Transcript: SickKids VS The Unknown

Introduction

Hannah Our memories make us who we are. And when memory goes wrong, whether through injury or disease, it's devastating. You might think that something so vital would be well understood. But though memory has been studied for thousands of years, we still know very little about it. Many brilliant scientists have devoted their lives to finding out where memory lives in the brain. One, an American physiologist named Karl Lashley spent his entire career picking apart the brains of rats, only to conclude that it was impossible to find an individual memory in the brain. His fruitless search inspired many to give up their own.

Sheena In the brain, it's kind of a daunting task. We're going to argue the most complex thing in the universe. And I think it's a little bit of hubris on our part to think that we can ever understand it.

Hannah That's neurobiologist Dr. Sheena Josselyn. She brings a healthy amount of humility to her work, studying the brain and memory specifically, which is the focus of her lab at the SickKids Research Institute. But she brings something else to her work on the brain, too, tenacity.

Sheena We are going to try and find out how it stores memories. Yeah, it's a big, big task and it's going to take a while and it's going to take many, many smart people working on this problem. But it's a really wonderful thing to do. You know, get up every day and try and solve one of the big mysteries.

Hannah Sheena has a collaborator in this grand endeavor, her husband, Dr. Paul Frankland. For almost 20 years, Sheena and Paul have shared a neurobiology lab at SickKids. Together with their teams, they explore memory at its most fundamental level: how memories are formed, stored, retrieved, erased and recovered in the brain. Experiment by experiment. Discovery by discovery. They have been partners in searching for the Holy Grail of memory research, and they found it. You're listening to SickKids VS, where we take you to the frontlines in the fight for child health. I'm Hannah Bank, and this is SickKids VS The Unknown.

Act One: Sheena and Paul

Hannah Okay. So before we take a deep dive into big existential questions, we thought we'd get one burning question out of the way first. How did you two meet?

Sheena We met in graduate school. Paul was in one lab up at the University of Toronto across the street, and I was in another lab. And as graduate students, you spend an awfully long time in the lab. And we met, and we've been together ever since.

Hannah We heard it all started with sharing pipettes.

Paul Sounds unhygienic.

Sheena That was pre-COVID. Yeah. I do believe that my lab, which had a little bit more funding than Paul's lab, would often find our equipment had sort of gravitated over to his lab, and I would have to go over there to retrieve it.

Paul Our labs were across the hall from one another and we actually started collaborating as well in graduate school and doing experiments together. So that was fun.

Sheena It really was the time in my career where I fell in love with science.

Hannah One of Sheena and Paul's first major breakthroughs concluded a century-old scientific quest involving something called an engram. Think of it as the physical trace of a memory in the brain. The theory was certain brain cells are activated when an important event happens and they form a circuit, an engram, that lives in your brain and can be reactivated with the right cues, allowing you to recall a memory. Scientists believed engrams existed, but no one seemed to be able to find one.

Sheena Yeah. So the engram has a sort of long and interesting history. So the theory has been around for over 100 years. Back starting around 1930, one very famous researcher called Karl Lashley set out to find an engram in the brain of a rat. So what he did is he would train a rat on different types of mazes and the rat would run this maze to find this little piece of food at the end. And rats are very smart. They have very good memories. So after a couple of days, this mouse could remember how to run this maze and find this piece of cheese at the end. Lashley would take this mouse and say, okay, I'm going to try and take out different parts of the brain of this rat, try and disrupt this memory. So the next time I place this rat on the maze, they won't have any idea where to go. So he did this experiment and variations of this experiment for about 30 years of his career. So he tried so many different ways in which to try and find an engram in the brain. And at the end of it all, he published this very important paper where he just basically said, I can't find it. It's an enigma. I have no idea where this memory trace is, where this engram is in the brain. This sort of finding of no finding was so influential that people sort of said, okay, this is a fool's errand. We're never going to be able to find this engram if it exists. Maybe it doesn't exist at all.

Hannah So scientists stopped looking for it. They stopped trying to get their hands on an individual memory trace. But Sheena and Paul had a hunch that they could find it and they started their search around the time they arrived at SickKids in 2003.

Sheena We had inklings that maybe we were getting a handle on the engram even before I joined SickKids, but sort of trying to prove to ourselves and to other people that in fact we had localized an engram in the brain was a pretty tall order. So we thought of many different ways of doing this. It was a big bet. We bet on our own ideas and we said, okay, we think that we can identify these certain cells that make up this memory. And the real proof of that would be to delete or somehow oblate just these cells and see if we got rid of memory. If memory looked like it was erased.

Hannah Unlike poor Karl Lashley, they had the advantage of 21st century scientific tools. Viral vectors and optogenetics sound like the stuff of science fiction, but so did their aim: selectively erasing a fear memory in a mouse. And yet they were optimistic they could turn their idea into reality. The first step was to give a mouse a fearful memory.

Sheena So what we do is we put a mouse in a place the mouse has never been before. The mouse is roaming around exploring. We play a tone and we give it a very, very mild aversive shock. So this is the type of shock, you know, like when you rub your feet on a carpet and you touch a doorknob, not enough to hurt anybody, not enough to cause pain, just enough to really startle. So the mouse, we think, is thinking what the just happened?

And we give it just one simple tone shock pairing. They have a very, very vivid memory of it, that we can give it the tone again, even two years after this and the mouse will show defensive responses to this tone. And that was the fearful memory that we could erase.

Hannah The second step was to find the memory in the brain.

Sheena So what we did is we looked for a fearful memory in this part of the brain called an amygdala. We looked in the amygdala for a certain population of cells that were really important in this memory. And we used a bunch of different, really cool genetic tricks. We used viruses, no, not coronavirus, but sort of helpful viruses to transport DNA or genetic material into a small population of cells. And our trick was to turn these cells into the engram cells. So this very small population of cells became really important in representing this fearful memory.

Hannah And the third and final step: erase the memory.

Sheena We found these genetic tricks that allowed us to basically kill this very, very, very tiny portion of neurons in this one brain region of a mouse. And when we killed it, the mouse acted as if they had never been taught this traumatic event. And if we killed another small population of neurons, nothing happened. So it had to be these specific neurons, and they had to be functional in order for the mouse to recall this memory.

Hannah How long did it take?

Sheena It took many, many years and many different iterations of trying to get this effect, to try and see if it would actually work or not. So there's always roadblocks and challenges in science. I wish that every day was like, you come into the lab, you make a big discovery, you have your lunch, you talk to people about it, you go home, and that would be amazing. But a lot of science is sort of grinding through things, trying to better refine your tool so it does more of what you want to do, a lot of reading, trying to figure out what other people are doing and trying to build off their ideas. Folks in the lab tend to work really, really hard. It turns out mice don't understand the concept of weekends really well. So we do our experiments, you know, seven days a week. I like to say 25/8 but maybe that's too much.

Hannah Do you remember sort of when you realized that you had actually made that discovery?

Sheena Yeah. So it was a really, really talented postdoc in my lab, Dr. Jin-Hee Han. And when he first found it, he came running into my office, which is right next door to Paul's office. And he said, I think we've found it. I think these mice can't remember anything. It's amazing. And so we got him to do validate it, to check it, to try it again and try and, you know, prove ourselves wrong because we don't want to say something that is incorrect. He did a bunch of other control experiments just to show that, yes, we do see this. We have erased this one specific fear memory in a mouse.

Hannah The team had succeeded where generations of memory researchers before them had failed. They had found the engram, demonstrating that they do exist and that they are the fundamental building blocks of memory.

Sheena It was a very big deal for us and we tried to, you know, shout it from the rooftops to tell everybody about our, I think, pretty cool discovery.

Hannah In 2009, six years after their search for the engram had begun, their achievement was set for publication in the journal Science, and it was expected to generate a lot of media interest. There was only one hiccup.

Sheena So when the paper finally came out, I was very, very pregnant and I thought, Oh, no problem, I'll just do some press as soon as that, you know, my child will be born and I will tell the media and everyone around the world all about this exciting finding. But then our daughter was about a week late. The wonderful thing at working at SickKids is here we're on hospital row. So we just ran across to Mount Sinai and I was induced. Paul and I came back here to the lab to work a little bit before going back over to the hospital. And I was doing press on this. I was talking to the Toronto Star and I had a computer in front of me and people were asking me questions and I was answering about it. And finally, one of the very wise nurses said, okay, time to stop doing that, time to really concentrate on this labor thing. So I ended up having an emergency C-section. And while I was on the table and they were about to open me up, the surgeon was asking me all these different questions and I was saying, Oh, we have a really good paper coming out. We have this really exciting finding. And he's like, Okay, keep telling me about it. So sure enough, by the end of it, everybody around us knew our really exciting finding. Everything happened all at once but I wouldn't have had it work out any other way.

Hannah Finding the engram in a mouse brain was a research homerun. And though the work could not be immediately translated into humans, it did mean that one day scientists might be able to erase fearful memories in people too. Something that has big implications for treating conditions like post-traumatic stress disorder. But before we talk about that, we've got one more big breakthrough to tell you about.

Act Two: Infantile Amnesia

Hannah What's your first memory?

Sheena I remember when I was in kindergarten, I lost a button on my jacket, and my teacher was really sweet to me and helped sew it back on for me.

Paul Similarly sort of traumatic, I think I was on a boat on a vacation with my family. The wind blew my hat off and went into the ocean and we tried to convince the captain of the boat to go and fish out the hat for me.

Hannah And what was your daughter's first memory?

Paul We often ask her about her memories, but I don't know what her first memory is. You remember? We must have asked her.

Sheena We asked her a bunch of times. And usually we get the eyeroll response.

Hannah I always get the eyeroll.

Hannah Ask anyone about their first memory, and they likely won't be able to recall anything before age four or five. This inability to remember early life is called infantile amnesia. It's a phenomenon that's long been observed but wasn't well understood. Until that is Paul and Sheena started studying it, spurred by observations they made of their daughter as she grew up.

Paul When we had our daughter 12 years ago, we were interested in memory in general, but we weren't so interested in specifically in say how children's memory changes over time. And that really made us interested because we had our own little experimental subject, if you like in front of us. So as she became more verbal, she would tell us about things which were important to her in her life. And and over a while, you could you could see that she was forming memories and she could remember things and she would tell other people about these events and so on. But now, with time, she also showed that she forgot those memories quite quickly.

Hannah Paul recalls one specific memory that seemed quite traumatizing for their daughter. But one day, she couldn't remember it anymore.

Paul I guess she was about two and a half years old. Something around that time. And we went to a zoo near Toronto. I can't remember the name of the zoo now. I've forgotten.

Sheena The memory researcher who forgets.

Paul Yeah, exactly. And we were there and we were looking at some some some animals and then this Canadian goose came over and sort of flapped its wings. It was kind of frightening, actually, even for me. But it certainly frightened our daughter Charlotte and she was like kind of traumatized by it. And she would tell the story afterwards about this incident where she said duck came over, went, quack, quack. I got scared. I jumped on Daddy. And then we went to see zebra. You know, that's that's exactly sort of a very sort of accurate description of what happened. And she would tell this story for like weeks and months afterwards, but eventually she kind of forgot it. So certainly if we ask her now, she has no recollection of this. And but even if we asked her about six months or nine months afterwards, she had forgotten this.

Hannah And what sort of questions did you ask and pursue as a result of this?

Paul Yeah. So the question we became interested in was about infantile amnesia. What in the brain, what about the brain makes it the case that these memories are so fragile and don't last very long.

Hannah Paul and Sheena focused on the hippocampus, a region of the brain that's important for memory of life events. But the answer to the question, what causes infantile amnesia, came as a big surprise.

Paul Yes, so the memory of that discovery is a little bit different because we weren't looking for it. We were doing an experiment with a totally different goal. The student in the lab came to me with the data and said, look, this control experiment didn't work. The animal seems to forget. And we go, oh that's bad. That's disappointing. But we looked at the effects and it was a big effect and we knew we need to understand this.

Hannah It took a few days of looking at the data and thinking about it for the team to realize what they had discovered.

Paul And then it started to make sense that what we've done in that experiment was to increase neurogenesis so increase the production of new neurons in a specific part of the brain, which is where that type of memory would be stored. And that led to the overwriting of that memory. So the memory is there. But you add these new neurons, it changes all the circuit, and then it makes it much harder to access that memory through retrieval. And so that's how we got there. This is probably the best ever failed experiment.

Hannah Clearly there was something that you didn't anticipate. And once you sort of made this discovery, what happened after that?

Paul So once we made that discovery and we sat around and thought about it and said, hey, wait a second, this looks like forgetting. This may be a way in which the brain forgets. Then I remember Sheena and I sat around—we always have lunch together—and we sat around one lunch and we, I think that lunch we came up with a list of experiments. If this is true, then all these things should work. And so the framework was super clear. The predictions that we could make based on this one observation were super clear. And we went on and spent two or three years testing those predictions.

Hannah What was it like to share that discovery with the scientific community and what was the response?

Paul In the scientific community, it was interesting because there was a bias in the in among memory researchers that something like neurogenesis seems like a really good thing to have, right? So that continued production of new neurons throughout our lives, that should be good for memory. And so it took a lot of convincing people that it can, not only can it be good, it can be good for making new memories, but at the same time it's sort of overwriting old memories. And so, you know, initially there was a little bit of a resistance, but I think with time, people have come around to the idea that it makes makes complete sense.

Hannah And what does that mean moving forward?

Paul So what it tells us more generally is about one way in which the brain forgets. You know, we all forget things. But it's a very sort of healthy thing to forget things. We don't want to remember everything. We can remember what we had for breakfast this morning and maybe even yesterday morning. But we certainly shouldn't remember with any degree of accuracy what we had for breakfast two weeks ago. It's a healthy sort of turnover of memories, and that is what you see in adults for sure. And then but in children, that is just much more pronounced.

Act Three: Why it Matters

Hannah Fundamental research or pure science, the kind of work Sheena and Paul do in the lab, is by necessity removed from the real world.

Sheena So when we were in the lab, we try and reduce things. So we have maximum control of everything that's going on. We don't want sort of real world things going on.

Hannah But that doesn't mean their work doesn't have real world implications.

Sheena I think it's really important to understand the basics of how a brain works. If we're ever going to try and make new treatments or new cures or anything for any type of disorder. We understand so much about the heart. A heart is a pump. We understand how the heart works. Not so for the brain. The brain is really unique. And one of the things that makes it really unique is that we don't understand how it works fundamentally. But we need to get that basic understanding of the brain and then we'll see, you know, where it will lead us.

Hannah Erasing fearful memories in mice and uncovering what drives infantile amnesia, these discoveries are helping to build a foundation of knowledge that enables further research and eventually better treatments for things like post-traumatic stress disorder.

Sheena So you could argue in PTSD, it is too much memory. Survivors of sexual assault or people coming back from war, some people can have PTSD where they have a very traumatic memory. It's recalled all the time. It's very intrusive, nightmares and all kinds of things that interfere with ongoing day to day life. The question there is, is the engram too big? Are too many neurons or too many brain cells engaged in the engram? Is the engram too excitable? I think that's a really interesting question, one that we can really leverage our understanding of these basic processes to try and help people with these incredibly troubling memories.

Hannah I asked Sheena if she thinks erasing memories raises any ethical concerns.

Sheena Yeah, super interesting question. Is it a really good idea to erase the memory of me embarrassing myself with karaoke a couple of weeks ago? Should we do cosmetic surgery of memories? And I think no. Bad things happen to us and we learn from them. We shouldn't go around trying to change our memories because that that really makes us who we are. That the old saying is that, you know, a child only has to touch a hot stove once in order to learn that stoves can be hot and stay away from them. Should we erase it? No. They should learn from that. We all should. And we as a culture should learn from the really horrible things that we can do to each other. But in the case of something like PTSD, where people are not functioning day to day, then it's, you know, an imperative to do what we can to allow people to become free of these memories.

Hannah Paul and Sheena's work on memory also has implications for dementia and Alzheimer's disease.

Sheena Some members of our family have dementia, and it's just they really do lose who they are. It's just really heartbreaking. For us, we want to be able to, you know, see what we can do with our fundamental knowledge of how memories normally are stored and try and see if we can key in on some mechanisms that might counteract this, you know, really devastating disease. And the pace of translating these very, very basic findings into some sort of clinical treatment is sort of maddeningly slow. And I wish that we could translate what we do in the lab into people much, much, much faster. The sort of alternative to this very slow, very sort of considered approach where we take safety really into account is if we were to rush and then we start testing these these non-proven treatments in our loved ones. And we certainly don't want that. Unless we start on this road, we'll never get to the finish line.

Hannah Paul and Sheena are keeping up the fight against the unknown. Beyond studies that have implications for PTSD and Alzheimer's, they're exploring aspects of memory that

play a role in depression, anxiety and fetal alcohol spectrum disorder. They're studying how social isolation affects memory and how rewarding memories influence things like substance abuse. Their findings are rewriting the textbooks on memory and demystifying the brain. We could talk to them about their work for hours, but we're nearing the finish line of this episode.

Hannah You must have really interesting dinner conversations, the two of you, about this.

Paul I think we would keep talking about our research if we didn't have our daughter because our daughter puts a stop to it. So when we get home and if we start sort of breaking into talking about work, she says, you're talking about work.

Hannah How old is she now?

Paul She's 12, but she's been stopping us talking about our research since she's been talking, I think so.

Hannah From SickKids Foundation, this is SickKids VS. Thanks for listening. If you want to support work like this, visit SickKidsFoundation.com/podcast to donate. And if you like this podcast, please subscribe and rate us on Apple or Google Podcasts, Spotify or wherever you listen to SickKids VS. SickKids VS is produced by me, Hannah Bank, Neil Parmar, Jasmine Budak and Gillian Savigny. This episode was written by Gillian Savigny. Sound design and editing by Quill. Productions support by Ayesha Barmania. For behind the scenes extras and show notes visit SickKidsFoundation.com/podcast.