Alan Hu Foundation Mental Health Lecture Series

Stress and Mental Health
Webinar by Stanford Professor Robert Sapolsky, PhD

John A. and Cynthia Fry Gunn Professor, Professor of Biology, Neurology, and Neurosurgery at Stanford University

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All right. Hello everyone. Good afternoon, good evening, and good morning. Welcome to Alan Hu Foundation Mental Health Lecture Series. I am Chih-Ching Hu, Co-Founder of Alan Hu Foundation and host for your webinar. Today Dr. Robert Sapolsky will present Stress and Mental Health. First of all, I would like to thank you all for joining us across the country and around the world. I would also like to thank Mental Health Association for Chinese Communities for providing simultaneous Chinese interpretation. Thank you MHACC founder and president Elaine Peng, and thank you Ida Shaw for Chinese interpretation. Alan Hu Foundation Mental Health Lecture Series aims to make mental health knowledge common knowledge. Alan Hu Foundation's mission is to promote mental health raise awareness and remove stigma surrounding psychiatric disorders, and support fundamental research for cures. Please consider making a gift to Alan Hu Foundation. Your gift will be 100 percent invested into foundation's mission to support mental health.

Today it is my great honor and privilege to introduce Dr. Robert Sapolsky. Dr. Sapolsky is a MacArthur genius fellow, John A. and Cynthia Fry Gunn professor, and professor of biology, neurology, and neurosurgery at Stanford University. He is also research associate at national museum of Kenya. His 2008 National Geographic Special on stress and his online lectures about human behavioral biology have been watched tens of millions times. The humor and humanity he brings to sometimes sobering subject matter makes Dr. Sapolsky a fascinating speaker. He lectures widely on topics as diverse as stress and stress related diseases, depression, memory, schizophrenia and Alzheimer's disease. His latest book Behave: The Biology of Humans at Our Best and Worst is a New York Times bestseller, a Washington Post the best book of 2017, and received the Los Angeles Times book prize. His articles have appeared in publications including Discover, Los Angeles Times, New Yorker, and the Wall Street Journal. His upcoming book is entitled Determined: The Science of Life Without Free Will. in today's webinar, Dr. Sapolsky is going to give a non-technical overview of the effects of stress and stress hormones on brain function.

Following the presentation, it will be a Q&A session. Please submit your questions using zoom Q&A function. The presentation is for educational purpose only and is not intended for medical diagnosis. If you have any persistent symptoms, please seek for professional help. With that I'm going to turn to Dr. Sapolsky. Welcome, Dr. Sapolsky.

Thank you. Is the sound ok?

Yes, a little bit noisy, but I think I can hear this okay.

Hello everyone. For some odd family circumstances, both of us are rapidly driving cross country. So we right now are at Eastern Wyoming. So maybe some technical limitations here. Okay, related to that, since early this morning, I've been completely stressed about whether this was gonna work or not. Whether this was gonna work with zoom, whether this is gonna work with Facebook, whether this is gonna work with FaceTime whatever. And as a result since early this morning, my body has been having some very interesting changes. It's been having a stress response. Since early this morning, I've been secreting a class of hormones called glucocorticoid. Somewhere around here today a hundred millions years ago, a dinosaur somewhere around here was being chased by another dinosaur, and as a result secreted the exact same molecules.

Yeah, Dr. Sapolsky. We have some feedback from audience that the sound is not good. It's hard to hear. So I think probably you need to try a slightly different direction to see if there is a cellular signal. I apologize to everyone that uh the sound quality is not good since Doctor Sapolsky is traveling right now.

Oh, again apologies. Is that any better?

Oh, this is better. And if any um background music can be turned off, I think that will help also.

Okay. So music is off. Good. Thank you. Okay. So let's just start again. With the last three minutes just demonstrated it was a very weird thing for a vertebrate animal to do, which is to get stressed for the reasons I've been stressed. A hundred million years ago, a dinosaur trying to avoid being eaten by another dinosaur secreted the exact same stress hormone that I've been secreting all day here worrying about the sound quality on this, and trying to pull this off, and encompassed in that what we have is an incredibly ancient piece of physiology. Whether you are a human, a primate, a mammal, a fish, a lizard, a bird, or a dinosaur a hundred million years ago, as far as you can tell, when you are stressed you have the exact same response in your body, and the critical starting point is we do something very strange with it, which is nobody's trying to predate me, there's no lions chasing me anything like that. There's a large dog pushing against me, but there's no physical stressor that would make any sense to a dinosaur, or a fish, or a bird. All that's happening is I'm being psychologically stressed. And what we have here is a central concept in the whole field. The stress response is what you turn on if you're being stressed like a normal animal. Somebody is intent on eating you, or you are very intent on eating somebody else because you're half starved to death, and for 99 percent of the beasts on this planet, when you turn on a stress response at that point, it's exactly what you want to be doing in order to survive this crisis. And the critical punchline of the entire field is we turn it on for hours, for months, for decades for purely psychological reasons, for reasons that no other animal out there in all of history has done a whole lot of. And the punchlines to the entire field is if you chronically turn on the stress response for purely psychological reasons, you're going to get sick. And what i'll be focusing on today is one of the realms in which the illness becomes more common is in the realm of mental illness.

Okay. So what we have here is a dichotomy between the way normal animals get stressed which is in response to a short-term physical crisis, Someone's trying to eat you or you're trying to eat somebody else, and chronic psychological stress. And what we see on the left here in this table is all the ways in which the stress response is perfect, exactly what you want to be doing if you were being a normal animal being stressed by a short-term physical emergency. Whether someone is trying to eat you, or you are chasing after someone else to eat them, if you're gonna get through this crisis, the first thing you need is energy. Energy mobilized not in your fat cells for some building project next spring, but mobilized right now to be handed to whichever muscles you're going to save your life. So the first thing you do is various stress hormones go to your fat cells, go to your liver, and dump energy into your circulation to power the muscles. Next thing that happens whether you are running away from a predator or if you were running after a meal, you need to increase your blood pressure, your heart rate, your cardiovascular tone, all as part of the strategy. Get that energy, get that glucose to your thigh muscles in two seconds instead of three, they're that much more likely to survive. Next what happens during stress is you turn off all sorts of long-term building projects like digestion. Digest breakfast tonight if you're still alive tonight. Don't worry about it right now. Growth. Grow tomorrow if you're still alive, don't waste energy on it right now. Likewise reproduction. Shut down the reproduction system, don't waste energy on it. Shut down everything that is not essential for the next three minutes. Finally, with the onset of stress, your immune system works better and that's a great way of defending you against you've been slashed open by this lion's claws and you're trying to avoid having some sort of pathological response. Okay, so what we see on the left here is everything you want to be doing if you are going to be stressed as a normal mammal. You are mobilizing energy. You are delivering it inward as fast as possible. You are shutting off the nonessentials. And what we see on the right is what happens if instead you were being chronically stressed for purely psychological reasons. If you were being a westernized human who's worried about taxes and global warming, and retirement, and traffic jams, and all of that where

you were turning on the same stress response as does a zebra running away from a lion or does a lion running after a zebra and you turn it on for purely psychological reasons day after day after day. And what we see here is everything that is beneficial on the left if you do it chronically is going to cause disease. At the level of chronically mobilizing energy because you were chronically psychologically stressed you were more at risk for adult onset diabetes, insulin resistant diabetes a type of obesity that is more common. If you were constantly increasing your cardiovascular tone because you were psychologically stressed not because you were running for your life but psychologically, and you were suffering from stress-induced hypertension, and you will damage your blood vessels stress into atherosclerosis. Constantly suppress digestion and for extremely complicated reasons there were more ulcers being formed. If you were a kid and you were chronically psychologically stressed and you keep shutting down growth, disrupted normal growth at its extreme that probably was one of the bizarre outcomes of medicine a disease children would have really for people with psychological reasons, psychosocial dwarfism. Next if you are chronically turning on the stress response, if you were a female mammal, your reproductive cycles will become irregular. They will stop all together, stress anovulation, stress amenorrhea. If you were a male mammal, testosterone levels go down, erectile dysfunction, all of that stops working. Finally if you were chronically stressed, short term what we saw was the immune system is enhanced, chronically, you suppress your immune defenses and you were in a position to be chronically prone towards inflammation. Okay so what we see here is this very clear punch line if you were going to be stressed like a normal animal on the left, you would better turn on the stress response. If instead you were going to be stressed like one of us one of us, smart psychologically neurotic westernized humans, and you turn on the stress results all the time for purely psychological reasons, you're more at risk for getting sick. So what this brings us to is when we are being chronically stressed we humans, we westernized humans, we neurotic westernized humans, we are being psychologically physically stressed. So this raises the issue of what is it that actually makes psychological stress stressful.

And if I can have the next slide, what we see here are the building blocks of psychological stress we can have. Yes, thank you. What you see is for the same external misery going on, you were more likely to feel stressed, you were more likely to initiate a stress response in your body, and you are more at risk for stress-related disease, if you feel like you have no outlets for frustration, if you feel like you have no predictability over what's happening, if you have no control, if you feel like life is getting worse, and if you have no social support. Great examples of this, a lab rat, take a monkey, take a college freshman volunteer, and give them random shocks now and then, and they're going to have a stress response. But instead give them some predictability, 10 seconds worth shock like, and you don't get the stress response. Predictability protects us from psychological stress. A sense of control protects us, outlets for frustration, social support, all of that. So what we see is psychological stress is built around lack of control, lack of predictability, lack of outlets, and lack of support. And as a great example, that's what the last two years have been all about.

If we can see the next slide, what we see is just a great example of chronic psychological stress, what's been going on during the COVID pandemic. Yes. Obviously it's been enormously stressful if you have been sick with the disease, if people have lost a loved one, but for all of us what we've been dealing with is a particular type of psychological stress, which is the difference between risks and ambiguity. Risk shown on the bottom left. Somebody sits you down and says, here, here's a box you can't look in there, but in the box there are 50 blue marbles and 50 red marbles, and reach in there and pull one out, and the deal is, if you get a blue marble, we're going to give you a million dollars, and if you get a red marble, we're going to beat you senseless, and knock your teeth out, and leave you unconscious in the street. Do you want to take the risk or not? And we differ. Some people have a high risk tolerance, others have a low one. We all differ. But under some circumstances, we are all willing to take risks. On the bottom right is the very different circumstance of ambiguity. Ambiguity is here's that box and there's a hundred marbles in there ,and all we're going to tell you is at least one of them is blue, at least one of them is red. Go in pick out one, and if you get a blue one, you get a great reward, red one, you're going to get a terrible one. You want to risk it? And people hate this circumstance. They turn on a massive stress response. Risk on the left, you've got a 50/50 chance. Ambiguity on the right, you've got anywhere from a 1 percent chance to a 99 percent chance, and everything we know about the brain shows that people hate ambiguity. It causes mas-

sive stress responses, a massive sense of discomfort. And what does the last two years been about? Not risk, but it's been about ambiguity.

If we can see in the next slide, since the 1950s, with polio vaccines, you get the vaccine and there's a risk, there's a risk when you get vaccinated that you'll get polio from it. What is the risk? One chance in 13.1 billion with that one all the time. What has COVID had been about? Ambiguity. What the risk of this? What's the risk? We don't know. We don't know how transmissible this is. We don't know how long it will be before there will be vaccine. We don't know how effective the vaccine to work. All the COVID is about this psychological stress of ambiguity, and that is a disaster for us.

Next slide. The next slide shows one of the features of what has been so stressful about this period, which is we are social primates. Every single primate out there during periods of emotional distress, what do you do? You, someone else, you hope they provide you with physical contact. You seek out social support. And what is the last two years been about saying, don't assemble with a group of friends, don't have a party with all of your like closest friends and colleagues, don't meet up other people in the way that family and friends used to. Instead, for the last two years we have been asked to give up the single most protective thing that primates do in psychological spectrum, which is having an interface one-on-one social support. That's left us in a terrible state.

Also the next slide shows us another feature of what's been going on with this, which is you begin to pay this price, and what you've seen the last two years, every one of those illnesses on the right has become much much more common. So this brings us to the critical last step there, yes, the effects of stress on your metabolism, your heart, your digestion, and your immune system, what about the effect of stress on your brain? And this is where we really see terribly relevant consequences now. Short term, back to the left side of this column, short term with the onset of stress, things happen in your brain over the course of a couple of minutes to a couple of hours, stress increases the amount of energy delivered to your brain, the amount of oxygen, neurotransmitters related to pleasure are released, you think more clearly, your sensory systems are sharper. What is this kind of stress about? This is what we call stimulation stress, that is not too extreme, not too severe, doesn't go on for too long, and under those circumstances what happens in your brain is wonderfully adapted. We love that kind of stress. But what if instead the stress is chronic? Our versions of chronic psychological stress, everything that goes on the brain, then there is a disaster.

If we can have the next slide. We have the first outpost of the brain where problems begin, a part of the brain called the hippocampus. I've spent the last 30 years of my life studying the hippocampus and what stress does there. This was the first part of the brain where people figured out that chronic stress is bad news. What does the hippocampus do is central to learning and memory. And what does chronic stress or chronic exposure to those stress hormones, those glucocorticoids, what do they do? They make neurons less excitable. They make them harder for them to talk to each other. They cause neuron connections to atrophy. They shot down the function of neurons. The neurons become vulnerable. They die more readily. You don't make neurons. The hippocampus atrophies. What we see this is why chronic stress does bad things to the learning and memory. And what we see is syndromes of chronic psychological stress like post-traumatic stress disorder, things of that sort cause damage to the hippocampus.

Next slide shows a second part of the brain in which damage occurs, and this is a brain region called the amygdala, and something very different happens to the amygdala. The amygdala is central to fear and anxiety all of that. What to stress you? What do the cortisol stress hormones do? They do the opposite within the hippocampus. They make the amygdala work better than it should, and what are we describing here, neurons become more excitable, they form new connections, the amygdala gets bigger. This is why if you were chronically stressed, you were anxious, you become frightened of things that other people are not scared of, you have trouble learning that you are safe. This is the link between chronic stress and anxiety disorders, and you look at people with ptsd post-traumatic stress disorder, and their amygdalas get bigger than are normal. So all of that's

relevant to memory problems during stress, anxiety. What we turn to now is the connection between stress and depression, and what we know most clearly are links to three different neurotransmitter systems. The first one, if we can have the next slide.

The first one was the first neurotransmitter that was implicated in depression, a neurotransmitter called dopamine. Dopamine, everybody knows about dopamine. Dopamine, it's about pleasure, it's about reward, and it turns out dopamine is central to the defining symptom of depression-anhedonia. Hedonism, the pursuit of pleasure. Anhedonia, the inability to feel pleasure, and we know that as a characteristic of major depression. Somebody suffers depression and great things have been happening in their life but they feel no pleasure, they have no anticipation. Depression is characterized by anhedonia, and it turns out this has lots to do with dopamine.

Now the next slide shows what people used to think what dopamine is about. Take a human, take a monkey, take a rat, and train them, put them in a room where when a little light comes on, a signal, that's the signal to work, press a lever, press a bar 10 times, and then you get a great reward. The human gets m&m, the monkey gets a raisin and whatever, and what you see is the very first time you get a reward from that is out of nowhere, your dopamine system activates like crazy. Okay so people looked at this and what they concluded was ah dopamine it's about reward. It turns out it's not actually about the reward. Now take that human or that monkey or that rat and get them to the point where they've been really well trained in this procedure, signal comes on, that means you do the work you get a reward, signal, work, reward, signal, work, reward, totally routine. When does dopamine get released now? Not after the reward, it gets released as soon as the signal comes on. What's that about? That's you sitting there saying, signal, yeah this is great, I know exactly what to do now, I press the lever 10 times, I'm gonna get this reward, this is wonderful, this is dopamine not about reward, this is dopamine about the anticipation of reward, and that's far more important than its role. Moreover if you block that rise of dopamine from happening, you don't get the pressing forever. It not only gives you the anticipation, it gives you the motivation to go and actually do the work he did to get the reward. Now we see something very subtle here. Okay, so what we see in this paradigm is you get the signal, you do the work, you get the reward, a hundred percent of the time you get the reward, it's completely predictable, you do the work, you get the reward. Now change conditions so that you get the signal, you do the work, and only 50 percent of the time do you get the reward, what happens to this point, what had been a completely predictable system now goes to 50/50 chance, and what you see is as soon as the signal comes on, dopamine goes through the roof. it goes incredibly high. why is this? because we've just introduced a critical term into our brain chemistry, the term "maybe", introduced "maybe" into the equation, and your dopamine system goes like mad, because you're sitting there saying, yeah I know how to do this, it's gonna be great, yeah, this is gonna be terrific, but no, I'm such a loser, I'm gonna mess it up today, but no, I'm feeling good about stuff, but then this bad thing happened to me five minutes ago, you go back and forth, back and forth, maybe yes, maybe no, teetering on this edge of optimism and what you see is that causes a massive increase in dopamine. In other words, dopamine is about anticipation, it's about motivation for reward, and when it goes its craziest is when you're not certain, there's a chance it's going to happen but you're not absolutely positive.

So next slide. What happens during major depression, what happens during chronic stress, you get depleted of dopamine in this part of the brain, and once we just described, you don't feel pleasure, more importantly, you don't feel the anticipation of pleasure, and even more importantly you don't have the motivation. What we just described one of the horrible symptoms of depression, which is psychomotor retardation. It's exhausting to do anything. It's exhausting to think anything. Everything is overwhelming because you've got no motivation, you've got nothing you're looking forward to, and forget about getting up and looking at ways to look at life in a more optimistic way, you don't even have the energy to get up and get dressed. So the depletion of dopamine plays a large role in the psychomotor symptoms of depression.

Next slide. The next slide shows the second neurotransmitter system that is relevant and this is, this whole feature of depression which is not only do you have fat sad thoughts, you can't stop them, one sad thing makes you

think of another sad thing, and another, and the other, and you sit there just lost in this negative affect, these negative depressed emotions, jargon for it, you ruminate. In depression, people ruminate on negative emotions, and that's you sitting there saying everything is a sign, that stuff is critical badly, it's going to turn out worse than even you expected, you were just lost in the thoughts of that, and what we see is, that's got a lot to do with a neurotransmitter called serotonin, and as it turns out, stress does very relevant things to serotonin.

Now next slide shows that inside your brain serotonin originates in one or two spots in what's called your brainstem, and then in red, a projection of serotonin-releasing neurons going all over your brain, and the area where it's most relevant to stress and depression is that this area called the pfc, the pre-frontal cortex. What's the pfc good for, regulating your behaviors, regulating your thoughts. What does serotonin serotonin do? It makes it easier for your pfc to control your emotions, to control your thoughts, to regulate things. What's going on during sustained stress, you get depleted of serotonin there.

Next slide shows that this happens with the onset of sustained stress, with depletion of serotonin, and with those glucocorticoids being secreted in excess, you also damage the prefrontal cortex, you cause the connections between neurons to shrivel up, and what you see then is there's less responsiveness in prefrontal cortex to serotonin.

And next slide. It shows that with chronic stress there's less serotonin as well, and what you have is a prefrontal cortex which normally under unstressed circumstances, you can have pretty good control over your emotions, you think something's sad, and you could then think, stop it, that's silly, that's not real, that's not actually going to happen to me, and you can stop it, and currently instead if you were chronically stressed and the prefrontal cortex has atrophied, what happens is you have a whole lot more trouble controlling negative emotions, and what we get then is is this rumination of depression. With chronic stress, your frontal cortex is depleted of serotonin, the frontal cortex gets atrophied, and suddenly you have a frontal cortex that can't help you to make stop thinking sad thoughts, and you just lost the rumination over and over forever, and what we see is probably the most famous, the most heavily prescribed anti-depressant drug out there is one that tries to compensate for this depletion of serotonin, a drug called prozac. Prozac is what's called an SSRI, a Selective Serotonin Reuptake Inhibitor. What it does is, it gives you more bang for your buck with serotonin, it counteracts the effects of chronic stress.

Next slide. Next slide shows the third neurotransmitter we need to worry about, one called norepinephrine system and what norepinephrine is. Dopamine, the loss of pleasure, the loss of anticipation, serotonin, loss in rumination, norepinephrine has to do with that psychomotor exhaustion, where it is just exhausting to get up and do anything, and with the onset of chronic stress, you get depleted with norepinephrine as well.

Next slide shows the norepinephrine system in the brain and starts in this one area called the locus coeruleus, and it is sending projections everywhere, and if there's not that much norepinephrine, you have tremendous problems mobilizing to do anything, and what we see of course in the next slide with the onset of chronic psychological stress we get depleted of norepinephrine precisely what happens.

Okay so let's get a summary of this. Let's go to the next slide after this, go to, yes, what we see here is just to summary the three neurotransmitter systems that implicated the most in depression, you get depleted of serotonin, you get rumination and negative thoughts, you get depleted of dopamine, you get the loss of anticipation, the loss of motivation, anhedonia, finally you get depleted of norepinephrine, and you've got psychomotor retardation, it's exhausting, it's overwhelming to get up to anything that might help you start feeling better, and what we see in all three of these cases is chronic stress, and you are depleted of serotonin, dopamine, and norepinephrine. Okay, so this gives us a tremendous sense of the neurobiology linking chronic stress, psychological stress with increased vulnerability to depression. Now that's all you need to know about the subject if you're interested in stress hormones and neurotransmitter systems, but it turns out there's far far more other things

going on if we can have the next slide.

Yes. The stress, the neurotransmitters, all of that like all sorts of other aspects of your body's functions are relevant to your vulnerability to depression. Top left, other hormones is not just the stress hormones, but other hormones affect every bit of brain chemistry relevant to dopamine, serotonin, norepinephrine, other hormones like estrogen and progesterone and what you wind up seeing is dramatic changes in the levels of the two over the course of reproductive life history when you were ovulating, when you were just giving birth, when you've just gone through the menopause, all of these involve massive changes levels of estrogen and progesterone, and it turns out that abnormal ratios of the brain and effect of dopamine and norepinephrine and serotonin. So we've got a hormonal level. Next on the top right, childhood, what sort of childhood you've had is going to have an impact on what sort of adults prefrontal cortex is, what kind of adult prefrontal cortex you are going to have. Childhood adversity makes you more vulnerable to clinical depression at adulthood, and what we see here in this study, very important is, low socioeconomic status, poverty, and what you see is by age five if you have been being raised in poverty, your frontal cortex is already developing more slowly on the average than more affluent kids' frontal cortex are. In another word, by age five if you foolishly pick a wrong family to be born into, you are already more at risk for all the consequences of adulthood malfunctioning, poor frontal cortex and higher risk of major depressive disorder. On the left, forget hormone during last month, forget your childhood, going back to when you were a fetus, it turns out the amount of fetal glucocorticoid, the amount of fetal stress hormones that you were exposed to, where are those hormones coming from, they're coming from mom, if your mother is chronically stressed because of poverty, because of chronic illness, because of refugee status, some such thing at least secrets moderate amount of glucocorticoids into the circulation, and what that will do is the glucocorticoids get to the blood stream of you, the fetus, and thus cause lots of prenatal stress by the way your mother is stressed and increases risk of diabetes as an adult increases risk of hypertension, increases risk of major depression, schizophrenia. Now what we see is in the next slide, or, I'm sorry, the right side of the slide at the bottom, there is taking things one step further back, forget when you were a fetus, what is even more comes out from nothing when we were genes and what we see here is an incredible feature of a story. Genes have a lot to do with depression. What version of genes you have does not determine that you will have depression or that you will have not, it's not a yes and no, it will determine whether you have an elevated risk or a low level of risk, and let me give you one example of how this works, because what we have is genetic makeup and interacting with environment, and this has to do with the gene probably widely implicated gene in depression, this was a group in university in 1990's did this started the whole field of it, that is a gene that is close to something called serotonin transporter. Don't worry about the details, they think this gene comes into three different flavors, and what people thought beforehand was having one of those flavors, and what all the rat and monkey studies did suggest was you maybe really at risk for major depression, and with the other flavor of the variant, you are being protected from depression, and have the second variant you will be half way in-between. Oh people really get excited, let's go study humans, and they did this massive study of 11 000 kids following more than two decades and the question was if you have a good version of this gene or if you have the bad version of this gene, does that affect your vulnerability to depression by the time you were 25, and what the answer was not necessary. All we know about the person's genetic makeup, you're not going to have much insight as to whether or not you were going to get depressed. It turns out that having the bad version of this gene puts you more at risk for depression if and only if you are also experience moderate stress during childhood. The more childhood trauma the more having the bad version is going to put you at risk for the disease. Have the good version and it hardly matters whether you've got a miserable traumatic childhood, but have the bad version, history of stress of severe stress, you have this increased vulnerability to stress-related depression. and what we see here is, it's not the gene, it's not the environment, it's the interaction between the two. Okay, so we've seen everything from this much, hormone levels, to child experience, to create a life, to genes, it turns out there's even more relevance than that.

Next slide. What we see is amazingly depression looks like a different disease in different cultures. Depression in western European cultures has a lot of different features than you see in east Asian cultures. Depression has

a different profile response to some of the medications in western European cultures than east Asian cultures. What is this about? Culture, what culture you were exposed to at birth had something to do with how your brain was assembled and what you see is somewhat difference depending on our cultures. Then on the right, there's differences in terms of evolutionary histories, if you are talking about genes for depression, genes are relevant, and what you see is it's widespread, 15 to 20 percent of the population of every culture on this planet will have major depression, enormous amount of work is required to understand why some people evolved with genes related to depression. Okay, so we've got brain chemistry, we've got psychological stress, we've got hormones, we've got childhood experience, we've got prenatal life, genes, cultures, all of these tell us about this disease. Thousand of people are affected by depressions, only about two third of them have health care, of those that do, only about half of them are actually helped by being given some anti-depressant medication, and as of those who do get help, about half of them have to stop taking the medication midway because the side effects are so awful. What this very fascinating statement we have, so more much we need to learn about these people whose lives are crushed by depression are not helped by method of western medicine because they can't afford access to health care, or because nobody understands how it works, or because research labs or researching lacks sponsors like that, what we see is a desperate amount of research work needs to be supported, what we see on the last slide is a very simple measure of how fix like that can happen, with organizations like this one, organizations built around the notion that depression strikes any family, depression does not care about your level of education, your social economic status any such thing, depression is the most common cold of psychiatric disorders, once you recognize that and show at next slide you see foundations like this one, like you know, foundation, what you see is a two-fold task being taken on, fostering research into trying to understand the brain chemistry and the hormones, of the genes and the evolution of the childhood experiences everything else that makes depression a disastrous disease, and the second thing is to de-stigmatize it, right, 15 to 20 percent of humans have this, it is not like some obscure psychiatric disorder that people normally have the energy, and they get to go up deep nature, to go and do something about, and if you're depressed, it's because you don't have function left, what we see here is a biological disorder, major depression is as real of a biological disease as diabetes, and you don't sit down with a kid with diabetes and say, oh, yeah, you know why are you complaining about this, what do you need to talk to yourself for stop naming yourself with this stuff, we don't say that to a diabetic because they have a biological disorder, you should not say that either to someone who lives with depression, we have a neurogenetic developmental disorder that's very sensitive to stress hormones, the exact same thing. Depression is a real biological disorder, it is not a sign that you don't have the function and backbone everybody else has.

So let me wind down at this point by thanking the foundation for supporting research in this area, for supporting education, for supporting destigmatizing. When we have a disease that 15 to 20 of people are destroyed by over their lifetime where, about half of those people never receive adequate medical care, and where the best estimates are three quarters of people with major depression never seek medical help because they have the stigma, and think it is something to be ashamed of, whenever we want to focus on first, this is the area we need to work on. thank you to the foundation for destigmatizing it.

So let me pause at this point and see if there are any questions.

Thank you so much to Dr. Sapolsky for the wonderful presentation. The sound quality, I apologize, is not that good to you, I want to apologize to the audience, but I think we already tried our best, we tested them many times today, but um. So let's open up to the Q&A. A question came in, can a typical hormone levels such as testosterone change our response to the standard operations of dopamine or other neurotransmitter?

Absolutely, and that's a great question. What we saw was, how something like the glucocorticoids could affect neurotransmitters, there are transmitters like norepinephrine, serotonin, dopamine all of that, what we see in turn is how other hormones can affect different version of the neurotransmitter. Every hormone out there like estrogen, progesterone, testosterone, oxytocin a long list of these affects functions of the brain that involve

changing how sensitive some parts of your brain are working out, and testosterone absolutely so, sensitivity to dopamine, short-term testosterone surges.

Right. So, next question, what qualifies as a stressful life event?

Yeah, well, if you were a zebra, the definition is very simple, which is a lion is left out and rip your stomach a little bit, and you still need to get out of there, and you are on the edge of sharp pain, and you'd better get stitches that is something of stress. What we see by the time this gets to us is what stress, stress is not somebody trying to predate me, stress is what you think there's a chance there is going to be, where there's a chance there's going to be a lot of traffic, or that your boss is going to yell at you, stress in those cases is something that's purely imaginary, and what we see is by the time we get to a human, stress consists of turning on stress response in anticipation of something happening that will not logically stressful to any other animal out there, to find human stress, it is imagining that something physically real is going to happen, but that is not really the case, and the punchline of all people is, if you do that chronically, you will get sick.

Okay, so the next question is, what could you suggest for people suffering from PTSD?

From sexual trauma, it's just a long long list of them, at this point there's varying opinions in the field, but i would say the majority of clinicians, nobody is ever cured of PTSD, the best case scenario is you learn how to manage it, you learn to keep it under control, you learn to recognize what circumstances trigger the worst manifestations of it, you learn to recognize what things help you to start feel safe again, but nobody ever actually gets cured from PTSD. If you're lucky, and if you have a lot of support, you manage it, you can keep it somewhat under control but you have to live with it.

Okay, thank you. The next question is, does early childhood exposure to chronic stress mean permanent impairment or can it be counteracted?

Okay, the bad news is adverse effects of stress early in life can be lifelong, for example there's an extensive literature right now of being exposed to a lot of maternal stress hormone levels while you were a fetus, and 60 years after you were born, you are about 20-fold more at risk for adults onset diabetes, oh my god, that is incredibly depressing, and it turns out prenatal stress like that and in late adulthood there's about a 20 percent increased risk of major depression. Yes, these things could be lifelong, so that's the bad news. The good news is, nonetheless, what we are learning over and over is very little about the brain and behavior is set in stone, parts of the brain like new neurons in response to the right sort of environment, virtually everything people used to think that was set in stone by the time we were 10 years old, 3 years old, and even younger than that, it turns out that neuroplasticity refunction the change with environment . So that's good news. But then the bad news part of it is, yes, there's all that neuroplasticity, the longer you wait, the harder it is going to be to bring about change with some of those interventions, in other words if you have someone who is completely broken by a life of terrible miserable, bad luck, and stress, it's gonna be much better if you try to do something for them when they're five years old than when they are twenty five years old, the older they get the harder to repair the damage.

And the next question, how do psychotropic medications interact with the stress handling system?

Well, those are exactly the drugs I mentioned before, Prozac and the other SSRI's mostly work on the serotonin system, there's a whole family of drugs, Wellbutrin, all of that work on dopamine and norepinephrine systems instead, and what you might guess is of course like there's 50 other neurotransmitters in the brain, and 49 of them somebody or other has seen evidence that there's something screwy with that neurotransmitter doing to depression, so there's important connections with all of that, so we see those interactions that are happening in terms of stress coming into interaction, what you also have is stress affecting how readily you can tell if you are safe, can you learn to recognize a safety signal that has something to do with learning of everything, if you are

chronically stressed, it is harder for you to feel safe, all sorts of common examples might as well, so tremendous stress, interactions with stress at every single aspect of brain function relevant to vulnerability to depression.

Okay, Dr. Sapolsky, I think we're gonna have the last minute and then we're going to wrap up the webinar, so here's the question, how can you link structural functional developmental properties to aggressive behavior?

Good, okay, that's a world of interesting issues brought up with that, and anyone looking at the news in Ukraine for the last two weeks realizes that if we don't know much about the biology of depression, we don't know much about the biology of aggression, and being awful as well you know what do. We know about that there's a huge amount of research, no surprise, making sense of why one person can be so much more aggressive and damaging than another person has something to do with brain chemistry, and has something to do with hormones, and has something to do with how much stress you've been under in previous weeks, and has something to do with your adolescence, and your childhood, and your fetal life, and your genes, and all of that, the exact same complicated sort of picture. I think probably the things that make the most sense is when you look at the part of the brain that is most central to aggression, it's the amygdala, so a little while ago, what we heard was, it's involved in fear and anxiety, in other words, you cannot understand the biology of one organism harming another one unless you understand the biology of that first organism feeling frightened, feeling anxious, feeling afraid. Aggression is so intertwined with a sense of fear, and in a world which you know a big devoid of the need to be afraid, this would be a much, much more peaceful planet. The other feature that I think is most important in terms of making sense of aggression is when we look at us as humans being aggressive to some other individual, to some other group, and we are asked to explain why it is we are angry at them, why we hate them, why what they're doing is awful whatever, almost certainly we come up with an explanation that is completely nonsense because we don't really know why we hate them, we try to come up with a rational explanation, a cognitive one, and it turns out we do not think our way to who we trust, who we love, who we hate, much more we feel toward them and we are driven in our moral judgment much more by emotion than we are by thought, and the bias among those people who study this sort of thing is, oh we're humans, we have these huge brains, from these huge vortexes, we think thought, thought is our pathway for understanding moral behavior and immoral behavior, and violence, and aggression, and empathy, and all of that, and it turns out that it is far, far from the case that, we are driven by emotional decision making rather than cognitive, rational decision making, what I think is, when it comes to aggression is, there are several reasons. The reason to be aggressive in the first place is fear, loneliness, anxiety, insecurity whatever, those were the emotions that brought out the hatred and reason, somebody had something that they were reasoned into the first place. I think to understand what aggression is, we have to understand why organism is lonely, afraid, insecure, resolve that, we can resolve the problem of aggression.

Right, wonderful, Dr. Sapolsky, thank you so much for the webinar, the presentation, and the Q&A session. We're going to close the event right now. We have a lot of questions but we don't have time to go through them. We'll see that whether we can have a further communication to answers.

Feel free to email me with those questions, if there are the questions come up a lot, I will be happy to answer them. Okay, thank you so much. Thank you everyone, again apologies, I never thought I would be giving a lecture leaning over one side of the car with a long large dog leaning against me, uh now in Western Nebraska.

No worries, that is just life, we have been doing that everyday. Thank you, thank you so much Dr. Sapolsky. Thank you everyone, I'm going to close the event now. Thank you, take care, and stay safe, and stay healthy.