Wired for risk: Cindy Ehlers on the science of addiction and mental health

Melissa Suran:

This is *Science Changing Life*, and I'm your host, Melissa Suran.

We often think of depression and alcohol dependence as deeply personal struggles—something shaped by our experiences, our choices, our emotions. But what if they're also written in our biology? Scripps Research professor Cindy Ehlers has spent decades studying the intersections of genetics, mental health and substance use. Her research reveals that alcohol dependence is about 50% genetic, but cultural and environmental factors like stress, trauma and even social support play just as big a role.

Cindy has also explored how disruptions to our daily rhythms—such as losing a job or a loved one—can make some people more vulnerable to depression. Today she joins me to break down the science behind alcohol dependence and mental health, and how these insights lead to real-world interventions. Welcome to the podcast, Cindy.

Cindy Ehlers:

Thank you for having me. I appreciate it.

Melissa Suran:

Of course. To start off, how did you come up with your theory on depression?

Cindy Ehlers:

I was the youngest scientist in a MacArthur Foundation-sponsored network to study the psychobiology of depression. And the foundation was particularly interested in what psychosocial factors influenced depression and how psychosocial factors interact with biological factors to produce the endpoint of people feeling that they have a very low mood.

It had long been known from the time of Freud that certain loss events are very highly associated with depression and feeling blue. For instance, an article that he wrote on mourning and melancholy. So, the kinds of events that are highly associated with depression are things like death, and divorce, and loss of a job—those kinds of loss events. And when people experience those events, we were able to demonstrate that they have disruptions in their biological rhythms. What happens is most rhythms in humans are controlled by light, but some of them are also controlled by social factors that set them. What can happen is when you have a loss of an important social factor in your life or an addition like the birth of a child, then your social rhythms change, and that changes your biological rhythms and causes kind of a social jet lag. And that social jet lag can lead to symptoms of depression in vulnerable individuals, particularly in women.

Melissa Suran:

It sounds like trauma is also a factor there.

Cindy Ehlers:

Yes, trauma is important, although trauma is more associated with anxiety than it is with depression. But this new theory of depression sparked a new therapy called social rhythm therapy, which is now available and very helpful for people with mood disorders.

Melissa Suran:

And what's the connection between sleep and depression? As we talk about things like rhythm, we tend to think of circadian rhythms.

Cindy Ehlers:

Exactly. There's a very close connection between sleep and depression. Our research group at the University of Pittsburgh was one of the first groups to demonstrate that dream sleep is associated with depression, and that disruptions in dream sleep can be an important marker of a person who is depressed; and in fact, that it can be treated by antidepressants, and that sleep may improve before mood even improves. So, there's a very important relationship between sleep and depression.

Melissa Suran:

Who's most at risk for depression and suicide, and why is that?

Cindy Ehlers:

Women are twice as likely to experience a clinical depression in their lifetime, and they're more likely to report suicidal thoughts. However, men are more likely to actually commit suicide. Now, heavy drinking is highly associated with suicide, and heavy drinking is more common in men. And alcohol itself can induce depression after heavy use, and people who are drinking heavily are often socially isolated. So, the combination of these events often leads to high risk for suicide.

Melissa Suran:

Do we know why women are so much more likely to have suicidal ideations?

Cindy Ehlers:

That's a really good question. It has to do directly with the fact that women have more depression than men. So, life events are more likely to create mood changes that lead to suicidal ideation in women.

Melissa Suran:

Back to alcohol dependence, when and why does it usually begin?

Cindy Ehlers:

Most people start using alcohol and drugs as teens. So usually, the risk for alcoholism begins during the teen years. And we have found that teens that drink at a young age are highly more likely to develop dependence on that drug. So, there's a number of reasons for that. One is that everything is more addicting to teens. So, teens are very emotional, and everything is more exciting to them—and so are drugs and alcohol. Also, teens tend to drink in a very deleterious way. They tend to binge drink, which is to drink large amounts of alcohol, or take large amounts

of drugs in a short period of time. And that kind of drinking is highly associated with developing dependence, and also with suicide.

Melissa Suran:

I'm also very interested in associated biological factors. Could you please explain the genetic connection to alcohol dependence in terms of how genes can influence addiction, or even how alcohol is metabolized?

Cindy Ehlers:

This is an extremely important question, and data suggest that alcoholism runs in families. We've known this for quite a long period of time. And in studying the genetics, we understand that about 50% of the risk for developing alcohol dependence is genetic, and the other 50% is less understood factors such as culture and the environment.

One of the well-known protective factors against developing alcoholism is differences in alcohol-metabolizing enzymes, which are found in different ethnic groups. The one ethnic group that's probably understood the best is Asians. In about 40% of Asians, one of the enzymes that metabolizes alcohol—aldehyde dehydrogenase—is less active. Because of that, they have problems metabolizing alcohol. And so, when they drink, they experience a facial flush. They often have headaches and high blood pressure and rapid heartbeat; and because of this, they're at very low risk for developing alcoholism.

Differences in alcohol-metabolizing enzymes are also found in African Americans, which also lowers risk in that group. We have found that one of the alcohol-metabolizing enzymes is also different in Hispanics and provides protection within that group. But it's also very important to note that cultural factors affect alcohol dependence *and* affect it differently depending on the cultural group. For instance, new immigrants—and we've studied this in Mexican Americans in San Diego County—that are experiencing difficulties in adjusting to the new culture. This is called acculturation stress, and we've found that acculturation stress can lead to loneliness and also lead to increased risk for developing alcohol dependence.

And among American Indians, the legacy of historical trauma—the loss of their lands, culture and language; and the genocide that was foisted upon them early on in this country—has led to a lasting legacy of trauma. And historical trauma is associated with increased risk for alcohol dependence and suicide.

Other factors such as religion are really important because they provide protective factors. If a religion bans the use of alcohol, then people don't get exposed to the drug, and so they have much lower risk. So, it's combined genetic and cultural and environmental factors that lead to the final risk in any one individual.

Melissa Suran:

It sounds like epigenetics also plays a role. It's a term that's coming up more frequently, especially as research has found evidence that trauma can create biological changes that can be passed down through generations.

Cindy Ehlers:

Yes, we'd like to be able to study epigenetics more and to understand how environment can turn on genes, which is what happens in epigenetics. The gene may be silent, but then an environmental factor can stimulate it, and then you can increase risk. And this is found, for instance, when you have famine in a group, and that can have a lasting legacy on that group of individuals.

Melissa Suran:

Another key term that's often mentioned is endophenotype. Could you explain to our listeners what that is and why it's so important to the study of genetics?

Cindy Ehlers:

Yes, endophenotype is important, and I'm really glad you brought that up. So, a phenotype is a trait that an individual has—like blue eyes, brown hair, how tall you are, how much you weigh. But an endophenotype is what's called an intermediary phenotype. So, it's usually a measure, often physiological, that is associated with the trait but is closer to the actual genetics. For instance, an endophenotype that we've studied extensively is heritable brain-wave measures. So, we can measure brain waves of an individual—and analyze them using very complicated, computerized quantitative analyses of their brain waves—and identify endophenotypes or markers in the brain waves that can then be found to be associated with genes. And when you have an endophenotype, it takes a smaller number of individuals to be able to get closer to the genetics than it does from just the phenotype itself.

And let me give just one other example: that is alcohol dependence. So, alcohol dependence would be the phenotype. Then what we have discovered is a brain wave that's associated with alcohol dependence, and we've found one that's also associated with risk for suicide. But let's say you come from a family that doesn't drink for whatever reason, but you have relatives in the distant past who were alcohol dependent. You may still have the endophenotype even though you would never show alcoholism because you wouldn't drink. So, it's a way of getting at these intermediary traits that makes it more likely to be able to identify what genetics underlies these important phenotypes.

Melissa Suran:

Thanks so much for that in-depth explanation. Now, looking back on your entire corpus of research, which of your findings were the most unexpected?

Cindy Ehlers:

Oftentimes, we find unexpected things—and I think that that's a very important part of research in general: to expect the unexpected. Otherwise, you'll miss a lot in the discovery process. And one of the things that I didn't really realize was how vulnerable the teenage brain is to drugs and alcohol. And I think most people know that drinking during pregnancy can harm the fetus because it affects brain growth, particularly during the third trimester, and can lead to fetal alcohol syndrome. But what I did not realize until I started studying it is very similar things can happen to the teenage brain.

So, the teenage brain is developing to its final form, and particularly cortical areas and areas that are involved in social and emotional development. Exposure to drugs and alcohol during that time can delay development and cause permanent changes in the ability of a person to then function over the lifespan. And so, it's very important that we understand that try to keep our teens sober.

Melissa Suran:

Right, and always remembering that age plays a crucial role.

Cindy Ehlers:

Exactly.

Melissa Suran:

Generally speaking, what are the greatest challenges of studying alcohol dependence?

Cindy Ehlers:

Teens that are using drugs don't really want to be studied, so it's harder to actually convince people that may have the most disability to participate in research. And also continued funding—trying to find stable funding to do studies that take over 20 years to accomplish. If you're trying to follow someone like a teen that's been exposed to trauma and alcohol, and then you want to see what happens to them in their 20s and 30s, you need the kind of funding that can allow you to follow that in a culturally appropriate way.

Melissa Suran:

Absolutely. And reflecting on what we've discussed about your research, which of your projects are you most proud of?

Cindy Ehlers:

Overall, I'm most proud of my 30 years working with the American Indian communities to help improve their lives. One program that we completed about five years ago in the community was a prevention program for teens. And since then, we have already studied and been able to show that teens that started drinking very young were much more likely to develop alcohol dependence. In fact, if you were age 13 and you started drinking, your chance of becoming alcohol dependent was 85%, whereas if you started drinking over the age of 18, you had normal risk for developing alcohol dependence. So, what we wanted to do was to put together a comprehensive preventive program to reduce teen drinking within the community.

And we did so by putting together an approach where we reduced their ability to obtain alcohol through shutting down convenience stores, selling to underage kids, and informing parents not to give kids alcohol. And then we did a lot of education in the community—because a lot of times it's educating parents and also law enforcement, where they think, "Ah, it's fine to start drinking when you're young. I did that, so I don't think there's a problem." So, education, and then also one-on-one therapy using motivational interviewing techniques to try to convince teens in a very non-threatening way to not drink until they were older.

We were able to show that this comprehensive approach reduced underage drinking and led to less drinking in the community, and we published it in the *American Journal of Public Health*. And so, the methods and the results are available to other people who would like to develop a prevention program that is like that one that we know is successful.

Melissa Suran:

On a similar note, I'd also like to discuss an app that you're specifically developing for the Native American community where the goal is to decrease alcohol dependence and suicide rates by incorporating teachings from community elders as well as cultural values. So, it's a unique way to translate the clinical research into health benefits, per se.

Cindy Ehlers:

This is in the very early stages of development, but we have had a fair amount of suicide among the American Indian community that we've studied, and we have over 20 people who have committed suicide in the population. And because we had studied many of these people over a long period of time, we were able to find out which factors were most associated with them having feelings of suicide. And in the teens, it was associated with losses: loss of a grandparent,

loss of a parent being moved from one family structure to another, say through divorce. These were the kinds of things that the teens said made them suicidal. And then drinking itself, which can cause depression, could be the final link in causing them to actually commit suicide.

So we decided that to be able to connect them back into the culture and back with other elders, that we would develop an app called *Voices of the Elders*, where they could go online if they were feeling lonely, and they could hear a tribal elder speak to them and tell them that their life was worthwhile, and that there are no Indians to spare, and that they could come at any time and get help.

We're in the process of putting that together, and we're going to beta test it among the teens and see whether they think it would be helpful for them.

Melissa Suran:

It sounds like having that personal connection is very important—especially during times of mourning and loss, when someone you looked up to is no longer there to offer guidance. So, the app isn't just about easing grief; it's also about filling the absence of that steady voice of reason.

Cindy Ehlers:

Exactly, that's a really good point. That's exactly what we're trying to accomplish.

Melissa Suran:

And what's the one thing you still hope to discover about mental health?

Cindy Ehlers:

We hope to know more about the genetics. We really need to study more of the genetics and to understand how cultural factors such as historical trauma may affect genetics through epigenetic mechanisms, as you mentioned previously. So, we've done some epigenetic sequencing in the population, and we're very interested in trying to pursue that to see if we can make some headway in that area.

Melissa Suran:

As an accomplished researcher—speaking of voices of reason to help guide people—what advice would you give to graduate students as well as up-and-coming scientists?

Cindy Ehlers:

My advice is that everybody needs to work in teams. You can get a lot farther working in a team than you can working by yourself in your lab. And I think it's very important to have mentors that you can go to continuously to help you talk through things; to help you through times when you're having problems with grants, or this or that. So, it's very important that the institute have mentors for people to be able to go to at any time and discuss their research and personal factors. Oftentimes, women come to me and ask, "How do you have a kid and be a scientist?" Or those kinds of things. And often, just having one conversation can make all the difference in someone thinking, "I can do that."

Melissa Suran:

And in what way do you think Scripps Research is uniquely poised to foster research on alcohol dependence, and even addiction in general?

Cindy Ehlers:

I think that we're in a critical inflection point. Right now, people like Hugh Rosen and Kim Janda are identifying new drugs to treat addiction. This is very important because there are very few drugs available that are actually effective in treating addiction. And we have lots of people here who can test them in preclinical and clinical settings. And then there's our group, which is engaging the community and studying the genetics. So, the critical mass is here. It's just important to be able to fund the structure so it can go on and be highly productive, to have that team of people that can really work together.

Melissa Suran:

And that's our episode. Thanks so much to Cindy for sharing her research and shedding light on the complex factors that shape alcohol dependence and depression.

Be sure to check out the show notes for more information on the cutting-edge work at Scripps Research and exclusive content from behind the scenes. If you like what you heard today, please subscribe or leave us a comment. Thanks for tuning in, and catch you next time on *Science Changing Life*—where listeners come curious and leave informed.