0:01 Dr. Mary Pat McAndrews
[Your Complex Brain theme music] Memory is not stored in one place exactly, but there are certain parts of the brain that are really important for being able to remember things, and we know this because damage to those really important parts causes very severe problems with being able to learn or retrieve new information.

Heather 0:21
[theme music continues] This is Your Complex Brain, a podcast all about the brain, the diseases that impact it, and the path to finding cures. I'm your host, Heather Sherman, and I have the great pleasure of working alongside the team at the Krembil Brain Institute in Toronto, Canada, a leader in brain research and patient care. In each episode, we'll take you behind the scenes into our clinics and research labs to meet the game changers of the future. We'll also empower you with the latest research to help you take charge of your own health. You'll hear directly from people who are living with brain disease, as well as their loved ones and the care teams who support them. Join us on a journey to unravel the mystery of your complex brain. [theme music continues then fades out]

[1920s gramophone music, Memory Lane by Fred Waring plays] When you think about your favourite memories, what comes to mind? Is it the championship win at your high school football game? [crowd cheers] Your baby's first words? [baby babbles] Maybe it's the lyrics of a song used to love?

1:35 Fred Waring
[sings] I am with you wandering through memory lane.

1:40 Heather
Or that amazing girls' weekend to celebrate a milestone birthday? [champagne pops, women laugh] [gentle electronic music] Without our memories, who are we? I often wonder, and you probably do too, how does our brain log and store memories? Where do memories go as we age? And, why do we remember some things and not others? Most importantly, is there anything we can do to improve our memory? I have so many questions and that's why I'm delighted to introduce today's experts. Dr. Mary Pat McAndrews is a clinical neuropsychologist and a senior scientist at the Krembil Brain Institute. She's also Division Head of Clinical and Computational Neuroscience at UHN. Dr. McAndrews' work focuses on investigating memory and language in patients with memory disorders, including epilepsy and Alzheimer's disease. And, Dr. David Gould is a neuropsychologist and a clinician investigator with the Krembil Brain Institute. He primarily works with patients living with epilepsy. Dr. Gould also regularly consults with UHN's memory and neurosurgery clinics, as well as the Canadian Concussion Centre. Thank you both so much for joining me on the podcast today.

Dr. Mary Pat McAndrews 03:05
It's a pleasure.

Dr. David Gould 03:06
Thank you. [gentle, electronic music fades out]

Heather 3:08
Okay, so this podcast is all about the brain and the mystery of how the brain works, which kind of seems perfect when you're talking about memory, because we all have memories but not many of us really know what's going on in our brain. So, Dr. McAndrews, can you start us off and kind of help us understand what is memory, exactly? How does it work?

Dr. Mary Pat McAndrews 03:27
Sure. Well, I guess I would first say that memories are really kind of stories that we tell ourselves about ourselves, and so there are ways that we encode and retrieve and represent all the things that have happened to us in our lives. That allows us to revisit our past, to plan for the future, and to solve real problems in the present, so it really is our own identity, I would say, is our memories.

Dr. David Gould 03:53
I would say that, over the last little while, we've started to appreciate that memory is actually a living thing, and so the same way that you learn a memory or encode a memory is different from how you retrieve it, and so there are a whole bunch of factors like how you're feeling at the time you've learned or had the memory, and how you retrieve the memory that impacts how we later recall it. And so, I'm starting to think of memory as a living organism that can change over time.

Heather 04:20
Oh, that's so interesting. So, tell me how and where memories are formed and stored in our brain.

Dr. Mary Pat McAndrews 04:27
Memory is not stored in one place exactly, but there are certain parts of the brain that are really important for being able to remember things, and we know this because damage to those really important parts causes very severe problems with being able to learn or retrieve new information. And so, one of those is my very favourite structure in the brain called the hippocampus, and it's actually called that because that's a Greek word for "seahorse" and, if looked at from a particular perspective, it kind of looks a bit like a seahorse. So, in my office, of course, is covered with sea horses of all different shapes and descriptions. So, that's really a critical piece. We know that if that part of the brain is damaged-- and it's damaged in many different kinds of conditions. Sometimes, if you have a heart attack, that can actually cause a lack of oxygen, and that part of the brain is really susceptible to losing that oxygen. Sometimes, you can have a disorder or disease like encephalitis that particularly affects there. Epilepsy affects there and, of course, probably the best-known disease or disorder is Alzheimer's disease where that damage really starts in the hippocampus before it starts to move in other places. But, of course, not everything is stored there. It's really important for us, being able to lay down new memories, and to retrieve certain types of memories that are probably stored all over the brain in different parts of what we call the neocortex. So, I guess we now understand, after many years of research, that while the hippocampus is really important, it's not the only structure that's responsible for what we've learned over the course of our lives, and how well we can retrieve that afterwards.

Heather 05:59
Hence, the mystery of our memory – still learning so much about it.

Dr. Mary Pat McAndrews 06:02
Absolutely.

Heather 06:03
Dr. McAndrews, I have heard you in the past describe this whole idea of memories and memory retrieval kind of like a scrapbook in your mind. Can you explain that to me?

Dr. Mary Pat McAndrews 06:13

Sure. I like to think of it in the following way, especially in memory for our own personal past experiences or what we talk about is autobiographical memory. Anybody who's gone through scrapbooks—especially of your parents' and grandparents' ages—recognize picking up the picture and saying, "What the heck is that? I don't know who any of those people are," and, "What kind of dress is that that they're wearing?" etc. So, sometimes we can retrieve information that seems almost lost to us in terms of the fine details of how we first came to learn that information. It might seem fuzzy or indistinct to us, and we just have the general gist: "Oh, that must be grandma because," of the following kind of thing. And sometimes, it's as vivid as though we were opening a picture that we just saw last week, because the brain has been able to store and retrieve all of those fine details. So, there's really a gradient in terms of the kinds of information that we can remember later. And so, a scrapbook might not be a bad metaphor. It certainly isn't something though, that is like a direct video recording that we can just go back and look at, and static in time, and never changing, and just as bright as before. There's definitely gradations in terms of the way that memory is delivered back to us again.

Heather 07:24
Fascinating. Okay, since I have you both here, I'm going to tell you a quick story. I'm going to ask for your feedback. [chuckles] [upbeat electronic music] When I was in grade four, we were learning about archaeology, which I loved, and our teacher wrote on the board this 45-letter-long word, which I'm going to tell you now: pneumonoultramicroscopicsilicovolcanoconiosis. It's a volcanic ash. [laughs] And, I'm going to say it again, because I'm not reading it right now. I'm literally recalling this from my memory: pneumonoultramicroscopicsilicovolcanoconiosis. It is amazing to me that it doesn't matter how many years have gone by or how long it's been since I've even thought about this word or said it out loud, I always can recall it perfectly. Meanwhile, I can't tell you what I had for breakfast. [chuckles] [Dr. McAndrews chuckles] So, what's happening here? Where has it gone in my brain that I can pull it out as this cool party trick when I need to?

Dr. David Gould 08:14
I think, as Dr. McAndrews was explaining, that your hippocampus was involved with encoding that memory, and so that young, beautiful hippocampus had this wonderful experience of learning something that you were interested in. You had the right amount of emotional effect associated with it, so you were engaged, and it formed this vivid memory trace that later got transferred to other parts of the brain. So, we call that to form of memory transformation, and it's later consolidated to other parts of the brain so that, when you need to retrieve it, subsequently, it comes out in very high fidelity. [upbeat electronic music fades out] And so, it's a very strong, episodic memory, and it's rich, you can mentally time travel, so it's got all the characteristics of a very good, high-quality memory that we think of as episodic memory. And so, that memory is relatively stable over the course of the lifespan.

We think of some reasons why you might not be able to retrieve that memory could be interference, so maybe you start to learn other words that get in the way of that word, so let's say you're learning other words that are kind of fancy and long and they start to interfere with that really long word that you learned. And then, only a very small amount of memory is actually decayed or lost, and so there's a normal amount of memory pruning that occurs. We don't recall all the instances of our life, all the quotidian things that occur, and so certain information is pruned away because we don't need to remember everything. It would be too cognitively overloading if we didn't delete our memory trash bins, and so, in the absence of a small amount of decay of information, we think of memory as being relatively stable over the course of the lifespan, especially those very high-quality, rich, episodic memories.

Heather 10:06
My mom, who was turning 87 this year, has another word about the same length that she remembers from her elementary years, so... But, you talk about this whole idea of pruning. Dr. McAndrews, I know that we've talked about this in the past, this whole idea of how our brain chooses to remember certain memories, and not others, and really the importance of being able to forget. Can you expand on that?

Dr. Mary Pat McAndrews 10:24
Sure. So, forgetting is really a good way of purging the information that isn't going to be necessary for us. Again, memory isn't really just sitting around to be a scrapbook. Our memories are meant to help us engage with the world, to solve problems, to predict the future, etc. And so, evolutionarily, we are geared towards trying to remember things that are really going to be helpful in that regard. As Dr. Gould said, sometimes that comes with an emotional kind of component, but often it also comes with a strategic component in the sense of, "Oh, I must really recall this because it will help me in the future". Anybody who's looked for their parked car in the Eaton Centre or somewhere else—you know, a big car lot—has recognized, fairly early on, that you'd better employ one of those strategies if you hope to find that car again because, otherwise, it's going to be lost to you forever.

Heather 11:19
I feel like you're talking to me. [laughs]

Dr. Mary Pat McAndrews 11:24
I think all of us have had that experience, for sure, so definitely using some strategies helps us to kind of isolate the things that are going to be really helpful for us in the future, and those kinds of memories are going to stick with us, especially if they can kind of make sense of the world for us. Anything that is not going to be helpful in that regard is probably going to be lost to us, and that's why we have, occasionally, some kinds of things that we call flashbulb memories; you know, you may have that experience, especially for events in the world that have had a very high level of emotional significance, right, like the 9/11 tragedy, etc. So, I personally can remember being on an elevator in Sidney Smith Hall when I heard about that from a friend of mine who joined me on the elevator. I have a very vivid recollection of exactly that experience, even though that's not at all necessary for my remembering what happened in 9/11. So, those kinds of things come along for the ride for those kinds of episodic experiences. But, as Dr. Gould said, for the most part, many of our life experiences aren't all that important for us to be able to remember later, and so it's actually a mechanism that the brain uses to be able to kind of withdraw those connections that aren't going to be useful.

Dr. David Gould 12:33
The aspect of novelty is an important one, and so some of these events that really stick out in our memory are things that are novel. You described, Heather, this wonderful autobiographical memory of what was probably a novel experience for you. It wasn't just learning how to read or write; it was the chance to learn about this archaeological term that you'd later use in life as a testament to your wonderful memory. [Heather chuckles] And so, things that are novel are better remembered. So, if you have a typical route home in your commute and something unusual happens, it's more likely to be memorable than just recalling your regular commute. I encourage people to think about, "How can I make information novel to promote memory?" If someone tells you something, just a regular piece of information, "How can I kind of store it in my memory in a way that makes it stick out and be novel?" So, if you're thinking about, "Well, I want to try to remember these items for a grocery list. How can I make kind of a funny, interesting novel story with them or visualize them in a particular way around my house,

that's novel?" because that'll make it more memorable than just the typical things like, "Eggs, and chicken, and celery".

Heather 13:38
Right. And, I think a lot of people probably do that without even thinking about it, but doing it intentionally is kind of interesting.

Dr. David Gould 13:44
Dr. McAndrews mentioned memory and emotion, and we also know that the other side of that could be that too much emotion can actually interfere with memory. And so, Dr. McAndrews described the perfect event of high emotional salience in this 9/11 memory, where it was enough that it caught her attention and it's memorable. But, sometimes too much emotional salience, like in a traumatic event like a car accident, can actually impair our memory temporarily. And so, we have a stress hormone called cortisol, and when we're feeling too much anxiety, it's somewhat protective for our body to produce it, but it stops us from forming memories in those moments. So, our hippocampus is not able to lay down new memories, and so sometimes people ask, "Well, why can't I recall an event?" and sometimes the reason is that the emotional salience was actually too high. And so, even though a certain amount of emotion is helpful for memory, if it tips over into being too much emotion, it can actually interfere with memory.

Heather 14:44
So, it's almost like our brain is protecting us in that way.

Dr. David Gould 14:46
I think so.

Heather 14:49
I wanted to ask just about the idea of the reliability of memory because, when it comes to those long-term memories, short-term memories, you know, there is some question as to how reliable our memory is and does that change over time. Can you help us understand that?

Dr. Mary Pat McAndrews 15:04
[atmospheric electronic music] Sure. So, I'll tell it in two different ways, and both are evidence based, right? So, they're both based on science. There's a lot of research that's been done on a phenomenon of eyewitness testimony, and especially about how individuals might be questioned in different ways, and the question itself might actually change your memory representation of what happened, right? So, if I ask, "How fast was the car going when it hit the pole?" that might be different than, "How speedy was the car going when it rammed into the pole?" for example. And, actually, it's been found that people's estimates are different by a number of kilometres-per-hour, just on the basis of that question, and then they'll recall that as being faster or slower. So, definitely, the way that memory can be interrogated or questioned can change the actual memory representation.

On the other hand, if there's not this kind of additional information or interfering information, actually, memory can be quite reliable. So, another colleague of mine was looking at autobiographical memory, and it's hard to actually figure out how reliable it is when you're telling stories because I wasn't there at the time you were learning about that particular type of ash. So, what he did was to actually stage an event, people walking around the Science Centre, and they had to walk in a particular way, and they were shown a particular series of displays, etc. And then, he tested their memory immediately and very

long after, and it turns out that, in fact, while they forgot some of the information, they didn't distort the information. So, the information that they recalled was actually highly reliable. So, it can be reliable if nothing is brought up to be able to interfere with it. You might forget some things, you might distort them slightly by saying, "Oh, I went to the Science Centre five times. I can't really recall which of those five times I saw this in", but without that kind of interference, your memory can actually be fairly reliable for individual events like that. [atmospheric electronic music continues]

Heather 17:06
Okay, that's good to know. It sort of begs the question though, how does our memory change over time?

Dr. David Gould 17:11
One way of thinking about that question would be to say to you, "Well, how has that memory of your event changed?" – the one you described involving learning the archaeological term. So, you're still able to retrieve it, I imagine you're still able to travel back in time and to re-experience that event and, in some ways, that is a really rich time capsule of your experience. And so, it may be stable over time, and it may actually remain stable over your lifespan, and so in terms of the life of a memory, it can actually be one that has a long and healthy life. [atmospheric electronic music fades out] And then, to the question of, "How does memory change over time?" we think that, in the absence of medical diseases or other sorts of forms of pathology, that memory can remain relatively stable over time, but we know that that rich, episodic memory system—the one that's able to lay down the type of memory that you're describing—can actually get slightly weaker over time. And so, that is something that we know, when we look up the normative values of how younger people perform relative to older people, that there is a relatively small, age-related decline in episodic memory, but it's something that is manageable and is something that's expected, but we shouldn't expect, also, to lose our capacity to form that rich memory. And so, when people ask, "Well, why can't I form that new memory?" I would say, "Well, what's going on at the time there that you can't form a new rich memory? Are you attending to the information? Is it significant? Is it novel?" And sometimes, we also need a couple more learning trials to be able to kind of learn new information, and that's also normal.

Heather 18:51
That's so fascinating, and you're right. I can even remember where I was sitting in the classroom and I can even see the visual of the teacher writing it on the board, so I never thought about it in those terms, but it really does make perfect sense. I wanted to ask you both though, because you work with patients who are living with epilepsy and also with Alzheimer's, what happens to the brain's ability to remember, when there is disease or damage or an injury?

Dr. David Gould 19:15
In both of those major medical populations you described, there's a lot of variability. For some individuals, there could be mild, moderate, or severe forms of memory impairment, but what both of those conditions you describe have in common is that they often involve the medial temporal lobe, and that's the same real estate in the brain where the hippocampus is—an important centre for generating those episodic memory—and so, for some of those individuals, because there is damage to that region, either from the network that's activated in epilepsy, or structurally, from damage to those particular brain structures, and then in Alzheimer's, related to pathology in that region as well, that memory can be impacted. And, it can be very subjectively frustrating, and some of the memory complaints we hear across both those populations is difficulty with memory of vividly recalling events and forming new

memories, and being able to retrieve that in rich detail, and so there are commonalities between those two conditions.

Dr. Mary Pat McAndrews 20:20
For epilepsy, we tend to think that the damage in that region can be fairly static, and that it doesn't necessarily progress in the same way as it does in a condition like Alzheimer's disease. So there, unfortunately, when I first started talking about the fact that, really, our memories are our identities, that's where the difference occurs. So, in the individual with epilepsy, while they're having difficulty retrieving some of those kinds of events—and it is very frustrating—they don't feel different. They don't feel like they're not themselves, or that they've lost themselves, and their partners don't feel that, or their loved ones. Whereas, in Alzheimer's disease, unfortunately, as it progresses, that's exactly the kind of phenomenon that happens with both the individuals and certainly with their caregivers, later on. I've had so many family members just express to me the fact that, because the memory has changed to such a great degree, they can no longer even celebrate some of the kinds of pivotal pieces of information or moments or things that have happened in the past, or make plans for the future, and it does feel kind of like grieving your loved one while they're still with you because, in some real sense, their identity is no longer the same.

Heather 21:36
Yeah, it's so sad. I know that you work with a lot of these patients and, as neuropsychologists, what is your involvement in terms of your role in their care? And, tell me a little bit more about the multi-disciplinary approach.

Dr. David Gould 21:49
Maybe I'll start with our epilepsy program. Within our epilepsy surgical program, individuals might be considering having epilepsy surgery to help remove the place in their brain where seizures are starting, and so, if their epileptogenic focus can be safely resected and offer them an improved quality of life because their medications aren't stopping their seizures, the question is also, "Well, what's the impact on thinking skills?" So, people are wondering, "Well, how is this going to impact my language abilities, my processing speed, my ability to problem solve, my ability to remember information?" And so, what we do is we characterize that by assessing those skills. [flowing electronic music] So, it's a lot like being back in school where you have all different courses and classes, and so we're testing different skills and different abilities, and we'll have people construct blocks to try to see their visual spatial skills, we'll have people answer as many words as they can think of to try to see their language fluency abilities, and then we'll ask them to remember information and draw information, and we're testing all sorts of skills and we're comparing them both to themselves to find out their own personal strengths and weaknesses, but also comparing them to age-corrected normative data about, "How do they do in these different domains?" And, at the end of the day, we get almost like a report card of the different areas of thinking skills to say which areas are stronger and which areas are weaker, and, "Does that fit with the type of surgical procedure that you're considering?" or some other things like, "How is that impacting you in daily life or at work?" And so, our job is to characterize cognition and be able to help people think about what could be useful, what kind of strategies could be helpful, and how that impacts their medical decision-making for a surgery or some other process.

Heather 23:37
And so, you're looking at the area of the brain, when we're talking about surgery, that may be resected or taken out and how that particular area would affect all of these different skills. [flowing electronic music fades out]

Dr. David Gould 23:47
Exactly. And, the way I explain it to some of my patients is I'll say, "Well, you know, we've looked at what your brain looks like, and that's like looking at a car, flipping open the hood and saying, 'What does the engine look like?' but we haven't taken it for a test drive." And so, our thinking tests are the way of seeing, "Well, what kind of thinking skills come from those different brain regions?" to be able to comment on, "What kind of predictions can we make for cognitive changes if you were to have surgery?" And so, people need to be informed about what kind of risk there is with a medical procedure like epilepsy surgery, so it gives them the chance to really understand, "Well, what could be the cognitive trade-off if I were to pursue this surgery that could be helpful for medical reasons?" like controlling seizures that aren't responding to medications, which is an exceptionally important medical goal that we know helps to improve quality of life in our patient population.

Dr. Mary Pat McAndrews 24:40
We also have some additional kind of tools in the toolbox these days. In addition to the kind of back-to-school that he was describing, [chuckles lightly] we also use a new technique called functional MRI, where we actually have individuals, while they're in an MRI scanner, doing various kinds of language or memory tasks so that we can actually see where, in the brain, those areas are active when they're doing that. It's a way that we didn't have 30 years ago to be able to actually look directly inside your brain and say, "Hey, is that area working the way that it should? Does that area suggest that it's really responsible and very important for something like language function?" And so, if so, "Should that area be spared during any kind of surgery because we know that that particular part of brain is going to be compromised from that surgical approach, and so your language or your memory might be compromised?" So, that's one technique that we use in all of our epilepsy surgery patients so that we can get another way of looking into the brain.

And then, finally, there's also a technique that we use both in epilepsy surgery and in brain tumour surgery, where we will actually work with neurosurgeons directly, and stimulate areas of the brain with electrodes, placed directly within the brain, so that we can see if we can disrupt a function by putting in brain stimulation. So, for example, I might see this particular part of the brain light up on my MRI scan and say, "Hey, that's really important for language," and then if I stimulate that area, do I actually disrupt language function? And so, then, we can have a really high degree of confidence that we know exactly what that part of the brain is doing, and what the consequences of having a surgical approach that would involve that part of the brain will do. So, that actually adds to the toolbox that we had for, you know, many, many years, that Dr. Gould was talking about, and just gives us a few more ways of being more helpful in surgical approaches to these particular types of conditions.

Heather 26:39
Well, how exciting is it for you to see these advances happen in your career?

Dr. Mary Pat McAndrews 26:43
It's fantastic. [laughs] It's wonderful. I reflect on the fact that I started in this work about 30 years ago, and if you had told me what I would be doing 30 years down the line, I would have never predicted or believed you to be telling me the truth. The advances have really been amazing. Obviously, there's still a ton to learn and a ton to be able to use some of these advances in the best way possible to be able to integrate them in our regular clinical practice. In fact, we're one of the very few surgical centres in Canada, that is using fMRI as a regular part of our clinical workflow.

Heather 27:19
Dr. McAndrews, I know mentorship is very important to you. [uplifting electronic music] We recently spoke with one of your former trainees here at Krembil, and here's what Sam had to say.

Dr. Samantha Audrain 27:35
I'm Sam Audrain. I'm a postdoctoral fellow at the National Institute of Mental Health in Maryland, and I'm a former UHN trainee of Dr. Mary Pat McAndrews in Toronto. I'm really grateful to have had Mary Pat as a mentor. Mary Pat really allowed me to explore the questions that I was really interested in. She really prioritized her trainees. That's something that I'm really, really grateful for – my experience in the lab. I spent six years at Krembil as a trainee. I entered the program, master's year, and then continued on with my PhD. I was mainly studying patients who have temporal lobe epilepsy and who experience what is called accelerated long-term forgetting. So, these patients could learn pretty normally and retain information seemingly normally on our tests of memory in the clinic, so we test their memory across 20 minutes on our standardized tests, but they have these memory complaints saying that their memory is really terrible, and they don't know what to do about. It turns out that a lot of these patients were forgetting things over longer time periods, so they would go home, for example, after their visit with us, and then they're forgetting rapidly the things that we had done at the hospital, for example. It really is a longer-term memory issue that they were experiencing, and it's only recently that we've started to identify these issues in some of these patients. And so, my time at the Krembil was really trying to figure out, "What's going on with these patients? What's the neurobiology that is causing this? Is it their seizures? Is it some of the structural damage that some of these patients can have in the memory regions of the brain? Or is it something else?" That's the kind of research that I was pursuing. [uplifting electronic music fades out]

[rhythmic electronic music] One thing that we were studying at the Krembil was trying to figure out the neurobiology of why these patients are forgetting, and so one of our studies at the Krembil was trying to figure out is the issue, having to do with the hippocampus, which is a really important brain region for memory. When the hippocampus is damaged, a lot of the time, these patients can't learn as well or remember things as well across shorter time periods, so we thought maybe it had to do with subtle hippocampal damage that was causing this issue, or it could be some of these longer-term processes that we think are involved in stabilizing memories, longer term. And, basically, our research suggested that it had to do less with damage to the hippocampus and more so to do with different kind of communication between the hippocampus and the neocortex, where we think memories are ultimately stored. So, that process of this communication between the hippocampus and the neocortex, after you learn something, seems to be really important in typical brains for stabilizing a memory, but they aren't really communicating as well in these patients, it seems like. [rhythmic electronic music fades out] And so, now that I've moved on and I'm in my postdoc, what I am trying to figure out is how that kind of hippocampal and neocortical communication is important for stabilizing these memories, long term, just in typical brains, and which specific regions of the hippocampus are important. So, there's different regions of the hippocampus that we can only really examine with higher resolution scanning, using stronger magnets. And so, that's one thing that I'm currently working on, trying to figure out so we can kind of get a better understanding of that whole process. And then, later, we can bring it back to patients and say, "Well, how is this working differently for them?"

[bubbly electronic music] What I find so fascinating about memory is how the brain can store this vast amount of information about our experiences. We encounter so much in the world, and although only a fraction of what we experience makes it into our brain, long term, that we can actually recall, I think it's

just so mind blowing that we can even remember anything at all from our childhood, for example. [chuckles] So, I think that is just super, super interesting and exciting to me.

What I love about science is that it allows you to be very creative, actually. [chuckles lightly] I know this is maybe not what people think about when they think about science, but what I have found is that there's a lot of creative thinking that comes into designing experiments and thinking of the interesting questions to ask, and the best ways to get at those questions. That's something that I just love.

Being a trainee at Krembil really helped to prepare me for my postdoctoral position that I'm in now. My goal one day is to become my own independent scientist. I'd love to have my own research lab, have the freedom to kind of answer my own questions and train the next generation of scientists. [bubbly electronic music fades out]

Dr. Mary Pat McAndrews 32:13
Oh, mentorship is one of the biggest joys, quite frankly, of my professional life. I've had many wonderful trainees in the past, some who have gone on for clinical professional lives, more of them who've gone on in an academic sense. I know, you just were having an opportunity to talk with one of the recent trainees, Samantha. Sam actually joined with my lab, initially, thinking that she wanted to be a clinical psychologist, and started taking some of the required courses for that, and then she came to my office, probably about a year and a half into the program, and asked if I would be terribly disappointed but she's fallen in love with research, and she just wants to dedicate her life to doing research from now on. And I said, "Of course, I'm not disappointed. I think that's a fabulous life choice, and I'm so happy that you've been able to find enough excitement in that and enough fulfillment in that, in working in the lab, to really want to dedicate your life to learning more about memory and memory disorders in a research capacity".

So, it's the best joy to be able to see trainees flourishing in the future, to catch up with them again at conferences later on and see how they've been able to advance the knowledge. And, I will have to say, at this point, some of my trainees are actually holding *my* hand in terms of being able to use some of the latest kinds of statistical techniques, because they're much more updated on some of this information than am I. But, it's just such a joy to be able to see that and to know that I've had at least a little part in shaping their professional and, hopefully, personal lives.

Heather 33:50
That's got to feel good. One other thing that I've always wondered about memory is how sleep impacts memory, and especially the lack of sleep. So, Dr. McAndrews, can you tell us a little bit about your research in that area?

Dr. Mary Pat McAndrews 34:00
Sure. Yes, sleep is a fascinating new area that my lab is getting involved in. We've known for a long time, obviously, even if we look back at our own lives as students, when we stayed up all night to cram for an exam and then found that our performance was suffering on the next day, that we really do need an optimal amount of sleep in order to be able to function at our highest level. But, in memory, there's a really interesting phenomenon that occurs, which we understand as consolidation of memories, and that is the ability to take what might be a fairly labile, transient memory trace and turn it into a long-term memory that is going to be able to be retrieved much later on. And, we've been doing some research, especially in our patients with temporal lobe epilepsy. We did some earlier research showing that those individuals display a phenomenon that we call "accelerated long-term forgetting", and that

means that they can do just fine at a 30-minute memory test, but over hours and days, they forget that information much faster than do individuals who don't have this problem with their temporal lobe. And, we found that, unlike healthy brain individuals, for whom the amount of sleep especially what we call slow-wave sleep—not dream sleep, but sleep where the brain is humming along at a very slow pace—in slow-wave sleep, for most individuals, that sleep actually promotes memory consolidation, so the longer the that you've been in slow-wave sleep, the more likely you are to remember information that you learned before you went to bed, basically. So that, actually is a promoter. But, in our patients with epilepsy, we found, actually, the longer you were in slow-wave sleep, the worse your memory was, the more forgetting we showed.

And so, now we're starting to track that down and trying to understand, "Well, why is it opposite to what we see in the healthy brain individual?" And so, we have the opportunity to study these individuals while they have electrodes, recording the activity in their brain. We do this, of course, for clinical reasons to understand where in the brain these epileptic seizures are starting from, but we can also look then and say, "What was happening in the brain during that night's sleep, when you were either forgetting a lot of information or being able to retrieve it?" and one of the things that we're starting to understand is that individuals with this type of epilepsy often show what we call interictal discharges during sleep. What does that mean? A brief blip, basically, where the hippocampus is not coordinating its relationship to the rest of the brain. It's actually not really a seizure, but just a tiny, little, very transient blip, and we begin to understand that the more blips you have, the more that interrupts that important information exchange between the hippocampus and the rest of the brain. And so, this is telling us that, at a fundamental level, this disruption of sleep is actually contributing to our patient's inability to remember things, long term. It's not just that they have damage in the hippocampus; it's actually that there's this discharge in the hippocampus that's disrupting the mechanisms that are absolutely essential for us to be able to lay down those long-term memory traces. [upbeat electronic music] So, this is an entirely new kind of understanding we have in terms of what might be happening in the epilepsy brain.

Dr. David Gould 37:30
As a neuropsychologist and a neuroscientist, it's interesting to hear about how the brain is trying to replay the day's activities by the hippocampus transferring information to the rest of the brain. And, as a clinical psychologist, it's also kind of interesting to reflect upon how our dreams are influenced by some of the material that's occurred throughout the previous day. And so, it gives two different perspectives that we know that the brain is laying down the memory, but we also know that what's occurring can kind of transform and be really interesting from a psychological perspective of how we feel and the psychological content of our dreams, as well.

Dr. Mary Pat McAndrews 38:09
I never remember my dreams.

Heather 38:10
Really? [chuckles]

Dr. Mary Pat McAndrews 38:12
I'm so bummed that people actually do say they can remember them very well. My husband does the same thing. I have no idea what I dreamed the night before. [chuckles]

Heather 38:19

Isn't that interesting? And, I dream so vividly, almost every night, so we're getting a little bit closer to understanding that. I think dream analysis is a whole other podcast.

Dr. Mary Pat McAndrews 38:28
[chuckling] Yes.

Heather 38:28
I think I could go on for about an hour about that. Just following up on what you were talking about earlier, Dr. McAndrews, in terms of the impact that we're learning of the hippocampus in memory, especially with patients with epilepsy, can that be corrected in some way? Is that sort of the next step of learning about how this works? [upbeat electronic music fades out] Is there a drug or a therapeutic that can help to regulate that, to help increase memory?

Dr. Mary Pat McAndrews 38:52
So, that's a fantastic 300-million-dollar question, [chuckles] because it's probably going to take $300 million to figure it out. I will say, in epilepsy, that's not the way that the research is going. In fact, there are some drugs, actually, because they suppress activity in the hippocampus, might suppress seizures, but they might also suppress the good activity that's important there, right? But, there are new therapies that are based on brain recording and brain stimulation that are being developed and, in fact, used quite readily in the US, a little bit in Canada as well – what's called responsive neurostimulation. So, the idea is to implant a device that will be able to detect when a seizure is occurring, and deliver, hopefully, a disruptive pulse to stop the seizure from spreading. So, that's one way of actually having an impact there. There are, in fact, people who are also starting to look at how might that affect memory, but the jury is still out on that one. But, I would say that there are also other ways that we're trying to understand whether or not there's a signalling within the hippocampus that can be affected by various ways in Alzheimer's disease, for example, and I'm part of a couple of studies that are looking at that in Toronto, actually. So, one study is actually looking at individuals with mild Alzheimer's disease and seeing whether, again, brain stimulation—deep brain stimulation, this time, the kind that you use in Parkinson's disease, for example—can actually be used to kind of get those memory circuits more available or more active – if they're too quiet, to kind of juice them up a bit. And so, if you're doing that, can you make the hippocampus a little bit more lively than it is and see whether you can affect memory that way?

And, another study that we've just started now is actually looking very, very early on, before you've even developed any symptoms of Alzheimer's disease, but in individuals who might be at risk for that because of genetic loading, for example, and here, there's actually a new hypothesis that, early on in the disease, the hippocampus might be too active and that's actually part of the problem, and you need to get it a little bit quieter. And so, we're actually using a drug that's used in epilepsy, but at a much lower dose, to see whether or not quieting down that activity can actually prevent that individual from progressing to what we think would have been their natural course of Alzheimer's disease.

So, there's lots of different research going on right now, but it's very, very far from clinical implementation at this point in time. Dr. Gould might also have some suggestions in terms of not directly manipulating that structure, per se, but also kind of looking at other ways of solving the memory problem by using other kinds of strategies, for example.

Dr. David Gould 41:42

Yeah. And so, for people with more advanced types of memory conditions, there are groups that are looking at cameras that are able to record events during the day and replaying them in the evening time as a way of reinforcing the memory from that day, and there is some evidence that this is beneficial, but it's still modest. And so, I think we need to have reasonable expectations about what we can do in terms of memory rehabilitation, but I think strategies can be very effective, and so, for epilepsy, we're working on a study where we are teaching particular strategies, and I think about it kind of like teaching people to be good students in school, that there are particular strategies that help people learn information in a more efficient way, and also help them to retrieve it. And so, for instance, if you're thinking, "Gosh, I have a family reunion coming up, and I can't remember which uncle goes with which kids," then, you know, one of the strategies that we'd look at it would be retrieval practice, to be able to practice pulling out that long-term information from your own memory.

Heather 42:46
How does that work?

Dr. David Gould 42:47
So, what we would do in that instance, would be that it would be up to you to pull out that information after it's been reviewed. So, you might review your family tree, and you would practice pulling out, from your own memory, which person goes with which family member, and it's like practicing taking a test. Instead of just study, study, study, you're actually writing a test, as a practice test, to be able to see, "Can I retrieve the information?" So, we know that that strategy of retrieval practice can be more beneficial than simply just rehearsing which family member goes together with which other family member.

Heather 43:24
And so, you're making those tangible connections.

Dr. David Gould 43:24
Yes. [glitchy electronic music] And importantly, you're practicing retrieving it from your own memory, because one of the challenges of memory is not just encoding the memory, but also pulling it out of your own memory storehouse. And so, if you're retrieving it on your own, you're giving yourself some retrieval practice, which could be beneficial for retaining that memory.

Heather 43:45
Dr. McAndrews, how, for example, would you remember that my name is Heather?

Dr. Mary Pat McAndrews 43:48
Ah, so I try and make associations. If I had a good friend named Heather, I might be able to do that and try and figure out ways in which you're either very similar to that Heather or different from that Heather. Unfortunately, I do not have another good friend named Heather. [Heather laughs] You are the only Heather that's in my orbit. So, under those circumstances, what I might say is, I'll take some particular characteristic, maybe, of, you know, features, and I might say, "Well, you know, Heather makes me think of Scotland, and I see that this Heather has kind of a reddish, golden hair, which makes me think of the reddish, golden hair in Scotland." [Heather laughs] And so, then I might be able to make that association and, when I look at your hair, then I think, "Scotland. Heather. Oh, we got it there." So, I think the best ways is whatever works for you. I don't think there's any one memory trick that will work under all circumstances, and so you should just use whatever is at hand. [glitchy electronic music fades

out] So, if you ever dye your hair and I pass you in the hallway, Heather, I probably will not be able to remember your name. [Heather laughs]

Heather 44:49
Oh, well, that could have gone a whole different way, so thank you for that. So, we've talked about how memories are formed in store. You've both talked about your care and your involvement with those who are impacted, and we've talked a little bit about this memory retrieval, but I wonder, are there any other things or strategies that each of you do personally to boost your own memory function?

Dr. David Gould 45:10
When we look at large-scale studies, we know that things like exercise, good nutrition, wellness activities, those things are associated with better cognitive functioning overall and healthier aging, as well as improvements on some of these areas like memory. It doesn't impact memory differentially, but it seems to be helpful for our thinking skills in general. And so, lifestyle factors matter, and we've also looked at the memory training games. There's a lot of online or virtual or pay-for-service types of programs where people seem to be in these brain camps or other sorts of kind of study environments, and they're purported to improve memory. And so, one thing we found when we've looked at that is that they get better at the tasks that they're training on, but it doesn't really translate into other aspects of their life. So, we call that transfer. And, the benefits of playing a game or working on a particular app don't seem to transfer to other aspects of their life, like, "How do I remember Heather's name if I see her at a party?" And so, one of our takeaway messages is that they're not harmful to do these brain training games, but they're also not differentially better than doing your own memory strategies where you're actually trying to work on your memory by using it. And so, I give my patients the challenge of, "Well, why not try learning by going to a museum?" or, "Why not try learning by watching a very interesting documentary and teaching someone else about what you just watched?" Those are ecologically valid ways of training your memory, and it keeps you active but you're also testing your memory. You have to learn as well as retrieve the information, and practicing using it and using good strategies to help promote learning and retrieval can help your memory, overall.

Heather 47:02
So, Wordle is fun but it's not necessarily going to help your memory.

Dr. David Gould 47:05
Correct.

Dr. Mary Pat McAndrews 47:06
But it's great for competition's sake...

Dr. David Gould 47:08
Yeah. [all laugh]

Dr. Mary Pat McAndrews 47:11
..against your partner. "I got it in three." I'd just add to that, for myself, personally, intentionality is everything, so when I was a college undergraduate, I had my own strategy for helping me study for a test, final exam, and that meant I had to be able to note down everything I thought was important on three index cards. That's all I gave myself. And so, that allowed me to try and sift through the information to categorize it, to make strategic decisions about what I thought was useful or not, and I just had to write it down on those index cards. I could throw them away afterwards. It didn't matter. I

didn't need to actually look at them again because I've now been able to kind of use that information, synthesize it, in a very intentional way. If you walk into my office, you will still see lots of little Post-it Notes. By the time I've actually cleaned them up, I no longer know what those notes were meant to do, but I'm always able to recall it just because I've actually intentionally written it down. [gentle, electronic music] So, that's my strategy, and I think intentionality, just like finding your car again in the parking lot, you have to be intentional about it. That will work for me every time.

Heather 48:17
And, for me, it's lists. If I make lists and then I remake lists and then I do it again and I colour code them, then I won't forget. [chuckles]

Dr. David Gould 48:24
And, each time you're reviewing that list, you're actually having a new memory exposure, and so, not only is it practically helpful because it's cueing your memory—it's giving you support to help you retrieve it from your own memory—but, each time you write it out or rethink about the list, you're actually re-encoding the memory. And so, I think it's a good strategy for multiple reasons.

Heather 48:45
Thank you both so much for being here today. I think every time we get answers, we just have more questions, so then, I guess, that's science for you.

Dr. Mary Pat McAndrews 48:52
Absolutely. It keeps us going. Thanks a lot, Heather.

Dr. David Gould 48:55
Thank you. It was a pleasure. [gentle electronic music fades out]

Heather 49:15
[Your Complex Brain theme music] Thank you to Dr. Mary Pat McAndrews and Dr. David Gould for joining me on the podcast today. Thanks also to Dr. Sam Audrain for sharing her journey as a Krembil trainee.

[theme music continues] This episode of Your Complex Brain was produced by Jessica Schmidt. Executive Producers are Carley MacPherson and Tobin Dalrymple, with production assistance from Dr. Amy Ma, Twayne Pereira, Sara Yuan, and Suzanne Wice. For more information about the Krembil Brain Institute, please visit uhn.ca/krembil , and you can reach us by email at krembil@uhnresearch.ca, but please note that, due to privacy regulations, we cannot answer any personal health questions. Thanks for listening. We'll be back in two weeks with another exciting episode. Have a great day. [Your Complex Brain theme music fades out]