Announcer: Bullet Proof Radio, a state of high performance.

Dave: You're listening to Bullet Proof Radio with Dave Asprey. Today's cool fact of the day is about the numbers in your brain. Specifically, it weighs about 3.3 pounds. It's about 60% fat, which means it's one of your fattiest organs, but especially if you're a woman, probably not the fattiest organ. You probably didn't know there are 100,000 miles of blood vessels in your brain, about four times around the equator of the earth, which is cool and you've got billions of nerve fibers called axons and dendrites, which you've heard me talk about before. Did you know there's about 100 billion neurons in your brain, but they're only about 10% of the brain?

They have that power because they reach out to 100 trillion plus trigger points, which is what you could call a neuron forest, and your brain can make about 23 watts of power when you're awake, which is not quite enough to charge your iPhone, but it maybe could if you weren't thinking. Your brain processes information at somewhere around one mile per hour up to 268 miles an hour. What that means is they're actually measuring how fast electrons flow in the brain, which is kind of cool. You can think both fast and slow as the title of a famous book would tell you.

All right, that was some cool stuff about the brain, and if that wasn't a case of foreshadowing where I tell you what we're going to talk about on today's show, then I've never foreshadowed. Before we get into today's awesome topic, today's guest is Dr. David Feifel. He's a master clinician, a certified neuropsychiatrist and very accomplished brain scientist who founded the Kadima Neuropsychiatry Institute in San Diego in 2017 after having been a full professor of psychiatry at UC-San Diego for more than 20 years. There's a couple things we're going to talk about today. One is that 10 years ago, he developed the world's first ketamine infusion program for psychiatric disorders, and integrated it into the UCSD's Center for Advance Treatments.

We're talking about one of the first guy's using ketamine in psychiatry this way, which is really, really fascinating, and because that wasn't enough for him, he's also one of the top guys looking at transcranial magnetic stimulation and ketamine in the brain. You wanted more brain hackers, you got more brain hackers. Dr. Feifel, welcome to the show.

David: Thanks, Dave. It's a real pleasure to be here.

Dave: How do you feel when I call you a brain hacker? Good thing? Bad thing?

David: I think it's a good thing. I love everything about the brain. It was a great intro, all those facts about the brain because I'm obsessed with it. It's cool. I'll take almost any description that involves the brain and I'm okay with it.

Dave: You definitely love the brain because you've written more than 100 research papers and book chapters and what not on different brain functions, and have really been at the forefront of your field for a long time. I always like to know what drives people to do what they do. Why did you become a preeminent brain scientist? Why that?

David: You may regret that question. You know, when I was younger, my first intellectual awakening ... You're a goofy high school student, then the one day you start to think seriously about things, but my first intellectual awakening was reading about quantum physics and realizing that scientists, like really serious scientists were saying that the reality around us ... These guys were hardcore physicists ... reality around us is not what it appears to be, and I'm sure you're aware, the what they call the Copenhagen interpretation of quantum physics is that consciousness actually is responsible for creating the material world around us.

Now, that's a crazy thing for a bunch of serious scientists like Niels Bohrs to say. I thought that was so cool, and basically I became really interested in consciousness. Once you start thinking about consciousness, it leads you to the brain, and one thing leads to another, and a few decades later I suddenly find myself in medical school, doing a MD PhD program and wanting to be a psychiatric and neuroscientist. That's the short version.

Dave: Did you actually clinically practice psychiatry?

David: I did, yes, and do.

Dave: You're still actually seeing patients?

David: Yes, yes. I'm in my office right now. There are patients my colleague is treating right now with ketamine. Just to give you the sense of what's going on.

Dave: Wow. You've done a ton of research. I find often times when people are writing hundreds of papers in an academic setting, they don't see a lot of patients.

David: Correct.

Dave: You've been hands on with patients your entire career then?

David: Yes. When I came to UCSD, I was primarily interested in research, and I didn't think that the clinical practice of psychiatry was all that interesting, but I thought the research aspect was great, along the way I fell in love with the clinical work. All my mentors said as soon as you get enough grants, buy yourself out of the clinical work so you can focus on the research. That's a very common thing in academic institutions. You have very renowned psychiatrists, or really it's true for any specialty, but they don't see patients because they're spending most of their time writing papers and going to conferences.

I didn't take that advice. I said gosh, I still love research but now I have this new found love for clinical work, so what I'm going to do is exactly what everyone tells me is the worst thing I do and that is I'm going to actually really try and do both well, and spend a lot of time doing both. I've done that. It's not been always the easiest thing but I'm really glad that I have.

Dave: How do you define the line between psychiatry and psychology for people who are listening? It seems like there's always some overlap there. Dealing with a past trauma, and a psychologist would put you on a couch, but in psychiatry, you might do something different. In your own mind, how do you tell people the difference?

David: You know, it's really arbitrary. I would even include in someways neurology. These are arbitrary divisions that have come up over the years due to political issues, or sometimes they're just historical. I think that if you think of Sigmund Freud, he's in many ways the father of psychological interventions, but he was also a trained neurologist, and he believed that ultimately all these disorders that he was trying to address were seated in the structure of the brain, but at the time, around the turn of the century, they just didn't have the tools to directly intervene. He believed that the therapies that he was developing were an indirect way of doing biological modifications of the brain. He wrote something, I think it was in 1893 about the scientific basis of psychotherapy.

It was very much neuroscience. I think that we're all dealing with mental states, and because of economic forces and insurance and so forth, psychologists, and because of their licensing limitations, focus on trying to change the brain by exchanging meaningful sounds with patients, and those sounds are words. Psychiatrists, in the last four decades or so, have moved away from that and tended to focus on trying to change the brain by exchanging magnetic pulses or chemicals, transfer them into patient's bodies. I think at the end of the day, the distinction is a gradient.

Dave: I am so happy that you said that. I've always had a hard time really telling the difference. When I set out saying something's wrong in my head, and I feel like I'm failing out of Wharton, which I didn't fail out of Wharton, but I think I came kind of close, something's not right and I ended up seeing this psychiatrist first fortunately because I wanted quantitative data that was going on in my head. Not necessarily to go see a psychologist and talk about what's going on in my head, but I think there's great value in that, and I've had great value from it. I wouldn't know if a friend called and said, “Who should you call? A neurologist?” You're saying it's all on the spectrum, so it depends where you want to start. Okay, that's helpful.

The direct interventions on the brain, neurofeedback, neuromodulation, transcranial magnetic stuff, is very cutting edge. In that sphere of brain hacking, I would put electrical stimulation and magnetic stimulation as some of the most cutting edge things out there, but you can buy home equipment to do electrical stim on your brain, which I started doing 20 years ago. Full disclosure. Magnetic stimulation you can buy for $500 and up online. Does that scare the crap out of you?

David: Yes and no. Yeah, it is a little scary that laypeople now have the ability to directly alter their brain. I think that the brain has generally a homeostatic mechanism that a lot of these things that are accessible to people at home probably are limited in how much severe harm they could do. We haven't yet released anything into the public market ... When people are doing self ECT, then I'll really get worried. I think a lot of the things so far are fairly benign, although of course, people always say, “Hey, we don't the long term effects of these things like transcranial stimulation and so forth, but they seem to

be low voltage.” On the other hand, I'm not sure just how effective they are in terms of their selectivity.

I think with things that I'm really interested in the direction I hope the field goes, I think are going to be much more sophisticated and not the kind of thing that will ever be available to the public.

Dave: Over years, I've had my own EEG for 20 years, usually more than one. After a certain point, I realized that it's probably not that wise to do brain surgery on yourself. I ended up starting a little company that does EEG neurofeedback in Seattle just because I needed access to someone who was going to tell me what to do. I can hook the electrodes up, but if you're part of the loop there, there are some forms that are generally supportive and good, and you can do those without expertise, but I also wouldn't work on my own race car if I was going to be driving it because I'd probably want a professional mechanic. That's where I look at the role of neurologists and psychiatrists to help us improve ourselves, but I've been really frustrated, Dr. Feifel.

Usually, if you go to a psychiatrist, “Oh, there's something wrong with your brain, and let's see if we can fix it.” I'm not that interested. I don't think there's much wrong with my brain today. I just want a brain that's twice as fast and twice as smart, and will live 10 times longer than Mother Nature wants it to be. It seems like whenever I ask for that, I get the response, “Well, more tests are needed.” I'm like, “Well, let me be the test already. Come on, here.” Where is your field on helping us get Professor X brains versus just heal depression, which is worth doing, obviously.

David: That field generally falls under the term neuro-enhancement, which is very interesting because starting about 10 years ago, there began a let's say an open discussion among brain specialists about whether this is ethical and something that neurologists, psychiatrists should do. There's a controversy, but a lot of people, and including there was an ethical committee from one of the neurological societies that looked at this, and came to the following conclusion. They said, “Look, it may not be the best use of physicians,” because traditionally the physician heals and takes pathology and tries to remediate it, but just like cosmetic surgery, it's not unethical. If a neurologist or psychiatrist could add a quality of life to somebody, there's nothing inherently wrong with that.

That wasn't accepted by everybody. It did provoke a lot of disagreement, so it is a controversial thing. The brain is interesting because it's different than every other organ. If you have a kidney, and your kidney is performing what it needs to do. It's clearing the toxins from your blood, that's fine. There's no point in making it to clear twice as much blood volume than you actually have in the same amount of time because it really isn't going to impact your ability to function. The brain, when is a brain good enough? You know what I mean? The brain is the heart and soul of who we are and how we perform, and what we accomplish. There's never a parameter saying this brain is serving its purpose because it may be normal, we may find that a brain is in the normal distribution, but can you ever not benefit from a brain that's performing a little better? I don't think so.

Dave: What is the brain's purpose?

David: Well. There's many answers to that, but as a segway into ketamine and the psychedelic drugs, I'll give you one of the explanations. I think, and this is counterintuitive, but it's a conclusion I've come to by listening to a lot of people who have had very profound life changing experiences taking ketamine, which is a psychedelic drug, and also from their experiences with other psychedelic drugs. I think one of the brain's major functions is to filter out reality. There's a reality that's out there that is counterproductive to our ability to do what we do in this world, and that is to advance and to reproduce, and to propagate the species. What the brain does is it filters out some of the really profound appreciation of the world, and it puts it into a categorical every day kind of knowledge that we have.

I realized this because I think that what the psychedelic drugs do, and it's interesting that there's so many different pharmacological mechanisms and they all seem to produce very similar profound subjective experiences where patients will come back and they will feel that they had this profound understanding of reality that occurred under the influence, but they don't feel it was like some sort of inebriated or intoxicated phenomena. They actually feel that the curtain was lifted, and they were able to appreciate the true reality, the reality in which we are not categorical. The world does not fit into verbal labels and categories, but everything is connected, and time is not this linear, unidirectional thing.

When they come back, and the drug starts to wear off, the brain comes back online. At least those parts of the brain whose job is to sensor. Think of them as the Chinese bureaucracy that makes sure nobody learns about the world outside through the internet. Not to pick on China, but any sort of authoritarian regime. It comes back on board, and realizes that some information from that outside world slipped in, and it works very quickly to try to eradicate any knowledge from the outside. I think a big part of the brain is to filter out reality so we can experience a different type of reality where we are each separate creatures trying to advance our own personal goals.

I think another big part of the brain, or at least let's say the human brain, people think about all the wonderful things that the human brain can do, but I think one of the most important differences in the human brain than the brains of other animals is the fact that it prevents itself from doing a lot of things that animals do. In other words, inhibiting impulses, inhibiting emotional reactions so that we can select a better behavior, so that we can delay gratification. That is huge, and there's a lot of processing power that goes into the human cortex, especially the frontal cortex to produce that what we call executive function, which is really just don't react to impulses coming from the lower brain, or at least, don't react right away. Think about it.

That was a huge evolutionary advance allowing us to accomplish all the things we have as a species.

Dave: It's awesome that you're talking about not reacting to impulses from the lower brain in the same conversation we're talking about psychedelics. I did ayahuasca with the Shaman around 1999 in Peru. I didn't try any psychedelics until I was 26, and found

occasional use seemed to be neuro-enhancing for me under the right conditions, not at a rave. There's this recreational use, then there's the let the brain see something it didn't see before, and then come back with more.

David: Right, and that's what we refer to as set and setting in psychiatry. How the same drug, the same pharmacological agent can have a very different effect on you depending on your expectations and the setting. If you're going and you're expecting to have this cool euphoric experience, it's just a way to blow off steam for a night, you're going to have a very different experience than if you're expecting to open yourself to something profound.

Dave: It actually makes me really happy to see that we're now, thanks largely to the MAPS Institute and Rick Doblin, who's been on the show, we're looking at MDMA for clinical trials as a medical use things, and we're now looking at psychedelic mushrooms where we know they raise brain derived growth factor and some other things. What's been missing from the conversation the whole time is ketamine, which has similar effects and is 100% legal for anesthesiologists and physicians to use. My wife's a medical doctor who did drug and alcohol addiction, and knows ketamine really well because she used it on patients in the ER.

It can be used the same way, and here you are, “Oh yeah, I did that in 2008.” It's just missing from a lot of these conversations about all these illegal substances where you don't know what quality you're getting, but we can get pharmaceutical grade ketamine that has a short life in the body and has some interesting neurological effects. Why did you start doing this in 2008? Why'd you pick ketamine?

David: Well, first of all, I think you're spot on. Before I go back and talk about how I started, it's a pet peeve of mine that there's all this attention about psilocybin and MDMA and LSD, which I'm really thrilled about it. I'm really excited at the prospect that in a few years, I could potentially have those in my armamentarium to add to ketamine, but what's frustrating at the same time is that a lot of the people, Michael Pollan, for instance, in his recent book talks about psilocybin and LSD, and I think the missing piece there is the fact that ketamine is essentially a psychedelic drug at the doses that we use, at the sub-anesthetic doses, and the exact same thing, so we're very close to the same kinds of things that he describes throughout the book. Patients experiencing is what my patients experience, and in fact, there was a study done not too long ago that gave subjects ketamine and LSD and psilocybin, and I believe also MDMA in different orders.

They randomized the orders, and after each experience, had them rate their experience on a scale that basically breaks down the psychedelic experience into 11 elemental kinds of phenomena. If you look at the ratings between psilocybin and LSD and ketamine, they very much overlap. Some of them have particular fortes, if you will, like ketamine is of course most strongly the disembodiment scale, which is the out-of-body, but the three of them look more closely overlapping than MDMA, which seems to be more euphorigenic than profound in a classic sense psychedelic or mind enhancing. If there's one thing I really would hope that this podcast starts to promulgate is the idea that ... A lot of my colleagues, who are aware of ketamine's remarkable impact on depression and

what a great breakthrough it is, are surprised when I say it's a psychedelic because they think of it as a dissociative anesthetic.

I'm really glad you brought that up. Going back to how I got into starting ketamine, really I had no idea it was actually a psychedelic myself at the time. I was just frustrated. Part of why I was excited about going into psychiatry was that I felt that in my career span that psychiatry would go through a kind of amazing revolution the way that thoracic surgery had gone through in the 60's with people like DeBakey and doing transplants where they learned to take a heart and put it into somebody else. I thought wow, we're going to do amazing things because neuroscience is really expanding and brain scans are becoming more powerful. I wanted to be part of this tremendous advance in the brain, and hoping that it would really lead to greater understanding of who we are and the world around us, and the quantum physics, and blah, blah, blah.

Then, years go by, and I was getting really frustrated because I realized that I'm still using the same tools like the antidepressants that essentially were no more effective than the ones that were developed in the 60's, and psychotherapy that really wasn't advancing. It was very frustrating. A lot of people don't realize that we have dozens and dozens of conventional antidepressants but not a single one of them has ever proven to be more efficacious than any other one, including the very first ones that were discovered in the late 50's and early 60's.

Dave: Like Depranil are you talking about?

David: Yes, like Imipramine, Tofranil was one of the first ones, and the MAO inhibitors. By the way, do you know the anecdotal story of how antidepressants were discovered?

Dave: I don't, but I love Depranil.

David: Well, interestingly enough, I'll just give you the quick version here. Tuberculosis in the earlier part of the 20th century was scourge, and there was no treatment for it, so people were placed in these sanatoriums, what they were called. Basically quarantined from society, and you could imagine the high rates of depression in these miserable places. They developed this drug called isoniazid, which is a precursor for one of the mainstay treatments we have today called iproniazid for tuberculosis. They introduced this breakthrough medication for tuberculosis into these sanatoriums, and one of the things that they unexpectedly found in addition to improving people's tuberculosis infections was the fact that suddenly people's moods were becoming more ... I remember the New York Times article, sunny. They were having more of a sunny mood.

People were perking up, and they were actually demanding activities from the administrators that didn't know what to do, and why was this suddenly happening. Some people actually became manic, which is always a signature of a bonafide antidepressant. Well, they analyzed the isoniazid and they found out that one of the properties it had was it inhibited this enzyme called monoamine oxidase, and it was already known that that enzyme is a major enzyme in the synapsis between neurons that is responsible for breaking down monoamines, which is serotonin, norepinephrine

and dopamine. People realized that wow, if this drug, isoniazid, prevents this natural enzyme from doing its thing and breaking down these neurotransmitters thereby increasing the levels of these monoamine neurotransmitters, they figured we can develop other drugs that do this. That was really the tricyclic antidepressants and the MAO inhibitors, which were the first medications.

It was also the impetus for the theory we now know is really pretty much bunk. The abnormal brain chemistry explantation of depression, which went like this. If these drugs increase these chemicals and produce an antidepressant effect, depression must be the result of low levels of these chemicals. Yet, in 50 years, we've never really found any compelling evidence to support the fact that people with depression or any other disease have abnormal brain chemistry. It's a much more complex story, but the myth still continues. I think it was a very useful expedient story for pharmaceutical companies because it was a way people could understand their drugs.

I was just very frustrated. You know, Dave, I was like I think I miscalculated. I don't think that this revolution is going to happen during my career. I think it's going to be the residents I'm teaching. The pharmaceutical industry is not producing anything more than just Me-Too drugs, and they're all focused on serotonin [inaudible 00:30:11] doing the same thing and not one of them is better than the other. Then, I started to scan the horizon for anything new. The two things that I'm involved with now both emerged around 2006 to 2008. The TMS, I had been keeping my eye on that for many years. I thought that was really an exciting, new paradigm shift in treating brain disorders and, to address what you were saying, to enhance brain function. The first TMS device approved by the FDA came out in 2008, and I jumped all over it and convinced my department to get it even though the chair thought this was some boutique ... I literally had to underwrite it with my discretionary research money. I'm not kidding because nobody thought this would go anywhere.

Dave: You're talking about the ten ton magnet that goes over? The really big one?

David: It's called the NeuroStar. It's like a big dentist chair. It's repetitive TMS. It was the first commercial TMS device indicated for treating depression. It was around that time I was reading one of the first papers from NIH from Carlos Zarate's lab about ketamine and this remarkable improvement in depression in people with severe treatment-resistant depression within hours. I actually was skeptical, and I wanted to do research on it, but I said before I invest in doing research and getting IRB approval, I'd like to see whether this is really as amazing as these papers say. You know, sometimes in research papers, you get statistical significance and it seems really cool, but then if you actually talk to the people, it's like, “Eh, yeah, it helped a little.”

I actually convinced UCSD, the powers that be, it took me many months, but I convinced them to let me start treating people with it. The rest is, as they say, history. I was just looking at something as a clinician, better tools, and I had no idea that this would lead me back to my original impetus for going into this field, and that is being an explorer of consciousness.

Dave: Both of those techniques, using the large magnets on the head and using ketamine, are out there. Have you sat down in the chair and put big magnets on your own head?

David: I have. As part of the training, we make everybody who gets certified in the device experience what it's like so they can relate to it.

Dave: How about ketamine? Have you used ketamine to go into other places?

David: Well, the honest truth is I haven't yet. I look forward to doing it, and I haven't yet. There's a couple reasons for that. One of them is it's a very controversial practice.

Dave: Oh yeah, very.

David: There's a lot of people in established psychiatry and medicine and elsewhere, who really oppose the idea of starting to give ... They feel it has a lot of potential, but we should study it for the next 20 years before we actually treat anybody with it. One of the things that-

Dave: Those people, by the way, they piss me off, okay? Seriously. 20 years before we can do any real work with something. Sorry, they're like speed bumps in the evolution of humans. Sorry. Keep going.

David: I realized that this is a very fragile kind of field, and what I didn't want was to play into that. I didn't want to be a Timothy Leary. The second reason was I feel like I'm in this previllous position where I'm the scientist and this sort of ground control. I feel like I'm ground control in Houston. I have all these patients who go off into these amazing places, and they come back and they report to me. Actually, we've created this special forum that every trip, a patient fills out this survey-

Dave: Tell me it's called the Special K forum.

David: It actually started out something like that. Then, we decided in case this ever gets published, we should give it a little bit more of a formal name, so we call it the PES. The Psychedelic Experience Survey. It was something more along the Special K moniker originally. I get to go from room to room and talk to people about these trips, and I feel like I'm trying to help bring this knowledge back from this other awareness into the mainstream. I feel like I'm an academic and a scientist but also a clinician and somebody exploring this really remarkable phenomenon.

Dave: I can see both sides of that. When I interviewed a professor from Vanderbilt who's been studying oral nicotine for Alzheimer's since 1988, he said, “Oh, no. I've never used it.” I'm like how could you not take something you've been studying for 20 something years? In terms of academic rigor, you can make that argument and it's worthy of respect. I'm mad because my plan was to have just experienced ketamine for the first time before I interviewed you, and a couple weeks ago, my executive producer for the show and I went down to see an anesthesiologist regenerative medicine friends of ours, whose also just been on the show. Dr. Matt Cook. He used ketamine in his practice with

stem cells and other things like that, and she has a horrible fear of needles. She's a very courageous, jump out of helicopters kind of personality but you show her a needle and her eyes roll up in her head and she hits the floor.

David: Wait, this is an anesthesiologist?

Dave: He's an anesthesiologist by training, but now he does regenerative medicine, fixes shoulders and stem cells. He's branched out, but he's years and years doing anesthesia with-

David: Who has the fear of needles?

Dave: My executive producer for the show.

David: Oh, I thought the anesthesiologist did. I thought that is a strange career choice.

Dave: No, that would not work.

David: Okay, gotcha.

Dave: I was going to go down and do ketamine, but he said, “We can use ketamine to help her get over that.” We actually shot the video of her doing ketamine for the first time, and she does it, and she had an IV for the first time in her life without full body convulsions and punching people. None of this was behavior she chose. She was embarrassed by it, and you could see she was terrified. She picked her hand up and she looked at the needle, and she pushed on it, and she said, “My fear is gone.” She's free.

David: Wow.

Dave: The difference from one little treatment. It was something that had just pushed on her for years. I'm a professional [inaudible 00:37:16]. She's trying to film me and saying, “Dave, I can't look at the needle because I'll pass out,” so she's trying to film me without looking. It all passed with one dose of ketamine.

David: Isn't that crazy?

Dave: Yeah. I was going to do it next, but she ended up taking all the ketamine [crosstalk 00:37:28]. She took all the time we had available so I'm going to do it with him another time. I can also say I haven't tried ketamine either, but I've tried DMT in the form of ayahuasca and psilocybin and LSD. Interviewed Stan Grof about it. None of these have I used super frequently, but all of them have provided value to my life, and I write about those in my next book. It's one of those things where functioning adult human beings are capable of using these on an occasional basis with intent to probably do some good, but I want to ask you because you're studying this stuff. Ketamine is a horrible party drug, but is there a downside to using ketamine therapeutically at these lower doses where it's not just a full on sedative? Is this something that's really dangerous? How dangerous is it?

David: I actually have data to support this because one of the frustrations I've had is the fact that the naysayers that we were talking about ... I think that in medicine, there's need for a healthy conservative approach because there are things that we can be a little bit too enthusiastic about, and in the history of medicine, there have been things that seemed initially to be really a wonderful breakthrough, and then we moved too fast, and they ended up causing a lot of harm.

Dave: Yes.

David: I think there's a balance. My frustration has been that the naysayers in their editorials and so forth, “We have to go very slow because we don't know the long term effects of these medications.” A lot of the treatments, like the treatment for depression requires repeated administration. It's not just a one time thing. The unfortunate thing, and one of the things that we're all working on addressing is that this amazing therapeutic effect, which can be instantaneous or within minutes and hours of a treatment, will wear off like dialysis. I call it psychic dialysis. It's amazing. Imagine your executive producer walks in with a lifelong fear of needles. One treatment and the fear is gone, but with things like depression and often times anxiety, it'll slowly come back, and then she'd come back again and it would be immediately ... Just like kidney dialysis, you know? It's dialysis for the mind.

They always talk about we don't know what will happen if you give this over and over again, which is required and which people like Feifel and other people have started to do, and we could get addiction. We know that people who use it illicitly and use it frequently in high doses can get bladder damage and there could be psychosis and so forth. What my colleagues and I did, because now there's quite a number of providers unlike when I first started who are doing this on a regular basis and have experience of hundreds of patients, many of whom have gotten it for months and years, so we created a survey and we did it very legitimately. We got it ran through the UCSD IRB, and it was a survey of the major providers. The survey was how long have you been doing this? How many people have you treated? Here are the major concerns. Addiction, bladder issues, cognitive decline, psychosis, etc.

We asked them how many of each of these have you experienced, and how many people have you treated? We presented this at an international conference of ketamine in Oxford, and we're writing up the manuscript, but the results are as we each individually expected. Exceedingly low. Exceedingly low. In fact, there were nine reported cases where the doctors felt that there was some evidence of addicted behavior, and when you look at the details, none of them can be attributed to ketamine. The patients either had preexisting addictions, and that's nine of 6000 patients. The rates are just better than some things that you can buy over the counter. My own experience of doing this for 10 years and talking to my colleagues, if it's done in a clinic, and I think there's a distinction here because the only cases that seem to meet the criteria of possible addicting behaviors as a result of ketamine were when the doctors were actually prescribing home use, like intra-nasal use.

What happens there is people get an immediate but short effect, and it feels good. They feel free of their symptoms, and then it goes away, so they want to feel that way again

and they do it again. Then, they get tolerance, and then they're using higher doses and they're running through their prescription faster. It becomes more intolerable to be anxious and depressed when you know that there's something that can take it away. That often leads to some bad behavior, and there's been at least one case reported in the publication where a patient was driving while experiencing a bit of a dissociative effect. If we limit it to the classic way of the way these treatments are done clinically, in the clinic, given as let's say an infusion or I tend to do a lot of intramuscular now, there's really been no adverse effects reported. I've had people now on it for five, six years.

Dave: It's fixed their depression?

David: Yes. I had patients who it's basically taken them from being suicidal to living a very full and complete life, and they return on a periodic basis and some of them have just stopped coming in.

Dave: Every time I hear something like that, and then I hear someone else, “More study is needed. Let's wait 20 years.” If you're that person, and you were going to kill yourself and someone says, “Wait 20 years.” Man. You got to look at the risk/reward balance, and if you're one of those people, the risk/reward is clearly in favor of doing it now.

David: I think, by the way, risk/reward is the key to medicine.

Dave: No, no. It's not. It says right here, “First do no harm.”

David: Which is a terrible motto.

Dave: It's wrong.

David: First of all, I hate that motto because first of all, it's a bunch of BS because the only way to do no harm is to do nothing.

Dave: Amen.

David: Every time you go under the knife, there's a chance of harm so why do we have a motto that we never even practice. Here's the other thing. A lot of time what that motto really means is do no harm to me, the physician. I'm not willing to stick my neck out and do this, even though it probably makes sense for this patient to get this treatment, I don't want to be the one who is out on the limb doing this. A lot of times, doctors are very skittish about doing something that's not really falls within the accepted dogma. I don't like that. I don't like that motto. I think the reality is, as you said, what medicine is is balancing the risks and the benefits and allowing a patient, assuming that they have capacity to make a decision as most people do, allowing them to make the decisions.

I can't make a decision for someone who's suffering and is willing to take a risk because this quality of life is not something they want to continue. It's so easy for me to say, “Well, this could harm you, or even in the worst case scenario, kill you so you shouldn't

do it, but if you feel like your life's a living misery every day, I'd want to take a reasonable chance even if it meant it could go the other way."

Dave: That's high integrity medicine right there where the patient gets to decide, and you help them to make the best decision possible. It makes me sad that we've created a scenario where your license may be at risk when you help a patient and that's unacceptable. That will get fixed because otherwise people will stop going to doctors.

David: Yeah, and they'll find other ways of getting the treatment, which I think happens now frequently.

Dave: Yeah, I don't like it that I have to buy some research grade chemicals to get my body to do what I want it to do, but hey.

David: I don't like it either. I'd much rather you come to me, and I can prescribe something that's been analyzed and the manufacturing process has been vetted by the FDA, and you know that each time you take it, it's going to be same quality, same dose and unadulterated.

Dave: I love your mindset there. Now, let's get back to ketamine. In my neuro-enhancement world, which has been a big part of my life for 20 years, and it's part of what we do at the Neuroscience EEG Feedback Clinic. There's three things I'm targeting in my own brain. I'm looking for neurogenesis. I'm looking for synaptogenesis and I'm looking for melanogenesis. I want more neurons, more synapses and more insulation around the neurons to make my brain function better, as long as I don't get so much that my brain functions like a bowl of spaghetti, which is the downside of that sort of stuff to put it in medical terms.

David: A good technical term, yeah.

Dave: There was a study about ketamine in 2010 that came out from Yale that said it improved depression but it also caused new synaptic connections between neurons in the brain, which is the Holy Grail of making a brain that's better than Mother Nature maybe wanted me to have. People have said for years it's because it blocks NMDA receptors, and for the neuroscience geeks, they'll know what that is. For everyone else, we'll talk about that in a minute. Then, in 2018, you talked about saying I don't think that's why ketamine works, that it might not be because of NMDA. How does ketamine actually work? Is it because depressed people get new synapses that cause their brain to fire in a different way? Is it because it's blocking some sort of NMDA or some other chemicals? Walk me through the layperson pharmacology or mechanism of action so we can all understand that.

David: First of all, it's important to know that anytime somebody tells you how ketamine works, or for that matter, how any antidepressant or any psychotropic works, or what causes depression, you should know that they're blowing smoke.

Dave: I love that.

David: The truth is, and it's embarrassing for me, a student of the brain for three decades now, it's embarrassing for me to say, “We just don't know.” The brain is ultimately a mystery. Just think about this. How does any of this stuff, all these 85 billions neurons and the chemicals, and the electrical firing, how does it create anything that we subjectively feel? Love, hate, awareness? It's an ultimate mystery, so we talk about correlations, about what we can see happening in the brain that goes along with this, and even there, it's so much extrapolation. I've seen so many things be the trendy thing that this is down regulation, up regulation of receptors, and so forth.

Right now, synaptogenesis is thought to be a good thing, and has been proposed as a mechanism for ... In fact, a paper just came out within the last month showing that all the psychedelic drugs, except Ibogain interestingly enough, share a common ability to produce rapid synaptogenesis. They're like fertilizer for the brain. I've seen headlines saying, “Scientists have discovered the reason why ketamine and psychedelics have their amazing therapeutic value.” I cringe a little bit because so many times I've seen us think that it was this, and it turns out that has nothing to do with that. Yes, we see that that happens. It makes common sense. It's common sense to intuitively believe that if you're able to cause brain cells to make more connections and emulate more, it'll do good salutatory things, but the truth is we just don't know.

I'll give you an example. I'll give you an example. One of the important things that happens in the maturation of the human brain, in the mammalian brain, is that there's actually a loss of synaptic, something called pruning that occurs around adolescence and continues on. In other words, we start off with a lot of connections, and then they get pruned down basically in terms of ones that are used get pruned down and the other ones get strengthened. There's a lot of abnormal brain states like autism that have been implicated in a lack of pruning down. Now, they have more connections and they have more cells, and yet, clearly that's not a good thing in those cases. I'm very wary of simple explanations like depression is abnormal brain chemistry or a deficit in your serotonin or something like that.

I wish we knew, but we are just scratching the surface. You can always look at the question a number of ways. You can look at the receptor, pharmacological, what it does, NMDA, the psilocybin and the LSD, they work on serotonin 2 receptors, which is a different mechanism. Or, you can look at it more in a global functioning way like I described earlier. What they basically all do is they eff up the function of the brain that filters out our awareness of certain realities, the connections between things. Whether it's through NMDA or serotonin 2A, maybe a better way to look at it is more at the psychological level, the meta functioning of the brain rather than the molecular level.

Dave: It's really fascinating that you say that. There's a certain class of people, I call them science trolls, and their basic mechanism of action is that didn't happen because it can't. The “it can't” comes via known mechanisms of action. If you look at almost medical intervention that is shown to work clinically over the past 100 years, the story that scientists have told themselves about why it works is almost always proven wrong 20 years later. It doesn't change the fact that it worked. We have this scientific arrogance that says, “Well, we know how everything works.” I think we might know about how maybe two percent of things in people's bodies actually work, and the rest of it we're

still pushing that, but that doesn't mean we should withhold useful therapies from ourselves because we don't have a clear story about how it works.

I just like the story of leprechauns. Maybe it all works because of leprechauns, but does it work is the first and foremost thing, and then we can decide if it's leprechauns or not. That's of secondary order academic importance if you can just say, “Is there efficacy and is there safety?” If so, let's start helping people, especially people who are suffering greatly because otherwise waiting til their dead so we can be sure we're safe doesn't seem very safe to me.

David: Yeah, I think that's really one of the short falls of institutionalized medicine. The fact that medicine got organized had a lot of benefit. You don't have the traveling-

Dave: The snake oil salesman.

David: Snake oil salesman, and who knows what you're getting and what it's going to do, but on the other hand, it can get so organized around guidelines and things like that that there's no longer any ability to really innovate, and there's so much fear about stepping outsides the bounds. Ultimately, it comes down to, and I'm beating a dead horse here, but about the risks and benefits for a given individual patient, their quality of life.

Dave: Talk to me about the typical dose of ketamine that's producing these antidepressant effects?

David: We dose in weight, and the typical anesthetic dose is probably four to eight milligrams per kilogram. The dose that we use starts anywhere from a quarter of a milligram, .25 milligrams per kilogram, up to two, sometimes two and a half, three milligrams per kilogram. Usually when we're giving it at that high dose is we're actually usually giving it in two injections to extend the trip. This is really interesting, and this is where ketamine and I think the other psychedelics diverge from the classic paradigm of medicine where it doesn't matter how you feel about the medicine, or whether you're aware that you're getting the medicine, or whether you're in a coma or you take it before you go to sleep, when we get the medicine inside your body, it's going to do its things. It's like, let's say, an antibiotic. The antibiotic doesn't care whether you're prepared for the experience or not. It's going to go and it's going to kill those bacteria.

With ketamine and the other psychedelics, your experience is paramount so that when we've been giving ketamine for years as an anesthetic, nobody jumped out and said, “Oh my gosh, all these people that we're putting under for surgery are waking up and their depression is gone, and we've discovered something.” For years, nobody knew that until we started giving administrations at sub-anesthetic doses where people are actually conscious through the experience and experiencing it, so isn't that interesting. You would expect it in classic paradigm of medicine. You're giving a higher dose when you put people under, when you use it as a full anesthetic. They should have a stronger antidepressant effect, but because people were asleep, and they didn't experience the trip, so to speak ... It's really funny because in my progress notes every day, I write, “Patient reports a really pleasant trip.”

There's no better medical term that's more appropriate. It's funny that I'm writing trip in all my formal medical progress notes for patients. This is really interesting, and you have to actually be awake and conscious to experience the effects in order to get the therapeutic effect, which is so cool.

Dave: You could almost term this as a microdose of ketamine, or it's a low dose similar to LSD. If you take a full dose, you're going to trip, and if you take a low dose, the microdose, you get a very different effect, which is generally cognitive enhancing for some people. Depranil, the antidepressant from a long time ago, you take it at full dose, you get all sorts of stuff. You take very low doses for antiaging, and you get a totally different effect.

David: That's right.

Dave: We have a history of looking at high dose and saying, “Well, if it does this, let's ban it or let's pigeonhole it.” I think playing with the dose curve, and looking at the patient's experiences is really cool and you were one of the early people to do that in clinical practice, and you've seen some phenomenal results. Let's talk a little bit about magnets on the brain. This is another one of those things where you say you're talking about woo woo stuff, you get crystal pyramids and magnets. We've got gear from Bullet Proof Labs where you put magnets on your bicep and you watch that bicep go twitch, twitch, twitch. You're inducing an electrical current on cell membranes with magnets, enough to cause your arm to move. You can say magnets don't affect the body. You're just wrong. For any skeptics listening, we know this. We know this medically, but you're focusing these on the brain to cause electrical activity in an area where there might not be enough.

How do you do that, and how do you know where to put it?

David: It's really unfortunate in a way that magnets happen to be one of the best ways of doing this because they carry so much baggage as this hocus pocus kind of thing, but we're using them in a very, very legitimate physics-informed way. In fact, the basis of magnetic treatment, for example, the main treatment is transcranial magnetic stimulation. Transcranial for crossing the brain, magnetic for magnetic, and stimulation being stimulation of the brain is a concept called Faraday's law. Michael Faraday in the 19th century, he was a physicist, and he discovered a very important principle that if you have a pulse magnet ... The key here is a pulsing magnet in proximity to anything that can conduct electricity, you will induce current in that material. Copper wire or whatever it is. If you ever see those high school science projects where a kid is riding a light bulb and making a light bulb light up, he's doing that because they've rigged the pedals to turn a magnet around copper wire.

It's a generator essentially. It's a generator, and that's how we use dams and waterfalls. They turn big turbines, which are magnets around wire and produce electricity to light up cities. The other thing is since brain cells, neurons, these hundred billion or so that you mentioned at the outset are essentially wires, organic wires, we can use Faraday's principle to cause those neurons to fire. They're built to fire. They're built to produce this current, this chemical gradient. It's a current that's like a battery. Batteries work on

differences between different ions, and the current runs down the length of the axon, gets to the end, and the only strange thing compared about the brain compared to any other wiring system in a building is that the wires aren't directly attached. There's a little gap, and it requires chemicals to be released when a wire fires to float across and to connect in a very specific way to the next wire.

There, those chemicals can either produce, if the conditions are right and there's enough of them being released to fire into the next one, or it can inhibit it. The idea of using pulse magnets is not a way out. It's really based on solid principles of physics. The idea was we know that the language of the brain mysteriously is the firing, the pattern of firing. At any given time, you've got these hundred billion, a little bit less than that, about 85, 86 billion neurons. They're firing in different circuits, and they're not all firing at once. They're firing in patterns of circuits. If you take a snapshot at any moment of the firing pattern, that correlates with our experience. If we're remembering a romantic high school relationship, and one day we're nostalgic, that's because circuits that connect to our memory association areas are firing.

If we're experiencing horrific fear, that's because circuits associated with our limbic system, or amygdala are firing. Firing is the language of the brain and we know that in every brain disease, or psychiatric condition or neurological condition, there are certain nubs, or nodes, in key circuits that aren't firing correctly. They're either firing too much or too little. The idea was rather than drop a pill in people's guts, in their stomach, that will get absorbed through their blood system, go everywhere in their body and interact with all the organs and produce side effects, and then cross into their brain and bathe the entire brain just to correct some firing in a certain area, a more direct way would be to use this Faraday's principle and direct the pulse magnet at the area that's firing abnormally and to physically go in there and try to correct it.

We know we can do that. You can Google TMS and you can find some great demonstrations of people in labs putting a magnet over their motor cortex, which is the part of the brain that controls the body, and if you place it here, which is the area that controls the contralateral arm, a person's arm on the other side will move. If you move it over to where their legs are, their leg on the other side ... If you move it all the way to other side, the other side of their body part ... It's really great. It's like a party trick. That in itself is not enough to create a correction of the brain, but what it is is we learned that if you do this over and over again, there's this plasticity that occurs. If you use high frequency pulses, you can produce what's called long term potentiation.

It's like getting a personal trainer for a part of the brain that's overweight and sedentary and out of shape. It's not going to start doing exercise on its own, so you need to get a personal trainer and you need to pull it out of the house, force it to do some calisthenics and job, and slowly over weeks, the person's physiology will change. Their cardiovascular system will get stronger, their muscles will get stronger and they can run more than 10 steps without getting winded. Then, the personal trainer can go away and there's a much higher chance that that person will continue to exercise on their own because it's not such a big bar doing it. That's what TMS does is we target the areas ... For example, in depression. I'm going to pull my brain out here, my model-

Dave: Model of the brain.

David: You assume it's a model. It could actually be one of my less than successful patients. There's a section right here towards the front called the dorsal lateral prefrontal cortex. Especially on the left side, we know that that plays an important role in a lot of things especially regulating mood. We know that when the activity is low there, people are more vulnerable to stress and depression. When it's high activity, they're more resilient. For depression, the protocol is target your magnetic pulse at this area specifically. Day in, day out, and over several weeks, just like somebody who's on a weight loss program, a fitness program, they will start to get in shape, will do more on their own, and then hopefully they're off to the races. That's the principle.

Dave: As a fan of neural enhancement, the two primary ways I'm exercising my brain aside from movement and brain exercises and what not, is I use high intensity light on the brain, which can cause some changes in the brain. It basically becomes stronger over time, and I use neurofeedback where I can train the parts of the brain that aren't firing at the speed, or with the strength, or at the frequency that I want so they'll do more. I'd love to add magnetic stimulation in so I can do even more of that. Are we to the point where you feel comfortable that there might be an application for TMS for those of us who want the brains of bodybuilders?

David: I think so. I think we're getting close to that. In medicine, usually the first focus is pathology. Abnormal. There's a lot of reasons for that. It's a more straightforward path, regulatory path, to produce something for a disease. I think commercially there might be more, from a business point of view, easier to make that a viable business, but then there's uses that then go beyond that to performance enhancement. We already know that you can do a lot of very interesting things with magnetic stimulation, including improving your memory. If you target it to the hippocampus area, it's been shown that people will have at least a short term enhancement of their memory. There are things that you can do to shut down areas that might be holding you back like areas where you're overly anxious about thing, or have social anxiety.

One of the things that I think is so exciting about TMS, right now I think we're in the infancy, and people will look back and say, “Oh my gosh. 2018, they were dinosaurs. They were using these big hulky machines, and targeting just one area at a time.” It's so unlimited because the concept is pretty straightforward. You change areas of the brain just like if you had a multi-band equalizer of your stereo back in the day, when I was in high school. You could adjust the treble and the bass. That's what you can do with TMS. You can really customize it for whatever a person needs. There's some technical limitations, but they should be overcome because it's just how could we get deeper, how could we do more than once? When it's just technology, and there's a market for it, smart people come up with ways around it.

Dave: That they do. My goal is actually to be abnormal. I want a brain that is above average so I can do more important things, and one that's happier than normal. It seems like this is what everybody wants on some level or another, so abnormality is a goal as long as it's the right abnormality, and that's the risk in all of this stuff as we talked about in the beginning.

David: Correct, right.

Dave: I've got one more question for you, Dr. Feifel. If someone came to you tomorrow, and they said, “I want to perform better at everything I do as a human being”, what are your three most important piece of advice? What would you tell them?

David: That is a really interesting. My inclination, my brain is going towards the social sphere, because I think at the end of the day, we are social creatures. Whatever you do, it always involves other human beings. Other human beings are always the gatekeepers to your success. You have to prove to other people that what you're doing is valuable and they have to like you. I would say being a better person in terms of your interaction with other people really can unleash your accomplishments and your success. We don't operate in vacuums. Even the most nerdy engineer can't really get much traction on the most amazing invention if nobody will listen to him, or people won't cooperate in terms of that.

I think that people who really genuinely, and not like a psychopath who can manipulate, but people who can really connect with other people and communicate, and make people really admire them and like what they're doing, that goes a long way, even many times compensating for deficits in other areas. That brings us back to the psychedelics. I think that the psychedelics have that ability. Before we go, one of the things that I wanted to do is I wanted to read you some of the survey responses from some of my recent patients. A lot of them that I get from people is love and connectedness, and just feel forgiveness. People who they were really pissed at, it's like okay, I see this issue in a bigger picture, and there's this transcendent forgiveness.

It may not be the specific response that you were looking for, but I would say social and then executive function, because executive function is really the master function that sits above all the other functions. By executive functions, I mean that unique CEO function that exists primarily in the frontal area of our brain that's the most recent evolutionary development, and really sits at the head of the table, and inhibits the impulses to act from all the other older areas, and allows us to be a little bit more thoughtful about those feelings and not just act on them impulsively. I was watching the news the other day, and it was talking about this trend of posting videos to try and shame parents, like soccer moms and dads who just lose it, and they start fighting with each other over their kid's games.

They would never normally do that. The idea is you post it and they get embarrassed and it inhibits them from doing this in the future. I can totally see myself acting in that way at times, so I totally get that. If our executive function was always as strong as it might otherwise be, we would never put ourselves in those embarrassing situations. We'd always give more thought to what we were doing. I used to do a lot of adult ADHD treatment. In fact, I started the first adult ADHD specific clinic for adult ADHD at UCSD in 1995.

Dave: Wow. [crosstalk 01:14:30]

David: It was so cool because you could change people's lives overnight with these stimulants. One of my first patients was this remarkable lady who was a science fiction novelist, but she only had published one, maybe two novels, but she had 33 that were two-thirds done and then she just lost interest and couldn't do it. Everything was disorganized, and her desk would pile up and she just didn't know what to do, so she would open a cardboard box, throw everything in there, tape it up and write the date on it and start fresh. Well, when I put her on stimulants, and she came in at the followup, and I asked her, “What do you think? Do you think it's made a difference?” She says, “You know, I wasn't convinced until ...” It was Monday I was seeing here. “... until yesterday.” I said, “What happened yesterday?”

She said, “My husband knew from the beginning. He just said you're totally different. You're listening to me. Your eyes aren't darting around.” I said, “What about you?” She said, “Well, we play trivial pursuit every Sunday, and he always beats me, even though I know more than him.” I said, “What was the difference?” She goes, “I never had patience to sit and think about it, so I'd blurt out the first thing that came to mind. On the medication, I actually just sat and I would think about the options, and I realized that I could eliminate a lot of them, and I won for the first time in memory. My husband said oh my God, you can not deny that the medication is ...” I said, “Yep.”

It's just that little bit of inhibitory power. I would say I'm not going to give you three. I'm going to give you improving our social brain and improving our executive function. I think with those two things, people are just going to kill it.

Dave: Well, if it makes you feel better, I just finished my next book, Game Changers. I measured what all sorts of high performers from all sorts of places came up with. We have a survey of 500 people saying what matters most. You're not too far off on that. In fact, two of the three big buckets were smarter and faster. The stuff you talked about there is in there.

David: All right.

Dave: You're not alone in that advice, but it's profound and useful advice. Of course, getting there, if you're listening to the show, saying how do I improve executive function? How do I improve my social environment? That takes some work, but it's work that's doable if you know it's important. Thank you for sharing that, Dr. Feifel.

David: My pleasure.

Dave: Your work can be found at your website, which is KADIMANP.com, K-A-D-I-M-A-N-P.com. Of course, that'll be on social and on the show notes, and things like that for people who would like to check it out more. It's fascinating work you're doing. Thank you for pushing the boundaries of using ketamine, magnets, and all the other cool stuff for making brains that have problems work better, and hopefully soon, brains that have no problems but still want to work better do it.

David: My pleasure. It was a lot of fun talking to you. Thank you for being an advocate and a master communicator of all the brain advances we're making, being somebody who lets the public know about these things.

Dave: You got it. Thanks again.