Episode 33 – Frederick Barrett: Psychoactive compounds to treat depression, addiction & inflammation

Drew (00:03):

Good day to you listeners, and welcome back to Science Changing Life with your one and only host Drew Duglan. And what a journey I have lined up for you today, or should I say trip always pushing the boundaries here. We delve into the breakthrough topic of psychedelic substances. I'm lucky to be joined by external guest Frederick Barrett, who is a cognitive neuroscientist based at the center for psychedelics and consciousness research at Johns Hopkins University. Dr. Barrett specifically covers the promise of these compounds in a clinical setting to help alleviate a number of neurological and mental health disorders. But before that let's discover how it was. Fred's initial passion for music that guided him towards studying, learning memory and emotion.

Fred (00:48):

I grew up in Philadelphia and for a good portion of my pre-college life, I was really devoted to playing music. I played the trumpet and I played the violin in a number of community orchestras, and I played the drums in punk rock turns, hardcore punk bands that persisted through college. I went to temple university for undergrad, for music education. At the time I knew I didn't know what I wanted to do with my life, but I knew I loved music and I liked helping people. And I naively thought there would always be jobs for music teachers. And, um, and at the time I was taking my psychology core courses, just undergraduate requisites, right. And getting really into it. So I decided to stay an extra year, get a double major in psychology and music ed. And, uh, I really began to get involved in research.

Fred (01:37):

At that point. I was involved in two different labs, one lab, the lab of Dr. Lauren Alloy at Temple studying hopelessness, depression, and, uh, another lab, Dr. Bob Weisberg, studying creativity. Then I was able to kind of use contribute to studies, looking at music creativity while I was also, uh, contributing to studies learning about depression. I just got completely addicted to the idea of, you know, conducting research, you know, who the, at that point, who the heck wants to treat people when you can do all this cool research and, you know, if anything hits, you can have an outsized impact on the world. And well, anyway, I, I found, uh, a grad school program at UC Davis in the lab at Petr Janata at the Center for Mind and Brain where I could bring everything full circle and use music as a tool to study emotion and memory in the brain.

Fred (02:23):

At about the same time I was friends with another grad student at UC Davis, who was a couple years ahead of me. And she was studying the effects of meditation on attentional, functioning and cognition. And it was Katherine MacLean. It was always her dream or at least I understood it to be that, to study the effects of psychedelics. And she graduated. She came to Hopkins to work with, uh, our, our mentor Roland Griffith, who was studying the effects of psilocybin and Katherine and, and Roland got some money to, to run a study, looking at the effects of psilocybin on meditation and, and the convergence of experiences that you can encounter during meditation experiences that you can encounter with psychedelics. And, uh, some of the money was going to be put aside for brain imaging. The day after the experience, there was, I hope that they might be able to index and study the afterglow.

Fred (03:14):

So, you know, there there's this change in, you know, stress and emotions that, um, you know, reduction in stress and, and a change in emotions that can occur a day or days. And up to a week after psychedelic experience, people like to colloquially call it the afterglow and wow, wouldn't it be interesting to, to study that and, and we should use music as it's told to do. I know a guy who does that. So Katherine sent me a series of emails, you know, how'd, you design your study, how'd you collect your data, how'd you analyze your data. How'd you interpret your data, how'd you find your subjects. And I jokingly, mostly jokingly sent her a tongue in cheek email response, um, hire me as a postdoc and I'll do it for you. And she said, okay. And I said, what really? Okay, great. Yes, of course.

Fred (03:54):

I would love to come to Hopkins to study the effects of drugs on the brain. You know, music is an incredible tool to do that, but we know, we know all sorts of things about drugs, you know, how they work in the brain and what receptors they hit and how they're metabolized and all these things. You know, music is complicated, because people are complicated, but drugs, drugs are the tool that I should be using to study, you know, altered states of consciousness, emotional functioning memory, and other things. So I came to Hopkins as a postdoc and, uh, and began to do that Katherine soon after left academia and, and dropped this whole study in my lap. And, and then I was off to the races, but, uh, I find myself in the peculiar situation now of contributing to studies that are showing remarkable effect sizes in, in relatively intractable populations that are suffering deeply in with disorders that are highly prevalent. And the initial signal seems to be that you might actually go a long way in helping people.

Drew (04:51):

Right. It's such a fascinating background. I mean, like you described in your earlier days, it's like you had this thought a few times, you know, what am I doing? And then it turns out that you've been able to bring that emotional sensitivity from psychology and you combined it with say your expertise in coding to make a good, really unique researcher. I would say, because so much of behavioral neuroscience now seems to depend a lot on this, uh, software too.

Fred (05:15):

Oh, absolutely. And I think that, you know, has, has really done me well, you know, and it's yeah, it's incredible. You know, I, I found myself at one point in grad school complaining to my advisor, uh, Peter, you know, like 95% of what of I'm doing is, is sitting behind a keyboard and struggling with MATLAB. And he said, well, would you rather be pipetting? And I said, well, in fact, no. This is the tool the time for sure.

Drew (05:43):

Definitely. And so it's fascinating, your lab is at this intersection with psychedelics and music and then helping certain populations. And you had just mentioned psilocybin. And so what is psilocybin? Because I think people is that the same as mushrooms, people might be familiar with that, but what is psilocybin?

Fred (06:02):

Yeah, so, so fungi generally and broadly are fascinating, incredible little chemical factories. And there are, you know, thousands and thousands of species of mushrooms, uh, each have their own chemical composition and the fruiting body of the mushroom, which is the thing we would pick up and eat from

the, from the store. If we were eating an edible mushroom, you know, safe edible mushroom, but the, those fruiting bodies are just the kind of outward expression, kind of the, the fruiting expression of the underground, mycelium, almost like a root network and the fruiting bodies of various mushrooms produce depending on their habitat. There are hundreds of species of mushroom that produce this peculiar chemical psilocybin. So yeah, psilocybin is the active psychoactive compound in magic mushrooms. Apparently, uh, you know, magic mushrooms have apparently been used for an unknown period of time, but a not insignificant period of time in the past, by a number of indigenous populations, psilocybin containing mushrooms are, are found on all continents, maybe at least six of continents, certain cultures of the world have, has identified them as important and utilized them in ceremonial offerings and ritual and, and for healing or for shamanistic purposes or other things like this psilocybin mushrooms you could argue, came to Western consciousness through, uh, Gordon Wasson, who, uh, was a Wall Street banker ages ago, you know, uh, almost a century ago.

Fred (07:25):

And he and his wife took a trek into the middle of, uh, Oaxaca. Mexico found a population of people who were using psilocybin mushrooms and the story of early research with psychedelics primarily with LSD. But of course there were studies with psilocybin, which comes from psychoactive mushrooms, mescaline, which comes from psychoactive cacti and, and then a whole host of related compounds that were developed or discovered it was it's mostly from what I understand, LSD that was studied in labs across the country and around the world. In the fifties and sixties, this all came to a crashing halt with the passage of the controlled substances act in 1971. And there were a small number of studies here and there scattered out throughout the nineties. And then it wasn't really until the first modern trial with psilocybin in the states in 2006, the people really began to start paying attention to it.

Fred (08:16):

Again, suffice it to say we use a synthesized compound rather than fungal matter for a couple reasons. One, if we have that synthesized compound, uh, generated by a medicinal chemist, we can really clearly and cleanly characterize that compound, store it under appropriate conditions. And we know exactly what we're giving people at all points. As I was kind alluding to, you know, the magic mushroom itself is the fruiting body of a, of a network of mycelium. There are hundreds of species of mushroom that contains psilocybin. Each species has its own average psilocybin concentration in any given fruiting body, but even within the same species, two fruiting body from the same, my network that are right next to each other, they can have vastly different concentrations of psilocybin or other compounds. And so frankly, if you are given a handful of fungi, there's no way of knowing how much psilocybin is in your hand.

Drew (09:10):

Definitely a solid rationale there for using the sort of chemically isolated psilocybin. So what kind of clinical studies have you been doing then and with what sort of patient populations and what have the results been like?

Fred (09:22):

Our lab at Hopkins and, and in parallel, a lab led by Steve Ross at, uh, NYU in 2016, published parallel studies, randomized controlled trials in cancer, patients showing very large effect size, incredibly impressive signal for the potential of psilocybin to treat anxiety and depression in these, in this population. And if you know anything about late stage cancer, the existential crisis that a accompanies

the cancer can be one of the most difficult things to treat about cancer aside from the actual cancer. So it's a remarkable opportunity to potentially give people their life back for the end of their life. But before those two randomized control trials, my colleague, Matt Johnson here at Hopkins in 2014, published an open label pilot study showing, uh, a remarkable effect of psilocybin in helping people to quit smoking. It was an open label, unrandomized, small sample proof of concept trial and 15 people.

Fred (10:19):

Uh, but the findings were that I think six months out over 80% of people were still abstinent cigarettes, biologically verified, and slightly less than that at one year, which just is, is almost unbelievable. And in 2015, a colleague Michael Bogenschutz at NYU published, uh, an open label pilot trial in patients with alcohol use disorder, showing that, uh, S Sabin therapy paired with a motivational enhancement kind of psychotherapy intervention drastically reduced the number of days drinking in the heavy drinking days of patients. There's ongoing research that, uh, hasn't been published yet by a colleague, Peter Hendricks at the university of Alabama, Birmingham, studying the effects of psilocybin in treating patients with cocaine use disorder. And now at Hopkins, we have a study in patients with opioid use disorder coming online soon in 2016, when we published our cancer trials, Robin Carhart Harris at Imperial college, London published an open label clinical trial in patients with treatment resistant depression, suggesting that in fact, psilocybin might be helpful in drastically reducing depression severity in patients with treatment resistant depression. These can be incredibly difficult patients to treat. Since then we published a study in patients with major depressive disorder, large that was published at the end of 2020. And our study over 70% of patients showed a, a clinically significant effect, which is a 50% of greater reduction in depression, severity from baseline.

Drew (11:47):

I mean, these are such, these are such striking effects and, you know, from anxiety and depression, all the way to addiction as well, which, you know, would be a massive application given the epidemic there with, uh, different drugs. So you mentioned effects lasting up to a year, I think, in, in smokers. So could you foresee some of these changes being permanent? Do you think people might have to sort of reup a dose, you know, every year or what would the dosing look like then? Would there be any negative side effects of these, uh, interventions too?

Fred (12:19):

Yeah. Excellent questions. And, and there's a lot to, lot to unpack here. I mean, so one, one thing to acknowledge is that despite all of the wonderful and fascinating things that I just said, you know, the number of people who have been treated with, with psilocybin specifically where a psychedelic general in the modern era is, is incredibly small compared to the number of people who need to be treated in order to support, you know, registration trials for the FDA, whereas, you know, cardiac or obesity or hypertension, you know, all, all sorts of medications going through registration trials, you need like thousands of people from all sorts of places over the world, uh, and thousands and thousands of observations to be able to, to claim that there's a therapeutic effect and that it's safe enough to bring to market even then in your phase four observation.

Fred (13:06):

And it's only then that you, you find certain drugs like one in 10,000 case of heart attack or aneurysm or something like that. And, and drugs that show those serious adverse effects can be pulled off the market after being marketed and sold. Right. Once we learn more. And so, yeah, we're way, way behind

anything, you know, any kind of data like that to, to really suggest like super low rates of potentially serious adverse effects that, that having been said still the effect sizes and, and the findings are pretty remarkable, but there's so much that we don't know. And there may be differential effects in different disorders. So between indications, substance use versus mood disorders, there may be different dosing regimens. We just don't know. We have no idea how long these will last. It may be that we have to play it by ear that some folks with major depressive disorder, I don't wanna use the C (cure) word, but, you know, have, have really indefinitely enduring, you know, therapeutic effects. Whereas other folks with major depressive disorder, they might need a re-up in a year. Maybe folks with treatment resistant might need far more frequent therapeutic intervention with psilocybin. Maybe it maybe after three or four different rounds than, than you see lasting benefit. But we, we simply don't know these are all great questions and they're all questions that are gonna have to be answered if psilocybin is ever approved as a medicine

Drew (14:22):

When working with different patient populations, Fred and the team are careful to screen for and exclude those who may have a family history of psychosis to minimize the risk of adverse events. That being said, is there a case to be made for challenging psychedelic experiences that help us to confront and integrate our shadows?

Fred (14:43):

You know, you can think of what people like to call bad trips or challenging experiences. These are experiences that can be characterized by feeling the physiological distress, grief, panic, fear, feeling like you're going insane or losing your mind and, and lone feelings of loneliness or isolation. These are all very challenging, affective and physiological like experiences that people can encounter during experiences with high doses of psychedelic drugs, especially the doses that we administer in clinical, uh, environments and, and, and clinical situations. There's a sense in psychedelic using communities that the worst trips are the best trips, because oftentimes most often I'd, I'd say at least within the clinic, these challenging experiences arise cause of challenging psychological material in a person encounters during their experiences. And on the other end, after the experience occurs and people integrate that within their lives, it's almost always part of the story and confronting these aspects of the self or a personal history or a person's life and dealing with that and working through it and, and maybe even more so the personal insights and the psychological insights that people gain through this process.

Fred (15:58):

And our best guess right now seem to be one of the core drivers of therapeutic effects. So it's almost like the bad trip in some cases, is the medicine, you know, there have been, I, I believe one or two instances of an individual who's gone through this experience and had to seek counseling afterwards because they had to finally confront the thing that they hadn't been confronting. And they went to like a few sessions and, you know, with, with a counselor or a therapist and, and then that was it. They kind of integrated it, they worked it out and they moved on.

Drew (16:25):

Sure. That is interesting. So could you foresee these being used at all for neurodegenerative conditions as well?

Fred (16:33):

Yeah, so that's interesting. So my colleague Albert Garcia-Romeu and, and Paul Rosenberg here at Hopkins are running a study right now in patients with, I believe mild cognitive impairment or early Alzheimer's dementia. And, and I believe they're targeting kind of cognitive and affective components. There's a, a growing animal literature to suggest neurogenesis, spinogenesis and synaptogenesis that occurs acutely. And then after psychedelic, uh, exposure, if it's the case that psychedelics have a neuroplastic effect, you know, it would, it would then follow that you'd wanna know whether or not that, uh, neuroplasticity that's induced by psychedelics could be helpful in treating neurodegenerative diseases. At the very least it's kinda slow the progression of the disease.

Drew (17:18):

This would be the remodeling, then, of neurons in the brain?

Fred (17:22):

Yeah, pretty much. Yeah. And other disorders could be reasonable targets - patients with Parkinsonian disorders. It may not be that psychedelics directly treat the disorder, but there's a literature suggesting that, uh, that stress, anxiety and depression early in, in the progression of Parkinson's disorder can, can speed the, the, uh, acquisition or the development of disorder. And isn't that terrible because the first thing you feel after you're told you have a Parkinson's diagnosis, you freak out because some people see it as, as like, you know, a point of no return. Like, wow, I'm gonna have this for the rest of my life and, and, and I'm gonna die with it. So it's, it's terrible that reacting strongly to that with anxiety and depression can, can speed the, the development of disorder, but, you know, wouldn't it be interesting of psychedelic intervention early on in that process would kind of relieve people of the stress and anxiety of the diagnosis.

Drew (18:16):

Got it. So I was at a neuroscience conference earlier in the year, and there was a panel on psychedelics and it did seem that a lot of the work was looking at how it affected our serotonin pathways, which a lot of people associate with sort of that happy feeling. So do we know, you know, mechanistically is that the predominant type of, um, neuron that these drugs sort of affect and remodel?

Fred (18:41):

Yeah. So it does seem pretty clear from decades of work, uh, in multiple species and multiple levels of analysis that it's the serotonin 2A receptor that, uh, and signaling at that receptor, that is the primary mediator of the trip, if you will. Yeah. Right. The psychedelic effect. And there's, uh, a, a bunch of human literature to suggest that that subjective experience, the trip itself is associated with therapeutic outcomes. So, you know, it, it, it follows then that signaling at this receptor, if it is indeed what kicks off all of these experiences that, that are associated with therapeutic effects, it, it follows that, that this signaling of this particular receptor is the apparent initial mechanism of all these effects with, with some of the subjective effects, possibly being, you know, the mind's manifestation of increased neuroplasticity, or there's a whole other thread to consider here as well, uh, which is work that's coming out of the lab of Chuck Nichols at Louisiana State University.

Fred (19:45):

Dr. Nichols is, is developing a really beautiful literature to suggest that psychedelics may have an anti-inflammatory infected in multiple different species in multiple different organs, in multiple different

processes. And, and, and that just kind of breaks things wide open, right? Like everything's related to inflammation. So if you can treat inflammation, you can treat so many different disorders. Who knows if that's actually true. I think we still have a long way to go to determine whether or not psychedelics have a neuroinflammatory or anti-inflammatory effect and, and how all of these things relate. But yeah, I think inflammation and neuroplasticity are the two hot models right now. Sure.

Drew (20:21):

Yeah. That was absolutely fascinating and such an exciting space. So I have one roundup question for you, which would be, if you could give a one piece of advice or your wisdom to anybody in the sort of realm of work or career progression, a life health self-improvement, it could be in anything, what do you think it would be and why?

Fred (20:40):

Uh, a lot of people ask how to get involved with psychedelic science and, uh, and my advice has been the same and it echoes advice that other folks have given, which is to not get involved in psychedelic science. There are lots of silos and, and lots of domains and disciplines within neuroscience, psychology, sociology, philosophy, microbiology, chemistry. There are lots of different disciplines that come together to really inform and, and help to define psychedelic science and psychedelic science exists at different levels in all of these disciplines and domains. My advice to people who want to get involved in psychedelic science is to get educated about something that you can use to study psychedelics, get your bonafides in that field, and then bring it to psychedelic science. And so that's what we need, and that's, what's going to help the field grow the most.

Drew (21:36):

Wow. I do really like that perspective, develop those tools that you could then transfer across to any field of your choosing. A big thanks to Fred for joining me today and perhaps giving us a glimpse of the future of treatment options for those struggling with mental health addiction or other cognitive disorders. And you can learn more by looking in the show notes where you'll find links to Fred's work as well as more exciting Scripps Research content. Remember to pass on the gratitude by rating the podcast, wherever you may be listening. And please join us again for future episodes in that intervening period, take care of your mental, stay curious and be well.