[00:00:00] **Stephen Calabria:** From the Mount Sinai Health System in New York City, this is Road to Resilience, a podcast about facing adversity. I'm Stephen Calabria. Today we have a special edition of Road to Resilience to celebrate publication of the third edition of the book that inspired this show's creation.

[00:00:18] The book is called Resilience, The Science of Mastering Life's Greatest Challenges, which can be found on Amazon and wherever books are sold.

[00:00:25] The newest edition was composed in part by John Depierro, Ph. D., an associate professor of psychiatry at the Icahn School of Medicine at Mount Sinai. Dr. Depierro is also the associate director of the Center for Stress, Resilience, and Personal Growth, which provides comprehensive programming to support the resilience and mental health of Mount Sinai faculty, staff, and trainees.

[00:00:46] Today on Road to Resilience, Dr. Depierro interviews Scott Russo, PhD, a professor of neuroscience and director of the Center for Affective Neuroscience, and the Brain Body Research Center at the Icahn School of Medicine at Mount Sinai.

[00:01:01] Dr. Russo delves into how his study of mouse models offers clues into how humans may bolster and maintain their resilience. We're honored to have Doctors Depierro and Russo on the show.

[00:01:13] **Jon Depierro:** Hello, my name is Dr. Jonathan Depierro. I'm an associate professor here at the Icahn School of Medicine and associate director of our Center for Stress, Resilience and Personal Growth, and I'm here today in the studio with Dr. Scott Russo, my colleague from Mount Sinai. So I'm going to kick it over to Scott. Maybe you could introduce yourselves to listeners.

[00:01:32] **Scott Russo:** Sure, Jonathan. Thank you very much. As Jonathan mentioned, my name is Scott Russo. I'm a professor of neuroscience here at Mount Sinai, a close colleague of Jonathan's, very interested in aspects of resilience and particularly to better understand the neurobiology of resilience, which is what my research program focuses on.

[00:01:50] I also direct the Center for Affective Neuroscience, which brings together clinicians and basic scientists centered around topics such as, for example, resilience other important mental health- related issues. So I'm happy to be here. Thank you again for having me.

[00:02:04] **Jon Depierro:** So you have a lot going on.

[00:02:05] **Scott Russo:** Yeah, it's okay. And two kids, so that also helps.

[00:02:09] **Jon Depierro:** So your work focuses on largely mouse models of stress and trauma and resilience.

[00:02:16] **Scott Russo:** We use a combination. I mean, my personal feeling is, is that when studying psychiatric illnesses, particularly depression, where a lot of the clinical data relies on self-report, I think using animal models in isolation where you can't rely on that type of self report, could be very limiting.

[00:02:34] So typically, the way that we start our projects is, through wonderful collaborative ties with psychiatry here, we start by analyzing biomarkers or brain mechanisms of psychiatric illness and then we take that back to our mouse models and study stress susceptibility in that context.

[00:02:50] So we use information that we gain from human cases of psychiatric illness and we then translate that back to relevant animal models.

[00:02:58] For things like depression and anxiety, for example, we use chronic stress and apply that to our animals as a way to kind of elicit symptoms and syndromes that we think are relevant to human illness.

[00:03:09] **Jon Depierro:** Yeah, it sounds like the work sort of goes two different directions. There's some work that starts in an animal model and then leads to drug discovery that then is tested in humans, or mechanistic discovery that then we see in humans when we look at them in the MRI or when we interview them.

[00:03:25] And also you can discover something in a human, then you go ask very specific questions in a mouse model that maybe our ethics board wouldn't let you do with human subjects.

[00:03:35] **Scott Russo:** That's absolutely right. That last point is particularly critical because we ultimately want to understand causality. Human research is incredibly important.

[00:03:43] Oftentimes we're limited to correlative findings, where we see a target, biological target X is associated with behavioral symptom Y.

[00:03:52] In the mouse, what we can do is, we can come in and we can test and prove that that biological mechanism is causally related to the behavior. So that's how we kind of use it.

[00:04:00] But it is bidirectional and you did mention that. There's been examples where we've started in mice without that pre-existing knowledge about the human condition and actually those studies have led to clinical trials and successful clinical trials, for example, of a potassium channel opener led by James Murrow and Ming Hu Han here.

[00:04:17] And then conversely, we take the similar approach in the opposite direction, where we identify the target and then develop the animal model around that particular target.

[00:04:26] **Jon Depierro:** Yeah, what you had mentioned about working so closely with clinicians is so important and so central to what we do at Mount Sinai.

[00:04:32] We get people doing different levels of analysis, different levels of work with patients or in the laboratory together in the same room, working together on projects. That transdisciplinary work is something we really pride ourselves on.

[00:04:45] **Scott Russo:** A hundred percent. You know, psychiatric brain diseases in general, but maybe psychiatric diseases in particular, are extremely complex, maybe amongst the most complex diseases that we've studied.

[00:04:57] And I think because of that, it requires a village and it requires a very diverse village with people that bring unique skill sets that range from clinical science to basic science and everything in between.

[00:05:08] **Jon Depierro:** So can you give us an example of how you've looked at resilience in your laboratory?

[00:05:14] **Scott Russo:** Yeah, sure. Yeah. Why don't I start with kind of a historical perspective? We have several animal models that we've developed. Uh, and again, as I mentioned before, these are based on the idea that applying a given stressor to a human is one of the major precipitating events that causes mental illness.

[00:05:31] So we apply various stressors to our mouse models, and one in particular is a social stress. This would be equivalent to, um, being bullied, maybe, if you will, and we apply this bully stress for chronic periods of time.

[00:05:42] And when we do that, our mice have unique individual responses to stress that range from being very vulnerable and exhibiting behavioral deficits and syndromes and symptoms that look a lot like depression, to those that are completely resilient and have no deleterious effects to that.

[00:05:58] And so, again, we try to kind of pattern our studies around the clinical literature in some ways and, and more, most recently, what we've found, and this was based on observations in humans following such traumatic bullying-like experiences or traumatic stress, individuals developed, or at least certain individuals will develop a syndrome that's marked by severe social avoidance, and prominent deficits in their ability to experience social contacts as being rewarding.

[00:06:30] We thought that we could model this in our mice. So we applied our, our social stress to our mouse model and we find effectively the exact same phenotype. Mice show reduced social interaction, and we proved that that was because those mice now viewed social experiences as being traumatic and not very rewarding, and so they avoided contact with them.

[00:06:52] **Jon Depierro:** Yeah. That's really fascinating. In the clinical psychology world, in humans we call that overgeneralization. So when a person goes through a traumatic event, they begin to associate that sense of danger with things that are directly related.

[00:07:08] So, for example, if they were in a car accident. They might feel anxious when they get in a car again, those first few times afterwards.

[00:07:16] But they also might feel anxious for things that happened to be around in the environment. Like the road they were on where the accident took place, or somebody else that was in the car with them, or they might avoid going out of their house entirely.

[00:07:27] So, something that's not exactly the traumatic stimulus, becomes, or gets all that emotion and memory attached to it. So it sounds like your mice, are bullied or socially excluded by one or two other mice in the laboratory.

[00:07:44] And then might expect that that's going to happen to other mice that they encounter and so they rather than enjoying hanging out with other mice,

they feel anxious and fearful and have almost a sort of PTSD response in the presence of a stimulus that's not actually threatening them in that moment, which is characteristic of human responses in PTSD.

[00:08:05] **Scott Russo:** Exactly. I think there's so much to be shared or learned because of these shared mechanisms. And, and you described actually our model perfectly on-target. So, effectively the way that we do this is, we usually select a large, fairly aggressive mouse that has a different coat color.

[00:08:21] It's a different strain. So it's kind of unique in that sense. It's a novel type of a mouse. It's an adult male or an adult female, and the social defeat ensues when that larger, aggressive adult male or female comes in contact with a smaller, more subordinate adult male or female.

[00:08:40] And what's really interesting is that those mice that experience that social subordination from those larger aggressive adults end up avoiding all social cues, independent of sex, independent of age.

[00:08:53] So if you put a small pup, same sex, same strain, they'll also avoid that small pup. So they do seem to really be generalizing this negative social experience, and that's then driving their choice to interact or not, and certain individuals choose not to interact under those circumstances.

[00:09:09] **Jon Depierro:** So you have a mouse model of schoolyard bullying.

[00:09:13] **Scott Russo:** Yes, indeed. Exactly.

[00:09:15] **Jon Depierro:** And the behavioral consequences that we see in that in young children, including depression and a lot of internalizing.

[00:09:22] **Scott Russo:** That's exactly right. And, what's great about this model that we now have is we've got behaviors that are very relevant to the human condition.

[00:09:30] We've got a model that, at least, ethologically seems valid and relevant. And, it seems like it aligns very nicely with the human condition. But now with the mouse, we're able to go back in and understand the brain circuits that control these types of generalized avoidance behavior.

[00:09:47] And that's really the benefit of our program is we can now go back in and with highly sophisticated and somewhat invasive tools.

[00:09:53] We can identify the brain regions that are activated in response to this bullying and then test whether or not they're the culprits in terms of driving the avoidance behavior that we see, the generalized avoidance behavior.

[00:10:04] **Jon Depierro:** So you've shown that you're very good at making mice depressed. Where does resilience come in? Do you see, for example, mice that are socially defeated and don't end up showing depression?

[00:10:16] **Scott Russo:** That's exactly right. Approximately, the numbers vary a little bit, but if you look across the broad populations of animals that we've studied over the years, a little more than half show what we call susceptibility.

[00:10:28] They have very, very strong and severe social avoidance and a whole host of other behaviors that we think are relevant to depression and anxiety, but the remainder of animals, much like humans that are exposed to stressors in the world, are relatively healthy.

[00:10:42] You know, they brush it off. They exhibit, uh, unique coping strategies and skills that we think protect them from the major deleterious effects of the stress.

[00:10:51] And maybe what's most striking is that for years, we thought, Well, some individuals, maybe they're just not getting bullied as much or they're just not remembering the negative experience, because maybe they have learning problems.

[00:11:04] But actually what it is, is that there's active processes, both at the behavioral level and then at the biological level, that can help us to really understand why and how animals can be resilient, even in the face of very deleterious and maladaptive stressors.

[00:11:17] **Jon Depierro:** So what are some of the helpful things that you see them doing?

[00:11:21] **Scott Russo:** So, there are behavioral strategies that they adopt within the session. So for example, you know, one of the maybe best strategies to limit the negative effects of bullying is to get out of that situation, actively remove yourself from that situation.

[00:11:35] And we do find that resilient mice tend to try and engage in behaviors that would allow them to more actively avoid those situations.

Sometimes they fight back. You know, they push back the bully and they can limit the bullying in that way.

[00:11:48] And what we find is that when animals engage in those types of what we call active coping processes, they're doing something actively to remove or limit the stress, those are the ones that tend more likely to be resilient.

[00:11:59] The susceptible mice are the ones that succumb and show these really severe behavioral phenotypes, oftentimes give up. They kind of throw their paws up in the air, take on a very docile body position, and allow the attack to ensue.

[00:12:13] So, that's an interesting kind of behavioral way of predicting which animals will be more or less resilient.

[00:12:18] **Jon Depierro:** And again, my clinical mind is lighting up because in the trauma literature, we see lots of different kinds of responses. We see the flight or flight response, which you're essentially saying is a marker of some of these resilient mice.

[00:12:31] They either try to fight their way out of the situation or escape the situation by physically escaping the situation. But in humans, particularly in humans, maybe this isn't the case in mice, but in humans who've had a lot of trauma in their past, there's more likelihood of a freeze response, shutting down.

[00:12:49] Sometimes their heart rate decelerates pretty dramatically. They might feel numb or have an out of body experience, where essentially, their brain is taking them out of the situation.

[00:12:59] And that tends to be associated with greater downstream effects. Those individuals who freeze during a trauma or afterwards as a way of managing emotions tend to be the ones with the most symptoms and most functional problems in their life.

[00:13:15] **Scott Russo:** That's really interesting. I think there's lots of parallels with our mouse model.

[00:13:18] And we and others have tested a bit, but there's definitely an enhanced fear and startle response in some of these mice following the trauma and we think that that actually is driving some of the more generalized fear to like these social targets, for example.

[00:13:32] A lot of the autonomic stuff starts coming online and a lot of the symptoms that you described seeing in human patients are what we visualize in our mouse models going forward from there, too.

[00:13:42] So yeah, no, I think there's so many parallels and now what we're really trying to do is, we're trying to dig into the biology of it. Cause at the end of the day, I think from a therapeutics perspective, PTSD is a very challenging disease to treat.

[00:13:56] And we need new tools in the toolbox. And we need a range of tools, from pharmacology to maybe, new methods like transcranial stimulation or deep brain stimulation, you know, that really kind of takes advantage of the broad literature and growing understanding of circuit biology that we have as a field.

[00:14:12] **Jon Depierro:** And new psychotherapies, too.

[00:14:14] **Scott Russo:** Indeed. Yes, I am a psychologist by training. Thank you, Jonathan.

[00:14:19] **Jon Depierro:** Or at least better spreading around of the therapies that we know work.

[00:14:24] **Scott Russo:** Absolutely, yeah.

[00:14:25] **Jon Depierro:** Because that's a major issue. Even with, drug studies, we have a really nice treatment that we know works. We need to train people to deliver it and getting it to the people that need it the most is always the issue, of pretty much any treatment in medicine.

[00:14:39] We could have a wonderful treatment, but it might reach only 10 percent of a population that needs it.

[00:14:43] **Scott Russo:** Yes. And you know, it's interesting you mentioned therapy, because I do think therapy is, from my training, it should be the, frontline treatment.

[00:14:50] I mean, that was what we should be aiming for at the starting point, and then moving to more invasive or challenging or therapeutic strategies using drugs, for example. But, you know, we've had several examples where we've tried to mimic mouse psychotherapy or develop mouse psychotherapy.

[00:15:07] **Jon Depierro:** I was going to ask about that. Are you becoming a mouse therapist?

[00:15:10] **Scott Russo:** We are. You know, it's great. I have a little couch. It's tiny. No, but seriously, you know, there are certain things, for example, that I think transcend organ systems, right? Organisms, different types of organisms from the rodent models that we use to humans.

[00:15:22] And one of them, for example, is, is social interaction, social contact. So, for example, if we take animals and we put them through this very long, bullying protocol and then we, phenotype them and determine whether they're susceptible or resilient.

[00:15:35] If we take those susceptible mice and we reintegrate them into social groups and let them normalize their social behavior in those ways and experience safe positive social contact, those mice can recover.

[00:15:51] There's even a possibility for us using more novel and interesting strategies. Cognitive enhancement, for example, which we know is great in humans for a lot of these conditions.

[00:16:00] We have some evidence that if we train animals in these cognitively challenging ways, that at the end of that training, we can promote a more resilient response following a stressor.

[00:16:09] **Jon Depierro:** They have a more flexible brain.

[00:16:11] **Scott Russo:** More flexible brain, and they can adapt and they can change their strategy, I think. So yeah, absolutely.

[00:16:15] **Jon Depierro:** That's really fascinating. I was thinking about, a lot of what we do in human work in treating a patient with PTSD is exposing them to new environments and helping them to feel safe in those environments, doing as much as we can to challenge assumptions they might have about how threatening something is, to have a space where they talk about their trauma and realize that it was in the past and it's not in the present to make that distinction in their brains.

[00:16:42] And to push themselves to do new things, rather than to avoid and withdraw. And it sounds like you've been able to do that. You can make someone sort of resilient at the end of the day after having gone through some amount of suffering.

[00:16:56] **Scott Russo:** That's right. And again, it's broad. I mean, you can use behavioral strategies. Kind of another interesting, maybe further upstream, strategy that we've used is a bit more invasive, where we've used new tools that allow us to isolate certain nerve cells in certain brain regions that we find to be associated with social trauma.

[00:17:14] And we can turn those nerve cells off using a fancy viral tool, which I won't get into the details, but we can turn those cells off. And what we find under those circumstances is that, those cells that are hyperactivated are actually detecting threat. Inappropriately detecting threat.

[00:17:31] **Jon Depierro:** False positives.

[00:17:32] **Scott Russo:** False positives, right? So you see this social target that's completely non-threatening. Maybe even cute and sweet if it's a pup. And those threat centers start going crazy in our susceptible mice. If we silence those, we can promote normal, healthy interaction.

[00:17:47] And I think if you wanted to kind of extend that to the human world, a great starting point would be, for example, TMS, when we can use certain protocols that would ultimately silence a given brain area.

[00:17:58] And we can maybe do that in the context of safe social interactions, clinically speaking, and then maybe what we would ultimately do is reduce the types of kind of social traumas that these individuals have experienced.

[00:18:11] **Jon Depierro:** And what you're alluding to also is some of the work that's being done here at Sinai. There's a lot of work on transcranial stimulation. There's also a lot of work from our colleagues on ketamine- assisted psychotherapies.

[00:18:23] So, taking a drug in the context of a supportive psychotherapy for PTSD or for depression, opening up the brain's ability to change and giving people sort of processing power as well during that time. Being with somebody who's safe and maybe relearning how to interact.

[00:18:41] **Scott Russo:** Yeah. That's a great point. You know, you mentioned ketamine-assisted. Also of interest to us is psychedelic-assisted psychotherapy. And I can say that in our models, both treatments, of course, it's harder to really control for the assisted therapeutic part of it, the human contact part of it, but both ketamine and psilocybin derivatives are antidepressant or they promote resilience in our social defeat stress model.

[00:19:04] So there's a lot there and I think a lot of corollaries that could be lined up nicely with the human literature to see whether or not it's similar circuits and similar mechanisms that these antidepressants are acting upon.

[00:19:15] **Jon Depierro:** I was thinking that you'd have them hold the hand of a nice, gentle mouse during their ketamine session.

[00:19:21] **Scott Russo:** We did, um, There was a series of studies a former trainee of mine did they tested whether or not having a buddy present while you are experiencing the trauma, whether that somehow blunted and, and it does in certain circumstances.

[00:19:34] It's not perfect. But there is this idea that having social support can blunt the negative effects and it can push more individuals away from a susceptibility phenotype and towards a resilient phenotype.

[00:19:45] **Jon Depierro:** So they they go back to their cages and say, boy, wasn't that awful? I'm glad you were there with me.

[00:19:49] **Scott Russo:** They commiserate with one another and the stress isn't so bad.

[00:19:52] **Jon Depierro:** Yeah, that's exactly also sometimes what we find in humans, too. Having somebody who's going through the thick of it with you, we actually saw that so much in the pandemic. One of the things that our healthcare workers found most helpful is having a buddy.

[00:20:05] Having somebody they knew on the floor with them, or a supervisor that they knew and trusted, that made it so much better. It was still bad, but it actually buffered against the development of PTSD and depression.

[00:20:15] **Scott Russo:** Yeah, that's really interesting. Imagine, mice can do the same.

[00:20:18] **Jon Depierro:** Yes, yeah, these are really powerful techniques that you've expanded upon.

[00:20:22] As we reflect on resilience, you mentioned mice, but I'm wondering about yourself. You do extraordinarily tough work. You apply for grants all the time. You have papers that go in and get nasty reviews, I'm sure, sometimes. What do you do? What are your strategies?

[00:20:40] **Scott Russo:** Oh, boy. Well, my wife is a psychiatrist, so that helps.

[00:20:43] **Jon Depierro:** My wife is a psychologist, so that helps.

[00:20:46] **Scott Russo:** So, it's very challenging. Like, I think it's, it's going to be individual for all of us. We all have to find our things that distract us from the challenges of life and make us feel optimistic about moving forward.

[00:20:58] Certainly having children, little children, to go home to is a huge help. You almost don't have time to reflect on the negative aspects of your day. You immediately go to parenting mode and you start thinking about what you need to do for your children.

[00:21:12] So, I've found that over the 10 years after, you know, my son was born and now my daughter, my rumination that happens at five o'clock until I go to bed has been really strongly diminished.

[00:21:24] And that's definitely helped me to maintain a more optimistic viewpoint. I exercise a lot. You know, I try to walk at least five or six miles a day. I do gym. I think exercise and diet are probably two of the most underrated therapeutics that we have in our toolbox.

[00:21:41] And there's so much evidence to suggest that these types of lifestyle changes are acting on some of the same mechanisms that antidepressants, for example, are acting upon, but they're doing it in a more natural way and, and I think that the lasting impacts of that is longer than it would be, for example, for more acute treatments.

[00:22:00] And then, lastly, it's funny, you have to be open minded. I, I just, I'll tell a, a little story about one of my students the other day. So if she's listening, maybe she'll laugh at this. But, she asked me how I was doing. I said, Oh, I've been really busy lately. Things have been a little bit crazy.

[00:22:14] And she was, she's very interested in mindfulness, and started asking me questions, kind of leading me down the mindfulness road. And it reminded me of a class that I took when I was respecializing in clinical psychology early in my training on mindfulness. This was 15 years ago.

[00:22:30] I had completely forgot about it, but some of those lessons I started thinking about and it really helped me to change my viewpoint. I started using some of those strategies, actively thinking about what was making me anxious,

and making some significant changes to that and trying to really listen to my body a little bit more.

[00:22:48] And that seems to be very helpful. So, mindfulness and meditation is another way that could be very useful for individuals if they want more naturalistic ways of promoting resilience.

[00:22:57] **Jon Depierro:** Yeah. I was sitting here thinking about how slow time passes when you turn off the TV. When I'm on the, on the days, maybe I wake up in the morning and I don't have the TV on, it feels like it's ages, but maybe it's just been a minute.

[00:23:10] But then, you could turn on the TV and you could watch six episodes of a show and by the time you know it, it's three o'clock in the morning, because you're not even looking at the clock. So I often tell my patients to do one thing at a time.

[00:23:23] In our busy world, focusing on one thing, particularly the thing that's directly in front of you at the moment, is usually the most effective thing to do. You could get bogged down in thinking about what you have to do five weeks from now, or a year from now.

[00:23:37] But doing one thing at a time and focusing on what the immediate need is, is very, very helpful. And even things like not eating while watching TV. Just, if you're eating, just eat. Don't try to do something else.

[00:23:49] Don't check your emails while eating because you're not going to taste your food and you'll get indigestion and you'll probably make a typo in your emails, because you're multitasking.

[00:23:56] Or maybe eating will have this negative association because you always do it while you're checking emails or dealing with something challenging. If you're just watching TV, watch TV. Don't try to have a conversation or eat at the same time.

[00:24:10] Those kinds of things are very powerful tools and it retrains the brain to be an attention mechanism. Because, it's so easy in our world, I know with my phone and with all the other things that we have, to get pulled in 16 different directions at once.

[00:24:24] And our brain can't do that. We're not a super, in some ways we are a supercomputer, but we're not a very good supercomputer at multitasking or

parallel processing. We can usually do one, maybe two things at the same time. And that second thing, usually not very well.

[00:24:41] **Scott Russo:** Yeah, yeah, no, that's really good advice. I think that is something that bogs a lot of us down. And, you know, trying to find ways of dealing with that. You know, you and I know very well, Jonathan, if we worried about all of our, of our upcoming due dates, we would get nothing done because there's so many of them. That's actually been a challenge for me.

[00:24:58] I don't know if it has been for you, but I, it's taken a lot of maturity and really growing and developing to be able to suppress those urges and increase focus. So, I appreciate that. I mean, I think it's a great skill set and one that we don't always focus on in psychiatry or in related areas as a therapeutic strategy to mitigate stress.

[00:25:17] **Jon Depierro:** Yeah, the thing I need to work on about my resilience is sometimes I overestimate how long it will take to do something and it, it makes it such a big thing in my mind. Oh, I have to write this paper and I have to make this table.

[00:25:30] I'm really putting it off. It's gonna take hours. And it turns out it takes 15 minutes, because you can take an old one and just change some numbers and then you're done, or at least you have a start.

[00:25:38] And then I'm always surprised when I do the thing and it doesn't take that long, and then I never, like, learn from that. It's always the, like, the next time I always think, you know, how long and how difficult something's going to be, and it often is not, because I've done something like it before.

[00:25:52] **Scott Russo:** That's funny you say that. I'm exactly the same way, I think probably most of us are. The question is, is, What kind of strategies would you recommend to hone that skill set?

[00:26:00] Because it is important, right? Like, I mean, I do exactly the same thing. You know, I gear up to write a big grant, for example, and I think it's going to take me exponentially longer than it does.

[00:26:10] And I'm, very, very anxious about it. How do you deal with that on a day to day basis? And how would you coach your patients to deal with that as well?

[00:26:17] **Jon Depierro:** Maybe those are two different questions.

[00:26:18] **Scott Russo:** Yeah, exactly.

[00:26:20] **Jon Depierro:** One of the things that I try to do, and I try to coach my patients in, is to do the smallest possible amount of the thing.

[00:26:28] So, if it's a grant application or a paper, write the cover page. Write two sentences. It doesn't even have to be two good sentences, but at least you've broken the ice.

[00:26:38] And if you did two sentences every day for two weeks, you'd have, at the end of the day, your aims page or whatever it is that you needed. So you break it up into these teeny, teeny pieces, almost an imperceptible amount of the thing.

[00:26:50] And then it gets the momentum going. And you say, Oh, it's not so bad, I've done this already, and I can just do a little bit over here and a little bit over here. And if you want to ask for help on this part, that's the other thing that I really encourage my folks to do, which is to reach out for help.

[00:27:04] If you have colleagues you're doing something with, carve out what section is for them and stick to it. It's easy to think, Oh, it's so much easier for me to do it myself. But then you end up taking on many more responsibilities and becoming resentful of other people for not stepping up, but you might not have given them the chance to help out.

[00:27:23] **Scott Russo:** Yeah, that's very good. That's very important feedback, I think. Or if you're the boss, being able to delegate. Being able to trust other people.

[00:27:30] **Jon Depierro:** To give up a little bit of control. Yeah, exactly.

[00:27:34] **Scott Russo:** Yeah, we have that problem in science, don't we? Science and medicine.

[00:27:37] **Jon Depierro:** We like to do things ourselves. We think we know best. One of the things this reminds me of is you had mentioned in an earlier conversation that sometimes you see mice that have sort of earned their stripes in some way.

[00:27:52] They go through something really challenging and they're almost better for it at the end of the day. You might describe them that way. Can you

tell us a little bit about those mice who've been through some stuff and learn from that experience?

[00:28:03] **Scott Russo:** Oh, absolutely. One of the things that predicts human pathology, not just psychiatric pathologies, but also organ system diseases, risk for cardiovascular disease, for example, is social status.

[00:28:15] In humans, we call it socioeconomic status and we base it on how much money we make. Maybe that's not the best way to measure social status. But anyways, that's our human definition in mice. We have corollaries of it. It's your dominant status within a hierarchy, within a cage of peers.

[00:28:31] And that's based on your access to food resources and otherwise other resources within the environment. So we predicted, much like would be predicted from clinical literature, the higher up you are on the socioeconomic ladder, the more resilient you are to a whole host of brain diseases and peripheral organ diseases as well.

[00:28:49] We predicted the same would be true in our mouse model. So the way that we did this, there are several tests that you can apply to determine social hierarchy. For example, who gets, who has access to the most food in the cage?

[00:29:02] That's one way. Who has access to the best resources for that? We take a cage full of mice that have an established hierarchy and we put the entire cage on an ice floor. So it's cold. It's cold to touch. It's not dangerous, but it's certainly uncomfortable.

[00:29:18] Nobody wants to walk around in bare feet in the ice. And one little tiny spot in the corner that can fit one mouse is heated with a heating pad and a small hut above the heating pad. The animal that's dominant, that gets the most food resources also gets the hut.

[00:29:32] And so these are ways that we can kind of determine mouse hierarchies, who's dominant, who's subordinate. And it turns out that we were only partially right that the more dominant animals would be more resilient.

[00:29:44] Actually, there was initially no difference. And when we dug deeper into it, we noticed something interesting about the hierarchies themselves that was important. So within a given hierarchy, you've got, say, five mice, and they're fighting, they're both, you know, they're vying for being the top dog.

[00:29:59] And as those hierarchies form, sometimes they're very stable. So one dominant mouse comes in and he or she just takes over everything and stays dominant throughout the entirety of the session.

[00:30:13] In other cases, they're much more plastic and you know, a dominant animal is being knocked off its perch by a subordinate animal and there's a lot of flexibility.

[00:30:23] We found that resilience promotion was dependent upon not only being dominant, but that you had to work your way to the top. So maybe you started out as subordinate and you really had to fight your way, claw your way to the top to become dominant.

[00:30:35] Those are the individuals that were most resilient to the, uh, deleterious effects of the stressors. And the way that we interpret that is, is that, that having to really, uh, experience adversity, much like in humans, helps you to develop coping skills.

[00:30:50] And that development of coping skills then translates into future experiences that are negative, i. e. being beaten up by a larger aggressive bully.

[00:30:59] Jon Depierro: And I can also imagine that it might put some new stressors into perspective. I'm not sure what goes on in the mice brain, but they might say something and mice speak like, Hey, this isn't so bad. I've been through worse before. I can take it.

[00:31:12] Scott Russo: Yep, absolutely. And conversely, right? So what about the animal that was really dominant and always dominant, right? You know, you could think about that as somebody that, you know, might have had a fairly easy go of things and didn't have a lot of adversity in their lives.

[00:31:27] They always kind of had access to enough resources and never had to really fight or, \ bully others around. And now they're experiencing this really uncontrollable social aggressor that they can't fight back against and I think maybe that also creates a situation in, in their brains that then causes them to be a little bit more vulnerable.

[00:31:45] Jon Depierro: They have no toolbox to deal with those things, because they never had to.

[00:31:48] Scott Russo: Exactly, yeah.

[00:31:49] **Jon Depierro:** I'm also thinking some of those dominant mice, it's probably not an easy go for them in terms of like their stress physiology. I could imagine, especially if there's a lot of other mice around, there's a sense that I have to like, maintain my position.

[00:32:00] I have to be on guard, I have to be vigilant. There's always going to be somebody coming to depose me. And I need to be like in this fight or flight mode all the time, which is probably an ongoing low level chronic stressor.

[00:32:11] **Scott Russo:** That's exactly right. You know, and one of the things that's clear is that, the state of the hierarchy really determines who's going to be resilient and not, depending upon their status.

[00:32:20] And what I mean by that is, in our laboratory, right, we have relatively benign conditions, we'll put it that way. You know, our animals live in very nice quarters, they overlook Central Park, they've got really good lives, they have free access to food, so they're never starving.

[00:32:33] There's no limitation in resources, really. And under those circumstances, these dominant hierarchies are established, and this is what it leads to. But let's go out into the wild, where those hierarchies are quite a bit different.

[00:32:45] There's a lot more competition for resources. And being the dominant animal under those circumstances is, like you said, highly stressful. If you were to take a blood sample and do a neurochemical assay to assess stress, all the stress markers that you would predict are through the roof.

[00:33:01] And we think actually, well, not just we, I mean, others have shown that that, increase or that change in physiology associated with dominance under those circumstances is actually deleterious to a lot of both your immune system, your resilience levels, your ability to kind of cope, as well.

[00:33:17] So, you know, it really is highly dependent upon hierarchy structure, society structure.

[00:33:21] **Jon Depierro:** Clinical psychology would say that chronic stress is a killer.

[00:33:24] **Scott Russo:** Yes. Yes, absolutely.

[00:33:26] **Jon Depierro:** And we see that in chronic PTSD, too. You probably see this in your animal work. Those animals that have been exposed to long-standing stress over and over and over again, they might develop behavioral patterns that are less easy to change.

[00:33:40] They're more ingrained. Their physiological changes are more significant. And we see that in humans. Patients that I've seen, for example, who've had PTSD for 20 or 30 years. Their bodies are actually much different than somebody the same age who maybe got PTSD and the symptoms are a month old or two months old.

[00:33:57] **Scott Russo:** Huh. That's interesting. You know we think about psychiatric disease and all the behavioral disturbances that arise from it, but in reality, these are whole-body syndromes. You know, if you look at comorbidities from, for example, PTSD or depression, there is exponential increases in risk for things like cardiovascular disease.

[00:34:16] If you have a chronic illness and you become depressed, you're much likely to bounce back from that chronic illness. So we've actually studied this a little bit in our mouse models because they're useful not just for studying behavior, but also for studying physical organ health.

[00:34:29] And I'll just give you an example, because it was a fun collaboration that we did here with Phil Swirski, who leads our Cardiovascular Research Institute. His lab is interested in cardiovascular disease and the negative effects of stress on cardiovascular risk.

[00:34:42] In particular, the formation and the progression of arterial plaques that then lead to cardiovascular events. What we found, actually, was that social stress increases the risk for cardiovascular plaque formation and rupture.

[00:34:55] So, in essence, our mice have an increased risk for heart attacks and stroke. And he then went on further to understand why. So, why would a brain disease, why would your perception of stress in the central nervous system, in the brain, lead to a disease like a plaque forming on the arterial wall and causing a heart attack?

[00:35:14] Well, it turns out that the brain actually projects directly out of the body, or out into the body, I should say, not out of the body, and it innervates bone marrow. What's important about bone marrow is, it's where we produce all of our immune cells.

[00:35:28] So now you've got this circuit, if you will, from stress centers in the brain that become activated when you experience psychological stressors. They then cause inflammation.

[00:35:38] They cause inflammation by secreting factors into the bone marrow which then lead to immune cells being more produced at higher levels and then released into the bloodstream.

[00:35:47] Those immune cells traffic to the cardiovascular plaque and that's what increases the progression. So we now have a specific mechanism to link brain to body to understand comorbidities.

[00:36:00] And it turns out the same resilient animals that are behaviorally resilient are also resilient to the deleterious effects on cardiovascular risk.

[00:36:07] **Jon Depierro:** That's no surprise, because there's that interaction, you'd expect both spheres to be resilient.

[00:36:14] **Scott Russo:** And, you know, human researchers have known this for years, but it's really nice. I think it's really rewarding to be able to see this in other species and then test potential common causal mechanisms.

[00:36:25] Now, of course, we can't do the same types of invasive strategies to test the brain-body theories in human depression and PTSD. But when we've analyzed blood samples, we do see similar immune profiles.

[00:36:36] So it does argue that there is a similar mechanism, brain to body, that's mediating the deleterious effects of stress on the immune system and peripheral organ disease in humans as well.

[00:36:46] **Jon Depierro:** And there might be treatments focused on the immune system that could be effective for depression and stress-related conditions.

[00:36:52] **Scott Russo:** That's exactly right. You know, there's been several attempts that have shown some promise. For example, infliximab, which is used for, I believe it's rheumatoid arthritis.

[00:37:00] It's a TNF alpha inhibitor. And then, Serucamab, which was an IL-6 monoclonal antibody developed by Janssen Pharmaceuticals that didn't pass FDA trials for its primary target, so it's no longer a drug that's being considered.

[00:37:13] But both of those trials showed some, um, positive effects. So, Serucamab, the IL-6 inhibitor, was able to reduce anhedonia in a depression cohort.

[00:37:21] And TNF alpha, at least in patients that have heightened inflammation, it was an effective antidepressant and was able to reduce depression severity based on a Hamilton D rating scale. So, very nice and could potentially be used clinically, I think, to treat certain types of depression.

[00:37:38] **Jon Depierro:** I'd love to hear over the course of your career, from graduate school to becoming a junior investigator to now senior investigator in charge of lots of folks, how has your thinking about resilience and stress changed over the years?

[00:37:52] **Scott Russo:** It's a really good question. I think early on, my thought process was that individuals experience stress in different ways, of course, and we, we knew that from the beginning, but that really this concept of resilience was more related to our bodies not responding in a certain way and therefore not causing disease, right?

[00:38:13] For example, in the case of stress eliciting some immune response in a more susceptible animal, well, a resilient animal simply doesn't have that same immune response it's lacking. Now we're really starting to think that resilience is not just the absence of a response.

[00:38:30] So, it's not a control condition for other, in other words, it's an active and different and unique response to a stressor that helps the animal adapt. And I think that was the concept that wasn't part of my thinking early on.

[00:38:44] And what's, what's interesting and I think important about that concept is that it opens up a whole new area of investigation. Rather than trying to reverse the pathological mechanisms that are induced by stress to treat someone that's depressed, what if we can enhance natural resilience mechanisms?

[00:39:00] What if we can make the response in the more vulnerable individual to look more like a resilient animal, and create a whole new class of antidepressant therapeutics in that way?

[00:39:08] I think, to summarize it in a word or two, resilience is active adaptation that's different than susceptibility, but also different than an unstressed context or condition.

[00:39:19] **Jon Depierro:** And that's kind of what you've come to over the course of your career.

[00:39:22] **Scott Russo:** Exactly. Yeah, it's been, it's been a slow evolution, but a fun one.

[00:39:25] **Jon Depierro:** And we see this in human work too. This is a bit of my soapbox. That there's been a lot of attention on understanding risk factors for PTSD, and maybe you look at thousands of people after a traumatic event, and maybe 15 percent develop PTSD, and you say that's the PTSD group, and you have a group that doesn't develop PTSD, and you call that the resilience group, and you sort of end it there, not really understanding why those folks who are the 85%, maybe who don't develop PTSD, are resilient.

[00:39:55] The other thing that your work, I think, begins to hint at, and certainly I see clinically, is that that might not be a sufficient definition of resilience. Simply not developing the pathological condition, like depression or anxiety or PTSD, after stress or after a trauma, that might not be the richest way of thinking about resilience.

[00:40:18] I, for example, think about resilience as that, plus understanding how people recover when they do develop symptoms, because we have to admit that there are stressors that are overwhelming, that do overwhelm even the most adaptive people. You know, we see our Special Forces operators get PTSD, they've had decades of training.

[00:40:40] The magnitude of the stress can overwhelm someone's coping. And the question for me, and the question maybe you're beginning to look at in your mice is, Okay, so that happens to you, you begin to show some behavioral changes.

[00:40:52] What can we do about it? What do you do about it? And that process of recovery is the added piece of how I think about resilience, because someone who is resilient from the start and someone who has recovered can look very similar months out, but we don't typically think of those recovered folks as resilient.

[00:41:09] We don't see the strength in our patients as much, I think, as we should.

[00:41:13] **Scott Russo:** I like that a lot. In fact, we've been starting to think in those terms, but, um, more and more, I'd like to integrate those concepts that you just mentioned into my research project.

[00:41:20] Can we develop animal models of recovery and see if we can promote active resilience during those recovery periods to make them well even sooner. I like that a lot.

[00:41:29] **Jon Depierro:** That sounds like a lot of fun.

[00:41:31] **Scott Russo:** Definitely.

[00:41:31] **Jon Depierro:** Yeah, this is all very fascinating work and I really thank you for your time in the studio and I look forward to talking to you more and working with you more.

[00:41:39] **Scott Russo:** Absolutely. This better spur our collaboration, but it's been a lot of fun. Thank you for having me. I really appreciate it and it's been fun talking to you.

[00:41:47] **Stephen Calabria:** Thanks to Drs. Depierro and Russo for appearing on today's show. For more information on Dr. Russo's work, check out the most recent issue of the Nature Journal, in which Dr. Russo and his team unveil new research into the role played by immune cells in times of stress.

[00:42:02] That's all for this episode of Road to Resilience. If you enjoyed it, please rate, review, and subscribe to our podcast on your favorite podcast platform. Road to Resilience is a production of the Mount Sinai Health System.

[00:42:12] It's produced by me, stephen Calabria, and our executive producer, Lucia Lee. From all of us here at Mount Sinai, thanks for listening, and we'll catch you next time.