Episode 5: Interview with a Neuroscientist – Alex Vaughan

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Matt:	00:07	Hello and welcome to the Numenta on Intelligence podcast. I am Matt Taylor and today I'm going to be bringing back the Interview with a Neuroscientist, a series that I started on YouTube. If you haven't seen that, I have several different interviews with neuroscientists who have come by the Numenta offices for one reason or another, including David Eagleman, Jon Michaels, David Schneider, Carmen Varela, and Eric Jonas. Today I'm going to continue that series and we are going to talk to Alex Vaughan of the company MapNeuro. He has been working at Zador Lab and has recently been recognized for his work, creating tools to help map the brain. So really interesting stuff going on there. So hopefully you enjoy this episode of the Numenta on Intelligence podcast.
Matt:	00:59	Today I have with me Alex Vaughan from Cold Spring Harbor Labs and a company called MapNeuro, which we're going to talk about both of those things at some point. Would you like to give yourself a bit of an introduction with what brought you into the field of neuroscience? What are you excited about?
Alex:	01:13	Sure. Uh, so my entry to neuroscience was actually a little atypical. I came in from kind of standard animal biology behavior, not anything having to do with medicine. I actually, the first animal I ever studied was a spider way back at Cornell and Ron W., and we were studying spider behavior and cricket behavior and basically trying to understand how these weird

little animals tick and, and kind of what makes them perform all of their crazy behaviors. And so I moved on from that and I ended up doing a PhD at Stanford where I, uh, where I did something kind of much more directed in the sense that I started working on fruit flies and fruit flies are this amazing model system in which we have over the course of a century's worth of work, gotten ourselves essentially perfect genetic control over a single organism.

Matt: 02:05 Right.

Alex: 02:06 So we can create mutations however we want. And by the time I came into the field, we could also use this, use these genetic tools to look at neuronal activity and to manipulate neuronal activity in the fly. And fly brains are very special. They have relatively few neurons compared to humans and every neuron does something unique and specific you can find the same neuron in one fly versus another fly. You can't do this in a person. So a lot of what I did was we were studying courtship behavior and flies and I would kind of go through and systematically turn on, some neurons, turn off some neurons, look to see how it manipulated courtship behavior, uh, and that. And after that I started working in a, in a more of the field of decision making in mammals and studied kind of how animals think, how they make decisions and moved from there to working on making maps of the brain and that's a lot of what we do now. And what, uh, what I can talk about, what we're doing at MapNeuro is basically building technologies and tools for maps in the brain. And in my current work, I'm technically still a postdoc and Tony Zador's lab at Cold Spring Harbor. And Tony has developed a bunch of technology over the years for what he calls molecular connectomics, which is basically a bunch of tools for tracing neurons throughout the brain that work really well, like much, much better than, than previous tools. So that's what we're building.

Matt: 03:30 And all the way back to fruit flies. I mean, you were working early in your career with genetic tools, applied genetics essentially to do neuroscience. I find that really interesting. I'd like to dive into that with you as one of our subjects we talked about today. What's more interesting from a broad standpoint are these, these molecules in your brain and this idea of molecular structure.

Alex: 03:52 So I would say the analogy is this, that in flies, because we have genetic tools, we can manipulate every neuron in the brain, uh, with arbitrary specificity and more or less do whatever we want to them. And this, this lets us understand the brain and if the fly

were a patient suffering from some sort of neurological disease, this would let us fix things relatively easily. In humans we have nothing like that. Nothing like that, control and in fact the only things we have in humans that let us say provide therapies are basically neuromodulatory drugs and these are drugs you've heard up. So they're things like serotonin and dopamine that people associate with reward and pleasure and addiction. And there's about half a dozen of these and the interesting thing about them and what makes them actually a little bit like the case in flies, is that they're in special circuits, special circuits there is that there's kind of one or two areas in the brain that express serotonin and they distribute the serotonin from a small pocket of neurons all the way throughout the brain. And everything that Serotonin does, it does through these neurons.

Matt: 04:59 So these molecules are flowing through the brain. They're moving.

Alex: 05:04 Yeah. So there's a bunch of neurons in one area, but most notably the dorsal raphae that express serotonin. And then they have these long range projections that reach all the way throughout the brain. They can reach inches and inches, which is huge for a cell, all the way throughout the brain.

Matt: 05:22 Wait, within a cell or through cells?

Alex: 05:22 Uh, so they, the molecule, the neurotransmitter of Serotonin is expressed in the cell and within this cell it's usually contained in what's called a vesicle. Uh, so this is basically a little, a little transport module, a little pod, more or less than what they do is they, they'll synthesize it usually in the cell body, which is in one location. They'll package it in one of these little pods and then it'll be transported all the way down down the axon to somewhere very far away, for instance, to your prefrontal cortex, which is the other part of the brain that doesn't make its own Serotonin, but in which Serotonin is critical for thinking and emotion and, and that sort of thing. And then at the right time, this neuron will release the Serotonin and the Serotonin then acts as a neurotransmitter. And what that means is basically it's passed from one neuron to another to change the activity of that second neuron. So there's a bunch of these that do really canonical things - serotonin and dopamine and norepinephrine, acetylcholine and these ones are particularly important because for the most part, every drug we have in the brain that helps people with depression or helps people improve their memory if they have Alzheimer's, every one of these targets, either the synthesis, the distribution, or the degradation of these neuromodulatory chemicals.

Matt:	06:41	Really important molecules. And are these important because they just have certain molecular characteristics that allow them to carry information or do you think there's a lot more that we don't know about?
Alex:	06:54	Yeah, so it seems like there's a couple things going on. One of the reasons they're important is that they seem to play a specialized role in computation. Uh, there are, there are kind of brain-wide changes that you want to make in order to alter behavior. And one of the ways that-
Matt:	07:13	Like global changes.
Alex:	07:14	Global changes, and norepinephrine is a great version of this. So norepinephrine you can find throughout your body, if you are nervous, say you're giving a podcast or something and you're a little a little excited, you would, you would have a little more norepinephrine than usual that's involved in the flight or flight fight or flight response.
Matt:	07:31	A stimulant, right?
Alex:	07:32	Yeah, so in the brain, we think that what it does is it controls attention, and we don't know a ton about this, but this is, this is the best theory right now. And so essentially when these neurons and the locus coeruleus release norepinephrine into the brain, they'll kind of wake up brain areas and say, pay attention to this. Pay attention to the sensory input that's coming in now and act on it as quickly as possible. And what it looks like, this tiny little set of cells here that, that release norepinephrine, what they do is they signal global changes in the brain and they so they, it's a very precise timing. So now is the time when you got to wake up and pay attention and do something, but it's more or less global. So, and the idea is basically that you need to be able to distribute this kind of signal to the entire brain at once. And these, these brain regions tend to specialize on that.
Matt:	08:22	And you take advantage of these molecular circuits in your company MapNeuro in really interesting way through viruses. And I'd love for you to talk about how do you use viruses and these molecules and how they, those circuits go through the brain to help map the brain.
Alex:	08:39	Yeah. So one of the things we're really interested in doing, uh, in, in our work is actually helping the field of neuroscience as a whole move beyond these four or five chemicals.

Matt:	08:50	Great.
Alex:	08:51	Uh, and a lot of the reason that we want to move beyond them is there's a 99 point nine percent of the brain or something like that doesn't express these chemicals, is doing different things and has connectivity maps that are hard to untangle. And what I mean hard to untangle, I mean, if you really want to know where a single one of the 100 million neurons in a mouse brain goes, like it starts here and it has this long production to a bunch of other areas,
Matt:	09:19	Axon and all of its dendrites.
Alex:	09:21	If you really want to know that, the way that you do that is you, you label one neuron in one animal and then you sacrifice the animal and you visualize, once you've kind of put the brain under a microscope, you visualize the anatomy of that neuron and so that's, that's the way that you can kind of get resolution over what single neurons are doing. Uh, and people who've done this for many years in particular for the neuromodulatory circuits that we were talking about and they've also tried to do it for many of the cortical circuits that are involved in learning and memory and motor control and sensory processing and everything else. But the problem is basically the tools that we have are one neuron at a time or maybe a few thousand neurons at a time, they're nowhere near efficient enough to create reliable maps of the brain that address the 100 million neurons you find in a mouse brain.
Matt:	10:14	You have to understand what the populations are doing.
Alex:	10:18	Yeah, and you have to understand the, you have to understand the map. So one, one analogy that I like to give is in neuroscience, people have been studying many, many different regions of the brain to see what they do, right? Uh, and so they can do this, either you have lesion experiments where you disrupt activity in one part of the brain or you can simply record activity in the same part of the brand and see what it does and behavior. And so using this approach, we have things like, we have motor areas, we have sensory areas, we have areas involved in decision making and we know where they all are. And you can think of these like subway stops in a city, right? There are all these different places and if you want to go to the spot where you're gonna, where you're gonna really, uh, make decisions, you go to the prefrontal Cortex, that's where you go. But it's like a subway map where we know where all of the stops are and we have no idea how to get between them. That's the big problem that we're, that we face. And there's been an

enormous effort in the last 10 years in particular to try to create some of these maps. Uh, and so one actually one outstanding project has been the Allen brain connectivity atlast. So the Allen Brain is uh, uh, the Allen Institute up in Seattle, founded by Paul Allen and filled with a tremendous collection of neuroscientists. They've done a project where they label neurons in one region and then they look at the projections of all of those neurons to a bunch of other regions. So if you label, say the prefrontal cortex, you might see projections back down to sensory cortex or to motor regions that are helping kind of output a decision. Um, and that might be a dozen different different areas.

Matt: 11:51 Yeah, because you're doing a lot in the prefrontal cortex.

Alex: 11:54 Yeah, you're doing a lot in the prefrontal cortex. Uh, and so what they did is it through a really heroic project, they did 500 of these maps tracing different areas of the cortex as they projected kind of across each other and in this dense network of connectivity. And they can make this beautiful map that shows you where all of the connections are.

Matt: 12:14 I think I've seen the visuals of this. This was really impressive when it came out a few years ago. I'll probably try and link to it in the show notes.

Alex: 12:22 That sounds great. They have an outstanding visualization people, I have to say, we've learned a lot from them. Uh, so, uh, there's one, so it was an enormous amount of work and it's been really useful. So now if you're looking in the prefrontal cortex and you want to know where these neurons go, you want to know who they're sending information to, which regions they're distributing information to, you can just look and figure it out. And there's one drawback of this approach, which is that in doing that you no longer have resolution over single cells. So you're labeling thousands of neurons simultaneously. And when you look at the projections, you see them all simultaneously and they're all very difficult to differentiate.

Matt: 13:02 Yeah, you can't tease them apart.

Alex: 13:03 Yeah. So going back to the subway metaphor, it's a little bit like saying, you know, I live in New York. It's like saying all of the people at Wall Street who were getting on the subway are simultaneously going to central park and the empire state building in Brooklyn. All right, that's just not true. Individual people go to different places and your individual neurons go to different-

Matt:	13:21	You don't have the resolution to understand the true map there.
Alex:	13:24	Yep. Yep.
Matt:	13:25	Um, so, but you're working on that.
Alex:	13:26	Yeah. So we're working on that. So one of the things that, uh, that Tony Zador at Cold Spring Harbor has been working on for many years, are ways to label neurons individually, socially, you can still use them for tracing. And one simple idea is you might label some neurons red and some neurons green and then you can see where the red neurons go and the green neurons go. And what we did is kind of abstract that concept out, such that we label neurons with a DNA barcode. And so what this means is, is we, we make a virus similar to the virus that the Allen Brain Institute used where they express a green fluorescent protein to label neurons. What we express instead is a short sequence of, uh, of DNA such that every neuron we infect is uniquely labeled.
Matt:	14:14	That's a huge difference. Before you would have had to detangle all of these different reds and greens and this is red, but which neuron did it really come from?
Alex:	14:23	Yeah and you know that that actually has been a really effective approach for, for many years, Josh Blackman, among other people, a pioneer to a technology called brainbow where they have lots of colors. They're beautiful
Matt:	14:36	They are.
Alex:	14:36	They're astonishingly pretty pictures. Uh, and using that approach you can trace maybe a dozen neurons at a time, maybe 20. It was actually, it was really useful for dissecting the fly brand. It's proved less useful in the mouse brain just because the mouse brain has so many more. So instead of using four colors or six colors or eight colors, what we do is we abstract the idea of colors into DNA. So every base of DNA has four possible letters that can be associated with a g, t, a or c, and you can think of those as four colors. And because we use a sequence of DNA that's 30 bases long, we kind of have four colors and then the next base we have four more and four more, four more and four more.
Matt:	15:21	So you can have a unique identifier for pretty much any neuron.

Alex:	15:23	Yeah, so we have, so we use a, a barcode as we call it, of length of 30. And I get those four to the power of 30 possible color combinations, which turns out to be enough to label something like every sand grain on earth, uh, which, uh, isn't that much more than the number of neurons in your brain, but it's probably enough.
Matt:	15:43	But you could theoretically map an entire human brain.
Alex:	15:46	You could, yeah. With, uh, with this approach, uh, on an enormous amount of work. And some luck, you could theoretically map the human brain.
Matt:	15:53	Tell us about the work involved here because it's not a trivial task even doing it this method, right?
Alex:	15:59	Yeah. So it's actually, it's a, it's very different than a traditional tracing experiment. In a traditional tracing experiment, you would find some way to label some neurons, you would say, in infect them with a virus that expressed a green fluorescent protein and then they would all be green and then you would take that brain, sacrifice the animal, put it under a microscope and you would visualize it. And this is amazing, right? You have perfect spatial resolution, essentially as fine details as you want to see. If you want to see the fine details of a synapse between two neurons, you can just kind of look and, and you can see the what are called presynaptic boutons that are, that are at the neuronal outputs and post synaptic dendrites that are kind of the inputs to the that next one, you have amazing spatial resolution. And what we do is we throw all of that out as quickly as possible. So if we're, for instance, looking at the projections from prefrontal cortex to other areas, we, uh, we grind up the area where we made our injections.
Matt:	16:57	Oh, you don't take these slices and have a beautiful rainbow like picture.
Alex:	17:01	We've, for the most part, we were getting back into that a little bit, but, but in the simplest part of the experiment, and I should say that this, this whole approach was pioneered by, by Tony Zador and a phenomenal Grad student in his lab named Eustis. Uh, and in particular, what Eustis's insight was, was you don't have to keep spatial information. You can infect a bunch of neurons to label them uniquely. And then at the injection site, if you grind it up, you'll see all of these barcodes and maybe you infected a virus that had a million barcodes and you labeled a thousand neurons. So there were a thousand barcodes that you end up finding in that sample. Once you go through the

sequencing process. The way we do this experiment is we take a virus that allows us to uniquely label neurons and we do an injection into, say, the prefrontal cortex to label these neurons. And every neuron is uniquely labeled with a barcode. The barcode, while the animal is still alive, the barcode is amplified by the cell and then it gets distributed along the neurons. So we have a protein come and grab onto this, this DNA barcode, it's an RNA form at this point and drag it along the process all the way out to its most kind of distal extent. It's the synapsis that it's making on other neurons and other brands.

Matt: 18:19 Is this a part of the molecular circuits you're taking advantage of is dragging these-

Alex: 18:24 Yeah, so one of the things we've tried to do is basically actually kind of precisely the transport machinery that I mentioned earlier that moves vesicles from place to place. We can piggyback on, on that kind of transport machinery to move our barcodes from place to place. So that's actually a really important thing that ended up working surprisingly well.

Matt: 18:44 It's fascinating. I think inside the cell, all the things that are going on and us being able to take advantage of that to increase things like this.

Alex: 18:53 A lot of that comes from really, really hardworking scientists who figure it out. Fundamental cellular processes, uh, that seemed maybe esoteric at the time, turned out to both have medical relevance and to lead to new technology.

Matt: 19:08 And we're talking about virology and genetics and very specific areas, a niche areas even within virology that could come to fruition and neuroscience and potentially no one ever thought that would be applicable here.

Alex: 19:21 Yeah, yeah, exactly.

Matt: 19:23 Very interesting.

Alex: 19:23 So yeah, so to, to, to finish the experiment that we ended up doing, we, we sequence at the site where we did our injection and that, that tells us which neurons interacted with which barcodes and when we want to know where each of those neurons projects, we sequence the barcodes that made it to other areas. So if there are 10 barcodes in the injection site and in one of the distal targets, we find three of those barcodes, then we know that there were three neurons that from the

injection, so that projected all the way over there to that other area. And if we see one of those barcodes in another area, then we know that that single neuron split and sent to axons to two different areas. And that's really where we get a kind of a real uptick in the amount of information. So instead of the traditional approach where you have bulk projections and again, every person is simultaneously going to Central Park or the Empire State Building, we're or to Brooklyn, we now know where every neuron goes on an individual level. Uh, and this has led to some, it's obviously we focus a lot on the technology, but it's led to some biological insights. So actually going back to what I was saying earlier about alarm signals in the brain. The first experiment that Eustis did was to trace the projections of cells that express norepinephrine in the locus coeruleus and to trace them on a single neuron basis. So where does every single one of those neurons go? And the previous hypothesis was basically that they were all widely distributed through the brain, sending a global kind of alarm or attention signal that would wake up the whole brain simultaneously. And that's not what Eustis saw, kind of, much to our surprise. He saw that this individual areas where a uniquely innervated by one neuron. So there would be an area, and or a better way of saying it is a single neuron can control one area and doesn't project to other areas. So there is some sort of anatomical specificity. There might be processes in circuits that allow you to kind of wake up the earth, the auditory part of your brain, wake up the visual part of the brain and modulate the brain in much more detail than we've done.

Matt: 21:35 Specifically in response to specific stimulus potentially as a part of a learned behavior. So yeah, that's very interesting. So you already mentioned that you worked at Tony Zador's lab at Cold Spring Harbor, but there's also this MapNeuro part of it. And I wanted to talk since you're, you're sort of on both sides of the fence here. You're, you're, you're a postdoc at Zador lab and you're also kicking off this business but you just got this award and some grant money for it with MapNeuro, which is exciting. Um, so what is this, what's the difference between, as a scientist a scientist and a business person? You know, what's the difference between the lab environment and where your priorities are there versus the business environment and how do you play those against each other?

Alex: 22:17 Yeah. Well, the first thing I should say is that, uh, on the business side, I'm still learning as I go. I'm very new to this. I'm trained as a scientist. I like to joke that anyone who wants to work with me, he gets to make the mistake of letting a business be run by a scientist. Um, but, uh, but it's been really fun so far

and, and kind of really, really interesting. The main idea that we're, that we're going for with this business is that we think that the technology that's been built in this Zador Lab over the last several years has legs. And it has legs in, in two senses. One is that we find that there are lots of other scientists who want this information, this information about the single neuron projections. And we-

Matt: 22:59 That's one of the reasons you're here, we're certainly interested in that.

Alex: 23:02 Yeah, exactly. And I spent a lot of my time doing, having this kind of conversation and trying to figure out what we can do now that we couldn't do before. And that's actually one of the goals of MapNeuro is simply to help scientists do this kind of experiment. And the reason for that is just that while we think we've done a great job making this experiment straightforward and routine in our hands, it turns out that people have different skillsets and some people are, for instance, very good at analyzing things but not so good at molecular biology. Some people are good at working with animals but not so good at molecular biology. Uh, and we are a lot of the goal of MapNeuro is to fill those gaps and to help people do this kind of experiment without having to-and is the worst case scenario-having to have a single person working for a year to replicate something that's already going on in someone else's lab. So it's essentially a meta-collaboration. It's, it's an effort to, uh, to provide, uh, uh, as much collaboration with the field as possible to help people do a kind of a new scale of connectomics.

Matt: 24:06 So as you're looking as, as MapNeuro grows in structure, you're looking for other labs that want to collaborate on this type of work, it seems like pretty closely with them because you want to understand what their priorities are and exactly how you can help develop ways of methods of doing what they need to do.

Alex: 24:23 Yeah. And getting back to kind of what I've learned over starting this business is you really have to listen to what people need and it turns out that you can't just make up what you think people should need or what it would be convenient for them to need and then offer that. And the example is basically just that we have the first thing we set up was, was a facility to do the core map seek experiments to do kind of the core molecular biology. Uh, and then we offered it to the world and it turns out basically that that is not enough, not enough to really help people. Uh, and there's a bunch of reasons for that, but the biggest reason is that it's really hard to adopt new technologies without fully understanding all of the caveats and all of the

difficult parts of the experiment and all of the ways it's going to fail that you might not even find out about until the experiment has done. And so people are both really excited about new technologies but also reticent to put an enormous amount of their own effort into them.

Matt: 25:24 So you're also, you not only need to offer them the technical services for the mapping, but also your expertise and how are they, how could they tackle this.

Alex: 25:31 Yeah, precisely. A lot of the conversations that we have that are super interesting for me are learning more about the kind of scientific questions they wish they could address and then telling them which of those we can actually, uh, we can actually get at with our, our technology. Um, but you know, it's been, it's been really rewarding because we see fields open up that haven't had access to many of the genetic tools, for instance, that I talked about in flies or even in traditional nice. And one of the things we're doing now is we're doing experiments in, um, in animals that are usually not studied very much because our approach can be used in mice. It can be used in rats, it could conceivably be used in birds, it can be used in other, other species of animals. Uh, and so the hope is basically that by taking away this one pain point of the hard parts of the molecular biology and figuring out how to do the experiment as a whole, we can kind of make it widely accessible for everyone. And, but there was a lot of learning. There are a lot of figuring out what people wanted and figuring out what the pain points were for them.

Matt: 26:39 Well, it's as, as new labs sort of adopt this and create own experiments, of course they're going to get data that lots of other people are going to find really interesting.

Alex: 26:48 We hope so.

Alex: 26:49 Alex has been here for the past day and I saw you give a presentation yesterday. They're just looking at that presentation, the ability for, for us for Numenta to understand not just the matter of the neuron, but what layers it goes to is, is really important. Especially we're talking about populations, you know, because all of our theories about the cortical column and what layers are doing, what, so getting better resolution about this population of cells in this layer of projects to this other layer and this layer, that's really important to us because it helps validate what we're thinking and raise new questions that we haven't thought about before. Like why is this happening? And that sparks innovation when you, when you

run into that thing, even if something says you were wrong, at least you know, you can go, you can go look for other doors.

Alex: 27:34 It's always interesting when we show that kind of data, it always make someone a little upset.

Matt: 27:40 Yeah.

Alex: 27:40 And I think what's going on is that, uh, the data that we tend to show is pretty high resolution. There are lots of neurons, we know their projections, we know in the case you're talking about their exact spacial location and in the field of neuroscience there's been a lot of implicit knowledge about where neurons are and where they go and it's built up over a century of really careful work, but it's also, it's combined a lot of different information in ways that don't, that don't always pan out.

Matt: 28:10 It's a bit tribal.

Alex: 28:12 Yeah, and people have longstanding beliefs that it must be this way and it turns out that when you can actually test it, uh, you will validate 90 percent of those beliefs and then in a very irksome way, validate about about 10 percent of them. So it's always a good sign when someone gets a little frustrated and then wants to do another experiment.

Matt: 28:31 Right, absolutely.

Alex: 28:33 That's the goal, right?

Matt: 28:33 I mean we're searching for the truth, you know, but you got to find out how things really work. I mean, that's, that's our whole mission is figuring out how it works so we can try to build it in software. So, uh, about MapNeuro, you've told us a lot about sort of how it works and the idea of you want a map or not high resolution maps of where neurons are projecting to. What are the questions that this technology might help us answer what, what things is this going to help with in the future?

Alex: 29:02 Yeah. So we are hoping, I would say to address three things and one is simply, there is a fine detail of neuronal circuits in the brain that if we can understand those will, I think give rise to not just an understanding of the brain but new technologies. And actually this is kind of the guiding principle of one of the main funding agencies that, that facilitated a lot of this work, which was the IARPA microns project and IARPA as you know, is

affiliated with the United States intelligence community and what they wanted. Oh, and we were part of this and as well as many other people using different technologies, uh, they wanted mechanisms to trace neurons in the brain to make machine learning better. The idea is that for things like deep learning and neural networks, they're hard. They're hard. It's hard to make them learn, it's hard to get them kind of off the ground, but if we can transport information over from the human brain or the mouse brain onto those artificial neural networks, then maybe we'll get a lot better at it.

Matt: 30:06 We could create our networks to more closely match what we're seeing in brains experimentally.

Alex: 30:11 That's one hope. The second is that we, we really want to just move neuroscience forward as a field, and I think one of the big technological stumbling blocks of neuroscience has been that there are 100 billion neurons and we don't know where they go. When you say it like that, it's just insane. Like what's the most important thing about a neuron? It's where it projects and who it talks to. Do you know that for any of the neurons you work on? No. The, you know, the brain is super hard in the sense and so we really hope to make, make progress.

Matt: 30:43 It seems like you're in the right space right now because people want this information and there's a, uh, there's been a lot more interest in just in neuroscience in general over the past 5-10 years for it seems from what I've, what I've seen and especially with the new hubbub about grid cells and stuff and how that all works with everything else that we're trying to incorporate from, from the past knowledge of neuroscience. So you're in a great place with, with MapNeuro and I'm really looking forward to seeing what you guys come up with.

Alex: 31:14 Thanks very much.

Matt: 31:15 You mentioned to me a paper that you're currently working on. I think it's on bioRxiv right now. It was about, it was about behavior and sparse coding in the frontal lobe. And uh, I mean we can't go over the whole paper, but what interested me about it is that it's all about how sort of populations of neurons that you've shown observing them through this, this technology you're talking about can show aspects of the behavior that's happening right now and you can decode based upon what neurons are firing, what they mean, what they're meaning. Can you explain that?

Alex:	31:50	Yeah, I'd love to. So this is actually a previous work that I did when I was in the lab of Adam Kepecs who's also at Cold Spring Harbor, uh, and working with an outstanding, uh, experimentalist Junya Hirokawa, he recorded, uh, the activity of neurons in a particular part of the rat brain, the orbital frontal cortex in the rat brain while the rat was doing a complicated behavioral task. So the rat had to, uh, had to smell an odor and, and basically figure out did it smell more like strawberries or did it, smell more like watermelon. And then we would vary the difficulty of that task by giving the rat mixtures. And to abstract this out, we were basically putting the rat in a situation where it had to make decisions that integrate a bunch of information. So integrating sensory information about kind of what, what the, what decision you should make, but also information about whether he should expect a big reward, if it's correct or a little reward and a and other kinds of information like that about the task.
Alex:	32:50	And one of the things we were looking for was basically we, at the highest level, we were trying to ask the question of whether neuronal activity in the brain makes sense. That's the simplest thing and the baseline hypothesis that people have had in particular for this part of the brain, kind of frontal, the frontal lobe and the decision making parts of the brain. The idea was was that essentially all of the available information that an animal has is utterly and catastrophicly mixed in a way that if you look at the activity of any individual neuron, it doesn't represent anything in particular. You know, it might, this neuron might be active when it smells watermelon, but it might also be active when the sky is blue and it might also be at be active when the animal expects a big reward and all sorts of kind of useless combinations. And the theory in some sense has been that these useless combinations are great because they allow you to make arbitrary associations, right? Like maybe want to make an association between a really good reward that you expect and the sky being blue. And that, that information has to overlap somewhere.
Matt:	33:59	You can do it.
Alex:	34:00	Yeah, you can do it. So what we showed instead is that at least in this part of the brain, in animals that are very well trained on a task and kind of very, very used to one task-
Matt:	34:13	Consistently-
Alex:	34:13	So we found neurons that represent psychological concepts in a really consistent and coherent and understandable way.

Matt:	34:24	Meaning abstract concepts. Things that are not associated with physical sensations even.
Alex:	34:28	Yeah. So they're, they're, yeah, they precisely right. They're not linked precisely to sensations, although there are neurons that represent those sensations, sensation of the watermelon versus the strawberry or whatever. But more psychological. So the, an example of this, you find neurons that, uh, that encode not just what decision the animal made, but essentially the probability that the decision was correct.
Matt:	34:52	Oh yeah.
Alex:	34:52	So if the animal goes right and it's high probability this neuron fires, a lot of it goes right. If the end, what makes it makes choice A and the animal has had a lot of evidence in that, in that favor, so the animals almost certainly right, this neuron fires a lot because the animal makes choice b. and it's also a good decision. The animal had a lot of evidence. This neuron also fires, but if the animal makes either choice without very much evidence than the, the animal is uncertain or should be uncertain and this neuron reflects it by firing very little. So that classically is called a confidence neuron. And this is one of the things that Adam, Adam Kepecs has worked on over many years, is identifying representations of, of not just the decision you're making, but a kind of meta-cognitive confidence in that decision. And we all know that when we make decisions we have confidence or not confidence in these decisions, but the idea that representations of, of that kind of an abstract concept and other abstract concepts that are related to decision making would be identifiable and kind of coherent and individual neurons, is the real, the real breakthrough, I think, of that paper.
Matt:	35:56	I think it's a really cool finding here because, uh, you know, we, we, I mean we always talk about how things in the world are represented sparsely by neurons in our brain, whether it's and especially in the sensory cortex areas.
Alex:	36:12	Yep.
Matt:	36:13	But we've always said, you know, as part of our theory that conceptually the same thing is happening, you're, you're, um, you're representing concepts and behaviors and that sort of thing and the same methods as you represent sensations. And so, um, it's, it's nice to hear that because it makes sense that you would build in your frontal lobe on top of all of those sensations coming in and you're going to build your

		representations in behaviors using those and with the whole behavior motor loop involved as well. Um, so that's really exciting stuff. Well, Alex Vaughan, thank you for coming in and being on the Numenta On Intelligence podcast. It's been a pleasure having you here.
Alex:	36:51	Thanks very much for having me. It's been great.
Matt:	36:56	Stay tuned for the next show where we'll continue the series of interviews with neuroscientists and I will be talking to Blake Richards, the associate fellow of the Canadian Institute for Advanced Research. That's the very next episode of Numenta On Intelligence. Thanks for listening.