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2 CENTER FOR THE STUDY OF TRAUMATIC STRESS  
3 DEPARTMENT OF PSYCHIATRY  
4 UNIFORMED SERVICES UNIVERSITY OF  
5 THE HEALTH SCIENCES

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7 BRAIN, BEHAVIOR, & MIND  
8 2025 SPRING CONFERENCE

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10 TUESDAY, APRIL 22, 2025

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22 provided by Uniformed Services University of the  
Health Sciences.

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

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2           **DR. NAIFEH:** Good morning, good afternoon,  
3 or good evening, depending on where you are.  
4 Welcome to the Brain, Behavior, & Mind 2025  
5 Spring Conference, sponsored by the Center for  
6 the Study of Traumatic Stress of the Uniformed  
7 Services University, in collaboration with the  
8 USU Department of Psychiatry, the Neuroscience  
9 program, Center for Deployment Psychology,  
10 Department of Family Medicine, and the USU Brain  
11 and Behavior Hub.

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

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

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

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

1 Conference website.

2 Please use the Q&A function at the bottom of  
3 the Zoom window to submit questions to our  
4 speakers at any point prior to or during their  
5 Question-and-Answer panel. You can submit those  
6 at any time as long as the panel has not ended.

7 When submitting questions, please note if your  
8 question is for a specific speaker or for all of  
9 the speakers in the panel.

10 Continuing Education credits are available  
11 for physicians, psychologists, and social  
12 workers for this event. We'll provide more  
13 information on that throughout the day,  
14 including posting information and links in the  
15 chat.

16 Lastly, a disclaimer: All statements,  
17 opinions, and assertions expressed during the  
18 Brain, Behavior, & Mind 2025 Spring Conference  
19 are those of the speakers and attendees and do  
20 not reflect the official policy or position of  
21 the Uniformed Services University of the Health  
22 Sciences or the Department of Defense.

With that said, we would like to start by

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

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

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

3 In short, this Conference exemplifies the  
4 vital connection between cutting-edge research  
5 and real world clinical impact, which is of  
6 paramount importance to both the Department of  
7 Defense and our broader healthcare communities  
8 at large. We have an exceptionally robust  
9 agenda for you today, featuring a wide range of  
10 timely and important topics. Over the course of  
11 the day, we'll hear about advances in precision  
12 psychiatry, exploring new prospects for  
13 advancing risk and resilience in mental health.

14 We'll delve into the brain and body connection  
15 in stress and depression, shedding light on how  
16 physiologic circuits influence psychological  
17 well-being. Later, we'll examine the  
18 neuroscience of parenting and perinatal mental  
19 health, a crucial area for understanding family  
20 wellness and early life development. Our  
21 program also includes innovative approaches to  
22 care, such as single-session interventions, that  
can bridge gaps in mental health treatment, and

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

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

13  
14 Our distinguished presenters include: Dr.  
15 Jordan Smoller of Harvard Medical School, a  
16 leader in psychiatric genetics and precision  
17 medicine; Dr. Scott Russo of Mount Sinai, known  
18 for his groundbreaking work on the neurobiology  
19 of stress and depression; Dr. Jodi Pawluski,  
20 from the University of Rennes in France, an  
21 expert on maternal mental health and the  
22 developing brain; Dr. Jessica Schleider of  
Northwestern University, a pioneer in brief,

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

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

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

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

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

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

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

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

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

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

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

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

1 a very stimulating and productive day ahead, and  
2 look forward to the discussions and discoveries  
3 that will emerge from our time together.

4 Welcome, and enjoy the Conference. Thank you.

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

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

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

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

1 2004, really, the child at that time of Luke  
2 Johnson, who was a basic science researcher  
3 working in Amygdala, now in Australia, and  
4 perhaps signed in today.

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

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

1 It is in those three realms that we struggle to  
2 learn and that we operate in order to help our  
3 patients and the world and, in particular, our  
4 soldiers, sailors, airmen, and marines. Through  
5 research, which, always remember, is basically  
6 observation, different tools of observation  
7 based on the area of research, but observation.

8 Through observation, we learn from our  
9 patients, from our friends, and from those that  
10 teach us from the bench as well as from the  
11 community.

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

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

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

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

13           That is our focus here in the Conference,  
14 and I look forward to our speakers leading us  
15 forward. There is a neurobiologic example of  
16 that, called the kindling model. Again, as a  
17 euphemism helpful to remember; if you, in fact,  
18 place an electrical probe on the cortex, you'll  
19 get a seizure on the brain. If you do that  
20 multiple times, you'll continue to get seizures.

21           After some point in time, it becomes  
22 autonomous. You no longer need to, in fact,  
place the probe. Many of our disorders, and

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

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

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

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

1 resilience.

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

15 We will now begin Dr. Smoller's  
16 presentation, which is titled, "Precision  
17 Psychiatry: Prospects for Addressing Risk and  
18 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

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2  
3 DR. SMOLLER: Well, thank you so much. It's  
4 really great to be part of this event. And I'm  
5 going to talk a little bit about precision  
6 psychiatry and what it may offer us in terms of  
7 addressing risk, resilience, and a number of  
8 unmet needs in the area of mental health. And  
9 I'll just start out with my disclosures, just so  
10 that you can take note of that.

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

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

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

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

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

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

19 So, let's talk first about this issue of  
20 clarifying the really diagnostic structure of  
21 mental illness. And this is something that I  
22 think we face clinically every day, right? One  
23 of the areas that we've seen tremendous growth in  
24 is the genetic research on psychiatric disorders.

25 And what you're looking at here is a graph that

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

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

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

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

11 So, looking at what we might think of as  
12 pervasive developmental disorders, like autism,  
13 as one group, mood disorders, anxiety disorders.

14 And what you see along the bottom is the  
15 timeline of DSM. And as this goes forward, you  
16 see conditions that are dropping out, some of  
17 them are coming in, and a reorganization of the  
18 diagnostic categories. When we get to DSM-5,  
19 something happens that rarely happens. And that  
20 is, instead of just splitting, we see lumping  
21 there in terms of autism spectrum disorder, but a  
22 continued sort of reshuffling of these other  
23 conditions. And, in fact, some now moving out  
24 from the anxiety disorder category into their own  
25 category, and certainly relevant here, trauma and

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1 stress-related disorders.

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

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

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1 your – you know, your eyes over to MDD, those are  
2 very strongly genetically correlated.

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

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

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

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

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

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

18 Let's move on to another topic for precision  
19 psychiatry: Risk stratification. We're not that  
20 good at knowing who is at risk for various  
21 conditions ahead of time, and that makes it  
22 difficult often to target preventive strategies.

23 One of the tools we have here is this burgeoning  
24 area of machine learning and artificial  
25 intelligence, coupled with the big data that are

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

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

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

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

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

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1 cases and controls for bipolar disorder.

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

18 And what you're looking at here is, this is  
19 a study of maybe nearly 200 people. Our first  
20 algorithm, which was based on natural language  
21 processing, plus the structured notes had a  
22 positive predictive value of 86 percent, meaning  
23 86 percent of the time when the algorithm  
24 diagnosed bipolar disorder, a blinded clinician  
25 doing the, you know, multi-hour SCID interview

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

7 We also — because we could then collect  
8 genomic data on using this algorithm — we  
9 compared the genetic components of our EHR  
10 cohort, which ultimately had about 3,300 cases,  
11 about 4,000 controls, to traditionally diagnosed  
12 large-scale genomic studies of bipolar disorder.

13 Bottom line was, they were very highly  
14 genetically correlated with the standard  
15 traditionally diagnosed cases. And so that  
16 really gave us some confidence that these kinds  
17 of data are very scalable and also can be very  
18 accurate.

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

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

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

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

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

25 So, these are some examples, but I want to

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1 actually focus on one other example where we've  
2 taken this even further, and that is in  
3 addressing the problem of suicide which, as I  
4 mentioned, is the second leading cause of death  
5 among young people, and the rates have been  
6 pretty steadily increasing over the last two  
7 decades. Now the use of electronic health  
8 records and health settings, we think, is a real  
9 opportunity, largely because most people who  
10 attempt or die by suicide are seen by a  
11 healthcare provider in the preceding month, even.

12 However, a minority of people who die by suicide  
13 disclose their suicidality to healthcare  
14 professionals. They're often not even seen by  
15 healthcare professionals, if they come to the ED.

16 They often don't have a documented psychiatric  
17 disorder and, you know, systematic reviews have  
18 shown that the clinical risk factors that we use  
19 are often not very predictive.

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

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1 validated risk prediction algorithms for suicide  
2 attempts or death. And the AUC, which actually  
3 got cut off here, was about 0.77. It detected 45  
4 percent of all suicide attempts or deaths, with  
5 90 percent specificity on average, about two to  
6 three years in advance.

7 So, encouraged by that, on the right, we  
8 said, could we see this kind of performance in  
9 other health systems? And we collaborated with  
10 our colleagues at five other healthcare systems.

11 Now, 3.7 million patients did the same thing  
12 and, effectively, their performance was the same.

13 We also conducted, on the bottom there, a  
14 detailed economic analysis asking the question,  
15 how accurate would risk prediction models like  
16 this have to be for them to be cost-effective to  
17 actually use? And the answer was that our  
18 algorithms - and now others that have been  
19 developed - do exceed those thresholds. They  
20 would be cost-effective if paired with evidence-  
21 based interventions or preventive strategies in  
22 actual clinical care.

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

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

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

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1 at the point of care to provide clinicians with  
2 this kind of risk-stratified information, to help  
3 them develop a safety plan and to help them  
4 consider what the options would be for this  
5 particular patient at a given risk level, always  
6 with the clinician's ultimate judgment and  
7 decision making as the, you know, the final  
8 arbiter there. But we are now in the process —  
9 we've just launched a large-scale, randomized  
10 trial of patients in the emergency department —  
11 4,000 — half of them being randomized so that  
12 their clinicians would receive this kind of risk  
13 information in the EHR, half without, and we're  
14 going to see, in this kind of setting, does this  
15 actually make a difference in terms of suicide  
16 attempts over the next one to six months?

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

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

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

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

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

11 First of all, overall hospitalization  
12 reduced suicide attempt risk in about 28 percent  
13 of patients, but it actually increased risk in  
14 about 24 percent. So, a model was trained to  
15 predict the conditional average treatment effect.

16 What that means is, if based on the data  
17 available, this person was expected to benefit  
18 from hospitalization, as we had just showed, you  
19 would hospitalize them. If they were expected to  
20 actually have an increased risk of suicide  
21 attempt with hospitalization, you would avoid it.

22 Otherwise, defer to clinician judgment. And  
23 simply applying that rule would have prevented 16  
24 percent of suicide attempts and about 13 percent  
25 of hospitalizations. So, this is really an area

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

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

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

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

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

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

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

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

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

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

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

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

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

5 And so that's really, I think, encouraging  
6 evidence, which we've extended elsewhere as well.

7 This was an even larger study, looking at 105  
8 potential modifiable factors – lifestyle and  
9 behavioral factors – that might be associated  
10 with reduced risk of depression. This, again, in  
11 the UK Biobank. What we saw, you're looking here  
12 at a graph where on the Y axis, you have this:  
13 the  $-\log_{10}(p)$ . So that's just a measure of how  
14 statistically significant the results are.  
15 Everything above the dashed lines in this graph  
16 is statistically significant, and you can see the  
17 different categories of interventions or  
18 behaviors at the bottom.

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

25 We then did this process of applying

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

7 We've also seen in other settings, social  
8 support, by the way, having this kind of effect.

9 These are data that we had from the All of Us  
10 Research Program during the early part of the  
11 COVID pandemic, and looking at to what extent  
12 people had social support in those periods. This  
13 was a study of nearly 70,000 individuals in the  
14 study. The bottom line was, social support had a  
15 pretty potent protective effect on the risk of  
16 developing clinically significant depressive  
17 symptoms. And if you had multiple sorts of forms  
18 of social support, emotional, tangible, or  
19 positive social interaction types of support,  
20 that was associated with 85 percent lower odds of  
21 developing depression. So, these are actionable  
22 kinds of things we can get by using real world  
23 data.

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

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1 mentioned previously, which is the idea of using  
2 genetic information as a potential biomarker.  
3 And many of you may have heard of the concept of  
4 a polygenic score. So, when we do these large-  
5 scale genetic studies, we often find variants, as  
6 I showed you earlier, that might be associated  
7 with a condition. Let's say it's depression or  
8 schizophrenia. But these are variants or DNA  
9 variations that by themselves have a tiny effect.

10 However, when you add them up, they can have a  
11 more substantial effect.

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

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

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

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

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

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

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

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1 connecting biomarkers of psychiatric risk to  
2 other health conditions.

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

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

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

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

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1 of.

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

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

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

3 But you really want to know, well, if it's  
4 not that good for something, you know, if you're  
5 predicted response to an SSRI, for example, is  
6 not very high – what else might you respond to?  
7 That's sort of the clinically relevant question.

8 And the nice thing about these models is that  
9 they can predict responses to different  
10 antidepressants. So, in this case, Tom was  
11 predicted to respond well to any of these  
12 medicines, although SSRIs were the best. For  
13 Megan, actually, mirtazapine was predicted to be  
14 the best choice. So, you can see how this kind  
15 of information could inform better decision-  
16 making.

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

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

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

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

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

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1 identified that they had lower levels of serum  
2 manganese.

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

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

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

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

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

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1 - really following those leads that could lead to  
2 some real change in ultimately clinical practice.

3 I'm very excited about the opportunities, but  
4 it's a complex field that's going to need to  
5 leverage and integrate all of the developments  
6 that we're now seeing in AI, and genomics, and  
7 epidemiology, in clinical psychiatry and,  
8 importantly, in implementation science, to bring  
9 these kinds of advances to the future of mental  
10 health care. So, I'm going to stop there and I  
11 will look forward to having an opportunity to  
12 answer some questions a little bit later. Thank  
13 you so much.

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

16

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

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

14           We will now begin Dr. Russo's presentation,  
15 which is titled, "Neuroimmune Mechanisms of  
16 Stress and Depression."  
17  
18  
19  
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NEUROIMMUNE MECHANISMS OF STRESS AND DEPRESSION

+ + + + +

DR. SCOTT J. RUSSO

+ + + + +

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Health Sciences.

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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

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

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

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

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1 bidirectional, whereby if you have depression and  
2 you develop cancer, your response to treatments  
3 is blunted, and the likelihood survival rate, for  
4 example, is diminished. Cardiovascular disease.

5 Patients with depression have an increased risk  
6 for developing cardiovascular diseases. But both  
7 of these relationships also go in the opposite  
8 direction. In other words, if you have cancer,  
9 you may also be more likely to develop  
10 depression. Similar data exists for all of these  
11 other illnesses.

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

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

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

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1 that are also found in these other conditions.

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

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

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

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

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

4 And what myelopoiesis is, it's an increase  
5 in the production and release of myeloid cells  
6 into the bloodstream. Myeloid cells include not  
7 just monocytes, shown here in the left-hand  
8 panel, but also neutrophils. And we see  
9 significant elevations in a subset of these  
10 patients across both. You can see it's not  
11 everybody. Some estimates from epidemiology  
12 studies have suggested that the immune  
13 dysregulation shown here represents about, you  
14 know, 25 to 30 percent of the overall population.

15 We don't see broad changes in other blood cell  
16 types. But what we do see is strong correlations  
17 with markers of stress.

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

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

11 Another feature of these patients is that  
12 the monocytes are also more reactive to stimuli.

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

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1           In addition, several years ago, a postdoc in  
2 my lab was very interested in the blood-brain  
3 barrier. This is the area that I mentioned  
4 earlier, which contains the neurovascular unit.  
5 And we hypothesized back then that in order for  
6 these immune signals or cells to interact with  
7 the brain, there must be some type of change at  
8 the blood-brain barrier. There must be some type  
9 of measurable interaction between these systemic  
10 immune factors and the blood-brain barrier. So,  
11 she collaborated with several of our clinical  
12 collaborators, first in Montreal, Gustavo  
13 Turecki, and second in Texas, with Carol  
14 Tamminga, who run psychiatric brain banks. We  
15 obtained nucleus accumbens tissue from patients  
16 with a diagnosis of major depression at the time  
17 of death. And what she found was that the  
18 endothelial cell-specific tight junction claudin-  
19 5, which is critical for blood-brain barrier  
20 health and forming the initial layer of the  
21 barrier that prevents things from our bloodstream  
22 to enter the brain, she found that there was

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

3           Functionally, what that would mean is that  
4 the barrier of a patient with depression might in  
5 fact be more open to peripheral factors perfusing  
6 in. I hope you notice that we split these  
7 cohorts based on antidepressant treatments, but I  
8 should caution you, most of these cases were  
9 suicide cases, and the fact that they were on  
10 antidepressants is based simply on toxicology  
11 screens at the time of death. So, we don't know  
12 if these medications were being taken as  
13 approved. We don't know if they were effective.

14           And we don't know what types of antidepressants  
15 were being used. It's just a broad category. In  
16 fact, when we do more controlled studies in  
17 rodent stress models, where we control the dosing  
18 and we measure treatment outcomes, mice that are  
19 exposed to the antidepressant imipramine, that  
20 respond positively from a behavioral perspective  
21 to that regimen, do in fact show evidence of  
22 blood-brain barrier normalization. So, it might

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

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

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

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

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

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

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

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

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

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

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

14 Okay. So, digging into this, it's really  
15 difficult to model psychiatric illness in mice,  
16 or rats, or even non-human primates, for example.

17 So, I don't want to make any claims about  
18 modeling depression in mice, or PTSD in mice.  
19 But what I do want to say is that our physiology,  
20 between mouse and human, is fairly well-preserved  
21 at some levels. And I think modeling the body's  
22 physiological response to trauma maybe is a bit

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

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

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

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

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

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

5           And thirdly, what are we really measuring?  
6 Are we really measuring social behavior? And  
7 what aspects of social behavior are we measuring?

8           One might interpret this type of avoidance as  
9 social fear, for example, rather than an  
10 uninterest or disinterest in engaging in social  
11 interaction, which is a little bit more  
12 indicative of some of our major depressive  
13 disorder patient cohorts.

14           So, we've kind of modified this strategy a  
15 bit. I'll just show you real quick a few videos.

16           We also, in addition to measuring interaction  
17 with a CD-1 mouse, we also measure interaction  
18 with juvenile, non-aggressive, same sex, C57 mice  
19 in their home cage.

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

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

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

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

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

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

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

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

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

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

22 But when we did this now, there was a bit

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 You can also see how those four clusters are  
8 expressed across control susceptible and  
9 resilient mice. And you can see that there are  
10 some clusters, for example, like cluster two that  
11 seem to be reduced in both susceptible and  
12 resilient mice relative to controls, others which  
13 might be increased or enriched, and still others,  
14 which are uniquely regulated in susceptible mice.

15 For example, this cluster is zero here. And so,  
16 this is the cluster that we focused on for the  
17 remainder of our studies.

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

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

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

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

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

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

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

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1 the plaque itself is organized in a very specific  
2 way. These dense lipid cores in the middle here  
3 are usually stabilized by a fibrous cap. And so,  
4 under kind of steady state conditions, we  
5 probably all have some level of plaque in there.

6 They're largely stable because the fibrous cap  
7 prevents this lipid core from bursting out,  
8 floating through circulation, and causing a  
9 cardiovascular event. The fibrous cap is made up  
10 of collagen, and MMP-8 is a collagenase, meaning  
11 that it can break down collagen.

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

22 This is work done with Ed Fisher and Ozlem

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

9 This paper is in submission. I'm not going  
10 to go through the details and what we did here  
11 because I want to focus my time. But I just  
12 thought I'd introduce this topic as a way to  
13 potentially think about MMP-8's action in brain.

14 Given the fact that it is a peptidase and can  
15 break down collagen and collagen-like markers,  
16 it's possible that MMP-8 in the central nervous  
17 system might be able to reorganize the brain's  
18 extracellular matrix, altering synaptic  
19 plasticity and changing behavior via that circuit  
20 adaptation.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22

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

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BRAIN, BEHAVIOR, & MIND  
2025 SPRING CONFERENCE

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

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TUESDAY,  
APRIL 22, 2025

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

1  
2           **DR. NAIFEH:** For our first question and  
3 Answer panel, we are joined now by Dr. Jordan  
4 Smoller and Dr. Scott Russo. Welcome. Our  
5 moderator for this panel is Commander Christina  
6 La Croix, who will help us address as many  
7 questions as possible during the allotted time.

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

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

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

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

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

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

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

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

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

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

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

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

**COMMANDER LA CROIX:** And have you or your

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

4 **DR. SMOLLER:** That's a really good question.

5 So one of the things that we can do when we  
6 build these models is identify what are the most  
7 influential features. And what we see is that  
8 it really depends on the outcome that you're  
9 predicting. It depends, to some degree, on the  
10 kind of modeling approach you're using. And the  
11 further caveat is that something might be highly  
12 predictive and yet not causally involved, right?

13 Because what you're doing is maximizing the  
14 predictive validity, but it might be that the  
15 thing that pops up top on the list is correlated  
16 with an actual causal factor. So one area that  
17 we and others are very interested in is causal  
18 machine learning or causal AI.

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

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

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

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

**COMMANDER LA CROIX:** Thank you so much. So,

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

4 DR. SMOLLER: Well, a number of people have  
5 been very interested in folate and the  
6 metabolism of single carbon metabolism. There  
7 are genetic variations that folks have looked at  
8 that are related to those biological processes.

9 There's been a lot of interest in, for example,  
10 MTHFR variation which, I would say, like many  
11 other sort of candidate genes with respect to  
12 psychiatric and behavioral outcomes, has had  
13 some interesting evidence supporting it, but I  
14 would say it's pretty mixed at this point.

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

1 at a genetic level are highly polygenic and  
2 highly complex.

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

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

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

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

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

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

1 ancestry. Still, although that problem has been  
2 pointed out, now, for over a decade, more than  
3 90 percent of the genomic data that are  
4 available worldwide are from people of  
5 predominantly European ancestry, which we know  
6 is a limitation, because some of the findings  
7 and, for example, polygenic score performance  
8 and all these kinds of things don't necessarily  
9 generalize very easily.

10         There's a lot of effort now to develop  
11 trans-ancestry, for example, polygenic scores,  
12 which is the approach that we typically now  
13 take. In the genetic data that I showed, about  
14 sort of cross-disorder function, those were  
15 largely from -- because of the size of the  
16 samples and the data that were available.

17 Although we did more recently do some work with  
18 the available non-European ancestry samples, to  
19 show that some of the findings were concordant.

20         But unfortunately, it's still vastly  
21 underpowered.

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

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

11 One resource that I hope people become more  
12 familiar with, is the All of Us research  
13 program, which is a nationwide cohort study, now  
14 enrolled more than 800,000 individuals and is  
15 very diverse along many axes. And so we are  
16 increasingly using those kinds of data as well.

17 So we are limited to what is out there,  
18 unfortunately, but at least on the EHR side,  
19 that has typically been pretty diverse.

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

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

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

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

1           **DR. SMOLLER:** Yeah, that's a good question.

2           I mean, one concern we always have is not  
3           adding to the onslaught of alerts and  
4           administrative work and all kinds of things that  
5           sometimes can be overwhelming in clinical  
6           practice, which is why we've done a quite a few  
7           focus groups to try to tailor these kinds of  
8           tools to what clinicians might find most useful.

9           We are in the process now of doing this  
10          4,000 person randomized trial, controlled trial  
11          of delivering this information. And so, we'll  
12          have a pretty large sense of feedback from  
13          clinicians and patients about obstacles,  
14          barriers, and so on.

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

1 insurance companies to buttress clinical  
2 decisions and so on.

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

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

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

1 psychiatric diseases.

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

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

          So for Dr. Smoller, do any of the factors

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

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

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

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

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

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

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

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

9 Have you considered such low intensity, far  
10 upstream interventions?

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

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

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

1 algorithmic evidence of highlighting folks at  
2 high risk.

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

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

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

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

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

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

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

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

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

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

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

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

1           So my opinion is that, if we could harness  
2 strategies, whether they be therapeutic or  
3 behavioral, to train the immune system, rather  
4 than to shut it off or turn it on, we want it to  
5 work properly and in kind of the sweet spot or  
6 the middle zone. And a good example of this is  
7 exercise. There's been a lot of discussion now  
8 about exercise and the benefit of exercise, but  
9 you know what exercise does acutely? It causes  
10 monocytes and an increase in pro-inflammatory  
11 cytokines in your body. Over chronic periods,  
12 though, it trains your immune system to respond  
13 kind of appropriately when it needs to, and I  
14 think that's what we need to harness in a pill.

15       Nobody has done that, to my knowledge, at this  
16 point. We've just used strategies where we shut  
17 it off completely and prevent it from elevating  
18 during stress.

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

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

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

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

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

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

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

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

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

10 **DR. SMOLLER:** Thanks so much.

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

19 We will now break for lunch, reconvening at  
20 12:45 p.m. Eastern Daylight Time, which is just  
21 under an hour from now. We hope everyone will  
22 use that time as an opportunity to go review the  
poster gallery on the conference website, which

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

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

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

19           We will now begin Dr. Pawluski's  
20 presentation, which is titled, "The Neuroscience  
21 of Parenting and Perinatal Mental Health."  
22

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THE NEUROSCIENCE OF PARENTING AND  
PERINATAL MENTAL HEALTH

+ + + + +

DR. JODI PAWLUSKI

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by the Henry M. Jackson Foundation, Inc.

## 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

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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

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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.

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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,

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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

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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

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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

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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

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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

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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

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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,

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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

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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

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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,

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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.

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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.)

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

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

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

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

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

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

+ + + + +

DR. JESSICA L. SCHLEIDER

+ + + + +

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

1  
2  
3 DR. SCHLEIDER: Thank you so much for the  
4 kind invitation to present some of our lab's  
5 recent work. We have a lot to get through, so  
6 I'm going to dive right in. And hopefully the  
7 discussion that follows this will be a lively  
8 one, because I'd love to discuss how this work  
9 may apply in the realm of treating and reducing  
10 traumatic stress symptoms.

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

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

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

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

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

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

11 And that's where I'm hopeful our lab can  
12 come in. I direct the Lab for Scalable Mental  
13 Health here at Northwestern. We started up in  
14 2018, and we've been hard at work towards our  
15 mission to design, test, and disseminate brief  
16 barrier-free interventions to reduce mental  
17 health problems at scale. Now, the interventions  
18 that I'm going to discuss during this talk aren't  
19 specific to PTSD or traumatic stress. However,  
20 given the prevalence of exposure to traumatic  
21 events, both big T and little T traumas, I'll  
22 mention the percentages of our various samples

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 These are a few logos of some of the single

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

15 Now, what do we compare our active SSIs to?

16 In this and other trials, the most likely and  
17 realistic, or face valid, ecologically valid,  
18 control condition would actually be nothing.  
19 That's the most likely thing that teens are going  
20 to access without an SSI like this when scrolling  
21 Instagram. But nothing is not a particularly  
22 scientifically compelling comparison condition,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 experiencing qualitatively?

2 One example of this work has been a co-  
3 design effort with LGBTQ+ teens, because they  
4 represent an enormous and surprisingly big  
5 portion of folks who end up accessing our  
6 interventions when we put them available online.

7 And so, we were able to get a grant from The  
8 Upswing Fund for Adolescent Mental Health to do  
9 some of this co-design work to learn from teens:  
10 how can we better adapt our depression-focused  
11 SSIs to meet your needs?

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

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

5 So, we took this feedback and ran with it  
6 and we decided that rather than trying to  
7 integrate those things into behavioral activation  
8 interventions, we would just create a different  
9 intervention that really did this topic justice.

10 And that's how Project RISE was born. Project  
11 RISE is an SSI that teaches about minority stress  
12 theory and why holding a minoritized identity,  
13 like sexual or gender minority identity and other  
14 intersectionally minoritized identities, can  
15 simply create a different kind and quality of  
16 stress that's not fair — you shouldn't have to  
17 deal with this extra layer of stress and this  
18 shouldn't have to be something that you learn to  
19 navigate in your life — but there are ways of  
20 coping, and Project RISE helps people make an  
21 action plan for finding hope and empowerment and  
22 strength and community and support even in a

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1 world that's not always fair.

2 And we built this intervention, which is now  
3 freely available on our lab website. We did an  
4 RCT of 538 sexual and gender minority youth, ages  
5 13 to 16. Again, recruited via Instagram, again  
6 with a waiver of parental consent, because it  
7 would be very unethical to ask teens to out  
8 themselves to their parents in order to take part  
9 in an online activity like this. And we found  
10 that Project RISE significantly improved  
11 hopelessness, self-hate, and internalized stigma,  
12 versus an information-only control. And that  
13 internalized stigma effect lasted two weeks  
14 later. So, we're now thinking about ways to  
15 integrate Project RISE with other interventions,  
16 such as the safety planning intervention. We  
17 have a grant to integrate both of those things to  
18 better serve the needs of the LGBTQ+ community,  
19 who are often kept out systematically of other  
20 resources.

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

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

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

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

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

13 The provider training is brief itself. It's  
14 first a 90-minute didactic, followed by a  
15 fidelity-checking, live-practice session of the  
16 SSC with one of our team members, and the SSC  
17 itself is designed to last from 30 to 60 minutes.

18 And the goal of this intervention is to help  
19 people get one small but meaningful step closer  
20 to a goal that matters to them.

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

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

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

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

22 And it's also something you can upload as

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

6 We've done several different trials on the  
7 SSC. All of them have been open trials to date.

8 There's a large body of literature, including  
9 RCT, suggesting the effectiveness of solution-  
10 focused brief therapy. So, these really  
11 illustrate the utility of the SSC on its own.

12 In one study looking at folks on outpatient  
13 waitlists for the SSC - both adolescents and  
14 adults - when the SSC was offered via  
15 teletherapy, folks who received it - which were  
16 80 percent of folks who were offered it - showed  
17 an 85 percent chance of significant decline in  
18 hopelessness and 80 percent chance of showing  
19 increases in readiness for change once they did  
20 get to the top of the waitlist. And reductions  
21 in anxiety and depression across two weeks,  
22 which, of course, is the opposite of what we

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

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

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

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1           So, Project Empower is a parent-directed,  
2           single-session, digital intervention that lasts  
3           20 to 30 minutes. It's based on an evidence-  
4           based treatment called the SPACE program, which  
5           came out of the Yale Child Study Center, created  
6           by Eli Lebowitz and Wendy Silverman.

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

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

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

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

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1 parent-distress tolerance, with an effect size of  
2 0.43 across two weeks.

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

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

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

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

22           So, one piece that we've encountered,

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

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

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

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

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

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

22 At this point, our lab is - rather than

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

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

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

21 This is a website, [SchleiderLab.org/yes](http://SchleiderLab.org/yes),  
22 that anybody can access and use any of our

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

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

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

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

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

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

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

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

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

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

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

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

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

5 So, to embed our SSIs into Koko, we actually  
6 had to reduce them in length even further,  
7 because nobody is going to do a 15- to 25-minute  
8 program online, if they're just scrolling social  
9 media - if they're not getting paid for it as  
10 part of a clinical trial. So, they had to be  
11 shorter in order for people to do them in this  
12 context. And simply by offering our SSIs after  
13 adapting them as just-in-time supports on Tumblr,  
14 6,179 adolescents accessed and completed them  
15 within one year. And because we'd already  
16 conducted many randomized control trials,  
17 including these same interventions, we could  
18 benchmark the immediate effects of the  
19 interventions in Tumblr against those that we had  
20 seen in larger clinical trials with longer-term  
21 follow up. And we saw that hopelessness reduced  
22 at least as much in the Tumblr-based SSIs as in

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

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

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

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1 resources when they're in acute distress.

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

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

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

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

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

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1       separately.

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

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

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

22 That's not necessarily because parents are

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1 saying no when their kids ask for treatment. But  
2 kids fear that their parents will respond in an  
3 invalidating manner – that they won't take their  
4 problems seriously, or that they haven't taken  
5 their problems seriously, or some teens don't  
6 want to burden their parents with an extra worry  
7 about their mental health because they see them  
8 struggling on so many other fronts in life  
9 already. So, parents aren't at fault for this  
10 necessarily. It's just that the reality of the  
11 state that we're in is that often youth cannot go  
12 to the adults in their homes to ask for support.

13 And about a third of the states in the U.S. do  
14 not allow adolescents to seek out mental health  
15 care of any kind without active parental consent,  
16 so that leaves many kids in a really tough spot.

17 Our qualitative research has shown this  
18 repeatedly, but we wanted to see if we could  
19 quantify it in a different way at a different  
20 level. So, we conducted a legal mapping study,  
21 testing whether parent consent laws are related  
22 to youth access to care among adolescents with a

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

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

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1 well. However, in states that require parental  
2 consent, that figure was only 37 percent. I want  
3 to highlight that 46 percent is still really low.

4 We should be aiming much higher than 46. But  
5 the fact that a law can be associated with such a  
6 large difference, such a noticeable difference in  
7 access, points to some barriers that may be  
8 really high priority in terms of dismantling to  
9 increase access to support.

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

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

11 (Whereupon, the above-entitled matter  
12 went off the record.)  
13  
14

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

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

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DEPARTMENT OF PSYCHIATRY  
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BRAIN, BEHAVIOR, & MIND  
2025 SPRING CONFERENCE

+ + + + +

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

+ + + + +

PAULA P. SCHNURR, Ph.D.

+ + + + +

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provided by Uniformed Services University of the  
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## P-R-O-C-E-E-D-I-N-G-S

1  
2  
3 DR. SCHNURR: Thank you. I'm so pleased to  
4 be here with you today to talk about  
5 psychotherapy for PTSD, where we are, and where  
6 we need to go. There are four parts of the talk.

7 First, I want to talk about PTSD clinical  
8 practice recommendations -- because I work in the  
9 VA, I'll focus on the VA/DoD Clinical Practice  
10 Guideline and then spend a little bit of time  
11 talking about psychotherapy versus medication and  
12 recommendations around that. Then I will move  
13 into talking about comparative effectiveness  
14 research and illustrate this with a study that I  
15 and colleagues did, comparing cognitive  
16 processing therapy and prolonged exposure. And  
17 lastly, I will end by talking about what we need  
18 to be doing to enhance treatment outcome in PTSD,  
19 and especially focusing on psychedelic drugs as a  
20 strategy.

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

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

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

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

25 So, we developed Clinical Practice

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

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

25 So, in the VA/DoD guideline, the

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

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

22 Twenty on this version of the CAPS was the  
23 standard for remission. So very pronounced and  
24 very durable effects.

25 The VA/DoD Guideline also recommends or

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

14 When you turn to medications, the  
15 recommendations are mixed and the options are  
16 fewer. There is a strong recommendation for  
17 sertraline, venlafaxine, and paroxetine, a weak  
18 recommendation for prazosin for nightmares. And  
19 that's essentially what the evidence suggests is  
20 effective for treating PTSD or nightmares in  
21 people who have PTSD. The Guideline strongly  
22 recommends against benzodiazepines and cannabis.

23 And this is for lack of demonstrated efficacy  
24 and known harms. There is Weak against  
25 recommendations for risperidone, ketamine, and

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1 prazosin for overall PTSD.

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

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

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

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

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

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

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

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

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

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

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

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

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

16 And what we found is that PE was more  
17 effective than CPT overall. 35 percent more  
18 likely -- greater likelihood of response in PE,  
19 46 percent greater likelihood of loss of  
20 diagnosis, and 63 percent greater likelihood of  
21 remission. And what you can see on the right of  
22 this slide are simply the percentages of people  
23 who achieved each of these outcomes.

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

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

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

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

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

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

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

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

12 PTSD is also not unique in terms of the rate  
13 of dropout that we see. This slide depicts the  
14 results of a meta-analysis published now almost  
15 10 years ago looking at dropout before treatment  
16 and during treatment in randomized trials. And  
17 in PTSD, 8 percent dropout before treatment, and  
18 then 27 percent dropped out during treatment.  
19 That doesn't look very good. But then if you  
20 look at depression, 22 percent before treatment  
21 and 36 percent during treatment. So, the  
22 takeaway from this slide and the prior slide,  
23 again, is that we have room to improve in  
24 enhancing the efficacy and the acceptability of  
25 treatment for mental health disorders.

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1           So, where we need to go with this body of  
2 evidence is that we need in PTSD to identify more  
3 effective medications and to enhance the  
4 effectiveness of both medications and  
5 psychotherapy. There's a number of strategies  
6 that we can use to do this. One is matching or  
7 tailoring. Using, for example, biomarkers to  
8 predict whether a person might be more responsive  
9 to medication or psychotherapy or PE versus CPT.

10          Personalized Advantage Index is simply a  
11 quantitative method of determining the advantage,  
12 how many points a person would additionally  
13 improve if they had their ideal treatment versus  
14 another treatment. People have also worked on  
15 flexibly tailoring protocols, both in terms of  
16 the amount of treatment, the number of sessions,  
17 as well as what's emphasized, depending upon the  
18 particulars of a given case but within the  
19 framework of that treatment.

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

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1 the shortest intensive protocols may be as short  
2 as a week. Usually they are two to three weeks.

3 And what we see with these protocols so far is  
4 that you get much greater completion. So, in VA,  
5 a recent study found that over 80 percent of  
6 people completed a course of evidence-based  
7 therapy, and that's -- in clinical practice,  
8 that's usually less than 50 percent. But what  
9 we're not seeing yet is that there's clear signal  
10 that treatment outcome improves, but  
11 theoretically it should if people have a greater  
12 dose of treatment.

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

25 And then, lastly, there are psychotherapy

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

5 So now I want to talk about psychedelic  
6 drugs. What I mean when I talk about  
7 psychedelics, first of all, classic psychedelics  
8 include a drug such as psilocybin and LSD, and  
9 these mainly interact with the 5-HT<sub>2A</sub> receptors,  
10 which are targets for the neurotransmitter  
11 serotonin. The effects of these drugs may bring  
12 on vivid visions or sensations, hallucinations,  
13 alter a person's sense of self, and promote  
14 feelings of insight or connection. Dissociative  
15 drugs include things such as ketamine and PCP,  
16 and these block the action of NMDA receptors,  
17 which are part of the brain's system for  
18 transporting glutamate. And while the  
19 dissociative drugs can alter perception, they're  
20 not like the classic psychedelics. Typically,  
21 they make people feel more disconnected from  
22 their body and their environment. And then,  
23 lastly, drugs such as MDMA, ibogaine, salvia work  
24 on a variety of brain functions to cause  
25 psychedelic or dissociative effects. Cannabis

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

3 The social and legal context in the U.S. for  
4 psychedelic drugs has been quite active over the  
5 past decade. But right now, cannabis and  
6 hallucinogenic drugs are classified as Schedule I  
7 by the U.S. Drug Enforcement Administration.  
8 That's the DEA. And it means they have no  
9 currently accepted medical use and a high  
10 potential for abuse. So, Schedule I drugs can be  
11 used in carefully regulated research and cannot  
12 be used clinically without a regulated exception.

13 Schedule II drugs are those that have benefit,  
14 but also a high potential of abuse or dependence,  
15 such as oxycodone and fentanyl, Ritalin. And  
16 then Schedule III drugs have benefit and a low  
17 potential for abuse or dependence, such as  
18 ketamine. And I'm aware that there is increasing  
19 interest in the abuse potential of ketamine, but  
20 it is relatively lower, at least at the present  
21 time, than we see for the Schedule II drugs that  
22 I mentioned.

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

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1 psilocybin in treatment-resistant depression in  
2 2018, and then major depressive disorder in 2019.

3 Pending a successful completion of clinical  
4 trials, then companies can request approval for a  
5 drug for a given disorder, which can then lead  
6 the DEA to reschedule the drug for clinical use.

7 Many states -- that's the federal landscape --  
8 but many states have passed legislation  
9 legalizing or decriminalizing cannabis or  
10 allowing it for selected medical use that is not  
11 evidence-based. In fact, PTSD is a common  
12 indication for medical marijuana. And I just  
13 want to make a note that DEA and DoD providers  
14 must follow federal guidelines and cannot  
15 prescribe marijuana, even in states where it's  
16 legal, at least at the present time.

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

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

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

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

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

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

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

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

25 Wherever the patient goes, the therapist

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

5 So, this slide is a graphic depiction of the  
6 MDMA protocol from Lykos: three preparatory  
7 sessions, an MDMA session, followed by three  
8 integration sessions, and then the cycle repeated  
9 two more times. So, each MDMA session is six to  
10 eight hours, usually eight, and psychotherapy is  
11 90 for the 12 sessions, 90 minutes.

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

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

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

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

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

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

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

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

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1 perceived as the lack of structure in the  
2 protocol.

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

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

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1           In our trial, which is being conducted in a  
2 VA setting, outpatient, we are randomizing 10  
3 veterans to standard or low-dose MDMA with  
4 outpatient PE delivered over a three-week period.

5           But this is still a much shorter duration and  
6 many fewer hours of therapy than the standard  
7 protocol. So, if this is successful, this could  
8 present a more efficient alternative for MDMA-  
9 assisted psychotherapy. But right now, our  
10 primary goal is assessing feasibility and safety,  
11 given concerns about potential anxiogenic effects  
12 of low-dose MDMA. So far, and we're early into  
13 the trial, and we're blinded to patient  
14 condition, we believe we're successful in the  
15 patients that we've seen so far in demonstrating  
16 feasibility.

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

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

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

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

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

20

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

23

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

11 CONCLUDING COMMENTS

12 + + + + +

13 TUESDAY,  
14 APRIL 22, 2025

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

1  
2           **DR. NAIFEH:** Thank you very much, Dr.  
3 Schnurr, for helping us understand the state of  
4 PTSD treatment research, including the  
5 challenges of MDMA-assisted therapy and other  
6 psychedelic therapies.

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

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

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

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

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

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

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

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

14 We see a lot more research done on  
15 depression, right? Postpartum depression, and  
16 actually not very much research done on anxiety.

17 And I'm speaking about research in terms of  
18 looking at brain changes in parents in relation  
19 to struggling also with a mental illness. So,  
20 depression, we're seeing a lot of more research  
21 out, showing that, indeed, different brain areas  
22 function differently in a mother who has  
depression compared to an individual who has

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

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

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

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

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

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

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

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

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

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

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

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

3 And so, the way I think about the  
4 medications we currently have for PTSD, is they  
5 address the symptoms and they bring the symptoms  
6 down, but they don't cure the inherent problem.

7 Now, I'm not saying, like, PTSD is an infection  
8 and we need an antibiotic to cure it. But the  
9 kind of model that we have in psychotherapy for  
10 PTSD is we have at least theoretical frameworks  
11 and we have some science behind the thinking of  
12 why a given treatment works, what the mechanism  
13 is, and how that addresses what is causing and  
14 maintaining the PTSD.

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

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

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

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

19 **COMMANDER SERPICO:** I was going to say  
20 Doctor --

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

**COMMANDER SERPICO:** Is that okay? Yeah.

1           **DR. PAWLUSKI:** I mean, jump in if someone  
2 has a more immediate answer. This is a huge,  
3 huge, huge question. And it also, for me, I  
4 think it depends on where you're located, right?

5       Different countries have different access to  
6 care, for example. I'm thinking mental health  
7 itself has a lot of stigma, mental illness,  
8 right? So I think we do need to change that.  
9 For me, when I talk about and I think about  
10 mothers and parents in particular, but mothers  
11 specifically, those who identify as mothers,  
12 there needs to be a cultural shift as to what  
13 that role is and what it means. And because,  
14 often, what we're seeing is just the pressure of  
15 trying to be the perfect mother, trying to  
16 fulfill all the roles, the literal cognitive,  
17 emotional labor, and physical labor that goes  
18 into expectations of mothers and the role of a  
19 mother. It is just overwhelming. And I think,  
20 in this regard, there needs to be some sort of  
21 shift.

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

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

6 But, of course, we need access to care. We  
7 need affordable care. We need care that works.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 problem.

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

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

1 telehealth, but it is a way to deliver  
2 intervention.

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

18       And the interventionists, I think, on  
19 average had about an 11th grade education, and  
20 the majority of the patients were not literate.

21       And so they had to retool -- because if you've  
22 done Cognitive Processing Therapy, you have  
worksheets, no less. So they had to come up

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

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

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

17 **COMMANDER SERPICO:** Thank you so much, Dr.  
18 Schnurr.

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

**DR. PAWLUSKI:** Yeah. This is another great

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

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

1 life.

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

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

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

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

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

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

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

9 And there are a variety of evidence-based  
10 protocols out there that have been shown to  
11 reduce general distress in the moment, and  
12 increase receptivity to seeking more care.  
13 We've actually, through a HRSA grant, been able  
14 to deliver single-session consultations to  
15 frontline healthcare providers during the COVID-  
16 19 pandemic and during lockdown, and found that  
17 they were highly acceptable and effective among  
18 frontline healthcare workers who were dealing  
19 with rapidly changing and incredibly stressful  
20 hospital-based contexts every day.

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

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

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

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

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

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

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

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

8 And we often use the term recovery when  
9 applied to people with serious mental illness,  
10 but I think we need to [missing word] our minds  
11 about this, and really think about recovery as a  
12 goal for everyone. And living a recovery life,  
13 becoming well, isn't just about decreasing your  
14 symptoms, it's really returning to life, and  
15 feeling engaged, and feeling healthy. And so,  
16 many, many practices that are not in a Guideline  
17 may still be useful when a person is being  
18 treated with -- well, hopefully with a  
19 Guideline-recommended treatment. But when a  
20 person is being treated with a standard therapy,  
21 there is a role for these other interventions to  
22 really get the person fully recovered.

**COMMANDER SERPICO:** Thank you so much. Our

1 next question is for Dr. Pawluski. You  
2 mentioned multiple macroscopic changes in a  
3 mother's brain. What microscopic changes are  
4 the causes of these macroscopic changes? Fluid  
5 volume shifts, increased number of cells,  
6 decreased number of cells, gain/loss of  
7 intracellular space, et cetera?

8 **DR. PAWLUSKI:** This is a great question. I  
9 mean, I typically work in animal models, so this  
10 is what we do, is we're looking at receptor  
11 distribution, various aspects of  
12 neuroendocrinology, neurotransmitter changes.  
13 And there's a whole book summarizing this  
14 research to date, so it's a huge field. But  
15 what we're seeing, in fact, is there are a lot  
16 of different changes.

17 And for me, I work more often looking at  
18 neuroplasticity at a cellular level, so looking  
19 at neurogenesis, and we recently did a review  
20 where we were looking at, what do we know about  
21 these cell changes across pregnancy, from animal  
22 models to what we see in humans? So, in humans,  
as I talked about, there's these structural

1 changes that seem to be this kind of decrease or  
2 this fine-tuning of the brain. And what's  
3 interesting, and I mentioned this briefly in my  
4 talk, is that I also showed when looking at  
5 neurogenesis in the hippocampus, there's a  
6 decrease in neurogenesis as well. There's a  
7 decrease in microglia. We've seen this in  
8 animal models across pregnancy in the postpartum  
9 period.

10 So there seems to be this shift. I mean, I  
11 talk about it as fine-tuning. Essentially, the  
12 brain becoming a bit more efficient. That's on  
13 a cellular level but, of course, there's other  
14 things driving this, right? So we see changes  
15 in neurotransmitter communication,  
16 neuroendocrine function. I mean, there's so  
17 much going on. There's not just one thing  
18 that's changing. It's the whole system is being  
19 modified and geared to care for the child. So  
20 it's really multi-level changes that we still  
21 are discovering. And when it comes to the human  
22 brain, of course, we don't have the techniques  
to delve into it, but because of the

1 similarities in systems and brain areas, we are  
2 getting a picture.

3 But it is quite complex, and we're often  
4 just studying one area. Some of us just study -  
5 - I love glucocorticoids, for example. But they  
6 don't work alone, and they interact with many  
7 different systems, and they just don't work in  
8 one brain area. So, it is really is a complex  
9 system. That's why I think the parental brain  
10 is quite so fascinating, is because it is so  
11 complex and there's so many changes happening.

12 But, in terms of these structural changes, I  
13 like to think of it -- there seems to be this  
14 fine-tuning, essentially. And I think that  
15 that's very exciting to see, especially during  
16 adulthood. And we have more questions than  
17 answers, perhaps, but I think it really is  
18 fascinating to see these changes and uncover  
19 more about what's going on.

20 So I don't know if I answered the question,  
21 but I'm happy if there's a more specific  
22 question or to refer to other literature to  
cover this in more detail.

1           **COMMANDER SERPICO:** You did. Thank you so  
2 much.

3           **DR. PAWLUSKI:** Thank you.

4           **COMMANDER SERPICO:** For Dr. Schleider, you  
5 talked about safety planning and crisis  
6 intervention. Can you comment on any other  
7 interventions focused on suicidal ideation and  
8 important focus in the Department of Defense?

9           **DR. SCHLEIDER:** Absolutely. So, the safety  
10 planning single-session intervention that we've  
11 put together is probably the most directly  
12 targeted to suicidal ideation in particular.  
13 However, we've also tested a couple of other  
14 interventions in randomized controlled trials  
15 that have shown promise. One of them is  
16 actually a crisis resource uptake intervention.

17           And what this is, is we actually partnered with  
18 our nonprofit partner, Koko, to develop a one-  
19 minute single session intervention to offer  
20 structured support to increase the likelihood  
21 that somebody will be motivated and able to  
22 reach out for immediate crisis support or help  
when needs are detected.

1           We tested this in the context of deployment  
2 via social media platforms, monitoring what  
3 people were typing into search bars. So, if  
4 they type something into a search bar that  
5 indicated they were having suicidal ideation,  
6 they would receive this sort of one-minute  
7 direct message-based intervention that would  
8 increase their odds of reaching out for help.

9           And what we found was that with this one-  
10 minute intervention, versus just offering crisis  
11 hotlines and text lines, the rate of uptake of  
12 crisis services boosted from 38 percent to 78  
13 percent within ten minutes. So we were really  
14 excited to see that we're not just able to  
15 target suicidal ideation directly in certain  
16 safety planning interventions, but we're also  
17 able to move the needle a bit on willingness to  
18 seek out support when those kinds of thoughts  
19 and difficulties arise.

20           We also have tested, in a randomized  
21 controlled trial, an intervention for non-  
22 suicidal self-injury, which is a separate issue,  
but often related and often co-occurring with

1 suicidal ideation in general. And that  
2 intervention basically teaches the concept that  
3 one can separate out their urges from their  
4 actions and helps people make an action plan for  
5 doing just that when thoughts of self-harm  
6 arise. And we found that does significantly  
7 reduce intentions to self-harm and increase  
8 capability of coping with self-harm-related  
9 thoughts.

10 So, there are several promising directions  
11 in this space, but a lot more needs to be done,  
12 especially targeting suicidal ideation in  
13 particular, which is often not the target of  
14 suicide-focused interventions. It's often  
15 reducing suicides, the behaviors. But the  
16 ideation can be a really important earlier  
17 target as well. So, I think there's a lot of  
18 room for growth in this space, but we have some  
19 promising need.

20 **COMMANDER SERPICO:** Thank you. Dr. Schnurr,  
21 do you worry about symptoms persisting due to  
22 veteran concerns for the status of their  
benefits?

1           **DR. SCHNURR:** This is not the best question  
2 to ask someone when there's only a few minutes  
3 left in a meeting, because there's a lot to say.

4           **COMMANDER SERPICO:** Yes.

5           **DR. SCHNURR:** But, yes, because I hear about  
6 it. Anyone who works with veterans has talked  
7 about cases where people have actually  
8 explicitly expressed concerns about how they  
9 might be reporting symptom improvement with a  
10 concern about how it would affect a disability  
11 pension. In the clinical trials that we do,  
12 where people are assured the research data are  
13 confidential and they are not released to a  
14 clinical record, we really don't see this as  
15 creating a kind of bias in which people aren't  
16 reporting their improvement.

17           The data from our electronic medical record  
18 suggests some evidence that people who are  
19 receiving disability compensation may appear  
20 less likely to respond to treatment. It's hard  
21 to interpret that, because disability  
22 compensation is supposed to compensate people  
based on the seriousness of their illness and

1 its impact on their functioning.

2 So, when we look within the medical record  
3 data, we actually may be seeing just a  
4 reflection of the fact that people have a  
5 pension, rather than people intentionally are  
6 not reporting. I think that it's still an open  
7 question and it's something that I think is  
8 important, especially -- I'm not a clinician,  
9 but the clinicians who I know and who I learn  
10 from suggest the importance of trying to  
11 communicate the value to patients of reporting  
12 as fully as they possibly can so that the  
13 provider knows how the patient's doing and can  
14 appropriately tailor the treatment, adding more  
15 treatment, adding different treatments, and so  
16 on.

17 **COMMANDER SERPICO:** Thank you so much.

18 **DR. NAIFEH:** Dr. Serpico, I wish we had time  
19 for all the other questions that are in the  
20 list. It's been great hearing from our  
21 speakers, but I know some of them may have to  
22 run. We are grateful to Dr. Pawluski and Dr.  
Schleider and Dr. Schnurr for being here to

1 share your expertise. Also, thank you to  
2 Commander Serpico. We only have a few minutes  
3 left, but I know that some of our speakers may  
4 need to go, so please feel free to do so.  
5 Before turning it back over to Dr. Ursano, I  
6 will ask Dr. Rachel Shor to provide some  
7 guidance about receiving continuing education  
8 credits. Dr. Shor?

9 **DR. SHOR:** Absolutely. So thank you again  
10 to all of our esteemed speakers for these really  
11 wonderful presentations and also to everybody  
12 who was able to attend the conference. My name  
13 is Rachel Shor. I'm a research psychologist at  
14 the Center for the Study of Traumatic Stress and  
15 the Continuing Education lead for the Brain,  
16 Behavior, & Mind Conference.

17 Continuing education is available for this  
18 event for physicians, psychologists, and social  
19 workers through the American Psychiatric  
20 Association. And so for those who are  
21 interested in Continuing Education credits, I'll  
22 ask that you please complete the evaluation and  
credit claim form that I'm going to be emailing

1 at the completion of this conference. And this  
2 form is going to include a link that includes an  
3 invitation code to access the evaluation for  
4 this particular event and that will allow you to  
5 claim Continuing Education credits within 90  
6 days of today's event. And all of that  
7 information is going to be included in the email  
8 that I'm going to send out. But if you do have  
9 any questions regarding completing this form or  
10 accessing the form, please feel free to contact  
11 me through our event website by going to the  
12 "Contact Us" page and choosing Continuing  
13 Education as a topic, and I will be happy to  
14 help assist in any way that I can. Thank you so  
15 much.

16 **DR. NAIFEH:** Thanks, Dr. Shor. Now, I will  
17 turn it back over to Dr. Ursano for some final  
18 comments. Dr. Ursano?

19 **DR. URSANO:** Thank you. Thank you, Jamie.  
20 What do you say when you've had such a wonderful  
21 experience? After a great meal, what do you  
22 say? You say, wow, that was wonderful. I  
enjoyed it. I enjoyed the people that I was

1 with, I enjoyed sharing the time with them, and  
2 they certainly felt stimulated and interesting  
3 that is -- in the discussions.

4 You know, we really did travel the world,  
5 figuratively and literally. I know, last year,  
6 I think we had 50 different countries sign up,  
7 and I'm sure it's at least that number this year  
8 and probably close to several thousand who  
9 registered. And we traveled it in a way that  
10 allows us to share a perspective, which is  
11 understanding that human behavior is complex.  
12 It takes a lot of work, but it also can be  
13 exciting. And it certainly has great benefits,  
14 truly from cell to community, from bench to  
15 bedside -- look forward to sharing it with you  
16 again next year. Back to you, Jamie.

17 **DR. NAIFEH:** Thank you, Dr. Ursano. Before  
18 we end, I would like to once again thank all of  
19 our outstanding speakers. I'd also like to  
20 thank the Center for the Study of Traumatic  
21 Stress and our other sponsors, the members of  
22 the conference planning committee, and our  
colleagues at the Center for Deployment

1 Psychology. And especially to all of you who  
2 attended today. We hope you'll join us again in  
3 the future for other Brain, Behavior, & Mind  
4 events, including our 2025 Fall Lecture. Please  
5 watch for those announcements, take care, and  
6 we'll see you next time. Bye.

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