#25 – We Oversimplified Psychedelics. The Brain Is Doing Something More Interesting (DMN Modulati... Transcript

(Transcripts are generated by AI and may contain errors)

Introduction and psychedelic science update

Welcome to the trip lab kitchen table conversations about integrative medicine and psychedelics. I'm your host and attending physician, Dr. Mariela Wood.

Hi everyone, welcome back to another episode of the trip lab. In this episode, we're going to go through some updates that have come out in the past few years about psychedelic science. So, we have come a long way in our understanding of psychedelics. As a quick recap, and I definitely go deeper into this in my prior episodes, the classic psychedelics, which we are focusing on today, like LSD and psilocybin were first synthesized in the midentth century and quickly became the subject of actual serious medical and psychiatric research. In the 1950s and60s, they were actually studied for a lot of things from alcohol use disorder and depression to end of life distress and use during psychotherapy. Then in the early 1970s, for reasons we can definitely break down in another episode, these compounds were classified as schedule one substances. And as a reminder, to be a schedule one drug, it means that the drug has no medical benefit and high potential for abuse, which as we have explored on this podcast is not the case for these molecules. But you can see why this needs to be a whole separate episode. So anyways, they became a schedule one drug. Because of that, research largely stopped. And for decades, scientific progress was frozen because these molecules became politically and culturally offlimits. Then in the 1990s, small groups of researchers began to reopen the door. And over the past 10 years, psychedelic research has absolutely exploded. We've seen modern clinical trials, advanced neuroiming, and a serious re-engagement with questions about consciousness, mental health, and healing. But even in the past few years, our understanding has deepened even more. Many of our early neuroscience explanations we had were very helpful. But we're finding out simplified as to be expected when we think about studying consciousness, which is what we're really doing when we study these molecules. They did give us a framework and a starting point. And if you've listened to my earlier episodes when I first started this podcast a couple years ago, you'll definitely hear me talk about those models. But today, we're going to do a refresh because some of the neuroscience that is coming out is truly fascinating. We're going to review what we know, what has changed, and why the newer science is, in my opinion, far more interesting than the original story.

Classic psychedelics and early neuroscience models

Not just what's happening in the brain, but what that tells us about the body, about healing, and about how change actually happens. So, to understand what's changed, I think it's briefly worth reviewing how we originally explained the neuroscience of psychedelics. And this again is the framework that I've used in earlier episodes on this podcast. So the classic psychedelics like psilocybin and LSD primarily act on the serotonin 2a receptor. They bind to this receptor and activate it but they do not increase the release of serotonin itself which is very much unlike compounds like MDMA which increase serotonin release throughout the brain and the body. The classic psychedelics work more through receptor level signaling. So this is one of the reasons that they are generally considered physiologically safer and why we often say their effects are primarily on perception, cognition, and experience rather than on cardiovascular autonomic systems in the same way. This also helps explain why classic psychedelics do not carry the same risk of serotonin syndrome that we worry about with other serotonergic releasers. Another core explanation we've relied on is reduced phalamic filtering. So the phalamus acts as a sensory gatekeeper filtering and prioritizing incoming information before it reaches the cortex. Under psychedelics, this filtering appears to be relaxed allowing more sensory, emotional, and internal information to reach conscious awareness. This has been used to explain heightened perception, emotional intensity, and the feeling that everything is more vivid or meaningful. We've also talked a lot about the default mode network or the DMN. So the DMN is a network of brain regions involved in self-referential thinking, autobiographical memory, rumination, and maintaining a stable sense of self. So the earlier neuroiming studies suggested that psychedelics were associated with reduced activity within the DMN, which became a popular explanation for experiences like ego dissolution or loss of rigid selfnarratives. So this is where an important pivot has occurred. So we'll come back to that because

what we're seeing now is better described as DMN modulation, not just simple suppression.

Finally, we've talked about neural entropy. So the entropic brain hypothesis proposed by Robin Carard Harris initially articulated in his 2014 paper and then refined over time most notably in later work by Carl Fryon proposed that psychedelics increase the variability and flexibility of brain activity moving the brain away from rigid habitual patterns into a more fluid state. This idea has even been extended into broader evolutionary narratives like the stoned ape hypothesis which has been most closely associated with Terren McKenna. So this hypothesis suggests that altered states may have played a role in expanding cognition and perception in early humans. So they thought that early apes ate psychedelic mushrooms which played a role in their brains evolving and expanding consciousness into our now human brains. Again this is purely a hypothesis but I think a very interesting one. So altogether these ideas gave us a really useful starting framework. We have the serotonin receptor activation, relaxed sensory filtering, reduced default mode dominance and increased neural entropy.

And all of these were really helpful. They helped us move beyond moral panic and into mechanism. But they shared a common limitation. They all treated the brain as static, modular and regionbased. when actually the brain is dynamic, worked and contexts sensitive. So let's take this further. I have four major conceptual upgrades that have happened in the past few years that I want to dive into today. First the DMN. Our understanding has moved away from simply DMN down reggulation and towards DMN modulation and network reorganization. The second is a shift from static brain maps to dynamic functional connectivity. Third is how we are reframing away from entropy as disorder and towards entropy as flexibility, constraint relaxation and predictive processing. And last, what I am most excited about is our understanding that psychedelics don't just work in the mind, but how it impacts the body in therapeutic ways as well. So, let's start with the DMN. One of the most common explanations you've probably heard and one I've definitely used myself in earlier episodes is that psychedelics downregulate the default mode network, the DMN. This idea came from early neuroiming studies by Kheart Harris in 2012 and 2014 showing reduced integrity or coherence within the DMN under psychedelics like psilocybin and LSD. And at that time this was a very important insight. It gave us a neural coralate for experiences like ego dissolution, reduced rumination, and the loosening of rigid self narratives.

DMN modulation and network reorganization

But newer studies, including ones also by carart Harris and others, have shown that that explanation is just a little too simple. The default mode network is not a single structure or a volume knob that gets turned up and down. It's a distributed network involving regions like the medial prefrontal cortex, posterior singulate cortex, and angular gyrus. regions that as we already knew are deeply involved in self-referential processing, autobiographical memory, and maintaining a coherent sense of quote unquote me across time. So we understand now that psychedelics don't simply suppress the DMN. Instead, they change how the DMN communicates with the rest of the brain. So more recent studies show that while within network coherence of the DMN does decrease between network connectivity increases particularly between the DMN the salience network executive control networks and sensory systems. So lots of science terms but essentially the DMN doesn't just quiet down it actually instead becomes less isolated very parallel to how people often feel during a trip and when they feel more connected to nature around them. So again, rather than the sense of self being turned off, what appears to happen is that the self becomes less dominant, less rigid, and more permeable to other streams of information. So emotional signals, sensory input, and intraceptive data gain influence. Networks that are usually segregated begin to communicate more freely. This helps explain something that the older downregulation model never quite captured. People don't technically experience less of what's important to them as a personal eye, which again we associate with that ego death. They often experience more of other things, memories, emotion, meaning, connection. So from a network perspective, this reflects a shift from modular processing toward global integration.

The brain becomes less compartmentalized and more interconnected. Another key update is that these changes are state dependent and time varying. Dynamic functional connectivity analyses show that the DMN's role fluctuates over a course of a psychedelic experience rather than remaining uniformly suppressed. This also aligns far better with subjective reports which include moments of dissolution followed by insight followed by reorganization.

So when we say DMN modulation, we're really talking about a rebalancing of influence. The DMN still participates

in cognition, but it no longer holds the same top- down control over perception, emotion, and meaning making. This fits closely with predictive processing models where psychedelics are thought to relax the precision waiting of highlevel priors, allowing bottom-up signals to update entrenched beliefs and narratives. So, seen this way, ego dissolution isn't the absence of self, it's the temporary softening of the brain's habitual model of self. And that subtle shift from suppression to reorganization turns out to be far more interesting than our original story. So once we stop thinking about the default mode network as something that's simply turned off or on, the next question naturally becomes, well, what is the brain doing instead? And this is where another major shift has happened in psychedelic neuroscience. Early imaging studies, not just in psychedelics, but across neuroscience, tended to rely on static brain maps. You take a scan, average activity across time, compare conditions, and describe differences as increases or decreases in specific regions or networks. And that approach gave us some important early insights. But it also assumed something that turns out to not be true. It assumed the brain under psychedelics exists in one stable state. We now know that this assumption doesn't hold. More recent analyses using dynamic functional connectivity show that psychedelic states are highly timevary which means instead of a single altered brain state the brain moves through multiple network configurations over the course of a session. So essentially the psychedelic brain is constantly in motion and this makes sense when you step back and think about how a trip goes. But now we actually have neuroscience that is catching up. So studies show rapid shifts in how networks couple and decouple including the DMN, salance network, executive control network and sensory systems and connectivity patterns fluctuate on the scale of seconds to minutes really. So this update is crucial because when you listen to people describe psychedelic experiences, they don't describe one uniform state. They describe waves, moments of disintegration, moments of emotional intensity, than insight, clarity, and reorganization. So, dynamic connectivity models align far better with this lived experience than static maps ever did. Another important implication is that no single scan can fully capture how psychedelics work. We can't study psychedelics as a snapshot in time because that snapshot is totally different depending on when you look, what the person is doing, whether the brain is at rest or engaged, and the individual's baseline network organization. So, this makes sense, of course, but it's really important that this is now explained neuroscientifically in the literature. This helps us explain why results across studies sometimes appear inconsistent and why that inconsistency isn't necessarily a flaw, but I think actually a feature of psychedelics and it helps us understand the mind better, too.

Dynamic connectivity and shifting brain states

So, we're seeing that psychedelics seem to expand the brain's repertoire of possible states, allowing it to explore configurations that are normally less accessible. Rather than pushing the brain toward one new pattern, they increase fluidity of transitions between patterns. So I think from a systems perspective this is enormous. It reframes psychedelic action not as a destination like a particular brain state you enter but as a process a period of heightened flexibility in which old patterns loosen and new ones can emerge. And as you can imagine this has really important downstream consequences. If the therapeutic effect were simply about landing in the right brain state integration wouldn't matter at all. But if the effect comes from moving through states, then meaning making, reflection, and postexperiencing processing become of the utmost importance, not something that's optional. This dynamic view also helps explain why psychedelic effects are so sensitive to context. The brain isn't being forced into a single configuration by the drug alone. It's being nudged into a more explorable landscape where environment, expectation, memory, emotion, and bodily signals all shape which paths are taken. So when we move away from that static brain map and toward dynamic functional connectivity, we stop asking questions like what brain state do psychedelics create? And we can start asking new questions like what kinds of transitions do psychedelics make possible? And once we shift what we're asking, I think the rest of the newer neuroscience, especially around entropy, relaxed constraints, and prediction start to make a lot more sense. So with that, let's talk about that entropy conversation. So early on, the entropic brain hypothesis proposed by Kheart Harris in 2014 suggested that psychedelics increase neural entropy, meaning greater variability or diversity in brain activity patterns. And this is powerful. This helped explain why rigid mental states like depression, addiction, and obsessive thinking may loosen under psychedelics. But as this theory matured, it became clear that the word entropy was doing a lot of work and sometimes being misunderstood. What the newer models clarify is that this is not randomness, which is often associated with the word entropy, so not just neural noise. Instead, psychedelics appear to increase the range of possible brain states the system can access. So, a helpful way to think about this comes from predictive processing models of the brain. In this framework, the brain is constantly generating predictions about the world and about the self based on past experience. So, these predictions or priors help keep perception and behavior stable and efficient. This is what allows us to go about our world and operate in a shared

agreed upon reality with the rest of the people around us.

And under normal conditions, those highle priors carry a lot of weight. They constrain interpretation and they keep perception, emotion, and identity within familiar bounds. What psychedelics appear to do is temporarily relax the precision of those highle priors. So this was reported in a 2019 study by Carheart Harrison Fryen. And let me emphasize this phrase, relax precision. The priors don't disappear. They just become less rigid. So when that happens, bottom up signals like sensory input, emotional states, interceptive information from the body gain more influence over the system. The brain becomes more open to updating its internal models. So this is where entropy gets redefined. Entropy in this context doesn't mean chaos. It means expanded flexibility. It means the brain can explore configurations that are usually inaccessible because it's constrained by habit, expectation, and deeply ingrained narratives. Another important note is the system isn't breaking down. It's temporarily becoming more plastic or flexible. So again, this also helps us explain why context and meaning matter so much. If psychedelics simply just scrambled the brain, similar to, let's say, electric shock therapy, expectation wouldn't shape outcomes.

Entropy, predictive processing, and flexibility

But if psychedelics loosen constraints on interpretation, which we now believe that's what they do, then set and setting become biologically relevant inputs, not just psychological add-ons. And outside of the neuroscience community, people have been talking about the importance of set and setting for ages. And now we just have an explanation, at least a current explanation that I'm sure will change of why. This also explains why people don't just experience altered perception. They experience new emotional associations, reframed memories, shifts in identity, and changes in how bodily sensations are interpreted. And these are exactly the kinds of changes you would expect if highle predictive models were temporarily softened, allowing new learning to occur. Importantly, this also explains why the effects of psychedelics are not inherently therapeutic. Flexibility can go in many directions. So without safety, guidance, and integration, relaxed constraints can just as easily reinforce fear or confusion. But when paired with supportive context, that same flexibility allows deeply entrenched patterns to reorganize. So when we revisit this idea of entropy with all this new neuroscience, we arrive at a much more interesting conclusion.

Psychedelics don't heal by creating disorder. They heal by creating a window of increased adaptability. And this leads perfectly into our next topic. From not just brain only explanations to brain body context interactions. So up until now, most explanations of how psychedelics work have focused almost entirely on the brain. So receptors, networks, connectivity, predictions.

And we actually often frame them this way to emphasize the safety of these molecules. You know, saying, "Oh, they just work in the mind." And yes, primarily what they do is change consciousness. But in my opinion, one of the most important shifts in recent years is a growing recognition that psychedelics do not just act on the brain in isolation. They act within a brain body context system. And this honestly makes sense because people report more than just visual or cognitive effects. They express feeling things more deeply. We see people report increased intense bodily sensations, changes in breathing and heart rate, waves of emotion that feel physical, and a heightened awareness of internal states. So, I think these experiences point us towards something that neuroscience is actually starting to take seriously now, and that's interosception, which is the brain's perception of signals from the body. Under psychedelics, interosceptive signals appear to gain salience. Sensations that are normally filtered out or interpreted automatically become available to conscious awareness. This includes signals from the autonomic nervous system, the visceral organs, and emotional circuitry that is tightly coupled to the body. So, psychedelics may not be increasing heart rate on a receptor level alone, like how we would think of a beta blocker directly lowering heart rate or blood pressure, but they increase awareness of our bodily sensations that are normally controlled beneath conscious awareness. And when we become aware, we are in a state where things like heart rate and blood pressure can fluctuate because of that awareness. So again, I think this supports what we know in mindbody medicine. So I think we really have to reframe the idea that psychedelics quote unquote just work in the mind. They actually heighten the brain body connection and our ability to access mindbody medicine. This also helps explain why psychedelic experiences often intersect so strongly with trauma, emotion, and identity. Trauma, as we're learning, is not stored as an abstract memory alone. It is deeply encoded in patterns of autonomic response, muscle tension, breathing, and visceral sensation.

Brain-body context and integration

So if psychedelics relax predictive constraints in the brain, they can also relax habitual interpretations of bodily signals. So sensations that were once labeled in our mind as a threat can be reexperienced, recontextualized, and integrated differently. So we know now even more deeply that context shapes nervous system state. and safety, trust, relational presence, and environment all influence autonomic tone, stress hormone signaling, and interceptive interpretation. And in a brain that has become more flexible and less constrained under the influence of psychedelics, this matters even more. This is why two people can take the same compound, same dose, and have profoundly different experiences and outcomes. So essentially what I'm saying is it's not just the drug, it's the system in which the drug is acting.

I think this shift also pushes away from a purely pharmacologic explanation of how the healing happens. Psychedelics don't insert new information into the brain. They alter how information is processed across the brain body interface. So temporarily widening the space in which learning can occur. So I'll say this again. This is where integration becomes even more essential than we originally thought. If the therapeutic effect were simply about receptor activation or network reconfiguration, integration would be optional. But if psychedelics open up a window of heightened sensitivity to bodily signals, emotion, meaning, and relationship, then what happens before, during, and after that window shapes whether the change consolidates or fades. This whole brain body context model also helps explain why psychedelic research is increasingly intersecting in fields like trauma therapy, somatic approaches, autonomic nervous system regulation, and of course, integrative medicine. And this opens so many doors to things that we're only beginning to explore like how sex hormones, menstrual cycling, stress physiology, and embodied experience may actually influence psychedelic responses. And this ultimately is where psychedelic neuroscience is heading. Not towards simpler explanations, but toward models that better reflect how humans actually experience change with or without psychedelics. So when we zoom out and look at the full picture, what becomes clear is that psychedelics were never doing one simple thing. Our explanations were simplified because the tools and language we had at the time were simpler. What we see now is far more interesting. Not suppression, but modulation.

Not a single brain state, but dynamic transitions, not chaos, but a temporary window of flexibility shaped by the brain, body, and context. So, I think psychedelic science hasn't just advanced by adding more data. It's actually asking better questions now, which is why we are finding out these new things. And as our models continue to evolve, so will how we understand healing, change, and the mind itself.

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