Speaker 1: Bulletproof radio, a state of high performance.

Dave Asprey: You're listening to Bulletproof Radio with Dave Asprey. You're going to love listening to today's episode because it is with the preeminent pioneer in the use of nicotine, not tobacco, but nicotine in a whole variety of age related and brain conditions with more than 30 years of practice.

Today's cool fact of the day is that we're discovering that kids are even more sensitive to light exposure than adults. A new study just came out that showed that showing preschool kids light in the evening suppresses melatonin almost completely, way more than it does in adults, which is a really important thing to understand.

The new study built upon a 2015 study where they looked at kids who are 9 to 16 and they found that these kids were even more sensitive to it when they were younger and the logic dictates but we don't have a study that says even young infants would probably be most sensitive. In this study, they used several different types of light. They went from a dim amount of light, which is about 15 lux, to a moderate, which is 150 lux, like a 60 watt bulb all the way up to 500 lux, like a bright, bright room and they did show a dose response.

The dim light suppressed melatonin about nine percent, the moderate light, one light bulb, by about 26 percent and bright light was about 37 percent in the younger kids and less so in older kids. Even brighter lights would do more than that.

The reason that this is a really cool and important fact of the day is that there are three things that bright light does in kids, and in adults, but more in kids in the evening and one is depression, the other is suicide and the other is cancer. Circadian disruption is tied to all three of those things and so today's cool fact of the day is keep it dim.

Today's guest is Dr. Paul Newhouse. Dr. Newhouse has a broad background in human cognitive medicine and neuroscience and has been for 30 years studying cognitive models in humans. He's the director of the Vanderbilt Center for Cognitive Medicine in the department of psychiatry and behavioral science at Vanderbilt. He's looking at the cognitive basis of neuro psychiatric disease.

The reason I wanted to have him on the show today is that his research focuses on specific mechanisms in the brain, like the cholinergic system, which is where acetylcholine, the big neuro transmitter that sort of stimulating affects things as well as the nicotinic cholinergic receptor system. If all that sounds super geeky for you, that's alright because we're gonna be talking about how cognition works and how these receptors are important for things like Alzheimer's Disease and other conditions and you're gonna learn a lot about what's going on between those ears of yours.

Dr. Newhouse, welcome to the show.

Paul Newhouse: Thank you. Glad to be here.

Dave Asprey: You have spent 30 years studying the brain and cognitive processes.

Paul Newhouse: Closer to 40 by now.

Dave Asprey: Closer to 40, alright, but who's counting?

What got you so interested, especially 40 years ago when this was, I think humans have always thought about what's going on in there, even going back to the ancient Greeks but what peaked your interest and has kept you engaged in this field of study for so long?

Paul Newhouse: Well, I think that I came out of medical school and I had an opportunity to work on a research unit at the National Institutes of Mental Health in Bethesda, Maryland and it was a really fascinating experience where we were studying in many ways for the first time, the cognitive underpinnings of these very unusual disorders like Huntington's disease and Parkinson's disease and Anorexia Nervosa. We were trying to in our own primitive way at the time, understand the underlying biology behind these disorders and what was happening to their mental processes as these neurodegenerative disorders took over.

I got fascinated with the idea that we could use the tools of cognitive science, of biology to understand what the mechanisms were that were going on in the brain, what goes wrong and then how we could probe that system to develop new treatments and new approaches to enhancing cognitive functions and the quality of people's lives.

Dave Asprey: You got interest and took off ever since. It's interesting that you started this work at the National Institutes for Mental Health probably right around the time it was basically spun out from the National Institutes of Health. This sounds like in the very early days.

Paul Newhouse: Well no, it was a fully formed institute by that point. This was in the late 1970s.

Dave Asprey: Okay, it was the early 70s. Okay.

Paul Newhouse: Yeah, so it was ... but it was a very unique group of people who were studying very curious disorders that other people hadn't made much headway with and we were taking sort of novel approaches so it was a bit, for a young student, it was a bit like being in a candy shop. We got to work on these amazing disorders with amazing people and patients and we were just really exploring the early days and when I came back to that work a few years later, I wanted to work in Alzheimer disease. I joined, I went back to the NIMH as a postdoctoral fellow and had an opportunity to join a group of people who were really ... we were

really kind of inventing things was we went along to try to work out what was going on in the brains of these people and this was the early days of brain imaging and what we would now call experimental pharmacology and trying to use drugs as probes to try to understand what was working and what wasn't working in the brain. I think we made a lot of headway.

Dave Asprey: It's changed a lot. A lot of the drugs, maybe some of the ones that you've worked on, things that were designed for Alzheimer's or a specific diseases are now being at least considered as cognitive enhancing agents in healthy brains. Does that scare the heck out of you or are you happy to see that?

Paul Newhouse: Well it doesn't scare me. I think that we have yet to really establish that drugs can enhance normal human performance, cognitive performance. One of the things that I've studied over the years is ways to impair people's performance and then look at how that changes with alterations and chemistry or pharmacology. It's very easy to use a drug to impair performance. It's much harder to show in any clear way that you've improved normal performance.

Now yes, if you knock someone's performance down, you can use drugs to bring that back up again but to improve performance from a normal baseline has proven to be very, very difficult and in fact, most of the drugs that we've studied as cognitive enhancers, actually show that in normals, they tend to impair performance as much as anything.

I think there's a very good biological reason for that, that we and others have published on over the years, which is this upside down U shaped curve of normal functioning. Most of us, if we're lucky, tend to function near the top of that curve and if we simply flog receptors with more chemistry or more drugs, we tend to push people over the top of that upside down U. If we're down functioning near the bottom, then absolutely, drugs and biological manipulations can improve us.

We're also understanding a lot more about circuit mechanisms and circuit dynamics and how that might impact people's functioning, especially the impact of drugs on their functioning.

Dave Asprey: It begs the question that there's an assumption that most of us are sort of within that standard deviation of a normal, in terms of our cognitive function. There's a time in my life where I would have sworn up and down that I was one of those but I was living in a house that had neuro toxins from water damage and a SPECT scan showed that my brain was absolutely ... well see I had room for improvement.

If we were to take, insert name of your favorite neurological workup for people whether it's an [EUG 00:09:16] or some kind of imaging, wouldn't most people have some areas of their brain that are underactive or overactive or not working very well?

Paul Newhouse: I think the answer is if you're saying most people, I think the answer is probably no.

Dave Asprey: Interesting, okay.

Paul Newhouse: Activity in the brain is not a linear construct.

Dave Asprey: Oh yeah.

Paul Newhouse: More activity is not necessarily better and less activity is not necessarily worse. One of the things we're learning about this [inaudible 00:09:50] turns out to be really interesting is that if there's a drug that enhances cognitive performance lets say in an Alzheimer patient, it may increase activity in areas that you want to be active for a particular task, lets say, but it may actually decrease activity in a different network that we see typically overactive in a patient.

For example, one of the things we showed in patients ... in a review paper that we published a few years ago where we looked at nicotine effects on brain activity, the data seemed to suggest that a cholinergic drug for example, might increase task relevant areas in the brain but it might actually decrease activity or decrease connectivity and now we're talking a lot more about connectivity than just activity.

It might decrease connectivity to areas that are less valuable or you don't want to be activated. One of the things we know about the brain as it changes with both the normal aging and with disease is that you start getting overreaction of a lot of areas that aren't used in younger ages or in patients without pathology. Now that may be compensatory in some sense but it comes at a cost.

What I'm trying to say, I'm sorry I'm going on about this but it's really just not just a linear construct. You can't say, "Oh, I need to increase the activity of these areas of my brain," it may actually be better for you if you decrease.

Dave Asprey: That is a fantastic explanation and one of the projects that I'm involved with is a neuroscience facility where we're doing 24 channel QEEG brain scans and five days of intensive neuro feedback where we can see, yes, [inaudible 00:11:44] these circuits are reactive and these areas are over connecting and if these areas maybe are only overactive in one frequency band and they're underactive in another, if you're looking at it from an electrical perspective and it gets very easy to look at something and say, could you draw a line between bad performing and high performing, it would not be a straight line, it's like a fuzzy swath and if one goes up and something else doesn't goes down, it's not gonna work.

I'm really happy that you're explaining that because even the real simple cognitive enhancer things like caffeine, nicotine that have been relatively well

studied for the last long periods of time, like you said, sometimes they do good things but sometimes they don't do good things.

Paul Newhouse: Even figuring out how they do good things is really interesting and we're still kind of at the beginning of that. I just wrote a proposal a few weeks ago which just went in last week to look at a novel molecule that we've developed here at Vanderbilt that we believe will be cognitively enhancing and this ... the way we want to look at this in patients, we've already got this molecule into humans now in our phase one study but we want to actually test this in patients and we want to take a totally new approach to testing it, which is not to use the same old approach that we've done before but actually to use brain networks as a measure of what we call target engagement.

We want to show that we can actually change the relative activity and connectivity of these well understood or well reasonably well understood brain networks, because that, to be honest, that's sort of where the brain is. The brain is not just a collection of cells, it's a collection of cells which then form themselves into networks, which those networks then interact to produce behavior and thought.

This is the challenge I think and makes it harder I think to develop these things because we're working at multiple layers of complexity.

Dave Asprey: My research into mitochondria suggests there's a mitochondrial network underneath that, where there's quorum sensing, the mitochondria talk to each other, both inside a cell and between different neurons. There's a communication network happening there and they communicate with other system in the body. There's multiple layers of networks that run throughout the system.

Paul Newhouse: Exactly. That's correct. There are subcellular networks at the level of mitochondria there are very intense relationships within cells and that's of course the focus of a huge amount of medical research is to understand molecular and cellular mechanisms.

Then there are sort of small system. I have a colleague who has developed a very clever set of electrical and chemical sensors to actually record from very small circuits within, lets say the primary visual cortex in the brain of a monkey. She can record from them and tell you what the local circuit is doing when they see, when that animal sees a certain visual stimulus and she can tell us what acetylcholine is doing right at that circuit level, that micro circuit.

Then we are taking it to the next level where we want to look at larger ensembles of circuits, which is what the complexity ... so you're absolutely right, there are multiple circuits that we have to be able to engage with.

Dave Asprey: One of the things that I discovered in my own path, I like to think that I'm a reasonably intelligent guy and I hit a time in my mid-twenties where my brain just wouldn't do what I knew it used to do and I was really struggling in grad school and when I was about 30 from this. It turns out that I did have thing inhibiting my cognitive function and by removing those things, I got a boost.

I continued doing other things that ... different studies different kinds of training, different substances, things like modafinil, that really did, at least from my perspective and from my external measure level of success, made a meaningful difference. I continue to do stuff today even in mitochondrial level things that seem to make, "Wow, I have more energy in my brain," just worked for longer, like the duration of cognitive function is a measure of enhancement as well.

I'm sort of looking at this as a hacker, which is my real background where you don't what's going on inside a system but you want to manipulate the system so look at inputs but you look at highest level outputs possible. When you're looking at networks like that, are you, in your studies, are you looking at measures of perceived energy or external ... what does everyone else think this person's doing or are we still down inside the brain when we're looking for the results of these things.

Paul Newhouse: No, we look at all of those kinds of responses. In human studies, we're very interested in what people perceive about their treatments as well as what they perceive their functioning to be. We have been working very hard over the last few years to try to listen better to patients about what they perceive their cognitive and behavioral functioning is. We spent a considerable amount of effort the on that. We take people's memory complaints very seriously because we think that they may have ... those complaints may have important implications for their underlying risk, for example, for cognitive disorders in later life. That's been a bit of an uphill climb but I think it's now accepted within our field that people's reports of how they're doing are important to listen to.

Now we ... this turns out to be very much a double edge sword however. We recently completed, one of my graduate students just finished her dissertation study, which was a treatment trial in patients who had post-chemotherapy, post-cancer chemotherapy, what they perceived as cognitive impairment, following the successful of their chemotherapy. This is so called, "chemo-brain," if you will.

We did a study with transdermal nicotine and we had hoped within the confines of a fairly short, low dose study that we would be able to see if there was a signal here, it's not a definitive study, just a small pilot study. What we found to our surprise was yes, there was a very strong therapeutic effect but so was the placebo.

Dave Asprey: Interesting.

Paul Newhouse: Patients improved dramatically on treatment but they improved just as well in over the exact same times course on placebo.

If we used subjective cognitive reports, in other words, if we used a structured instrument that allowed us to ... for them, it was developed by another investigator in the cancer field who had developed this instrument specifically to look at people's perception of their functioning.

What we found, and she published a lot of work on this and it looked like a very solid instrument and what we found was that's incredibly responsive to placebo effects. Now that's very interesting and not to be dismissed at all because placebo is really interesting and how people's brains react to the involvement of being in a treatment trial and getting treatment and having people listen to them carefully and take what they're saying seriously is not ... we don't sneeze at the at all. It demonstrates the challenge in trying to establish an efficacy.

Right now, what we've concluded from her study is we can't conclude.

Dave Asprey: How frustrating.

Paul Newhouse: We've concluded that the study wasn't designed well enough to allow us to make any definitive conclusions about the effectiveness of nicotine in this case.

Anyway, I think there's a ... she was initially quite disappointed in this result but now we think we've ... I've convinced her actually, there's a lot of interesting results gonna come out of this it just won't be that she expected.

Dave Asprey: It's that the age old problem for anything from yoga to any pharmaceutical agent. How much of it is because we believe that it works versus because it has an effect independent of our belief.

Paul Newhouse: Well, I think it's even more than that though. It's not just that our belief that it works, it's the impact of visiting with a person who tests you every few weeks or coming into a clinic where people take you seriously. It actually can produce benefits to your cognitive functioning, your mood, your energy level.

If you see somebody that you have a good relationship with and you trust and who takes you seriously, we know that your treatment will benefit, right? We know that ... that's the basis of every good doctor, patient relationship is establishing trust and confidence. That's not to be ... we take that very seriously. It's more than just belief.

Dave Asprey: That's a fair point. I have a friend, Robby, who makes something called the X pill and he read a bunch of studies on placebo and said, "Well, I'm just gonna make a little purple pill that everyone knows doesn't have anything in it," and you basically write on your own, what the little label on this is and then you take the pill just to tell yourself that's what you want, which sounds incredibly stupid but

... he's done a reasonable amount of science, not an NIMH level of science but enough to say, "Wow, people get at least a placebo effect from taking something that's labeled Placebo."

For things like motivation and willpower and other things that are kind of surprising, I spent a couple hours chatting with him and said, well this is surprising but if we look at something like nicotine where we know that it has a mitochondrial enhancement effect, we know it raises PGC 1 alpha in a way like exercise does and we know that there's a plausible mechanism for this to work and we'd expect it to work, is there a way to ever know that it is effecting chemo-brain? Would you measure this at a subcellular level? Would you measure this at a network level or is it really about these higher level perception things?

Paul Newhouse: Well I think it depends ... I think you have to ask the right question before you know how to measure something. If you're looking to measure people's perception, then you have to measure their perception. If that's your outcome measure, you have to design a study that is long enough and adequately dosed enough and with the right design, and there's a lot of really bad clinical trial designs out there. Things that failed, we've seen this Alzheimer's field littered with failure, not always because the agents are bad but because the study designs were bad. They asked the wrong question, they asked it in the wrong way, they did an inadequate study.

I guess, the question is yeah I think you could design studies to adequately address chemo-brain for example. It turned out that the one that we designed didn't do that but we learned from those mistakes and we say, "Okay, now we should design something a little bit different."

You're right, we should look at other outcomes. If we do this study again, which we're hoping to get funded to do, we will look at brain circuitry and we will look at other outcome measures that's might be proxys for the eventual target.

Dave Asprey: I do owe you a thanks because back in 1988, you were the first person to propose augmenting the nicotinic system to treat Alzheimer's disease and I've come across a few of your papers and I'm a relatively outspoken fan of nicotine as apart from tobacco and smoking, which have clear risks, but nicotine as a purified agent seems to be a really potent cognitive enhancer for at least a set of people, including me and probably even has some health benefits, depending on which benefits you're looking at even though there might be other counteracting things.

What made you look at these pathways or look at nicotine as medical therapy so early on?

Paul Newhouse: It's like everything else, it's a little bit serendipity. I came into a lab at NIH where people were looking at cholinergic drugs and I looked around and I said, "well

what's no one else looking at?" And I said, "Well, I seem to remember from medical school that nicotine activates the same system, why don't I look at that."

In those days, there was no patch, there was no gum. There was no spray or vape or anything like that so we had to actually make our nicotine for intravenous use, we had to infuse it. We had to basically create our own pharmaceutical, which we did at NIH with the help of some very clever pharmacists and we actually created an intravenous formulation of nicotine that we could infuse gradually into people and we had to learn to do that, we had to learn to do it safely and so it was tolerable.

Right away, we began to see some hints that there were ... that this was active in a very rapid way. That sort of got me launched into sort of, I'm just asking the next question, which is what are these nicotinic receptors doing in the brain? They had only just been identified at about the same time.

Simultaneously with my interest, a guy named Ken Kellar at Georgetown, who's still there. Ken Kellar was doing the really, the first identification in the human brain and in the rat brain of where these nicotinic receptors were. Where these receptors were for nicotine. We'd always been taught, oh there are no nicotinic receptors in the brain or almost none.

Like a lot of things we're taught, they turn out to be wrong. Ken did some of the first identification of nicotinic receptors, other people quickly followed with even better techniques to image these receptors and to show where they were and what they did and that launched a whole field, which is still continuing to this day of understanding where are these receptors, what do they do, and what do they not do. Now how can we take advantage of those receptors to move the brain around, move cognitive processes, emotional processing and then use that therapeutically potentially.

Dave Asprey: I think you might be ... [inaudible 00:27:20] it sounds a little bit humble when you say potentially because you've studied nicotine, at least the nicotinic system in the brain for mild cognitive impairment, the chemo-brain, you talked about, the Alzheimer's disease and even you're looking at things like HIV and aging and down syndrome and just all these very disparate things, all boiling them down to just one receptor in the brain.

You must believe that there's some meat on the bone, for lack of a better word here.

Paul Newhouse: Well yeah. I think ... I'm not sure I would use meat on the bone but what I would say is that we think that nicotinic stimulation is a modulatory system, it modulates, not necessarily mediates but modulates a whole set of other neuro-transmitter systems and biological processes. It's a very ancient receptor system, phylogenetically. What we think it does in the human brain or in the

primate, excuse me, in the mammalian brain, is that it doesn't transmit information directly that much itself, that's mostly glutamate. Glutamate is the major sort of excitatory transmitter.

What nicotinic receptors do is they act like gain enhancers. The modulate the gain of a particular neurochemical event. If you stimulate a nicotinic receptor that's sitting pre-synaptically or sort of in the end of an axon and you get more bang for your buck when a signal comes along.

What we think it can do is amplify an already existing signal. Now you know, if you've ever played with amplifiers, that if you amplify a signal just to the right amount, you actually increase signal to noise but if you over amplify it, you just get noise.

Dave Asprey: Right.

Paul Newhouse: That's what we think ... that's why we get this upside down U shape curve, because you want to sort of find the right exact amount of extra amplification that give you the best signal, if you will.

Dave Asprey: What a beautiful analogy. I've never heard it explained that way. I'm pretty open about this. I am ... I just love nicotine. I've never smoked in my life. I did half a cigar once, it made me sick when I was 20 something. Other than that ... using patches or sprays or lozenges on occasion for writing my books and for giving a really powerful on stage thing, maybe my brain benefits from that kind of amplification.

Paul Newhouse: That may be. One of the interesting things is we don't really have a great grasp yet of who will benefit and who won't. It's pretty clear that there's a collection of people who smoke or use tobacco or use nicotine in some recreational way or who get benefit from it.

A few years ago, about a decade ago or more, I had a graduate student and she was really interested in ADHD, Attention Deficit Hyperactivity Disorder. She was interested in, you know one of the things we knew about these people is that they smoke a lot, well why was that?

We began to look into what were the potential effects, neural effects of nicotine on cognitive processing in ADHD. We knew that amphetamines for example were used, they helped ... stimulants helped patients with ADHD and what we found by actually taking this into the lab was that there was a cognitive process of what we call behavioral inhibition that nicotine really seems to help in these patients. In other words, it kind of slows down their brain a little bit and reduces impulsive responding in the lab. What we showed in a paper some years ago was that you could actually use this lab measure to predict how effective a nicotinic treatment might be in a real world test.

We could say, okay if we got this degree of improvement in this particular task in the lab, which is called the stop signal task, which is a measure of how quickly you can stop a response, a prepotent response, that actually mapped on pretty well to how well the drug would work in a clinical trial.

We began to realize that there's some people out there who really benefit from tuning their brain a little bit this way maybe. They just want to be ... many of us, if we have depression for example, or mood disturbances or anxiety, we might benefit from tilting us just slightly to the right or the left and that's what nicotine may do.

For example, if ... we always used to ... we joke our lab that nicotine, in some respects is the perfect psychotropic drug because if you're de-aroused, it will arouse you. If you're over aroused, or hyper-aroused, it will calm you down. It will bring you more into sort of that middle ground.

The guy in the movie who's gonna be executed and they offer a last cigarette, right?

Dave Asprey: Right.

Paul Newhouse: There's a reason there, because it's anxiolytic. It's anti-anxiety, it reduces anxiety. If you're de-aroused, it may actually wake you up.

That's different from amphetamine, which won't do that. Won't do that. Amphetamine has a kind of linear uni-directional effect. It just simply flogs your dopamine and noradrenaline receptors until you basically run out of transmitter. That doesn't really tune the system very well.

Dave Asprey: My limited experience with amphetamine as a prescription in business school is that it made me want to either hide under a desk or hit people.

Paul Newhouse: Exactly.

Dave Asprey: It was not at all like nicotine. That's for sure.

Paul Newhouse: But if you had ADHD, you see-

Dave Asprey: Which I did, yeah.

Paul Newhouse: What you might find is that stimulants may actually improve your ability to inhibit inappropriate impulses or improve your ability essentially to be on task, for example.

It really depends and I always try to explain this to people that the effect of any drug that has this sort of bi-directional effect is really dependent on where you start. We can show even in rats, if you buy 100 white rats from a supplier and

you give them nicotine, you will find some of them will really get a better cognitive performance, some of them will get worse. It really depends on which, where those animals started.

The ones that perform really well without nicotine will get worse with nicotine and the ones that are poor performers will show improvements.

Dave Asprey: That leads to a really important question for people listening to the show. There are a lot of people who think they're really good performers but aren't performing at the level they're capable of. There are a lot of people who are good performers performing at their limit and then there are people who know they're not performing at their capability set, how would you if you're one of those people for whom nicotine might be a useful substance?

Paul Newhouse: Well, that's a tough one. I'm not sure that we know how to tell people.

Dave Asprey: Could you just try it and see if you feel better?

Paul Newhouse: There is ... it's a free country. People try these things.

Dave Asprey: I'm not asking it from a libertarian perspective there-

Paul Newhouse: No, I understand.

Dave Asprey: Is it something that you would ... you'd be like, "Wow, I like my life better on this. It's probably working." Or is there other stuff involved?

Paul Newhouse: People do [inaudible 00:35:42] experiments all the time. If you feel anxious or you're annoyed or upset or stressed, you might have the gin and tonic or something or glass of wine and you'll say, "Oh, this really helped. I feel much calmer now."

For most people who try nicotine who believe there're not functioning that well, I would better that for most of them, I would objectively demonstrate that it doesn't improve their performance, but does it benefit their subjective perception of their performance? That's a different story.

There were studies back in the '70s that looked at, for example, amphetamine effects on performance and what I believe that they showed, if I'm remember correctly is that people felt that they were performing much better but weren't in fact.

Dave Asprey: Almost all of the cognitive enhancers, whether modafinil or even some of the brain training suffer from that same ... that same problem where you think you are but you don't know if you are and I've ... over the years of working on my own brain, I do know things like lost words, where I just can't think of

something. That is ...its vanished from my life and it used to be a common source of stress for me. There's some external things.

Even doing that day to day finger tapping test, the very basic measures of short term executive function, it seems like it can be all over the place. I would love to be able to offer people, listening to the show, how do you know where you are in what spectrum. Are you a person who's working at your capacity?

When someone is considering nicotine or any of the other cognitive enhancing substance that are out there like that, they're always going to be suffering from this, "Well I think it worked, therefore it did work," self-inherent bias. What is the mechanism, or is there a mechanism, like a daily test or something that you could do or something that you might use in a study that would be accessible to people to just let them check in and see whether they're wasting their 50 bucks on whatever this cognitive enhancer is or whether it's actually benefiting them?

Paul Newhouse: Well, this is a very rapidly developing area. You're talking about something that is now being labeled as ecological momentary assessment, EMA.

Dave Asprey: Cool.

Paul Newhouse: The idea here is, can you take cognitive assessment out of the lab and put it in ... can you put it out there for people to give you data?

One of my ... one of the postdocs in the center is developing in the study with a guy at Washington University who is developing phone based, iPhone or Android phone based platforms to do real worlds assessments, right on your phone. That data will get fed back in and what she's interested in is looking at people with this subjective belief that their cognition is changing and she wants to be able to test them over a long period of time and actually look at brain imaging periodically.

Scan them and then also get this sort of ecological momentary assessment and do something ... there's this concept of so called burst testing where we ... I send you Dave, I send you a link and on your phone and I test you once an hour for the next two days or once every day for the next seven days. Then I don't talk to you again or I don't send you a link of the next month or two and then I do it again randomly.

The whole idea is to get some kind of database where people's functioning is looked at over a length of time because one of the things that you talked about a moment ago made me think that our cognitive functioning for all of us is a very noisy process. This hour, I might be really good but an hour for now when I'm a little drowsier and it's the end of the day, I might not perform as well. We're very attuned to this in our lab because we focus a lot on testing people at the same time, the same time of day in the same situations as much similar as we can make them because we know there are circadian effects in cognitive

performance, we showed that when I was running the lab for the US army that your cognitive functioning actually runs on a 12 hour cycle and actually pretty tightly linked to your core body temperature and that people perform better in this at these hours of the day poorer at those hours.

It's never a sort of fixed thing. If I can do EMA, if I can actually test you in real time, in the real world, I can get a much better idea of your long term performance. Yes, I think we are getting close to be able to roll this kind of thing out for people.

Dave Asprey: That is one of the most important things I think happening in neuroscience, although there's a lot happening right now because I've become just keenly aware probably because I suffered from toxic mold stuff that really did remove blood flow from parts of my brain, at least remove oxygen levels at a time in my life. I noticed, when I was having a decline and I developed this whole lifestyle tool set of things where I don't have the dips like I did before.

I'm never at 100 percent all the time but I go from 100 to 85 instead of from 100 to 50 back to 100. I managed to reduce the dips and it's had a profound impact on my performance. Enough Bulletproof followers have had very similar results from things like ketones and lots of these other things including nicotine that it seems like that's hackable but we don't have great data other than "Wow, I sure like my life, I feel good and I don't just fall asleep after work like I used to."

Getting the data is going to be transformative, especially when we get the data ourselves, instead of it going into a study that we don't actually get to know whether what we're doing works. If you put on your future hat, 20 or 30 years from now, where do you think we'll be with cognitive enhancement?

Paul Newhouse: Well, I tend to focus most of my energy on obviously looking at ways to enhance cognitive function in disorders because I'm a pathologist. That's what a physician is, we are pathologists of a type, right? Unlike your job, my job is not to enhance normal cognition, my job is to look for ways to normalize or mitigate the impact of disorder.

Now, what I have focused on is as you alluded to early on is the idea of that we can take for example cholinergic stimulation, and I don't mean just nicotinic but other cholinergic approaches and we can apply those to conditions that look like accelerated aging.

We know for example in down syndrome, down syndrome patients survive to their 50s, 60s, 70s now easily 'cause we fixed all the cardiovascular problems that they used to have. They get fixed easily now, or relatively easily but they age faster. We know that patients with HIV survive much better than they used to but their bodies and their brains seem to still age faster than everyone else's.

We have a number of conditions where we think they resemble accelerated aging, we think that cholinergic stimulation, or nicotinic stimulation might be sort of agnostic to the disease state and I think that's what the kind of tools we're looking for.

A colleague of mine at the University of Utah and I are just writing a grant that's going on Monday to propose to the National Institute on Aging that we develop a novel method on cognitive training for patients with early memory loss that focuses on a different network in the brain than typically has been done up to now. We want to focus for example on the cognitive control network, not just memory systems but actually focus on networks that are involved in essentially executive function. We think we can train them in a way that will enhance and will provide what we call transfer effects, both near transfer and far transfer effects to a whole range of cognitive functions.

I think, if I put my future hat on, I think we're gonna become much more sophisticated about this. We're going to do what my colleague, Reisa Sperling at Harvard calls COMBAT, which is combined, in her case, she calls it Combined Alzheimer therapies-

Dave Asprey: Nice.

Paul Newhouse: Or COMBAT to combine approaches.

It won't be just a cognitive enhancer anymore, it will be a cognitive enhancer plus specific brain training to target a specific set of networks or network or networks to enhance, if you find that your son or daughter is not doing well on this particular aspect of school, maybe specific training on tasks which enhance that network could enhance that ability to function.

Instead of bio-hacking your mitochondria, maybe you're gonna get a lot more bang for the buck by targeting a particular neural network, either chemically, with training or both in the same way that you would target if you wanted to run faster or lift more weight or do something else, you would target the network that's involved.

Dave Asprey: That is profoundly awesome and I look at all of this stuff as there's a return on investment for the amount of energy you out into to any therapeutic, whether it's a physical exercise, a brain training exercise, a pharmacological solution, whatever it is, there's always a cost and it's how much time, energy, money and is there a biological cost in terms of side effects and how do you stack those most effectively to get the most return in the least time.

I feel like we're getting enough data now that maybe someday we'll get there to the point where we know we're getting the maximum returns.

Paul Newhouse: We may know for example that intervening at the molecular level to prevent the depositing of abnormal proteins may reduce the risk of developing dementia or Alzheimer's for example. We may have to intervene at much earlier ages if we only took that approach but if we combine that with neurotransmitter based approaches, with cognitive training and with molecular approaches, we may have a much more powerful wrench on this system to keep your brain healthier.

To me, the most important thing is to keep your brain healthy in aging, because that's when you see the big decline, it's not in middle age, its aging.

Dave Asprey: Now, I've got to ask you something. You've been active in research for 40 years, which means by any measure you're at least in your early 60s. You look very, very healthy. I run an [inaudible 00:47:38] non-profit group for [inaudible 00:47:38] your skin looks great and you look like someone who's aging well and clearly your brain is working at a high level. What do you do to take care of your own brain?

Paul Newhouse: Well, so you know it's funny. I was talking with a colleague this morning about sort of a new center idea that we're developing and we're gonna call it something like the Center for Healthy Brain Aging.

Dave Asprey: Love it.

Paul Newhouse: What do I do? I, if you look at the data that's out there and the National Academy of Medicine actually produced a report on this last year, the best data is physical exercise, right now. If you look at all of the data, the best data out there suggests this gets back to your [BDNF 00:48:25] idea that you mentioned some minutes ago, which is that physical exercise seems to have the most ... the biggest effect size and even that, it's not that large but it's a bigger effect size. I give a lecture every year where I say, well here are all the things you can do, none of them have a very big effect size by themselves but if you start combining them, now you're talking.

Physical exercise, intellectual challenge, problem solving, socialization, mindfulness mediation, improving emotional health, all of these things seem to be linked to healthy brain aging. The trick is how to combine them and one of the ideas that I've had, haven't done it yet but I want to do it, is to develop a clinic essentially where people who are concerned about brain aging come and get consultation and how their lives can be tuned in middle age to kind of prevent these problems.

We don't have to cure Alzheimer's disease, we just have to put it off until you die of something else, right?

Dave Asprey: What a pragmatic and awesome statement. Yeah, that's exactly right. As long as you put it off long enough, it's a non issue.

Your approach is very much aligned with the work I'm doing. I'm in my mid-40s and I know that it had mild cognitive impairment in my mid-20s and-

Paul Newhouse: Except we wouldn't have called it mild cognitive impairment.

Dave Asprey: No, we wouldn't have. I had, lets see, Daniel Amen called it a toxin induced brain damage essentially. Suddenly it wasn't working well but I had the symptoms that would actually highly correlated with the cognitive impairment that you study. I don't want to go back to that and I'll do just anything to not have a brain that works that way.

In your idea that what if we just put a small investment in now that saves a large investment later along with all the pain that comes with it. I got to ask though, I mean is there a nicotine patch under your shirt sleeve there?

Paul Newhouse: There is not. There is not. I try not to take the drugs that I'm studying because it would less me less subjective.

Dave Asprey: But that's no fun.

Paul Newhouse: No, it's fine. I'm a cancer survivor, I take good care of myself. One of the things you learn in life is that you can do all the right things and take good care of your self and life will still kick you in the behind.

Dave Asprey: That is true.

Paul Newhouse: I have a wife who's a dietician who feeds me very well and takes good care of me and I've had some wonderful physicians who take good care of me and try to enjoy myself and work hard but also try to lead a balanced life and that's, I think I'm gonna do fine but you're right.

Some of us are of course trapped with our genetics, that's at big issue. Genetics are not ... I'm not a determinant, I'm not a genetic determinist but we are realizing that certain genetic risk factors are present and we have to look for ways to mitigate those and manage those risks but even in genetically high risk people, we're starting a study now to look at a long term prevention trial in genetically high risk individuals for Alzheimer's disease and those studies are actually ongoing now across the country and around the globe.

One of the questions is, is it enough to simply do this molecular intervention or do you have to change lifestyles. I think it's gonna turn out to be that life style is gonna have as big an effect size as anything.

Dave Asprey: Your ... all the things I've seen make me think that it cannot be an either, or, when you combine the two, you get more than ... two plus too equals five kind of a situation.

I have one more question for you Dr. Newhouse. Based on just all the things you've experienced in your life, including your academic research but not just that, if someone came to you tomorrow and they said, "I want to perform better at everything I do as a human being," what are you are three most important piece advice, what would you tell them to do?

Paul Newhouse: Perform better at everything, well I guess I ... the first thing I would do is set realistic expectations.

Dave Asprey: Awesome.

Paul Newhouse: I mean I would like to perform better at lifting weights for example but I have to set realistic expectations about how much my body is gonna let me lift without hurting my back. I think the first thing is to set realistic expectations and pick one or two things that you want to improve in your life and focus on that and I think you're gonna ... I think people who try to set too many or too high expectations are bound to get disappointed.

I, just as with patients, what I do in my clinical practice with memory disorder patients is to set small goals to make them achievable. We're going to manage these particular problems and we're going to try focus on treating this problem and we're gonna make everyone's quality of life better and I think that's a reasonable, even true for normals, those of us who would like to improve.

I was a bike racer at one point, I used to do competitive bike racing years ago and one of the things I learned was I didn't have to get better, I just had to get older because I started moving up in the classes and my performance relative to other people, got better and better 'cause they all dropped out.

Dave Asprey: Don't decline as rapidly as everyone else, that's a good strategy.

Paul Newhouse: That's right, that's right. Keep doing it.

I think setting realistic goals is the first thing. I think that improving one's care of oneself is really important. I think adequate sleep turns out to be even ... we haven't talked about that at all but one of the things that I've become convinced of that I wasn't sleeping as much as I should have been and so I focus more on getting better and longer sleep. I think that's improved cognitive function and actually seems to help clear the brain of some of thee abnormal proteins. There's some evidence for that, weak evidence, but there is some evidence.

Then I think I would focus on enhancing ones emotional life and I think, I'm convinced that mindfulness approaches may be extremely valuable in terms of improving one's ability to focus and attend to information. I think we multitask way too much. I fault myself for this as well. We're not really ... there seems to be a capacity limit to how much we can do simultaneously and I think that I've become convinced, at least personally the way you have, that I've become

convinced that mindfulness has become beneficial to me in terms of allowing me to improve my focus of attention, if you will. It's a skill. It takes training, it's hard work but I think it actually helps in a way, train the mind.

I think mindfulness, and then a regular physical exercise program, I think is incredibly valuable from all sorts of perspectives, both physical, cognitive and emotional. I think if people did just those things, and tried to do less of the bad things, don't drink too much, drink a little but not too much, what's Michael Poland's famous idea about your diet, eat plants mostly. Eat plants, don't eat too much and don't eat too much meat. I think all of those things, I think most people would find that their quality of life improved and maybe even their perception of performance.

Now we don't know about their actual performance until we actually measure ... can figure out a way to reliably measure it.

Dave Asprey: What an awesome answer. At least your perception of performance will improve and that will feel good.

Speaking of it, what is your favorite type of mindfulness practice? Maybe something you do, or something you've seen that's most effective.

Paul Newhouse: You know, I'm a simple guy so I just use MBSR, which is associated with Jon Kabat-Zinn. I tend to ... I'm a creature of habit, so I tend to use his approach 'cause it's the one I learned. I'm not saying it's the only one or even the best one but it seems to work for me.

Dave Asprey: Well you're definitely doing great work and you have been for, going on 40 years now. It's always useful to know both how you think about it and some of the tools you use.

Dr. Newhouse, I just genuinely thank you for your continued work in this field for decades and I think its made a meaningful difference, some of your research has been really informative for me and I think that you've moved the needle for a lot of people with a lot of conditions and it's had reverberations throughout the field. Thank you very much for being on the show and thanks for your work.

Paul Newhouse: I appreciate it. You're very welcome and stayed tuned, we've got a lot more exciting stuff coming. We're developing new molecules as we speak and we're rolling those out and new approaches. I'm just getting started.

Dave Asprey: Well sign me up of the early adopter list, I'll be on it.

Paul Newhouse: Alright, thanks.

Dave Asprey: Thanks.

If you'd like to know more about Dr. Paul Newhouse's work you can look up the Center for Cognitive Medicine at Vanderbilt and they're always looking for people in trials or people who would like to support the research and this is really worth your research to support.

Paul Newhouse: You know, it's what I tell people now, that if you want to cure Alzheimer's disease, volunteer for a study.

Dave Asprey: I love it. Thanks again Paul.

Paul Newhouse: Alright, Dave, it's a pleasure. Take care.

Dave Asprey: Take care.