

So, when we look within the medical record data, we actually may be seeing just a reflection of the fact that people have a pension, rather than people intentionally are not reporting. I think that it's still an open question and it's something that I think is important, especially -- I'm not a clinician, but the clinicians who I know and who I learn from suggest the importance of trying to communicate the value to patients of reporting as fully as they possibly can so that the provider knows how the patient's doing and can appropriately tailor the treatment, adding more treatment, adding different treatments, and so on.

COMMANDER SERPICO: Thank you so much.

DR. NAIFEH: Dr. Serpico, I wish we had time for all the other questions that are in the list. It's been great hearing from our speakers, but I know some of them may have to run. We are grateful to Dr. Pawluski and Dr. Schleider and Dr. Schnurr for being here to

share your expertise. Also, thank you to Commander Serpico. We only have a few minutes left, but I know that some of our speakers may need to go, so please feel free to do so. Before turning it back over to Dr. Ursano, I will ask Dr. Rachel Shor to provide some guidance about receiving continuing education credits. Dr. Shor?

DR. SHOR: Absolutely. So thank you again to all of our esteemed speakers for these really wonderful presentations and also to everybody who was able to attend the conference. My name is Rachel Shor. I'm a research psychologist at the Center for the Study of Traumatic Stress and the Continuing Education lead for the Brain, Behavior, & Mind Conference.

Continuing education is available for this event for physicians, psychologists, and social workers through the American Psychiatric Association. And so for those who are interested in Continuing Education credits, I'll ask that you please complete the evaluation and credit claim form that I'm going to be emailing

at the completion of this conference. And this form is going to include a link that includes an invitation code to access the evaluation for this particular event and that will allow you to claim Continuing Education credits within 90 days of today's event. And all of that information is going to be included in the email that I'm going to send out. But if you do have any questions regarding completing this form or accessing the form, please feel free to contact me through our event website by going to the "Contact Us" page and choosing Continuing Education as a topic, and I will be happy to help assist in any way that I can. Thank you so much.

DR. NAIFEH: Thanks, Dr. Shor. Now, I will turn it back over to Dr. Ursano for some final comments. Dr. Ursano?

DR. URSANO: Thank you. Thank you, Jamie. What do you say when you've had such a wonderful experience? After a great meal, what do you say? You say, wow, that was wonderful. I enjoyed it. I enjoyed the people that I was

with, I enjoyed sharing the time with them, and they certainly felt stimulated and interesting that is -- in the discussions.

You know, we really did travel the world, figuratively and literally. I know, last year, I think we had 50 different countries sign up, and I'm sure it's at least that number this year and probably close to several thousand who registered. And we traveled it in a way that allows us to share a perspective, which is understanding that human behavior is complex. It takes a lot of work, but it also can be exciting. And it certainly has great benefits, truly from cell to community, from bench to bedside -- look forward to sharing it with you again next year. Back to you, Jamie.

DR. NAIFEH: Thank you, Dr. Ursano. Before we end, I would like to once again thank all of our outstanding speakers. I'd also like to thank the Center for the Study of Traumatic Stress and our other sponsors, the members of the conference planning committee, and our colleagues at the Center for Deployment

Psychology. And especially to all of you who attended today. We hope you'll join us again in the future for other Brain, Behavior, & Mind events, including our 2025 Fall Lecture. Please watch for those announcements, take care, and we'll see you next time. Bye.