From Running Rats to Brain Maps

Sounds of May-Britt dancing, hooting, clapping cheering, her saying they believe in us, excellent science.

Nancy: That's what it sounded like 10 years ago, when Norwegian neuroscientist May-Britt Moser got the news that every researcher dreams of.

Nancy: It was Monday, Oct. 6. May-Britt Moser was deep into the weekly lab meeting where PhD fellows and postdocs share their latest findings. The results, from Charlotte Alme, were particularly fascinating. The meeting went overtime. And then, at 10:10, (phone ring AX) the phone rang.

May-Britt So I was sitting here discussing the data with Charlotte. And I was wondering, should I answer this phone? I normally don't answer phones that are from people I don't know. And then I thought, behave!

Nancy: It wasn't just anyone on the other end of the line, of course. It was Göran Hansson, secretary of the Nobel Committee for Physiology or Medicine, with the news. May-Britt Moser and Edvard Moser, along with their mentor and colleague John O'Keefe from the University College London, had just won the Nobel Prize in Physiology or Medicine for their discoveries of two types of brain cells that work together to function like a GPS in the brain, enabling animals -including us - to know where they are and navigate to where they want to go.

(Archive tape) **Nancy**: What did Edvard say?
May-Britt: We don't know, he doesn't know. He's on a plane to Munich.
Nancy: Oh no!
May-Britt: Oh no! I think that they're trying to call the pilots.
Nancy: So I have to ask you the question, which is, how do you feel?
May-Britt: Crazy!
This is so great for the whole group.
For the faculty, for NTNU, for Norway, for our politicians, for the research council.
It's so great because people believe in excellent science in Norway

Podcast music intro

Nancy: I'm Nancy Bazilchuk and you're listening to 63 Degrees North, an original podcast from NTNU, the Norwegian University of Science and Technology.

The 2014 Nobel Prize in Physiology or Medicine and the discovery of the specific cells that help us navigate radically changed the way neuroscientists looked at how the brain works.

Earlier discoveries mainly concerned how the brain handles information that comes in directly from the outside world – like sound, sight and smell.

But location and space? Knowing where you are isn't really a result of a sensory experience, as Edvard Moser explains it.

Grid cells, the type of cells that the Mosers discovered are a critical part of the brain's GPS system. They're found in the innermost reaches of the brain, far from direct lines of information from the outside world.

To understand why that's so important, think about vision. There's a nerve, the optic nerve, that goes right from your eyes into your brain. It's like a hotline between the eyes and the brain. There's no question where the signal comes from.

Grid cells, in contrast, while far from inputs from your senses, are nevertheless responding to a specific aspect of the environment – where you are and how you find your way.

The brain has found a way to organize its own internal understanding of space. That matters because it offers some of the first concrete insight into the mystery of how the brain computes things. And these types of neurons are found throughout the animal kingdom, from mice to rates to monkeys and bats and humans.

How did May-Britt and Edvard Moser figure this out, and why does it matter? What was the path that led two people, she raised on a farm and he, the son of an organ tuner, become celebrated neuroscientists? It's an improbable story of persistence, passion, curiosity and not a little bit of luck.

And, I was there to witness at least part of it. When we at the Communication Division got the call that May-Britt and Edvard had won the Nobel Prize, I hustled down to their offices and recorded everything. Later, when they had to write their biographies for the Nobel Prize webpages, I interviewed them to help them write a first draft.

The sound files that make up this podcast are from that time. They're a cool little time capsule from those heady days right after the award.

But… I made those recordings long before this podcast was born. So that scritchy-scratchy sound you may hear as you listen to the Mosers tell their stories – that's me, scribbling frantically so I had a backup in case the recorder failed! Just pretend you're a fly on the wall, watching history being recorded!

Nancy: May-Britt and Edvard met briefly in high school – which isn't as coincidental as it might seem, since they both grew up on islands not far from each other, on the west coast of Norway.

But it was in Oslo, where they were both students at the university there, that they really connected. Edvard did 15 months of military service, so even though he was a half-year older than May-Britt, she was already a university student when he came to start university, still quite uncertain about his studies.

As it turned out…. May-Britt was puzzling over the same problem, too. They met through a mutual friend.

Edvard: I still didn't know what I wanted to study. So I had considered nuclear physics. That was one of them. And then I met May Britt, and she had done a lot of different things. So we both were in the situation that we didn't really know what we wanted to do. And then we thought that perhaps let us try psychology.

May-Britt:
We decided that it would've been extremely interesting to study psychology, because then we could learn about the brain. And then I was connected to my childhood because I was so eager to understand why we do things.

Nancy: May-Britt's childhood summers on her family's farm were spent watching animals and wondering why they did what they did. At one point she even studied snails as they nibbled on grass. Studying psychology reflected her childhood curiosity.

Nancy: But the University of Oslo didn't have a ton of neuroscientists. Internationally, the field was rapidly developing, but still in its early stages. Just a few years before May-Britt and Edvard took up their studies, researchers David Hubel and Torstein Wiesel had received the Nobel Prize for their studies of how the visual system developed in mammals for their work in the 1960s.

As undergraduates, the Mosers found their way to Terje Sagvolden, a psychologist who was working with the neurochemical mechanisms of hyperactivity in rats.

May-Britt: It was quite exciting because.. first of all, we could work with rats. And that was interesting.

Nancy: But already here, May-Britt was thinking big.

May-Britt:We pushed him really hard. Can't you go into the brain? Because we want to understand why they are hyperactive. But he didn't have the tools or anything in his lab. He just wanted to do behavior, but he taught us statistics and…experimental design. And we learned a lot of behavior theories together with him. It was really exciting. But we always pushed him, "why can't you?"

Nancy: Edvard and May-Britt spent two years during their undergraduate studies working with the hyperactive rats, and published two papers based on their work. But it was a seminar by another University of Oslo researcher, Per Andersen, that convinced them his lab should be the next stop in their journey.

Nancy: Per Andersen was an internationally recognized neuroscientist who was named a Foreign member of the Royal Society and the National Academy of Sciences in the US for his groundbreaking work. He was a kind of research superstar in Norway and had his own TV show, “Your Fantastic Brain” on the Norwegian Broadcasting Corporation’s main TV channel.

Edvard: We actually decided to go to Per Anderson because he was working on plasticity in the brain that includes mechanisms of learning and memory. And that was really close to what we found interesting in psychology too.

Nancy: There was only one problem. Per was not a big fan of psychologists. He himself was an MD/PhD.

Edvard: We went to Per and asked if he could take us into the lab. And of course he said, no, no, because he had a big lab. And he didn't really want to take in more people. Another thing was that he was somewhat skeptical to psychologists.

May-Britt: he really didn't want us, and we knew that.

Nancy: But the couple was determined to change his mind.

May-Britt: I remember that I felt I was glued to the chair because I decided I'm not going to leave this room before he's accepting us. And you know, I'm known to be kind, but very stubborn. And he was extremely stubborn, <laugh> And then to experience these two people glued to the chairs, in his office, he was just...: I don't want to, and I just, you have to, you have to take us.
You have to accept us. And then he, I think he just realized he couldn't kick us out. He just gave in.

Edvard: After that, he said, okay, I will give you a test.

Nancy: But this was not what you might think of as a test, in an academic context at least. No, Per Andersen wanted them to build...

Edvard: A water maze, which is an entire new lab, actually a pool where a rat swims to find a hidden platform in milky water, so that they can't see it.

And then he gave us a few papers, and we started reading, and then we started building this.

May-Britt: What he said was if you are going to do your masters here, then read this paper, see if you understand this paper. And then build the water maze lab. And if that is a success, you are allowed to do a master thesis in my lab.

Nancy: The paper in question was written by Richard Morris, who developed the concept of a water maze while he was at the University of St. Andrews in Scotland in the early 1980s. It remains widely used today to as a test of spatial learning and memory in lab animals.

May-Britt: And, it was just a very simple, I think it had three pages. So the method was not very detailed.... But still, I remember that I said, oh, wonderful. Because then, we also want to do PhD with you (laughs).

Edvard: He wanted to us even to build the pool, to physically build it. But then at least we convinced him that we could buy it from one of these factories that make like fish tanks.

Nancy: They couldn't know, but even this small task, of building a lab from scratch, would prove to be very valuable in the journey that they're still pursuing today, 10 years after their Nobel Prize.

Edvard: Then after a few months, we were having rats swimming in the pool and finding the platform. And we did everything like it was described in the paper.

And then we started on the project to find out what is the role of the hippocampus in this navigation behavior.

Nancy: OK, time for a little translation: The hippocampus is a part of the brain that has been known to be critical in memory formation since the 1950s.

So this research actually involved removing a little piece of the rat's hippocampus to see if that area would affect the ability of the rats to find the hidden platform.

This required some VERY careful work. The rat brain is roughly the size of a small green olive. And the hippocampus, deep inside the brain, is roughly the size of an elongated sunflower seed!

Per wanted May-Britt and Edvard to look for a phenomena called Long Term Potentiation, abbreviated as LTP, which is a key mechanism underlying memory foundation but….

May-Britt: We thought that we need to find out whether the animals can learn when they have these lesions.

May-Britt: And then we have to make controls. So if we leave the middle part, we have to check, do they learn if you remove the dorsal, do they learn when you remove the ventral? And how does this look? And we are thinking like we were trained with Terje.

Nancy: A little more translation here: the dorsal part is the back part, while the ventral part is the front. BUT…. because of the way the hippocampus is shaped, like a fat curved sausage or a banana, it's also lower than the dorsal part. And Terje, of course, is Terje Sagvolden, with whom they worked as bachelor's students.

May-Britt: And then suddenly we realized that when they had a lesion in the dorsal part, they didn't learn. But if we had an equally big lesion in the ventral, they did learn. So there was a difference in this sausage that was so similar. And then we had to start to read anatomy.

Edvard: So essentially they lost old memory of location. But that was only after the dorsal lesions. So the ventral ones, the ones at the bottom, they didn't have the same effects. The hippocampus was at that time already known to be involved in this behavior. So we actually found out that it was only a part of the hippocampus, the more dorsal or upper part that was actually involved. So that was, that was our master thesis.

Nancy: May-Britt and Edvard actually wrote a joint thesis, which was not uncommon at the time.

And here was another bit of luck.

May-Britt: And then Per, because he was the president of the European Neuroscience Network, allowed us to bring a poster with our master's thesis to Sweden, Stockholm. Apink poster. And then, Richard Morris passed the poster.

Nancy: May-Britt loved pink, and she liked teasing Per, who probably would have preferred the poster be white. But May-Britt insisted that the poster be pink.

May-Britt: And he saw this and he said, wow ...
This is so exciting. The dorsal-ventral difference. And we had used his water maze, and he found it so interesting.

May-Britt: And then he said, why don't you come to Edinburgh and work with me? And he gave a plenary talk at that meeting, and he mentioned our poster, really, at this meeting. And I was like, whoa, the big Richard Morris is mentioning us!

Nancy: These results would eventually be published in the Journal of Neuroscience, which was a pretty big deal for two master's students. And starting with their meeting Richard Morris, who invited them to work with him, the doors began to open.

Nancy: Fast forward a little. Now married, May-Britt and Edvard both succeed in getting funding from the Research Council of Norway to do their PhDs with Per. This was extremely unusual because the grants were scarce and the Research Council generally liked to spread these grants to different universities. They traveled several times to Edinburgh to work with Richard Morris during their PhD studies. And… soon they were a family of four.

Nancy: It may seem incredible that having kids didn't slow the couple down. May-Britt says she just brought the kids to the lab. It seemed like the obvious solution. Their older daughter…

May-Britt: … was born in 91 in June, and we started the PhDs in 91 in January. So….we were so naive and so driven by forces, like, I don't want to be a housewife. We want to understand. Then we were sort of blind of, are you allowed to do this? Should you do this? Is this good for the child, for you, for the environment? We didn't care. So I think we were ….just in this bubble. But she was happy and we were happy. And when I had to go to the lab, Edward was sitting there looking after her, and then I would go.

Nancy: You may think this is part of Scandinavian egalitarianism, giving women the same freedoms and opportunity as men. But …

May-Britt: I didn't have the freedom. I just took the freedom. I think that is the difference. And I took the freedom and Edward and I took the freedom in such a way that people didn't think of stopping us. And they saw that we didn't do it because we were angry or tough, it was just that we want to learn, to understand. And we just expected things and the environment to help us on the way towards this vision.

May-Britt: And we never questioned that.

Nancy: They also had lots of support from friends and family. Edvard's parents would help, May-Britt's brother and sister-in-law helped, Richard Morris's wife helped when they were Edinburgh… the list is long.

May-Britt: People were extremely nice.

Nancy: Since May-Britt and Edvard had already been traveling to work with Richard Morris in Edinburgh while they were writing their PhDs, the natural next step was to do a postdoc with him. Here again fate intervened, in the form of Edvard's PhD thesis.

Edvard's dissertation looked at Long Term Potentiation, and found that the type of measurement that was commonly used was highly sensitive to temperatures in the brain itself, to the point where it could give misleading results if brain temperature wasn't factored into the measurements. It made him realize that if he and May-Britt really wanted to understand what was going on in the brain, they needed a new technique.

Edvard: it really made me quite keen on going to the individual cell recordings.

Nancy: And there was one person in particular who had already made major discoveries by making recordings from individual neurons: John O'Keefe, then at University College London.

O'Keefe, with whom the Mosers shared the Nobel Prize, had discovered specialized neurons in the brain in 1971 that he called place cells. Place cells are found in the hippocampus and are triggered in response to an animal entering specific places in its local environment.

Nancy: But there was one little twist: Remember, Edvard and May Britt were doing postdocs with Richard Morris in Edinburgh, with whom they'd had ongoing contact ever since he noticed their pink poster at the European Neuroscience Society meeting. Edvard thought he would be able learn to do individual cell recordings with Morris, but Morris himself didn't actually have experience with this technique.

Edvard: (47:22) So then he rather suggested that I go to O'Keefe and spend some time there to learn the technique, which was very kind of him because he was paying my salary.

Nancy: Edvard spent just three months in early 1996 learning how to do single cell recordings from O'Keefe. This involved inserting an extremely thin electrode in the hippocampus of the rat, so thin that it could squeeze in between the neurons in the brain. The end of the wire wasn't insulated, so it could pick up the electrical activity from nearby cells without damaging them. Not surprisingly, it's pretty delicate work.

Edvard: (48:14) So, he spent a lot of time with me, showed me everything from how to do the surgeries, how to make the electrodes, how to do the recordings, how to interpret the signals on the screen, how to analyze the data. And, also we talked a lot about the literature, what was known, what was not known. So it was really very intense training. So absolutely formative for our future.

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Nancy: May-Britt had a month with O'Keefe in the London lab too. She overlapped with Edvard's last month with O'Keefe.

May-Britt: (01:09:49) Edward had been there for two months, so he could sort of train me. So John didn't have to do it twice. But, I sat with John for surgeries, and he was excellent. So I learned so much. And also the way he treated the animals, and, just the experience of being in that lab meant a lot for me.

Nancy: It was a good thing that this training was so efficient, because fate was about to intervene again, big time. And this time, their fate would involve.... a bomb shelter.

Here's what happened.

In 1995, even before May-Britt and Edvard had finished their PhDs, a position opened up at the university in Trondheim, in the Department of Psychology. Terje Sagvolden from their bachelor days at the University of Oslo encouraged them to apply.

Edvard: It was one position in Trondheim... we sort of did it without really intending to take the positions, but we were encouraged to do it by Terje Sagvolden. And then, okay, we didn't put much effort into it, and didn't expect anything, because when we applied, we didn't even have the PhDs. So, we really didn't expect it. But then suddenly they called us in for an interview, and that was a total surprise.

Nancy: As luck would have it – again – the Psychology Department was expanding and they were able to offer May-Britt and Edvard *two* positions.

Edvard: They had a lot of flexibility, but nonetheless, it wasn't only about the positions. We also said we needed a lot of equipment, a new lab and everything. So it was quite expensive. But, we got it all. When we came to the interview, we had this long detailed list with every single piece of equipment, cost, companies, everything. I think they were so impressed by the level of detail in this list.

Nancy: Looks like Per Anderson's challenge to build the water maze paid dividends!

Edvard: We just said that this is what you need to build up. And then, that kind of convinced them even more. So we actually got it all. We didn't really know whether we should accept it or not, but in the end, we did accept it. And then the condition was that we come already in August 96 for the teaching. And that of course, completely shortcut our plans, because we wanted to either stay much longer with John O'Keefe, for a couple of years at least, or to go to Arizona.

Nancy: Arizona was where neuroscientists and former John O'Keefe postdocs Bruce McNaughton and Carole Barnes were doing groundbreaking work on recording from multiple neurons, not single cell recordings. So that was especially tempting. Spoiler alert: the Mosers would work with them eventually.

Nancy: The space the Mosers were given to build their lab was in a former bomb shelter in a part of Trondheim called Lade. They bought a little place nearby. Even though there were just two of them and they also had to teach, they managed to build everything. They also had to take care of the rats, run experiments, and of course, care for their girls. It didn't take long before they were able to run recordings.

Here it might help to understand how they actually ran their experiments and what they were recording. The rats were outfitted with electrodes on their heads – like little caps. The wires didn't impede their movement, so the rats could move freely.

During an experiment, the rats would be put in meter square boxes where their job was to chase around after little bits of chocolate. Fun! The electrodes would register a signal every time the neuron it was placed near would fire. This signal was sent to a computer, where it could be heard as an audible pop, like popcorn popping. Here's an actual recording of place cells firing during an experiment.

As the cells fire, they also show up as dots on a computer screen that corresponded to the location in the box where the rat was when the cells fired.

So for example, with place cells, the researchers could see that specific neurons always fired when the rat was in the same place in the box.

Edvard: The lab was up after half a year. So then it was operative, and we started doing these recordings. And after a year or so, we had the first cells, very excited about that. We're in a department of psychology, so, not everyone else was equally excited, but at least we had a good time.

Nancy: They had a lot of questions about these place cells.

Edvard: One of the first questions we started on was actually how is this place cell signal that O'Keefe discovered generated?

Nancy: And they had a way to answer this question, not just because they were able to do recordings. Remember their big breakthrough in Per's lab, the subject of the pink poster? There, they documented that different areas of the rat hippocampus played a wildly different role in how a rat remembered things. Anatomy was key.

Edvard: That's at least a major reason for the success is that we, unlike most other groups in our field, have used anatomy to guide us, to constrain the possibilities, and to create ideas.

Nancy: And once again, luck – and something else – played a role. Back when May-Britt and Edvard were finishing their master's degrees and puzzling over their findings, they reached out to a Dutch neuroanatomist, Menno Witter, then at VU Amsterdam, the Free University of Amsterdam. There's a fax that documents this exchange that hung for years on the wall outside of Edvard's office - early evidence of collaboration.

And at the same time as the Mosers were trying to figure out the different connections in the brain, they were also building connections out in the research universe.

Edvard: And for that reason, it's been so important that first Menno collaborated with us, and then later that he came here.

Nancy: And the Mosers found other ways to get help. They applied for funding from the European Commissions's Framework V(FIVE) programme, and got a grant in 2000. The money allowed them to build a consortium of seven groups with researchers from across the globe – and with whom they had worked in one way or another during their academic career.

Edvard: They were people we already had worked with, partly at least. And, they had the type of knowledge we needed.... An important part was to find out where this signal came from, and also to go out to the area outside the hippocampus, namely the entorhinal cortex.

Nancy: Time for a little more brain geography here. If you remember that the hippocampus is shaped like a tiny banana, deep inside the rat brain, then the entorhinal cortex is an even smaller structure - the size of a corn kernel – that is at the lower bend of the banana.

They were able to explore these areas because the EU funding success triggered a series of other grants.

Edvard: And suddenly around 2000, 2001, 2002, we had a lot of funding and that included also the center of excellence.

Nancy: The Centre of Excellence was a 10-year long grant awarded in 2002 by the Research Council of Norway. The Mosers called this group the Centre for the Biology of Memory.

This cascade of money, and collaborators from the EU Consortium, like Menno Witter and Bruce McNaughton and Carole Barnes, the researchers from the University of Arizona who May Britt and Edvard had wanted to work with, turbo charged the research coming out of the lab. For one thing, they had begun working with tetrodes, four electrodes that could record simultaneously.

Nancy: Now they were closing in on grid cells, even though they didn't know it. They began experimenting with trying to disrupt neural circuits in the hippocampus.

Edvard: One of the first things we then explored was the origin of this place cell signal. And we did that then by making small lesions in the hippocampus to interrupt the intrinsic circuit of the hippocampus.

Nancy: That didn't seem to affect the place cells at all.

Edvard: So that sort of led us then to look at the direct inputs that do not go through with the intrinsic circuit, and went out to the entorhinal cortex and started to record there, still in collaboration with Menno.

Nancy: What's interesting is that lots of researchers had already recorded in that little corn kernel shaped area, the entorhinal cortex, and had recorded signals, but no on had managed to make any sense of what they had recorded.

Nancy: And suddenly…

Edvard: So, this turned out to be the area that then contained the grid cells.

Nancy: Well..... not so suddenly. It was more like the Mosers were inching towards finding the grid cells. By this time they were working in the medial entorhinal cortex.

Edvard: Then, so already in 2004 in this area, cells have spatial activity. They have multiple firing peaks, and it looked quite regular. I didn't understand it quite.

Nancy: Here's what it sounded like - a cacophony of noise. But remember, the researchers were mapping each time the cells fired on their computer. As the cells fired, they showed up as dots on a computer screen that corresponded to the location in the box where the rat was when the cells fired.
That allowed the researchers to see that the cells looked as if they were firing in a certain way.

Nancy: There was one crucial missing piece that would eventually make the hexagonal pattern of how the grid cells fired clear.

The researchers were testing the rats in boxes that were one square meter in size. They were seeing the beginnings of the hexagonal patterns that grid cells make when they fire.

But.... it wasn't quite there.
So....after an eventful series of meetings at the 2004 Society for Neuroscience gathering in San Diego, they realized that if they needed a bigger box. Not a meter square box, but one that was four square meters. They also built a circular box with a diameter of two meters.

Edvard: (01:11:44) And then we extended the size of the environment and then saw the hexagonal pattern in it.

Nancy: And....

Edvard And that was the discovery of the grid cells.

Nancy: SHAZAM!

They announced the findings in a publication in Nature in the summer of 2005.

That was nearly 20 years ago now, and much has happened since. The Nobel Prize was a highlight, of course, but both before and after the award, the laboratory was growing and funding has continued to stream in.

The most notable funding award, among many, was being named a Kavli Institute in Neuroscience, one of only 7 internationally, and the only one in Scandinavia.
The Research Council of Norway also continues to support the Mosers' work, most recently with its third 10-year grant of a Centre of Excellence, which extends until 2033.

As the centre has grown and expanded, so have discoveries themselves. Many relate to new specialized cells in the brain, such as speed cells and border cells.

But more and more look at computation and networks, such as a network of cells in the lateral entorhinal cortex that encodes for episodic time. All this has been accelerated by the continuing development of new technologies to look deep into the brain to see what is happening.

Nancy: Ten years ago, when I recorded these interviews with May-Britt and Edvard, I asked May-Britt what her vision for the future was.

May-Britt: (01:46:26) And I feel that very strongly that I want things to happen. And what I think is extremely important here, and I think that will happen, is that we can build an institute that will grow in different directions, but having this ambition, we want to understand how the brain is generating cognitive processes. I think that having people with different backgrounds and just excellent people, good quality people, and friendly people, still ambitious, coming together, that is exactly what happened to Edward and me. So different and then coming together. And then it's just an explosion of ideas and creativity and using the different qualities that we have.

Nancy: Sounds about like what has happened, May-Britt! I'm Nancy Bazilchuk, and you've been listening to 63 Degrees North, an original podcast from NTNU, the Norwegian University of Science and Technology.

This podcast has been written, recorded, editing, produced and sound designed, by me, Nancy Bazilchuk. Thanks to May-Britt Moser and Edvard Moser and their stellar head of communications, Rita Elmkvist Nilsen.

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