DANNY LENNON: Nick, thank you so much for taking the time to talk to me.

NICK GANT: My pleasure. And welcome to sunny Oakland.

DANNY LENNON: Yeah. It's been great so far being able to see around this wonderful city you've been in. And I've had the pleasure of seeing your facility here and the lab. So, we'll probably talk a bit about that. Before we get specifically to the lab, maybe fill people in on your background that has led you to doing the work you're currently doing.

NICK GANT: Yes. So, it's kind of in three prongs. I'm an exercise physiologist, I'm a nutritionist and I'm a neuroscientist. So, I started off with an undergraduate degree in Sport and Exercise Science and then an MSC in Exercise Physiology. I did that at Lufburrow, and I met Clyde Williams there and then I worked in his lab for a couple of years doing everything - exercise, nutrition. Getting involved in quite a lot that was coming out of Lufburrow at that time. And then I did my PhD with him. I did my PhD in Fluid and Carbohydrate in Extreme Environments. And then, postdoc, in a lab that at the time Clyde Williams was sharing with Ron Morin's group. So, I got to see some of the stuff that Ron Morin and Susan Sheriffs were doing

out of Lufburrow at that time. Then, I moved here, and I saw quite a unique opportunity with the Center for Brain Research we have here at the university and the capabilities there to start answering maybe some of these questions that tend to be avoided in nutrition. Nutritional neuroscience is a whole area that's difficult to get into and exercise physiology. So, unanswered questions relating to exercise nutrition has been ... what I've been doing. It's hard to do and that's my excuse for the lack of productivity, but we've managed to pick some of the low hanging fruit in those areas.

DANNY LENNON: Yeah. I think that's the one thing that will strike people maybe when they start looking at some of the work you've published that there is this novelty to a lot of the research questions that you've kind of asked in that, as you said, there's almost like a Venn diagram of these different areas that you have this interest of an intersection between them. Do you think that adds something to the questions that you're able to come up with versus being stuck in one particular silo?

NICK GANT: Yeah. And, as I said, it's difficult to do. It's very nichey but also very important and I think the role of the brain in nutrition, particularly excise nutrition, is totally undervalued. Well, not undervalued, but I always say we're in the pre-muscle biopsy needle sort of era when it comes to brain. I remember sort of in the late sixties you saw this exponential growth in research after that technology was available. We're still pre- that in the field in that our advanced techniques in nutritional neuroscience have to be done independently of whole-body exercise in particular. Or we have to have a reductionist approach, where we look at a single joint sort of movement, if we're looking at exercise. And scanning the brain in particular, which is one of the frontiers, is very difficult in a naturalistic ecological validity ... valid environment. You know, we're trying to develop those technologies so people can eat at a table while we look at the brain. But in my work, we have to stick people

inside the bore of a noisy magnet and try and pass things to them and make sure they don't choke on them and all of these other things. So, it's technically difficult, but in my view, it is one of the next frontiers along with the genomics where we're going to make the biggest gains and hopefully, we might be part of that over the next couple of decades.

DANNY LENNON: Right. So, before we get into some of the nuts and bolts of the research, you've just been very kind in giving me a tour of this wonderful lab that has been able to be built here. Maybe give people an insight into ... I suppose it's only relatively developed, as you've said, and so you've been able to put some pretty cool stuff in. What are some of the things you're most proud of after being able to design the lab the way you wanted?

NICK GANT: Yeah. So, we're able to have a good sort of research kitchen environment and a natural eating area that we're sitting at now. An area for people to study and do cognitive testing and panel type food testing, which is really important for any good nutrition department. Then we're able to have an exercise facility where things are environmentally controlled, not just talking about temperature here, talking about all the other things I need to control to make when I'm measuring brain function, light levels, noise levels are very important. So, our exercise facilities are equipped with ways of tracking the eyes. We've got a virtual reality system attached to all of our exercise equipment so people can be immersed fully in what they're doing, and we can present them with stimuli whilst they're exercising. And that doesn't usually happen in the neurosciences that we've ... in our previous papers, we finished exercise and then tested the brain's a bit, before and after model. And then we've got some advanced neuroscience techniques that we could include in those paradigms right here. So, noninvasive brain stimulation techniques like transcranial magnetic stimulation, transcranial direct current stimulation. And I also have a

commercial sort of gray driving simulator. So, one of the problems with a lot of the nutritional neuroscience I do is people say, what ... you know, how is this drop in the amplitude of a rapid eye movement? What does it really mean? Am I going to get knocked off my bike because my eyes aren't moving quickly? Well, we can then say ... get you driving a car and seeing how many speeding tickets you pick up where you're deviating in the lane from where you should be, what signals you are missing from the GPS and really put it in context. And I guess the final thing that's great is being part of the Center for Brain Research. I have to walk not far from here to get to a 3T MRI scanner. So, we incorporate in most of our studies ... the funded studies, at least, FMRI or MRS to look at concentrations of metabolites in the brain or tractography. So, that's an excellent thing to do. We're moving ... we're actually hoping to move even further in the imaging to, you will have seen in the lab was using near infrared spectroscopy to have a look at how much blood was or how much hemoglobin was in the prefrontal cortex of the person in the lab. We're going to move that on to hopefully an imaging set up where we can get MRI like data from people whilst they are in a natural environment. So, I think we'll make some big gains and over the years I'm going to try and target some of the mechanisms in nutritional neuroscience area that have been relying on sampling the gutter, which is the blood and looking at neuropeptides appearing in the blood, which don't tell us a great deal. And the areas of exercise science mechanistically, the brains control when its role as a consumer and a controller of everything we do.

DANNY LENNON: Right. Yeah. It's fascinating to see that there's not any applications for exercise, but there's also ones that quite clearly will have implications outside of that for day to day living as well as just general health. To maybe start on at least initially with the exercise type stuff. I know a lot of your work has been based around trying to at least rescue some of the downsides we see from exercise and juice fatigue. And so, there's

probably a number of elements to that when we use that word fatigue. So, what's the best place for people to really think about what that word should mean in the context we're talking about? How do we define or think about fatigue?

NICK GANT: Yeah. I think it's reasonably well defined in the neurophysiology literature and that is when we're fatigued, we have biochemical changes occurring at the level of the muscle or what we would call distal to the neuromuscular junction. Energy depletion, changes in pH temperature and so forth that lead to the peripheral fatigue. But then there's a central component that's easily measured. So, output from the motor areas of your brain, the motor cortex and other areas, is dampened or reduced. And we tend to see that as a reduction in output from the brain that's perhaps in order to protect you from doing any voluntary damage may be because if you carry on, there'll be some damage to peripheral or central tissues and that's technically and historically been called central for tea. But that's really one of the only ways of quantifying it successfully. And we do that, but it's very hard to do during whole body exercise. You have to normally stimulate the brain and measure flection of the elbow or the knee or something like that. But it's always within the wider context of everything else that's happening within the brain. Everything that makes you the source of the biggest noise in our experiments. So, your personality, your mindset, your mood, fatigue, previous experience, how you're pacing, exercise. And of course, that's been captured in this central governor model of exercise fatigue, which not many people ... there's been a lot of publications but not much data collected in that field. So, it's a theory in that respect. So, what I try to do in the lab is remove all of those extraneous variables by looking at things, not necessarily just stimulating muscle contraction, looking at how much the muscles fatigue and how much of the central nervous system has been involved. We try to make other reflective or things beyond your control that still show us in an underlying

way how the brain is functioning. So, central fatigue could be you're feeling too hot, your bum is hurting, your rating or perception of the intensity of what you're doing is higher than it should be. And of course, these are all valid ways of measuring it. In fact, you don't need all the equipment I have here. You need an RP scale really to gauge how somebody is doing. But with the RP scale, you don't know it's because they just had an argument with a girlfriend that morning, had the wrong thing to eat. So, there's so many variables come into the equation. We try to get rid of them. Now, we don't have to get rid of them with brain imaging because we can see large activation networks. But when we're interrogating the motor system, we tend to get rid of them. So, fatigue is very hard to define and it's different for everyone and it's pathological at its extremes. And it's based on a whole series of factors which are governed by the central nervous system and by the central nervous system including you in that ... your behavior.

DANNY LENNON: So, from study to study, we may see a focus on specific characteristics related to fatigue that we're going to try and assess, particularly with this study. And that may be different from depending on the context of what we're trying to look at.

NICK GANT: Yeah. So, I think, we're at the stage now in the literature where we think the kind of fatigue that accompanies certainly prolonged exercise and it may be the same for prolonged cognitive work, is an imbalance of certain neurotransmitters. We've moved away from the original serotonin hypothesis somewhat. There's been a few blind alleys there, particularly in people looking for precursors they thought might influence the synthesis of that neurotransmitter. Most of the consensus is around the brain catecholamines, so, dopamine and noradrenaline. And we know that these have very high turnover rates when the brain is very active and when they're turning over all the time, they tend to become out of whack or depleted and we get a change in excitation and inhibition within the areas where

they're required for important neurotransmission. Of course, most people are familiar with a drug which alters both of these profoundly and that is caffeine. And even with all the research we've done on selective dopamine and noradrenaline, reuptake inhibitors, we find caffeine often just as good as all of the illegal ones. And that enables the ... indirectly through adenosine antagonism, an increase or super normal levels of those neurotransmitters. And it seems to restore, in my opinion and our research, a lot of the fatigue induced deficits. So, it's certainly that we see in exercise performance. And I'm also including energy depletion in that. We've got some work that we should be publishing soon where we've made people ... well, they were hypoglycemic because their blood glucose levels were below four. And the amount of central fatigue we could gauge in our kind of realistic power dime was no different with a placebo ... sorry, with being well fed regularly with sort of normal carbohydrate intake recommendations during exercise and being depleted of sugar. So, that's no breakfast and then three hours of intense exercise and things like that. So, I think, the imbalance in neurochemistry is the biggest cause of this and targeted drugs that are illegal and don't damage you or against the context of ... or the spirit of fair play and things like that are the best way to do that. And going on from that, I think the brain is quite metabolically robust when it comes to its energy status. But we have this weakness of failure in neurotransmission in areas of the brain that work very hard during exercise in particular. I always default back to exercise because it's one of the most demanding things, certainly in terms of signaling the brain can do, sort of generate a huge amount of electricity to recruit a huge amount of muscle and you can measure that increase in metabolic rate quite easily across the brain by looking at blood going in and out. You can sometimes you take that withhold cognitive work, but the areas of the brain involved in those processes are so much smaller and don't have such fluctuating energy requirements that from an energetic

point of view, they're less easily perturbed or at least they sit there dumb and happy at a similar energy requirement for most of the day. Whereas you can of course, as most of your listeners will know, just getting up out of your chair has a profound change to your whole-body metabolism and in particular your brain.

DANNY LENNON: So when we consider this huge turnover and these potential changes in neurotransmitters that are happening and this attempt to try and at least mitigate some of that through a stimulant like caffeine, at the risk of this being too broad of a question with something like caffeine, for example, and this may be difficult to quantify, just to what degree can we mitigate some of those changes going on and how much of a rescuing effect can we possibly have on some of these induced fatigue states?

NICK GANT: Yeah. That's a really good question. You've given me a hard one to try and answer, you know, it's very individual with caffeine, number of factors that listeners might be familiar with in terms of how mature your central nervous system is, how much you habitually take in your diet and all the rest of it. But generally, our research shows that with, let's take that three-hour paradigm we're quite familiar with the prolonged exercise. We measure a separate motor system than the skeleton motor system. We measure the ocular motor system because then we don't have to worry about the peripheral fatigue in those muscles because the muscles in your eye credibly robust to fatigue, they're moving thousands of times a day and they weren't exercise during the cycling anyway. When we measure that motor system, which does get impaired indirectly by exercising the muscle, which is one of the big findings in the study we published in Nature Scientific Reports, you fatigue the legs, the eyes slow down because those two motor systems can ... the fatigue can spread and it may be ubiquitous phenomenon or at least the neurotransmission failure may spread across the brain. With those types of studies, a moderate dose of caffeine, I'm going

to say we did four or five milligrams per kilogram body weight in the middle, so at 90 minutes, completely reversed that. And when we take it before exercise, obviously we get ... so we get eye movements and oculomotor system that's amped up. It's even more active than before. So, that's one of the things that leads me to believe at least the central component of fatigue is very much linked to those neurotransmission systems and decreased tone in them. Of course, as soon as we bring the peripheral systems into it, we'll see probably a far greater proportion of the fatigue, say coming from maybe depletion in the muscle, liver, and all of the other factors that other people have measured far more than we have. And so, we think, probably about 10% of that probably lies within the brain. 10%, as you'll know, is well within the margin of being first or last in any kind of elite sports. So, this is why these people who seem to, and again, there's not much data to support this, be highly resistant to perturbation of those systems - that bloody minded, crazy attitude to sport, seem to do really well.

DANNY LENNON: Yeah. When we think of like the general class of stimulants outside of caffeine, are they all having effects via the same mechanism? And if so, what type of differences do we see from compound to compound?

NICK GANT: Yeah. By and large. So, if we're talking about the things that are used socially, the same things, they're generally plant based caffeines of one type or another, coming from different plants, but by and large, the adenosine antagonism is the ... seems to always be the main mechanism. There are other things that we caught, we use, and we test in this lab. I do some commercial work with people looking for the next big brain food, psychotropics and normally some kind of weird and wonderful extract. But their effects are usually subtle compared to the stimulant. So, they're usually within the same family, but they often can differ with some plants in terms of the pharmacokinetic response. So, this is

quite important because it leads to the time at which the peak level occurs within the blood and the central nervous system, but also how quickly they're metabolizing expelled from the body. Now there's a whole number of other factors that are probably more important than that - how healthy and big your liver is. And there are some factors now involved in that that can be tested. Genetically and commercially, those tests are available. But that's the category we tend to use. In terms of the area of stimulants that are used in ... for psychiatric medicines, they tend to ... we've published some studies with methylphenidate, with Ritalin and with other SSRI antidepressants that have either an anti-smoke ... sorry, smoking cessation, medicine, bupropion. They're all banned in sport. But they, at least in our studies, they seem to target the ... well, certainly the jewel one's target noradrenaline and dopamine in a similar way to caffeine does naturally, and of course those things that are banned for other reasons. There's important criteria why you wouldn't take those. And of course, what they do in somebody who's depressed, for example, is they reset that natural balance in those neurotransmitters that's lacking in them, at least for certain people who get depressed. Obviously, they don't work for people who have no specific reason for the depression that's chronic. But they're doing the same thing. So, we're, and of course we being here within the Center for Brain Research, we involve psychologists and neuropsychologists and sometimes anesthetists in our work when we're doing serious stuff. So, we're able to look at things in a little bit more extreme than most people can in that field.

DANNY LENNON: 100%. I do want to move on to creatine because of a lot of questions in this area. And I think what you've done is particularly fascinating in highlighting at least that the role of creatine traditionally for a lot of people who are sports nutritionist as well-known it's impact on performance per se. But at least, and this has been known for a while, but at least in the last

couple of years become more and more aware of the potential impacts on cognitive function, even mitigation of neurodegenerative disease and some other things it's been hypothesized to work with. From that aspect of the brain specifically, where did this kind of first link come with creatine and why is it that it can potentially have effects at the brain?

NICK GANT: Yeah. So, I mean we publish some ... we started publishing this a few years ago now and there's quite a nice study we put in the Journal of Neuroscience where we bought all of this together. Of course, my background in exercise nutrition and really familiar with the peripheral effects and muscle of creatine when I came here, some other colleagues ... and we have a brain bank here where Kiwis donate their brains when they die, and they'd started staining for the creatine transporter. Now when you find a tissue in the body that has high and fluctuating energy requirements, you see quite a lot of creatine transporter. Obviously, the muscles are a big example of that, needs to draw the creatine in to buffer both temporally and spatially, the energy requirements of high intensity stuff that glycolysis and everything else it doesn't catch up with very quickly. And when they stay in these brains, they saw extremely high levels in the motor system. In motor cortex, we'd say M1 and the highest, in fact in cerebellum, which is important area at the bottom of your brain for controlling movement. So clearly the movement areas of the brain have the highest energy and fluctuating energy requirements because they require creatine. Other areas that do the same kind of task all day long, auditory cortex for example, doesn't have as big and as fluctuating ... doesn't have as much creatine transporter. So, we wanted to develop a paradigm where we could actually measure that creatine in the same way we would in muscle to figure out whether that was really happening. So, we developed a magnetic resonance spectroscopy protocol in the magnet up here, in the MR machine up here, where we supplemented people with our standard sporting type loading protocols. So, 20

grams of creatine per day in five-gram doses for a week. And we measured them before and after and we saw, and we use other techniques as well, like we have a brain mimicking phantom with different standards for creatine, so we can work out the actual concentration increase. And when we do that, we saw that ... oh, there's a few other things we do. I probably should mention for some of your listeners. We make them perform some movements and we work out exactly what areas of the brain are active in moving their muscles. This is something that we see lacking all the time in nutritional neuroscience. We see people saying, this is what I did with a particular food or diet. These areas of the brain have been measured when this has been done in MRT and therefore they're implicated in this, but they've never performed the task they were doing in MRI. One thing you quickly realize is that their activation networks that you measure when you're resting, lying in there doing nothing, are completely different to when you're doing the functional tasks. So, we always have functional tasks involved in our paradigm. So, in this case, they produce a force. With FMRI, we look at areas of the brain that are lighting up. Then we position a virtual cube inside the brain, inside that area. And we look at how much creatine increases in that area after the supplementation. And it's a substantial amount that we can easily quantify. We did a bit of a back of the envelope calculations on this and it's ... we think it's around a millimole per liter increase, which ... well, we know it's around a millimole per liter increase, but the calculations showed us that that would probably be enough energy to cover all signaling activity for a few seconds within the brain. Now that ties in nicely to what creatine supplementation does in muscle. It can cover all ATP synthesis requirements rapidly for around that period of time before anaerobic glycolysis gets kicking going and when free ATPs is diminished. So, that gave us ... and we published those data and we thought there is probably something in this if it's that much energy. So, we wanted to really smash people with a protocol. So, exercise is not going to do that. As I said, my

view is that exit ... that the fundamental brain function is quite, the brain is very metabolic flexible, and it's quite well adapted to using different energy sources during exercise. So, we use a hypoxia protocol. So rather than taking away the fuel, we take away the fire it burns in. And so, we expose people in the lab, typically in those studies to 10% oxygen. So that's half what you have in the room here for around 90 minutes. And we measure a rafter test including your psychological ones so that you and I, if we didn't have an underlying concussion, that's something else we've looked at, but we'd probably tolerate that reasonably well. People tend not to tolerate it and pass out if they are anemic or something like that. But typically, people can tolerate that. And we can do an hour and a half's worth of neurocognitive testing. And most of our people are highly intelligent university students. We take them down to a level of cognitive function where the neuropsychological tests would suggest they'd fail to cope with the normal demands of independent living, that sort of thing. So, it's a real smash over the head. But what that then reveals is all of the deficits that can be addressed by the creatine. And what we find is that a range of cognitive functions, attention and memory are ones of them, and we know those areas are sometimes not that well perfused. And the overall neurocognitive index score that we get from these clinical tests improved significantly. So, that gives us a good idea when combined with the brain imaging, that there's been a real effect of the creatine on normal people who are otherwise stressed and fatigued. We also did some neurophysiology in those series of studies. So, we stimulated the brain electromagnetically and looked at excitability of the whole call to come out to pathway. So, we asked people to produce force with their arm and we saw a significant ... what we've proposed is a beneficial effect on the excitability of the motor cortex. So, there's a clear neurophysiological, neuro-psychological and neuroimaging basis for suggesting that creatine supplementation has a neural effect as well. And what I think has been

happening for years in this field is people have been measuring maybe one rep max or multiple repetitions in sport. And some of that effect at least has come from a central nervous system. And of course, they've indirectly suggested it was muscle by measuring the amount that muscles improve, the brain has improved as well. And other tissues have the receptors in as well. Liver to some extent that really know what it's doing there. Sperm of course, they've got to swim under water, holding their breath for a long time to get a lot of creatine. The other thing that drives me to carry on using creatine compared to some of the other drugs we use, particularly in the clinical areas, is that it's reasonably safe. No collection of nephrologists or renal physicians have ever come up with a statement suggesting that it isn't, but it's well known that if you have an impairment in renal function, you shouldn't be taking it. We had a scandal here a couple of years ago where it was suggested in the U.K. media, I think it was The Independent, that Jonah Lomu who had an underlying kidney condition was killed by taking creatine in the '90s. Or, I know, and I've heard from his team doctor here when he was at Counties Medical and the all blacks that that categorically didn't occur. He was ... but there's still the worry out there and some of your listeners may have taken it and suspected they've had some kind of kidney pain. Of course, when you look at the amount of actual substance that the kidneys are having to filter per day, when you're on a loading cycle, it's a lot. It's within the realms of what normal kidneys can deal with, but not if you had an underlying condition. So, we want to move on and we are now with different clinical populations because as you mentioned prior to our work, there was a lot of smaller studies on different clinical populations that have conditions that are defined by either neural biogenesis of energy problems or some other kind of problem with them, usually with the mitochondria, so they have impaired production glycolytic or oxidative metabolism in some way, and the creatine seems to have to help restore some of

their function. There's also a couple of studies showing increased cognitive function in vegetarians, which not particularly well controlled. And of course, regular listeners of your podcast will know that we never make any inferences from just one study. But of course, there's no creatine in a vegan diet and it has to come mainly from eating the muscle tissues or the brain if you wish of other animals.

DANNY LENNON: Right. And at least mechanistically that makes some type of sense because from a sports nutrition side, most people are kind of aware that you do see probably more pronounced impacts of creatine supplementation. Someone who already has low muscle stores of that comparative to the relatively high. Just to tie back to previously what you were saying and correct me if I'm wrong on any of this, we've talked about disability. For once, someone has put on some creatine for a certain period of time. It's essentially because of that increased energy availability that at the brain is, it can have impacts at least acutely on some of these cognitive function tests. How does that relate to potential chronic long-term effects at the brain when someone's considering a long-term cognitive health or neurodegeneration? Do we see or where do you feel the state of literature is in relation to creatine on that aspect? And does that differ to the benefits that you just talked about or is that just a continuation of those, if that makes sense?

NICK GANT: Yeah. No, that's a good question. You know, everything you've said is correct. Of course, I need to start my answer with saying we don't know because it hasn't been those chronic studies. And of course, the people that first started taking creatine in the mid-nineties are just getting to the age now ... they were taking it, the elite athletes in Boston Olympics is where it boomed. They're getting to the age now where they might see whether a career of a long period of taking this supplement has helped with their brain function. But I suspect that when there are very high levels systemically the brain will have

a super elevated level of creatine, which is then always available for times where when there is either a rapid and severe requirement for energetic function in the brain, but also where it might be mildly compromised. So, one of the big degenerative things that happens is we don't blow the cobwebs out as well in the brain. We have lower levels of perfusion and important places like the hippocampus where memory goes and all the rest of it. I think there's a role for creatine in a backup substrate that does not require the profusion to be there in such high high levels and things like that. But it's all highly speculative. I think there is definitely a role ... and colleagues starting to explore this, as it being there as a prophylactic for any serious neurological problem you may have. So, for example, it's a stroke represents an extreme ischemic event in the brain. Typically the type of stroke that most people get in old age at least, and therefore there's a time before you can have either clot busting drugs or the brain sorts itself out, that there's a lot of tissue dying and it's been shown in the mouse model of both stroke and of ... we'll stick with stroke, that creatine supplementation beforehand reduces the size of the infarct and improves the recovery of the animal. So, you know, I'd see a day where it's taken prophylactically for people in those sorts of situations. And we've done some specific work here with a mild traumatic brain injury and because it's got the link with sports, it's really important for most people and mild traumatic brain injuries, as most of your listeners will know, one of the things that so many sports people in contact fighting, all kinds of sports, even noncontact sports with large changes in velocity and things, expose their brains too. And an area where we think the research, we're about to publish hopefully shows ... we'll be some of the first to show that creatine supplementation has a direct benefit in that subacute period. So, maybe I go on to -

DANNY LENNON: Yeah. I was ... hundred percent wanted to ask about this because as people know, I have a keen interest in this area and I find particularly even

in mainstream sports news now, I think it's becoming more and more well-established of just how massive a problem this is for a number of sports, particularly in combat sports, which I talk about quite a bit. And so, this area of where potentially we can kind of mitigate some of that is extremely interesting. Can you maybe just expand on what is it about a concussion or a traumatic brain injury that means that this rescue of energy availability by creatine would be effective? What is actually happening with these TBAs?

NICK GANT: Yeah, sure. So, when you get the concussion, of course most people rapidly recover within the first couple of weeks, but those that are mild and don't, are typically associated with a substantial amount of organic damage. And certainly, in the sub-acute period, most of the problems associated with that organic damage beyond that, all bets are off because there's post-concussion syndrome and highly complex psychological disorders that people develop beyond that. But most people would fall into that category. So, some of the neurons are shared or damaged and are torn by the impact. Let's say it's an impact. Even heading a football too hard, which people never really consider to be a force like that. And that's what most people focus on. So, there's a neuron or damage. There's some rewiring needed for the signaling to work again. But more importantly than that, those neurons are ripped away from their support network of glial cells. So, neurons, most parts of the brain, they're only really less than a quarter of the types of cells that are in the brain. The glial used to be just thought of as connective tissue or filler. These cells connect those neurons to the blood vessels. They store energy. Astrocytes store meaningful amounts of glycogen. Nobody in sport really talks about that glycogen store. I do. And I think we should more. So, they get torn ... the neurons may move and get torn away from that. So, they're torn away from something that's connected to the vessel that has glycogen, that's role is produced the substrate that the neuron uses. So, this

damage causes a window of metabolic vulnerability. So, during that time people are mostly symptomatic. If they tried to do too much cognitive work, they develop stress, headaches, fatigue. If they tried to do physical work, they typically develop a headache or they have some coordination problems, things like that. And therefore, the standard way of treating concussions like that is cognitive and physical rest. That's mainly what you do. And that's terrible for somebody because they want to get on and recover. So, we're looking for a way that could support active recovery. So, what the creatine does, of course, is provide a substrate that's there in the neuron, does not require oxygen, and does not produce any waste product that needs to be cleared into the vasculature in any way. So, it's really a rescue in the same way really, I've just described for stroke really of having creatine available to aid the recovery. So, it may be important at the initial period of the impact to have it there. We haven't managed to do an RCT yet where we supplement people prophylactically, but we've looked at people in the subacute phase. So, what we do with them is the hypoxia. We can't actually expose them to the levels of hypoxia we do with healthy people. They develop to many symptoms and often become quite upset and fatigued. So that actually shows you that their brains are far weaker than ours. In fact, one of my colleagues has shown that even 10 years after a concussion with hypoxia you can reveal those underlying symptoms. So, what's happening in the brain is rewiring. There's some neuroplastic effect after the concussion that's reestablishing the networks that were damaged. But what we think happens to those networks, it's a bit of a quick and easy, quick and dirty job that's reasonably fragile. And what I mean by fragile is it does the job. But most of the adaptation and resynthesis of everything that needs to occur is probably based around those glial tissue takes a bit longer. So, things work again, but immediately when you stress them energetically, which you can do through severe cognitive works or very physical work or in our case hypoxia that affect

deficits come straight to the surface again reveals that weakness and the person's in a lot of trouble. So, I mean, good physicians that work in this area, sports medicine doctors test their concussion patients on a treadmill test to see when the symptoms ... when they become symptomatic cause it's clear you need to have the brain stressed energetically for some of these things to occur. So, in that study we found that the cognitive functions I mentioned earlier on ... I should add a bit more detail. This is a crossover randomized control design. So, there's this five week wash out period between having creatine or the placebo. So, there's a lot of spontaneous recovery occurring in their function anyway, but that spontaneous recovery certainly in the neurocognitive testing is much better when there was creatine present. So, we think it's ... and of course I'm not a dietician who can give advice to anyone, but we think it's a reasonably safe, commercially available therapeutic strategy you can do outside of medical supervision that could be applied to people. To be honest with you, a lot of people I speak with who are in the most prone sports, they're typically running at things quite quickly. A lot of them are taking creatine because they're running quite quickly. And so there might be some degree of protection already there. I don't know what the ideal dose is. Like I say, we've just started this really, so we've used the dose that we know has been tried and tested for loading in muscle. The threshold for maximum uptake rates may be lower in brain. It may persist for longer. You may not need as big a dose. It will be certainly better for clinical populations if it works out that we don't need a bigger dose because they're already taking enough pills for their other comorbidities and you know, unless if you try to ingest creatine in any other way, but mixing it with water, it amounts to a lot of capsules or a lot of compressed tablets per day. And you feel like a real junkie whilst you're doing it.

DANNY LENNON: Right. Yeah. I think there's a lot of interesting aspects that we can get into there. So, it's this

essentially being able to provide that energy at the time where it's needed, where the brain isn't able to do it effectively or as it normally would. We will circle back to creatine but just while we're on that, because it reminds me of this other area that's been hypothesized in relation to TBIs from a nutritional standpoint, has been the provision of ketones to try and do some of the similar things that we've just talked about with creatine. Essentially being able to provide the energy substrate at a time where we know there's going to be the shortfall because of that brain trauma. What was your current position and perspective on the hypothesis of ketones either indulges me from a ketogenic diet or exogenous ketone supplementation for some of this TBI mitigation?

NICK GANT: Yes. So, I'm glad you mentioned ketones because it's a real hot topic. But my position would be, we don't know yet, but of course there is probably 99% of people promoting certainly endogenous ketosis who make those claims on voice and opinion. There's probably stronger than the literature would suggest. So, we perhaps need to step back a bit and think about key tones, ketosis and brain function. It's a really interesting area. Some of the theories you suggested, some are related to how the ketones themselves change the concentrations of certain neurotransmitters like gaba and glutamate and some advantages around having a different neurological profile during that time. And some are on the alternative provision of energy when there's a reduced supply from say systemic glucose being available. That's an interesting one. Let me talk about the brains of metabolic flexibility because most people classically trained, they tend to think about muscle and we talk, we think about fat and carbohydrate oxidation rates and all the rest of it. The brain is very different. As most of your listeners will know, there's not high rates of fatty acid oxidation in the brain. And there's not high rates pass through the blood brain barrier through and there's an enzymatic barrier and another thing. So, a lot of the textbooks would say the

brain is exclusively reliant on the concentration of glucose in the blood. That's not entirely that accurate. And I think normally when we think about carbohydrates supplementation, particularly during exercise, it's one of the third or fourth benefits that gets rattled off for sports drinks. So, you have maintenance of a sparing liver glycogen, maintenance of high rates of carbohydrate oxidation. Then somewhere below that you have improved cognitive and brain function through maintenance of blood glucose. In terms of cognitive function, you can actually become quite hyperglycemia. Your function won't change too much. You'll feel bad and there are a number of other reasons you're conditioned to and sensitive to glucose. But we get people quite hyperglycemic. Rats can go down to two, one millimoles per liter in glucose in the blood until their brain function start to compromise and the brain's quite metabolically robust. Something else that happens during exercise, people don't think about as much, blood lactate is some are saying now preferred source of fuel for neurons. So, the brain is a net producer of lactate, but during exercise, it starts consuming it and it starts consuming it and that lactic never goes back into the blood. It's oxidized in the neurons. In fact, those astroglia cells I mentioned earlier on that store glycogen, they turn it into lactate, not ... it doesn't enter the neurons as glucose in any way and the neurons turn down and they oxidize that. And lactate is also thought to be what we call a volume transmitter within the brain in that it has an important signaling. This is important when we talk about ketosis, particularly with exercise science because one of the markers people use that either a diet is producing lower metabolic stress during exercise or a training regimen has, is lower lactate production that they've measured systemically. Now, nobody knows whether that was quite helpful for the brain. It might be some exquisite mechanism whereby when your muscles are working really hard beyond what oxidative metabolism can support, that extra lactate has been scooped up by the brain because it is working very hard to

drive those muscles. So, of course when we talk about glucose and lactate, ultimately, they both come from carbohydrate sources of energy and the lactate perfuses ... well, it's really pushed into the brain by the concentration that's in the blood in the same way that ketones are. So, ketones appear, and they're oxidized by the neurons. And that process isn't quite as tightly governed or controlled in terms of the absorption, the transporters. We need gluc one and all these other things as carbohydrate and therefore it's available to be oxidized. And it could be the same principle as the creatine. You've got an alternative fuel source that's available there and we don't know yet. When I say alternative, I need to be quite guarded because we don't also know whether there's some competitive inhibition of other fuels when it's around. So, if the mitochondria are busy dealing with that, all those competitive down regulations of PDH or something, the brain loses some metabolic flexibility in the glucose. And one thing that I propose, or I feel I'm pretty sure about is that glucose metabolism within the brain, or at least reasonable levels of carbohydrate endogenously in the brain are required at that level where you know, you need to achieve your peak performance or optimal performance. I think it's the same as muscle. So, let's say you're on a carbohydrate elimination diet, most people seem to be able to function perfectly well cognitively on that diet. There's no long-term ... or we have long term data from epileptics actually. So, my view is that whatever the liver is producing in terms of the glucose and the ketones which seem to track ... the ketone bodies produced by the liver seem to track really well with the brains requirement as you enter deeper into ketosis. But we don't ... but those people aren't all elite performers in whichever field you might be in and cognitively elite performer or an athlete. And of course, something we know from ketones and even the biggest kito diet zealot would probably agree now that peak power outputs are not often obtained with ketogenic diets. At least not unless glucose is reintroduced in this time for

those enzymes to be ... to regulate. The same may occur in the brain. And so, the brain may have a peak power output problem. We know excitability in the motor system is reduced when we deplete carbohydrates or during prolonged exercise. And we know from some of our work where we reintroduce carbohydrates through drinking that excitability increases again. So, if we have this excitation and inhibition problem, sorry, a need for huge rates of flux through glycolytic pathways, that may be something that ketones don't support either when supplemented or in the endogenous form through fasting or ketogenic diets. And that might be important for some people. But I get a feeling it's important for such a small percentage of elite performers that they're not the kind of people who would be getting injured and other things. But again, I think there's far too many people promoting, manufacturing and all the rest of it with ketone supplements. So, I'd like to be clear that there's a small amount ... or, well, a lot of it's based around one pathology, which isn't related to what we were talking about, but epilepsy. Kito people make huge inferences from the epilepsy field. Having a ketogenic diet or carbohydrate elimination is a really effective strategy for reducing the occurrence and severity of these tonic clonic seizures. And regardless of the mechanism of either injury or congenital problem that's led to epilepsy, what happens is hyper excitability in the branding. We've just been talking about optimal excitability. They have large networks of neurons that are very close to rapidly depolarizing. So, they're about to fire off. And for some reason, they can do that without warning or any particular ... well, there may be a particular trigger. Now, that's reduced. There’re people who've been on ketogenic diets for most of their life. I think in the 1900s it was first proposed. Some suggest, as I mentioned before, that there's something about the ketones. It might alter the balance of some neurochemicals. I think it comes down to, again, a peak power output problem. So, a tonic clonic seizure is incredibly violent, physical and energy

demanding event. You know, afterwards, people ... muscle soreness. You break bones having one of these things. So, it's akin to an extremely high-power output athletic endeavor. I think we have widespread glycogen and carbohydrate depletion within the brain with that type of diet. And therefore, when the brain really needs to kick off with something like that, it doesn't have ... the neurons are further from their potential to depolarize because they don't have the energy available. Either the lower carbohydrate status keeps them further from that point or when they have the trigger that deep polarization doesn't spread as far because of the lack of energy that's available. So again, all of these things are hypothesis, but compared to the weird and wonderful things I hear some people talking about that one seems to make more sense. And again, I would just like to reiterate, I think people who are on prolonged periods of intermittent fasting or ketogenic diets don't seem to do too badly cognitively. You certainly can't measure any impairment. And in fact, there's a lot of reports typically now associated with intermittent fasting that people feel sharper and less fuzzy during the fast and then when they break it or when they get back on the carbs, in the case of the keto diets, they don't perform as well cognitively. And it might be that those individuals are just a bit more sensitive to those rapid excursions in insulin and glucose that most people eating regularly throughout the day have all day long. Look in that postprandial period, there's a huge cascade of neuroendocrine signaling happening. Things we can measure, things we can't measure yet. It seems possible that some people have disruptions perhaps in key transmitters that happen when they eat. And it's certainly the case in the breakfast literature in my opinion, that when you have rapid excursions in glucose and insulin after certain types of high-glycemic loads from breakfast that there can be periods where that happens. Of course, we know with rebound and reactive hypoglycemia, we see the cognitive effects of that quite easily. And just ask someone who suffers from that. So, my answer

to all these questions is it's very complex, but you should be very careful if you hear someone making some outrageous or quite strong claims in any of this area. But you should also, particularly if you suffer from one of these disorders, carefully watch the scientific literature coming out in the area of brain supplements that improve the brain's ability to store energy. Creatine we talked about. Brain supplements that can regulate the perfusion within the brain to make that improved. Beet root and dietary nitrates of one which is in that area and one we haven't talked about yet, but ones that are able to mitigate some of the inflammation. So, I've mentioned that the brain has an energy deficit caused in the case of concussion by the organic damage occur to the brain. That damage is associated with inflammation and that inflammation, at least most of it, the same with muscle, appears to be counterproductive for function. And the area of reducing agents, antioxidants seems to be a good area to explore in the brain field, measuring inflammation quantitatively within the brain is very difficult. But certainly, combating inflammation and the energy deficit or the energy crisis after a brain injury or any other kind of neurological insult seems to be two of the biggest hot topics for the future.

DANNY LENNON: Right. So just on that, if inflammation is happening, maybe even localized at the brain and that can be difficult to measure, would a kind of systemic marker like C-reactive protein, tell us anything of like if we see that's elevated, trying to have a nutritional intervention that brings that down, would that tell us anything about what we're potentially doing at the site of the brain or is it kind of like guesswork that maybe it makes sense that it would probably have an effect?

NICK GANT: Yeah. That's a hard question, Danny. So, I guess ... we have markers that tell us certainly how much the brain has been compromised is what's leaking out and what's now getting in. And we have some techniques that can tell us ... imaging

techniques when there's been severe damage and a lot of it doesn't show up. But in terms of knowing how much of that inflammation we need to address with some kind of reducing agent, we don't know. Look, I think some of it is useful. Of course, if you reduce the inflammatory response, you may reduce some of the adaptation that occurs as well. But an inflammation within the brain, typically chronically is known to be very bad for brain function as anybody knows who's studied inflammation. So, we don't know. But those markers that you can pick out from the gutter, the blood ... the gutter really is selective and what comes in and out of the brain and what we can measure in the blood are probably going to be what signals the work that's done in that area.

DANNY LENNON: Sure. I just wanted to clarify one thing in case people had a question because I think you've already mentioned it, but just to kind of clarify. You've talked about this energy deficit that can happen at the brain and therefore that's why we've seen things like creatine work. That's why there's a hypothesis that an exogenous source like ketones can potentially do something. And I know you've touched on ... but just to hammer home for people, why is it that we can't just do that with glucose for example? And we know the brain uses that, just provide more of it. And would that not do the same thing as an exogenous ketone or creatine?

NICK GANT: Oxidative glycolysis or the production of lactate from astrocytes is probably impaired in some way by the damage that occurs to the tissue structurally. So, these glial cells I mentioned, there's far more of them than neurons. They are required to be the link between the blood supplying or the supply of exogenous or endogenous glucose. And the neuron, the site where it needs to be used. Other things can ... and that's an active transport mechanism. Other things are a little bit more passive, including glucose, which seems to basically be pushed into the brain depending on how the blood and the ketone bodies. So, the concentrations of those

close to the neurons where they can be taken in an oxidized are probably going to be higher when there's a severe perturbation to the structural function of what we might call the brains' glucose supply system. If we use the exact terms, it's too long winded. The place where the glucose is stored, so the glucose is stored predominantly in those other cells. So, if you think about muscle, it's stored in the muscle. It's not stored in the muscles. It's stored in a helper cell, releases lactate and then diffuses into the neuron. The lactate does. It's actually transporting to the MTC mechanisms. But if that's absent, then it's an area where ketones could be used. But look, if you're thinking about supplementation for ketones to provide that alternative in terms of how we're involved, all bets are off in terms of what might happen because the body's not evolved in situation where it has extremely high levels of ketones and glucose. Of course, starvation ... most people know who've tried to get into ketosis takes a few days if not longer, and you easily come back out of it again. I don't think the brain is involved in an environment where it has high levels of ketones. It's an artificial situation and other energy substrates that aren't depleted. That might be this magic bullet the ketone researchers are talking about for enhancing performance. But it also might be restrictive or reduce metabolic flexibility for a glucose source energy. So, we really don't know. So, it would be very reckless to say to someone who is liable to have a brain injury or suffering from one take ketone bodies ... sorry, take ketone salts or esters or generate your own through a ketogenic diet. If you were trying a ketogenic diet for the first time after a brain injury, that might could be catastrophic if the, you know, in terms of all the other things and having the keto flu on top of all the other problems you have at that time. But I'm sure there are a lot of, you know, researchers and former guests of yours that might suggest it would do no harm. So, the only harm I think it could do, given that we've all done ketosis before, it's perfectly natural thing. We all did it as infants. And there's some

discussion as to whether we've kept all of that ability since infancy or some brain areas have lost their ability to do it. And in rat models, some brain areas seem to have lost it beyond infancy. It seems sensible that we would have retained it for periods of starvation and retain optimal function with it because there's no point needing to go out and hunt and gather food if ketosis doesn't provide you enough energy to do that. But there's no evidence that high levels of it in combination with high levels of glucose are being available, creatine even more bizarrely and artificially and everything else. I really feel that the brain is highly reliant on glucose-based source of energy for a lot of things. And you see that in the fact that those glycogen stores I mentioned in astrocytes become depleted after exercise, certainly in rodents and can be super compensated afterwards in the same way that muscle camp. Super compensation is some kind of adaptation that's occurring acutely probably to prepare for the next bout of extremely high and fluctuating energy requirements to the brain. I think we all see that in the reductions in, as I keep saying peak power issue and high intensity stuff that tends to happen with people who aren't metabolically flexible. You know, having ketones available in sugar could also be the ultimate in metabolic flexibility. We just don't know yet.

DANNY LENNON: Right. And that's the thing I think with biology that we often see, there's almost no case where you get all upsides pretty key if you start playing around with this stuff. Like you say, this artificial situation where you have, again, we couldn't naturally get to a place where you have these elevated ketones as well as all these other energy substrates. And so very rarely we find we can have like the best of all worlds. And in the case of biology there's always seems to be a down regulation of this or some sort of side effect somewhere along the chain.

NICK GANT: Yeah. That's a really good way of summarizing and listeners will probably take that away as the

main message. You pay something and you rob something else to do it. Yeah.

DANNY LENNON: Yeah. Two quick questions to finish off cause we're close to time here that I wanted to get your thoughts on. One was the potential impact of nicotine on cognitive function and maybe other related areas at the brain. I've only seen a couple of papers, I think I mentioned to you that have kind of looked at this kind of link between nicotine and the acutely impacting cognitive function. Anecdotally some people will tend to use nicotine for certain work-based tasks to be more productive and so on. What is your current perspective on any of that stuff? Is there something to that idea that nicotine can acutely impact cognitive function?

NICK GANT: Yes. I think it probably can. I think that the evidence and I think people that are addicted to nicotine will tell you this, at least they have a strong withdrawal ... replacing a lot of withdrawal symptoms, certainly, but physical and mental performance seems to be capable of being improved by nicotine substantially. The problem is we would never want to recommend it and therefore my opinion, even research it because it's so highly addictive. You know, you could in many ways be ruining the life of somebody through addiction by promoting it as a nootropic or performance enhancing substance. So, we have thought here about quantifying some of those effects, but we don't think it's an ethical or moral thing to do. Firstly, exposing people to something that's highly addictive. Remember the addiction now is probably the most important thing because you can ingest nicotine to the body without the worry of all of the cosmogenic stuff that comes with the tobacco. However, some of the things that are oxidized in even a vapor are carcinogenic in high quantities. Of course, you could use a patch for a low dose or whatever. But exposing to something that could ruin their life through a chronic addiction is not something we want to do. So, I don't want to say anything even if it’s to people who are already addicted to

nicotine and just want to optimize the way they take it to enhance performance. It's akin to caffeine, lower sort of levels of dependency in that if you take caffeine, you can optimize the way you take it, so you get the most beneficial performance effect by reducing its consumption at certain times and all the rest of it. But I don't want to even say we endorse or think too much about doing it now because of that.

DANNY LENNON: Right. Sure. And the final thing that I wanted to bring up, and we probably can't do this most much justice in the smaller time we have left. And it could be probably a whole podcast episode in itself, but it'd be remiss of me not to bring up carbohydrate mouth rinsing and potential mechanisms behind that because of the work that you've done. So again, to put you on the spot, if we were to kind of pull this down to some kind of key points that you want to make people aware of and they can maybe go look into a bit more, what are some of the important work that you've uncovered on the mechanisms behind carbohydrate mouth rinsing and its potential for performance?

NICK GANT: Yes. So, maybe we can put a couple of papers in the episode notes. A couple we've published with the neuroscience. My aim always been to fill in some of the mechanistic information. Everybody seems to have tested it in their pet sport to see if it works or not, but very little is given to working out the mechanism behind it. So, we've done a few studies here. We've stimulated the brain electromagnetically to see whether the quarter motor track becomes more excitable. So, the areas of the brain that control movement, are they really enhanced in some way the moment at least when carbohydrate enters the mouth? And they are substantially. And the force production that accompanies them is the same as when glucose then appears in the blood peripherally 10 minutes later. But you don't get the same neural effect. So, we think it's a unique signaling mechanism. It comes through these powerful projections from the olfaction and gestation we have in the

mouth. We've also done it within the brain imaging environment in a different way to others have in that we've actually measured force production and got the individuals to produce force whilst we rinse through the mouth a carbohydrate containing a noncarbohydrate tainting similar tasting solutions. And we've isolated the areas that are involved in producing force and shown that they are more active when carbohydrate is in the mouth first placebo. We've also shown, interestingly, we don't have the time to get into it in detail, but visual areas of the brain are more active when they're looking at exactly the same symbol on a screen. So, there's a heightening of the senses as well. So, we filled in some of the gaps to show that it is a brain-based effect that influences the motor system immediately, which other studies haven't. But we're also starting to rethink our hypothesis behind this, which has always been traditionally that perhaps the brain is sensing glucose at a time where you're using a lot of it and it's becoming depleted and then it gets a signal that help is on the way when in ten minutes time I'm going to get glucose, therefore I can release the safety break I've put on the voluntary activity because I'm going to be having more glucose available to do that. I don't think that's probably the case now because in our FMRI studies we see no degradation in the activity we see in subsequent rinses. So, if there's that complex behavior going on, you would think that on the fifth time the brain has already had that signal. And where the glucose is appearing, it's diminished. So, I think its probably part of a more ancient evolutionary mechanism that rewards us for finding carbohydrate that was probably a highly prized nutrient when we were looking, scurrying around looking for it. And it promotes what you're doing to keep on doing what you're doing. So, the motor system is more active. The senses are heightened. So, as you're scurrying around trying to find more of it, you're better at doing that. Okay. And that's quite a wide-ranging hypothesis. But tying it back to the mouth rinse in literature, it's not just the case that this

happens. I mean the mouth is a hugely powerful sensory organ. And if you have things in your mouth that you're conditioned to like or you drink during sports for example, there's going to be a classically conditioned reflex to that ... not a reflex, but a response to that that makes you perform better. So, you put anything that tastes nice in your mouth, in my opinion, you could detect some effect and maybe effects that are beneficial when there's something noxious in your mouth. Some of these things that are highly stringent, like the menthol, that's the equivalent of the coach slapping the strength athlete round the face. The sensory operators in our mouth has a direct main line into the limbic system. These neurons have one sign up. That means that the signal gets there very rapidly and quite forcefully and has no really way of being influenced by anything else. Whereas you think we look at something that we think is pleasant visually thousands of signups are a long process that can be highly influenced by other things that are happening in our lives. So, listeners should really read those papers because I think that ... I'm convinced now that we've uncovered the neural origins of it, that it's a real thing, but I'm not convinced it's just constrained to a carbohydrate or in this case, maltodextrin, glucose, polymer taste. It's probably lots of other things involved.

DANNY LENNON: Yeah. 100% for everyone listening, we'll of course link up to all those papers and previous ones that we've talked about today. So, just to round this out, Nick, for people who want to either find you on social media or find out more information about the lab or publications that's going on, where's the best place on the Internet for them to go check that out?

NICK GANT: Well, I'm hiding down here in New Zealand and I'm not a big social media guy.

DANNY LENNON: Smart move.

NICK GANT: I have a Twitter account, NickGantNZ, that I update maybe once every couple of years, but

I'm for people to contact me via that. And the lab has a website, lab.gant.kiwi. Again, which we rarely update. But we can put some of those links onto the page and I'm happy to talk to anyone about any questions they have in this area.

DANNY LENNON: Awesome. Yeah, so I will link to those and as I said, other papers that we've mentioned throughout the episode today, as well as where you can contact Nick if you have questions and hopefully, we don't bury you with an influx of responses. So, with that, Nick, I'll finish on the very final question that I ask everyone to round out the podcast. Completely detached from what we've talked about today, if you wish, it's simply, if you could advise people to do one thing each day that would benefit any area of their life, what would that one thing be?

NICK GANT: Okay. Well, I'll keep it attached to what we've been talking about today. I think David Goggins, the ultra-endurance athlete, former Navy seal, former obese person, has this mantra where he says: Do something that sucks every day to stay mentally strong. Now I'll put the neuroscience behind that. The brain responds positively and adapts well to acute stresses, whether they be physical stress like a bout of exercise or taking a cold shower or cognitive stress like doing some meditation that's quite difficult or something like that. That seems important to stop the brain getting too fuzzy and we've got some good neuroscience that backs that. So, you need to make yourself uncomfortable. And I try to do it every day in whatever way works best for you or you need to. When you stop doing that, that's when you see a bit of deterioration. So, when we get old and retire, we drop a couple of IQ points because we're not having acute stress in our day, having to meet deadlines, those sorts of things. So, you've got to do something that challenges you and pushes you behind your comfort zone every day to stay sharp and keep the brain adapting and plastic in my opinion.

DANNY LENNON: Wonderful. And a perfect way to finish with that. Nick, thank you so much for first showing me around this amazing lab you have and for taking the time to talk to me.

NICK GANT: Thanks, Danny.