

Your Brain is Tough Transcript

Stephen Calabria: [00:00:00] From the Mount Sinai Health System in New York City, this is Road to Resilience, a podcast about facing adversity. I'm your host, Stephen Calabria, Mount Sinai's Director of podcasting. It turns out our brains are tougher than we'd thought.

Every challenge we face, joy we experience, relationship we build, they all leave a mark on our brain. On today's episode, we have Dr. Eric Nestler, a renowned neuroscientist and the dean of the Icahn School of Medicine at Mount Sinai.

Dr. Nestler spent his career exploring how stress, trauma, depression, and addiction reshape the brain and why some people recover while others remain stuck.

We'll explore what modern neuroscience can teach us about overcoming adversity, protecting our brain health, and cultivating resilience, not as an abstract ideal, but as something each of us can strengthen one experience at a time.

Dr. Eric Nestler, welcome to Road to Resilience.

Dr. Eric Nestler: Thanks for having me.

Stephen Calabria: So sir, you've spent decades studying why some [00:01:00] people develop depression or addiction after adversity, while others seem to emerge stronger. One might call it brain resilience.

When people hear the phrase a resilient brain, what do you hope they understand that they may not already know?

Dr. Eric Nestler: Sure. There's broad variation in the ability to adapt or cope with challenges that we face in everyday life. Two examples of that would be our vulnerability to become addicted after trying a drug of abuse, or the ability to remain functional, happy, healthy, despite being subjected to horrible stress.

And in fact, we know that in both of those circumstances, most people are able to avoid serious illness. So in the case of drugs of abuse, an example would be cigarette smoking. Almost everybody would try a cigarette or so during high

school or college, [00:02:00] but the vast majority of people do not become addicted to nicotine.

So we would describe that as a brain that is at least partly resilient to the addicting effects of nicotine. Similarly, we know that unfortunately, people get exposed to horrendous levels of stress in combat, in war zones, or physical and sexual abuse in the community, but most people somehow manage to function okay despite that stress.

So there's something about most individuals that enable more coping and while a smaller subset of people are vulnerable. One critical point to make is that a brain that is resilient to one thing might be vulnerable to another, and vice versa.

So I don't like to think of people being resilient or not resilient, because I think most people are resilient to some [00:03:00] things, it's just that they're also more susceptible to other things.

Stephen Calabria: One of the things that has stood out in several recent interviews you've done was your father and your relationship with your father. You've talked about your father's love of music and perhaps- Yeah more importantly, his recall of that music later in life.

Dr. Eric Nestler: Yes.

Stephen Calabria: How did that influence the way you see the potential of the human brain?

Dr. Eric Nestler: Yeah we know that there's something about music, but all art, visual arts, performance arts. There's something about art and humanities overall that influence the brain in ways that are different from conventional ways, basically asking somebody to think of something.

Music, art, accesses parts of the brain that are different, and therefore, art and music and related approaches allow people to understand brain function in ways that would [00:04:00] otherwise not be possible, and likewise be able to help people with a brain disorder who otherwise are not responding.

The particular example to which you're referring about my dad was that he was very demented later in life. He was well into his late nineties, and he was mostly silent, hard to engage him in a conversation. And then all of a sudden, music came on from his young adulthood, and he would start singing the lyrics of the song.

And it would be amazing. And my own children, who were young adults at the time, were just flabbergasted at the capacity of music to draw out parts of my dad that were still in his brain, even though they were otherwise inaccessible.

And that's what we're finding in general whether it's using music in the neonatal intensive care unit to help babies develop during this very precarious early phase of their lives, whether it's people [00:05:00] with Parkinson's disease using dance to move with a fluidity that otherwise they would not be able to muster, or whether it's people with Alzheimer's disease or related dementia like my dad being able to appreciate some aspect of social interaction and cognition that was otherwise unavailable to them.

Stephen Calabria: For years, it seemed many people thought the brain was relatively fixed after childhood. Today, we know it's constantly adapting. How does that ability to change shape the way we think about recovery from trauma, loss, or chronic stress?

Dr. Eric Nestler: Yeah, absolutely. So this was something in medical school 40 or so years ago. I learned that the adult brain is mostly fixed, and that if pieces of the brain and its functions are lost, they're lost forever.

And we know that's just not true, that the brain retains enormous [00:06:00] reparative capacity throughout life, and that the brain really can recover from severe injury and disease even through advanced aging.

It offers tremendous hope for people with a brain injury or illness in that it means we can optimize that repair and regeneration of function, and make a person respond better.

Stephen Calabria: Not only does that repair exist, but it's also a biological process, an active process. How does that play out inside the brain?

Dr. Eric Nestler: We're still learning precisely how that occurs. We do know that in the vast majority of cases, it does not involve the generation of new nerve cells.

The one thing that remains true, from what I learned decades ago, was that the brain, except for very small parts of the brain, does not generate new nerve cells. So when we lose nerve cells and lose their [00:07:00] function, it means that other nerve cells need to pick up that lost function.

And we're understanding how it is that nerve cells in a different circuit, in a different part of the brain adapt to the loss of other nerve cells in order to replace a function that's been absent or lost.

And our goal now is to better understand that so we can promote that process, enhance it, and increase the extent to which it occurs.

Stephen Calabria: You mentioned earlier that two people can experience the same hardship or the same trauma but have very different outcomes. Why does the brain respond so differently from one individual to another?

Dr. Eric Nestler: We think that the individual differences across individuals and our ability to adapt in a coping manner with challenges in the environment are partly genetic and partly non-genetic. [00:08:00] The genetic piece in some ways is the easier one to understand.

We now can sequence a person's entire genome. A genome is three billion nucleotides long comprising about 20,000 genes, each of which encodes a protein and that subserves a function. That's a tangible process for discovery.

We don't have all the answers yet. There's still a tremendous amount that we need to learn about how each gene, each protein contributes to brain function, but it's a tangible process that is now well underway.

So we can identify now the individual genes acting in individual types of brain cells that are the reason why one individual is more resilient or more susceptible to a particular challenge in the environment, say, a type of stress.

The other half of the equation is more complicated. And I think that is best illustrated by the [00:09:00] fact that we do many of our studies on what's called genetically inbred animals. So this is a type of mouse or rat that is genetically identical to the rest of the groups of animals. It's like having hundreds of identical twins in a laboratory with an endless supply.

So we can demonstrate that these individual variations in vulnerability or resilience to a drug addiction-like outcome or a depression-like outcome in an inbred line of rat or mouse is very robust, even with a constant genome, proving that genetics are only part of the process.

The question becomes then, what is that other piece? That is largely the environment. Every environmental exposure we have throughout life conditions [00:10:00] us to either be more vulnerable or more resilient to the next

challenge, starting in utero with the stage of an embryo and a fetus to childhood, adolescence, and then throughout adult life.

The positive aspect of that, we can actually train the brain, train a person to be more resilient, and that is an active area of research that we could get back to if you'd like.

Stephen Calabria: Are there similar processes going on in the brain of someone suffering from depression and someone sufferings from substance use disorder, or is it impossible to bifurcate the two?

Dr. Eric Nestler: I think there are areas of commonality. Both of the syndromes involve symptoms which we refer to as reward. Reward simply means the extent to which we're made to feel rewarded good, satisfied by something that happens to us.

Many people take drugs of abuse partly to feel good, to feel [00:11:00] better, to get that reward. Possibly the people who are more vulnerable to addiction are those who have a reward deficit, who can't get that good feeling on their own by a good social interaction, a good meal, or something like that.

So going back to the commonality of addiction and depression, likewise, involves a deficit of reward. It's called anhedonia, a loss of interest in pleasurable, rewarding activities, and so that's where the two syndromes overlap.

Stephen Calabria: Many listeners have experienced significant trauma whether it be from an illness, losing a loved one, abuse, or other life-changing events.

What have you observed to be the best, most effective, and practical ways people can bounce back from hardship?

Dr. Eric Nestler: There are many ways that a person can enhance their resilience to stress, and these have been written up extensively. [00:12:00] I'd recommend a book by our former dean, Dennis Charney, called Resilience.

I think it really is a wonderful exploration of how individuals have found a path toward resilience, and it provides steps that people can take to boost their own resilience. What are the crucial ingredients?

They are things like learning how to be confident, gaining a social network where you have social supports, understanding the nature of the stress and what caused it and what it means for you.

And there is robust evidence that people can dramatically help themselves become more resilient, to a point obviously in the face of hardship. And so it's something that we recommend very strongly to everybody.

After all, I tell my own children this, I tell my students and other trainees and young faculty this, [00:13:00] that life is unpredictable. Life comes along with things that are sometimes not good, hopefully not devastating, but sometimes devastating also.

And the goal in life is to learn how to adjust, cope, adapt, and do the best you can under the circumstances. And that is a great lesson, and it's something that I think we all need to embrace and get better at, particularly in the age of stress that we've created for ourselves in the modern world.

Stephen Calabria: I'd like to linger on your point about social support for a second. Because in three years of hosting this show, it seems to be the one variable present in virtually every resilience story.

Could you talk a little bit more about the role of others, your people who have your back, in getting through difficult experiences?

Dr. Eric Nestler: Absolutely. We all know, regardless of what walk of life [00:14:00] we have or what the challenge may be, that having others to speak to, to share feelings and thoughts with, to get advice from is extraordinarily important.

And I, yeah I think it's, goes even further than that to the extent that it's likely that our social nature is in our DNA, that humans are a social species, like most mammals, that really require social interaction.

You could take a rat or a mouse in the laboratory and restrict its ability to interact with other mice or rats. After a period of a few weeks, we see dramatic declines in that animal's ability to function normally, eat right, sleep right, interact with other mice or [00:15:00] rats when given the opportunity to do so.

So I think it's the way our brains are wired because of our DNA that makes us dependent, and I use that word very deliberately, really dependent upon positive social interaction. We require it for health and wellbeing.

Stephen Calabria: Okay, so if someone is experiencing intense loneliness and doesn't feel the presence of a social network or social support, they could be suffering from depression, and they could perhaps think to themselves, "Maybe I'm just not a very resilient person."

What would you say to those sorts of folk?

Dr. Eric Nestler: First of all, I would remove the blame 'cause I think that, it's like I'm not resilient, it's my fault. That's not at all what we're saying. If a person is feeling that they're getting sick, that they're getting depressed, there are many ways to get help.

And if they're [00:16:00] concerned that crescendo of symptoms is being caused partly by loneliness and social isolation, they should seek help to become more involved in social settings.

There are many social networks, community groups, church organizations, sports organizations where positive social interactions are nurtured and fostered, and people should really seek those kinds of interactions and know that they're not facing something alone.

Stephen Calabria: For that same person who might be going through a difficult period, people often feel a kind of pressure to bounce back after hardship. Yeah. They're told, "Oh, just get over it. It'll pass. Just cheer up. Smile."

From a neuroscientist's perspective, is resilience really about returning to who you were before, or is it about becoming someone new altogether?[00:17:00]

Dr. Eric Nestler: That's a really important point. We all know in popular culture, pull yourself up by your bootstraps, right? Bounce back. That's not so helpful to people.

What's more helpful is to work with a person and help them use the tools within their own brains that enable them to overcome adversity and build that kind of resilience and coping ability, which as I, as we've discussed, is definitely possible.

Now, a person can get sufficiently impaired, sufficiently sick, whether it's depression or severe anxiety, post-traumatic stress disorder, or something like that, where the natural, the tools of natural resilience are just not strong enough.

And for those people, we need to figure out other treatments. For example, antidepressant or anti-anxiety medications. And we know empirically that when [00:18:00] people get severely depressed or severely anxious or have severe post-traumatic stress disorder, simply utilizing one's own innate tools is not enough. They need the help of medication.

And in fact, one way that we view medication is to boost the capacity of resilience. I will also say this is a good point to mention that one of the reasons why we're facing such an increase in the incidence of anxiety, depression, and PTSD, I think is due to the lockdowns instituted as a result of the COVID pandemic.

I think the lockdowns initially can be understood from the context of a new virus the world had never seen, we not knowing what that virus would bring, and us seeing our hospitals being overwhelmed.

And I'm talking about March, April 2020, being overwhelmed, overrun by people dying from the virus. [00:19:00] Where we went wrong was by maintaining the lockdown way too long. So I think back to the fall of 2021 to the Omicron craze, right?

Everybody remembers that fall where all of a sudden this mutated form of COVID was more infectious but less harmful. Meanwhile, anybody who wanted a vaccine was vaccinated, which also made the virus less harmful.

Almost no one who was vaccinated who got sick with COVID needed to go to the hospital. No one, unless they had an immune-compromised state. Yet we were telling people in Christmas 2021 not to be together with your families, because of COVID.

That was a big mistake that we should own up to and learn never to do again, because a lot of the consequences that we're seeing now in the high levels of stress and [00:20:00] stress related illnesses, I think is because of that extended lockdown.

Stephen Calabria: There seems to be a degree of subjectivity around these areas of depression and anxiety, and substance use disorder. Is there a set upon, agreed upon scientifically based diagnosis as to what constitutes either of these things?

Dr. Eric Nestler: You hit the nail on the head. The major challenge in psychiatry is that in 2026, we do not have an objective laboratory test to diagnose any of these illnesses.

No brain scan, no genetic test, no blood test, and that's the difference between psychiatry and every other branch of medicine. I have spent my 40-year career as a psychiatrist trying to get us to a better place, and I have not yet succeeded.

I feel I've contributed to the basic biological knowledge of these illnesses. Now we need to translate that knowledge into [00:21:00] improved diagnosis. In diabetes, there's no question. I can measure insulin blood levels.

I can do a glucose tolerance test and very clearly, quickly understand whether a person is insulin deficient and they need insulin, period. Very little ambiguity. In psychiatry, we use a list of symptoms called the Diagnostic Statistical Manual, or DSM, to diagnose depression or anxiety and differentiate those illnesses from the normal feelings of sadness and anxiety that everybody feels as part of living.

But that's just a list of symptoms, and those listed symptoms is simply not sufficiently objective.

Stephen Calabria: Also, during COVID and during lockdowns, we saw data that substance use disorder surged among certain populations. Your work has transformed our understanding of addiction and depression by showing that [00:22:00] experiences can literally alter how genes are expressed in the brain. Does that also mean positive experiences can help rewrite that story?

Dr. Eric Nestler: Most definitely. Just the way harmful, damaging, hurtful experiences can produce bad effects on the brain and cause addiction, depression, post-traumatic stress disorder, good things can have the opposite effect, and we know that's the case.

In fact, that's one way to boost resilience, is to be more active and exercise, eat well, have more social interaction, challenge your brain with all sorts of interesting, novel ways of thinking and calculating and feeling about things.

And that will change the brain through very fundamental processes involving changes in gene expression, changing the circuitry of the brain to make the brain more resilient. So we definitely think that the brain's [00:23:00] capacity for repair and resilience is the flip side of its capacity to be hurt in vulnerable situations when bad things happen to us.

My main point of reference for the surge in drug addiction as a result of the COVID pandemic and related conditions is that we were losing, at the peak, 100,000 Americans every year from drug overdoses.

That's just a staggering number 100,000 Americans dying of a drug overdose every year. I was in high school and college during the Vietnam War era when my generation was torn apart over the Vietnam War, where the total military casualties were on the order of 58,000 people over a 15-year period.

And here, we were losing, and still are losing, almost twice that number every year from drug addiction, and our country has not harnessed nearly the resources it should or could to [00:24:00] help people with that illness.

So my lesson from the experience is that we need to invest a lot more in brain research to understand these conditions, and then utilizing the results of the research to come up with better paths for treatment.

Stephen Calabria: Much of psychiatry has historically focused on treating illness. Our work here at Mount Sinai on one's health span, not the span of one's life, but the span of one's health, is one focus of our work here at the Icahn School of Medicine at Mount Sinai, at which you are the fearless leader and dean.

And I would encourage our listeners also to check out our special Health Span miniseries in our video talk show- The Vitals, available on YouTube, Apple Podcasts, and Spotify.

Your work has a similar focus about treating not just illness, but also health and making sure folks are actually healthy throughout their lives. Do you think that's [00:25:00] where the future of mental health care is headed?

Dr. Eric Nestler: Absolutely. In fact, I would extend that to the future of care across all organ systems involved.

When I went to medical school, again about four decades ago we were taught how to be doctors, and doctors at the time meant how to help people who come to us when they're sick, and that's the way medicine has been fashioned over the past century, say.

We're now at the cusp of a fundamentally new way of looking at the field of medicine to not only treat people who get sick, but also to prevent disease in the first place. Now, this has been talked about for many decades.

It was certainly talked about when I was a medical student. But we never really put our money where our mouth was in terms of health prevention.

We all know, for example, that insurance companies in general, to a certain extent, [00:26:00] will not pay for prevent- much preventive care as they will f- to help pay for people who get sick and for the treatments that are required and proven effective.

So we need to invest more in how to keep people healthy and prevent disease in the first place. This is very much part of our view of Mount Sinai as a learning health system.

So our view is that everybody who comes through the doors of Mount Sinai, outpatient clinic, hospital, whatever, from the moment you're born to the ripe old age, that you get your genome sequenced. That genome is stored in the cloud, analyzed over time.

We will gain more and more insight into the meaning of your genome over time as we learn more about it, and that will be coupled with everything in a person's electronic health record, every imaging test, every blood smear, every pathological analysis, digital devices that we're wearing, our [00:27:00] activity levels, our metabolism measures, and so on.

Putting it all together and informing what a person's risks are and try to capture those risks, change a person's lifestyle, institute better health surveillance, catch a cancer before it forms, for example, and promote health in that way.

Same is gonna be true for the brain. We need to figure out how to promote brain health by boosting resilience making a person less vulnerable to stress later in life, we need ways to identify people who are beginning to show the first evidence of a neurodegenerative disorder like Alzheimer disease or Parkinson's disease or ALS, Lou Gehrig disease, and before the first nerve cell dies, be able to capture that evidence and then institute protective measures.

Very much along the lines of the way statins are now used to lower cholesterol and thereby [00:28:00] prevent atherosclerosis and heart disease, that's what we need for the brain, ways to identify risks early so that we can institute measures to prevent people from getting sick.

Stephen Calabria: You mentioned the rise of effective medications earlier and pharmacologic interventions. There is an old response or trope among some folks that they don't want to use a crutch, they don't want to rely on something

else, that the perfect platonic ideal person is someone who is just able to deal with their problems without having any outside help. How would you address that kind of notion?

Dr. Eric Nestler: Yeah, I would simply say that there really is no appreciable difference between an illness that affects a peripheral organ and an illness that affects the brain. The brain is a physical substance just like the pancreas and the heart and the lung.

And so a person with diabetes whose, say, pancreatic beta cells have died because of an autoimmune [00:29:00] reaction, so the person is not now making enough insulin, they need to take insulin in order to live, in order to survive.

A person who gets severely depressed, their brain has been damaged for whatever reason, and just like in the case of diabetes, the brain is not able to repair itself on its own, and it needs a boost.

And it's very distressing. As a psychiatrist, I've heard this argument for many decades. I think the society has mostly grown past that for depression, antidepressants. We still face it severely for drug addiction.

Perhaps the best treatment today for drug addiction remains this 12-step programs, Alcoholics Anonymous, Narcotics Anonymous, and similar support programs, which could be enormously effective for people.

But my big beef with those programs is that they dissuade people from taking medication. So, for example, if I'm depressed [00:30:00] and I got into a syndrome of addiction, likely partly because I'm depressed, my ability to not take drug is gonna be boosted by treating my depression.

And for somebody at the 12-step program to say you can't treat drug addiction with another drug," they're wrong. It's just empirically, factually wrong, and we need to just need to educate people to that point.

Yeah, this is a good point to also add that there's a lot of interest in the notion that sometimes we are too fast to use medication to treat psychiatric disorders. I don't think a person would say that for schizophrenia or bipolar disorder.

Those conditions need medication. But for depression and anxiety, how severe should it be? How long should you be sick? How impaired should you be before one starts a medication? There's not a [00:31:00] crisp, clear, definitive answer to that question.

I think when a person is impaired and not functioning well enough for a period of a number of weeks, it's time to start thinking of medication.

But we lapse into the ease of treatment where a person can come in for the first time they ever see a doctor and a little bit down in the dumps, and instead of the doctor looking for ways to boost that person's natural resilience, just prescribes an antidepressant medication.

That's wrong also. And so we need to hit it right and balance the two. It's always better to try to help a person use their own powers of natural resilience, which are extraordinarily strong. And if those don't work, then use medication.

Stephen Calabria: Finally, what's one misconception about the brain you'd love to see disappear?

Dr. Eric Nestler: It is the capacity of a brain of a person to adapt and [00:32:00] respond in a positive manner. You don't wanna count people out, and you don't want to look at someone who has gotten sick and think of them as weak. That's not fair. It's not true.

You have to think of that as a situation where they've been subjected to a particular set of circumstances to which their brain is not well-adapted to cope and help that individual overcome it, because that person could well overcome many other things that many other people could not.

And we need to, look at brain disorders as being akin to every other field of medicine.

Stephen Calabria: Thank you very much, Dr. Nestler.

Dr. Eric Nestler: My pleasure. Bye-bye.

Stephen Calabria: Thanks again to Dr. Eric Nestler for his time and expertise. 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 [00:33:00] platform.

Want to get in touch with the show or suggest an idea for a future episode? Email us at podcasts@mountsinai.org. Road to Resilience is a production of the Mount Sinai Health System.

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.