#37 – Do Psychedelics Leave Biological Fingerprints? How Psychedelics Influence Stress Physiology... Transcript

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Introduction: Do Psychedelics Leave Biological Fingerprints?

[music] >> Welcome to the Trip Lab, kitchen table conversations about integrative medicine and psychedelics. [music] I'm your host and attending physician, Dr. Mariella Wood.

Hi everyone. Welcome back to the Trip Lab. Today we're diving into an incredibly interesting topic in psychedelic science, and that is do psychedelics leave biological fingerprints? And I wanted to do this topic because there are some remarkable, early I will say, studies that are starting to ask whether a psychedelic experience can leave measurable traces across different layers of human biology. So this includes DNA methylation and epigenetics, changes in immune function, inflammatory markers, stress hormone signaling, and actually even early research looking at cellular aging and longevity pathways. And the studies are fascinating, so we're definitely going to dive into all of them. But also, one of the other reasons that I really wanted to do this episode is because for a long time, medicine has treated the mind and the body as if they are separate. So mental health in one box, physical health in another. But mental experience is not separate from biology. It is biology. Thoughts, emotions, trauma, fear and safety, connection, meaning, all happen through the body. They definitely do happen in the brain, but also the nervous system, the immune system, and the endocrine system. So the ways that our cells communicate with each other. So really today, we are tackling a bigger question. If a psychedelic experience can shift perception, emotional processing, memory, identity, and our felt sense of safety or connection, how far does that ripple through the body? So let's start with the basics so we can really understand the body first. And what I actually mean by {quote} biological fingerprints. And of course, we already know that psychedelics affect the brain. I think that's pretty clear at this point. But I think understanding how is important because again, the brain and the body are not separate.

How Psychedelics Act on the Brain and Body

And because if these molecules can create profound and lasting effects in this organ, the organ that influences the rest of the body, then it makes sense to ask whether we might see changes throughout the body as well. So just a quick recap, the classic psychedelics, which are LSD, psilocybin, mescaline, and DMT, which is in ayahuasca, those act on the serotonin receptors, especially the 5-HT2A receptor. And right off the bat, of course, these receptors are found in the brain, but they are also found throughout the body, including the gut, blood vessels, platelets, immune cells, and other peripheral tissues. So when psychedelics act on the serotonin receptors, they actually don't cause the release of serotonin.

>> [snorts] >> Instead, they activate the receptors directly and create downstream effects that can change communication between brain networks and influence neuroplasticity, which is the brain's ability to adapt, change, and form new connections. And again, remember, the brain is essentially the control center for the rest of the body. So let's move on to the rest of the body. And I think the first notable system to understand is our stress response system. And specifically, we call this the HPA axis, or hypothalamic-pituitary-adrenal axis. And the hypothalamus and pituitary glands are actually located inside the brain. The adrenals sit on top of the kidneys.

So this axis is all about communication between the brain and the body when a stressor arises. And that stressor can be emotional, psychological, physical, or environmental. So acute anxiety, trauma, lack of sleep, overexertion, illness, pain, poor nutrition, when we're talking about physical stressors, blood sugar swings, or environmental exposures like microplastics, smoking, things like that. So the body responds to all of those different forms of stressors in the same overlapping pathways. So, what happens is the hypothalamus, again in the brain, releases CRH or corticotropin-releasing hormone. Then that signals the pituitary gland, again in the brain, to release ACTH or adrenocorticotropic hormone.

Then ACTH travels through the bloodstream to the adrenal glands, which release cortisol and other stress-related

compounds. Then after that, the whole body gets pulled in. So, cortisol influences blood pressure, heart rate, blood sugar, digestion, immune function, inflammation, reproductive hormones, mood, sleep, and truly so much more. So, essentially, stress really is a full-body biological event. Okay, so we have that. Next, let's talk about DNA methylation and epigenetics. So, epigenetics refers to the way our cells regulate gene expression.

Stress Response, Epigenetics, and Immune Basics

To really understand this, we do have to go back to basic biology. So, our genes are made of DNA, which are the biological blueprint that we are born with.

And our DNA is essentially instructions to make proteins. So, DNA gets transcribed into RNA, and then RNA is eventually what gets translated into proteins. And these proteins get built from amino acids, hint hint, which is why nutrition is so important. And then eventually go on to form enzymes, receptors, hormones, structural tissue, immune signals, transporters, and essentially everything in our body. However, what people don't realize is that, while yes, our DNA is the backbone, it is actually not our final destiny. So, every cell in your body essentially has the same DNA. But, a liver cell behaves very differently from a brain cell or a skin cell or an immune cell.

So, why? Because different cells turn different genes on or off depending on what they need to do. And there are external factors that can actually influence this. Enter epigenetics.

So, this is the process that regulates genes are more active, less active, easier to read or harder to read. And one of the most studied epigenetic mechanisms is DNA methylation, which is when a methyl group, which is a small chemical group made of one carbon and three hydrogen atoms, gets added to the DNA. And depending on where that methyl group is added, it influences how easily a gene is expressed. So, what influences that epigenetics? Actually, quite a lot. So, of course, normal developmental changes and aging, but also stress, trauma, inflammation, nutrition, toxins, medications, sleep and exercise, alcohol, infections, and other environmental exposures. So, essentially, this is the biology of how and why lifestyle matters so much. And very interestingly, these epigenetic changes are actually being studied in psychedelic science, which we'll get to.

But, okay, next system. Again, we're still just recapping understanding the body a little bit more before we get into these studies. So, next I want to mention the immune system. So, when most people think about the immune system, they probably think about fighting infections. And yes, that definitely is a major part of what the immune system does.

But, it also does so much more. It is constantly scanning the body, responding to injury, cleaning up damaged cells, looking for cancerous cells to fight off, coordinating whole body repair, regulating inflammation, and communicating directly with the brain and the nervous system. And one of the main ways immune cells communicate is through signaling molecules called cytokines. So, these are essentially chemical messengers that help immune cells talk to each other and coordinate what kinds of responses the body needs.

And some are inflammatory and activate defense and repair. Others are regulatory and calm the immune system. And while we're on inflammation, one other thing I will point out is is inflammation is actually not inherently bad. It's all over social media, anti-inflammatory, anti-inflammatory, so I really wanted to point that out.

We actually need inflammation to heal, fight infections, and respond to injury. The problem arises though when it's chronic, excessive, or poorly regulated.

But back to the immune system, we are finding out more and more every year that the immune system is deeply connected to mental health, the gut microbiome, hormones, pain, metabolism, and a lot more.

Very interesting, and we'll get back to it as it relates to psychedelics in a minute here. So, last other thing that I want to briefly chat about is cellular aging markers. And this is a huge topic, and there's a lot of fascinating science that has come out in this field. And I do have another episode on longevity medicine that dives deeper into aging biology, if you want to check that out. But for today, the big idea is that researchers are starting to ask whether psychedelic compounds may influence some of the pathways involved in how cells age, repair, and respond to

stress. And some of those pathways include cellular senescence, which is when cells stop dividing, but they don't fully die off. And those cells can accumulate with age or after injury, and they can release inflammatory signals that affect nearby tissue. Researchers are also looking into telomeres, which are the protective caps at the end of the chromosomes. So, these help protect DNA during cell division, and telomere shortening is one of the biological processes associated with aging. There's also oxidative stress, which happens when there's an imbalance between free radicals and the body's antioxidant defenses. And again, a little amount of oxidative stress is normal, but too much can damage cells, proteins, lipids, mitochondria, DNA, and contribute to aging processes. We're also looking into DNA damage responses, which are the systems our cells use to detect and repair DNA damage. And having those healthy repair systems is essential for cellular health, aging, cancer prevention, and resilience.

Okay, great. We'll be done with the basic framework first. So now, let's dive into what we are learning in the psychedelic space and how psychedelics are likely impacting all of those pathways. And I will say right off the bat that these studies are early, but it is actually in humans and the data is very interesting. So first, I want to talk about a paper recently published this year, 2026, in Translational Psychiatry.

Psilocybin, Immune Markers, and Cortisol

So they looked at whether psilocybin-assisted therapy, specifically for alcohol use disorder, was associated with measurable changes in DNA methylation. And specifically, they saw changes at certain CpG sites, which are areas where we often see methylation occur, and changes in co-methylation modules, meaning sites that appear to change together.

And I think even more notably, these changes were specifically related to genes involved in serotonin signaling and immune function. They also found that certain baseline methylation patterns may be associated with how effective the treatment is. So basically, what that means is that epigenetic patterns may eventually help us determine who is more likely to benefit from psychedelics, which is completely fascinating. Now, of course, in this study, what we don't know is whether these changes were due to psilocybin alone, the whole therapeutic process of the psychedelic experience, or the subsequent reduced alcohol use because of the treatment.

All those things definitely go together, but the study doesn't really parse out which one it was. But even if it was not specifically from the psilocybin, this could potentially be huge, especially for alcohol use disorder. If psychedelics can help people drink less, change behavior, sleep better, and ultimately shift out of a chronic threat state, then all of that can also lead to positive epigenetic changes. And I think this is truly where psychedelic science is forcing us to take an integrative perspective in care.

We are never really just studying a drug effect in isolation. What we're really studying is a complex intervention that includes pharmacology, consciousness, memory, emotion, nervous system state, behavior, environment, and relationship. So, all of those things very different from the way that we usually study medications. So, okay, that one was fascinating. Next, let's move into the immune system.

And as we talked about, the immune system really is doing so much for our body and communicating with all body systems. So, a 2023 study published in brain, behavior, and immunity looked directly at whether psilocybin caused acute or lasting changes in immune status in healthy volunteers. So, this was a placebo-controlled study with 60 participants, and researchers measured inflammatory markers like TNF alpha, IL-6, and CRP, and other immune signaling markers before and after a psilocybin experience. And what they found is that the psilocybin group had acute reductions in TNF alpha and persisting reductions in IL-6 and CRP 7 days later. They also found that these changes were connected to brain chemistry and mood. Specifically, the reductions in TNF alpha were linked to lower glutamate concentrations in the hippocampus.

And even more interesting, the greater the reductions of IL-6 and CRP, which are inflammatory markers, 7 days later, the more participants reported persisting positive mood and social effects. So, this really does suggest that immune system changes and mental health changes are moving together.

And if we zoom out a little bit, I think this actually makes a lot of sense from what we know about physiology outside of psychedelics. The immune system is deeply responsive to stress, threat, sleep, trauma, infection, nutrition, gut

health, and so much more. And you've probably experienced this. If you've ever been under an immense amount of stress, and then shortly after got sick, had a pain flare, had gut symptoms, skin flare, or just physically felt inflamed, you have experienced this mind-immune connection. And this is well studied. Many stress-related conditions, including depression, PTSD, chronic pain, autoimmune disease, and burnout, have all been associated with altered inflammatory signaling. So, taking it back to psychedelics, these molecules induce powerful experiences, where people are moving through awe, surrender, love, forgiveness, memories, grief, and connection, and they definitely are psychological experiences, but they are also biological events that may be shifting the relationship between the nervous system, immune system, and felt experience. And before I move on from the immune system, I will also mention a 2024 preliminary study that looked at cytokine production after a psilocybin experience. And they did see alterations after psilocybin, but the specific pattern of changes were not the same across patients, which I think also makes sense, because everyone's immune system is vastly different and very context-dependent.

So, this study tells us that the changes were real, but more studies need to be done to understand the specific changes as it relates to cytokines in an individualized way. Okay, related to the immune system is the HPA axis, which again, hypothalamic-pituitary-adrenal axis. So, essentially, our stress response and cortisol center. So, this whole system, and again, hypothalamus and pituitary in the brain, adrenal sitting on top of the kidneys, is involved in regulating our stress response, ultimately releasing cortisol, which is our primary stress hormone.

Neuroplasticity and Brain Connectivity Changes

And what is fascinating about psychedelics is that they appear to interact with this system in a way that is way more complex than simply {quote} {unquote} calming it down. So that immune system study that I mentioned earlier also measured cortisol and they found that psilocybin actually activates the HPA axis during the experience. So specifically in the study cortisol increased and peaked around 80 minutes, started to come down by 150 minutes and by 360 minutes there is no longer a significant difference compared with placebo. So it's gone back down to normal. So acutely during the experience psilocybin actually activates the stress system. Which I actually think is really important to point out because some people, especially if you're taking psychedelics in a social setting or microdosing, a lot of people are taking it with the goal to {quote} {unquote} relax or calm down. But that may not actually be what's happening inside the body. So the psychedelic state appears to actually be more activating, which I do think also makes sense when you think about the emotional intensity of a full dose experience. But I think what we really want to know is what happens after that stress response peaks and calms down by the end of the trip. And there was a study published this year in 2026. It was an animal study published in current biology that gives us some answers. So the researchers looked at how psilocybin affects neurons in the hypothalamus, which are the key neurons that regulate that HPA axis. And they found that psilocybin activated these neurons and improved stress resilience, which is huge. And I think the term resilience is key. So our goal is actually not to get rid of all stress or constantly be in a state of calm. Our goal is to support the body to become more resilient and dynamic when a stressor arises. So we want to be able to move in and out of that stress response at appropriate times. The body is meant to be dynamic, not just zen and calm all the time. An interesting side note in this study, they actually found that female mice showed stronger behavioral, endocrine, and neuronal responses, ultimately leading to more stress resilience than the male mice did. So, just the very tip of the iceberg showing us that we really do need more research about how female bodies respond to psychedelics. And well, really everything differently. But, back to this topic. There's also really interesting preclinical research looking at psilocybin in stress-induced models of depression. A 2025 study found that psilocybin improved depressive-like behavior and cognitive recognition impairment in stressed rats. And if you really want the nitty-gritty science, specifically they saw that psilocybin downregulated ACTH and corticosterone, increased BDNF, and modulated endocannabinoid systems as well. So, to expand out, think about the bigger picture.

Psilocybin seems to affect much more than just the serotonin system when we're talking about the body. And this truly brings in a full mind-body medicine approach to healing. Okay, next. We cannot leave out neuroplasticity. So, this is probably one of the most common words you hear in psychedelic medicine research.

So, I don't think it's novel at this point that psychedelics increase neuroplasticity. But, as it relates to this episode, specifically looking at lasting biological markers, there's some interesting stuff here. So, psychedelics are actually starting to be described as psychoplastogens, which is a term that refers to compounds that promote rapid and sustained changes in neuroplasticity.

So, this idea really took off after a 2018 paper called psychoplastogens, a promising class of plasticity-promoting neurotherapeutics. So, what does that all mean? Very briefly, neuroplasticity is the brain's ability to change. This is how we learn, adapt, form new associations, recover from injury, and it's actually how therapy works and how habits change. So, basically, it's how the brain updates its model of the world. So, going a little bit deeper, psychedelic science specifically is looking for markers of this, like changes in dendritic branching. So, dendrites are the branch-like extensions of neurons that receive signals from other neurons. Dendritic spine density, synapse formation, so synapses are the communication points between neurons, and signaling pathways involved in growth and remodeling. One of the most common biomarker studied is BDNF, or brain-derived neurotrophic factor. So, this is a protein that is involved in neuronal survival, growth, synaptic plasticity, and learning. So, let's look at the psychedelic research. So, there's an LSD study that showed acute changes in BDNF. And we have an ayahuasca study that showed changes in BDNF were associated with the antidepressant effect.

However, a recent systematic review and meta-analysis looked at 29 different studies and did not find reliable increases in BDNF.

Cellular Aging, Longevity, and Psilocybin

So, ultimately, the data is mixed and emerging. We definitely need more research looking at other markers of neuroplasticity, like synaptic proteins, mTOR-related pathways, and other markers of gene expression. So, biomarkers related to neural plasticity, we're not really there yet. There's nothing consistent.

But, we certainly do see lasting functional MRI changes after psychedelic sessions. And functional MRI, or fMRI, is actually a really fascinating tool because it measures changes in blood flow and oxygen use as a way to estimate which brain regions are more active and how different parts of the brain are communicating with each other.

There's a 2024 study that followed participants before, during, and 3 weeks after a high-dose psilocybin experience. And we see widespread disruption and reorganization of functional connectivity throughout the brain.

Some of those changes resolved after the acute effects wore off, which I think makes sense. But reduced connectivity between the anterior hippocampus and the default mode network did persist. Other studies, more interestingly I think, have also found that changes in brain connectivity and emotional processing after psilocybin were associated with improvements in depression symptoms.

So, the changes we see on imaging correlated with depression improvement. Okay, we had to talk about neuroplasticity. But let's move on to probably one of the most surprising biological fingerprints when it comes to psychedelics, cellular aging, which is essentially markers of longevity. And I have a few podcast episodes on longevity medicine if you want to understand this field in more depth outside of psychedelics. So, check out episode 29, which is the integrative roots of longevity medicine, or episode 20, which is about NAD+ and longevity. But very, very briefly, longevity medicine is not just about the number of years we have been alive.

Aging also happens at the cellular level. And again, as I mentioned earlier, the field is looking at cellular senescence, telomere length, oxidative stress, DNA damage, mitochondrial function, which is a personal interest of mine, and the ability of cells to repair and respond to stress. And interestingly, the idea that psilocybin could affect biological aging did not start with the study we're about to discuss. A 2020 paper proposed what the author called the psilocybin telomere hypothesis. So, the idea was that because chronic stress, depression, anxiety, and other negative psychological states have been associated with accelerated biological aging and shorter telomeres, perhaps the lasting psychological effects of psilocybin could also translate into measurable changes in biological aging. So, that paper was just a hypothesis.

But then, in 2025, researchers actually did a study to test this hypothesis. And the results were pretty remarkable, I will say. So, in the lab, they treated human cells that are involved in producing collagen and wound healing with psilocin, which is the active metabolite of psilocybin, and found that the treated cells continued dividing longer. So, lower doses of psilocin extended cellular lifespan by around 29% and higher doses extended lifespan by around 57%. And they also looked at how this happened, the hallmarks of aging. And specifically, they saw longer telomeres, lower levels of oxidative stress, and changes suggesting less accumulated DNA damage. And I think

most notably, researchers did not see evidence that the cells had undergone any cancerous transformation.

So, I really emphasize that point because this is a really important paradox that I don't think is talked about enough in longevity medicine. Many pathways that promote longevity overlap with the pathways involved in cancer.

So, cancer cells are essentially cells that have escaped the normal controls on growth, division, and cell death. So, biohacking your way out of aging is not necessarily risk-free. If we keep stimulating growth and regeneration without fully understanding the downstream effects, there definitely is the potential to also support processes that we do not want, like cancer. And other side note, this is also one of the reasons that I'm still very hesitant about many of the peptides being used in the longevity space.

Because for a lot of these compounds, we simply do not have robust long-term human data. And in some, we don't have any human data at all. It's all mice studies or animal studies. So, I think they're really exciting and the mechanisms do sound really intriguing, but I think we do need to understand the tradeoffs before broadly recommending them. But okay, back to the study. So, after those remarkable findings in human cells in the lab, the researchers decided to study aging again in female mice. So, they gave them psilocybin once a month for 10 months and found that 80% of the psilocybin-treated mice were still alive compared with only 50% of the mice in the control group. They also saw improvements in fur quality, which is so cute that that was a research outcome. Hair growth and hair color. So, anyways, fascinating. And there's more studies, too. I think another interesting one is a preclinical research study showing that psychedelics enhance mitochondrial stress resilience in the prefrontal cortex. So, okay, bringing this all back to the bigger picture. Mental health and cellular health are not as separate as we have treated them in the past. Improving psychological health can also ripple downstream into physical and cellular biology. So, yes, a psychedelic experience may begin with those serotonin receptors.

But the downstream effects appear to spread very widely through stress pathways, immune signaling, gene regulation, behavior, relationships, sleep, and potentially even cellular resilience. And honestly, this should not be surprising. Grief changes the body.

Chronic stress changes the body. Connection, safety, and meaning changes the body. So, why would we assume that a profound in consciousness would remain only confined to the mind? Psychedelic science is becoming much bigger than we initially suspected. It really is forcing us to ask whether emotional healing can change physiology, whether changes in consciousness can influence cellular signaling, and whether the environment around a treatment is part of the biological intervention itself. So, ultimately, I think the real question is not whether psychedelics change the body along with the mind.

I think the real question is why did medicine ever separate them at all? Thanks for listening to the Trip Lab. If you liked this episode, please subscribe and share so we can get the conversation started about integrative medicine and psychedelics to destigmatize it and fully explore what this could mean in the world.

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