Kavli Institute for Systems Neuroscience and Centre for Neural Computation

Annual Report 2014

Norwegian Centre of Excellence

NTNU – Trondheim
Norwegian University of Science and Technology

May-Britt Moser. Photo: Geir Mogen

A year for the history books

So many truly remarkable things have happened in 2014 for us at the KI/CNC that the year feels almost surreal. Each passing month made us feel both humbled and overwhelmed. Everything we've worked for over the past three decades has now reached the stage where the lab's professional development has skyrocketed, as has recognition for what we have achieved. I would like to take you through this year's highlights, with the recognition that it is impossible to name and thank everyone who deserves recognition.

The year began ceremoniously at Columbia University, where we accepted the 2013 Louisa Gross Horwitz Prize for "discoveries that have illuminated how the brain calculates location and navigation."

The Horwitz Prize is Columbia University's top honour for achievements in biology and biochemistry research. We shared this prize with John O Keefe. Eric Kandel, who introduced our award lectures, described it this way: "To begin with, it celebrates, as do all the Louisa Gross Horwitz awards, science at its best. Second, the Award celebrates an extraordinary collaboration between May-Britt and Edvard."

Shortly afterwards, we learned that we had been selected for another award, the 2014 Karl Spencer Lashley Award, given by the American Philosophical Society "in recognition of their discovery of grid cells in entorhinal cortex, and their pioneering physiological studies of hippocampus, which have transformed understanding of the neural computations underlying spatial memory." (We attended the award ceremony for this prize in November, right when we were in the thick of festivities for another, slightly more well known award that I will describe later in this text.)

March brought not just prizes but the publication of several important studies. You can read more about these publications – one on border cells, and one on smells and memories – elsewhere in this annual report. March also brought the news that Professor Yasser Roudi had been selected for the Fridjof Nansen prize for young scientists, for his work in the field of theoretical neuroscience.

April brought the news that both Edvard and I had been elected Foreign Associates of the US National Academy of Sciences. I am the first Norwegian woman to have received this recognition, and we as a couple are the youngest Norwegians ever to be elected.

In May, it was Menno Witter's turn to be recognized when he was elected board member of the Norwegian Health Association's Dementia Research Programme. Menno was our first group leader in neuroanatomy, and while all of us at the KI/CNC work with basic research, it is his work that is closest to having clinical implications.

In May we also learned that we were selected for the 2014 Körber European Science Prize. This is both a great honour and comes with a large sum of money, which we were able to invest in laboratory equipment. The prize of €750 000 is awarded by the Hamburg, Germany-based Körber Foundation. In announcing this award, the foundation said that it was "yet another recognition of their seminal finding of specialized neurons called grid cells, which are critical in helping all mammals, including humans, find their way."

The long spring days also found us preparing for the summer's highlight, the second annual Spitsbergen Neuroscience Conference, which we host on the magical arctic island of Svalbard. More than anything, we will remember the great talks, the science, the sharing of unfinished thoughts and work in progress. We want to thank all of the participants for sharing their time and minds with us, exploring what lies at the frontiers of neuroscience.

We also learned during the summer that Kavli researcher Kei Igarashi had been honoured with the Young Investigator Award from the Japan Neuroscience Society. The Society said that he had received the award "for his current studies in the lateral entorhinal cortex, together with his previous studies of the olfactory system." You can read more about his research elsewhere in this annual report.

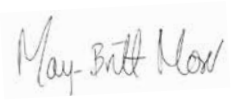
"Edvard and I are deeply grateful for all the attention, recognition, support and help we have been given"

In September we once again assembled a wonderful group of brain researchers in celebration of the Kavli Prize. This happens every other year, and after the Kavli Prize is awarded in Oslo, the neuro- and nanoscientists come to Trondheim to give lectures, attend symposia and meet with all of us and each other. Our good friend John O'Keefe was one of the 2014 Kavli Prize winners in neuroscience and Stefan Hell was here as the nanoscience winner. The two prize-winners had a good visit and discussion in the lab with Edvard and me, during which we discussed research and microscopy.

It is hard to believe that just four weeks later we would learn that we had been selected for the greatest academic recognition a scientist can achieve, the Nobel Prize. I'll never forget October 6: the phone call from Göran Hansson, secretary of the Nobel Committee, the long minutes afterwards before I dared to tell anyone, the combined shock and joy of the experience, and the whirlwind of festivities and attention in the aftermath, culminating with the Nobel lectures and award ceremony in Stockholm in December.

The timing of the Nobel Prize lectures was also extremely fortuitous, because both Edvard and I were able to present new, unpublished findings in our lectures. Two articles were published detailing these findings just after the December ceremony. One describes how the brain makes maps and memories for different rooms, with Charlotte Alme as the first author. The second explains how the brain puts a twist on internal maps to make them more robust, with Tor and Hanne Stensola as first authors. You can read more about both of these research areas later in this report.

Edvard and I are deeply grateful for all the attention, recognition, support and help we have, both now and the decades that we have worked to find out how the brain generates behaviour. Without the support and hard work of the many graduate students, post.docs, staff members, government and university officials and funding agencies and foundations, we would have never been able to achieve all that we have. We offer our deepest and humblest thanks to you all.



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May-Britt and Edvard Moser holding their Nobel Medals, during a visit to the Nobel Foundation's offices.

Photo: © Nobel Media AB 2014 Alexander Mahmoud

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A stream of exciting discoveries

May-Britt and Edvard Moser shot to fame in 2005 with their discovery of grid cells deep in the brains of rats – the discovery that resulted in their winning the Nobel Prize in 2014. But the couple is also responsible for a string of other scientific discoveries..

This is their story.

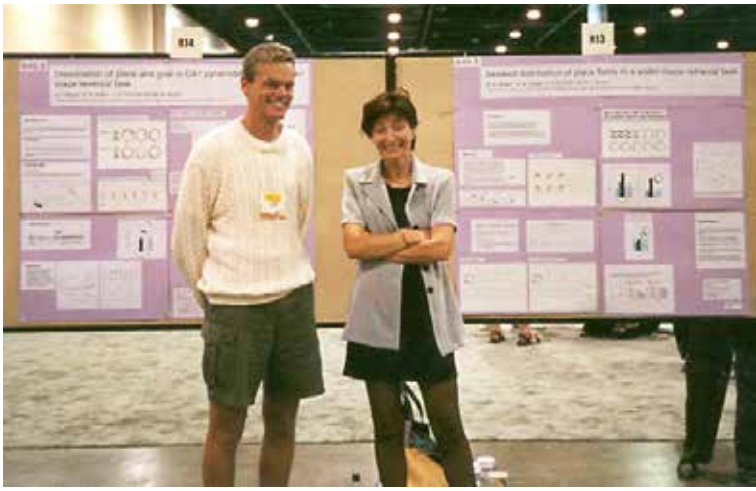
May-Britt and Edvard Moser's passion for neuroscience and the brain began in the early 1980s, when they were both psychology students at the University of Oslo (UiO). Their studies exposed them to classical psychological theories, such as behaviourism, as well to pioneering work being done in the newly developing field of neuroscience, where scientists were beginning to link external stimuli to neural responses. This in turn brought them to Per Andersen, a UiO neuroscientist whose work with the neural mechanisms of memory and a phenomenon called long-term potentiation (LTP) had led to ground-breaking findings.

The grand slam
Mari Trommald, May-Britt Moser, Paula Pedarzani and Edvard Moser, four of the six PhD candidates who defended their theses the same day. Their supervisor Per Andersen is in the middle. Facsimile from Universitas 1995.

The couple realized that Andersen's research might allow them to explore their own growing interest in linking neural activity with animal behaviour. But first, they realized, they would have persuade Andersen, a famous medical doctor who already had more than enough graduate students, to take them on.

Persistence pays

One day in 1988, the Mosers, by then a married couple, met with Professor Andersen. They knew that he would be reluctant to accept them as graduate students, given his already huge stable of students. But the pair simply refused to leave Andersen's office until he gave in – a strategy that in the end succeeded. Andersen agreed, with one catch: they could study with him

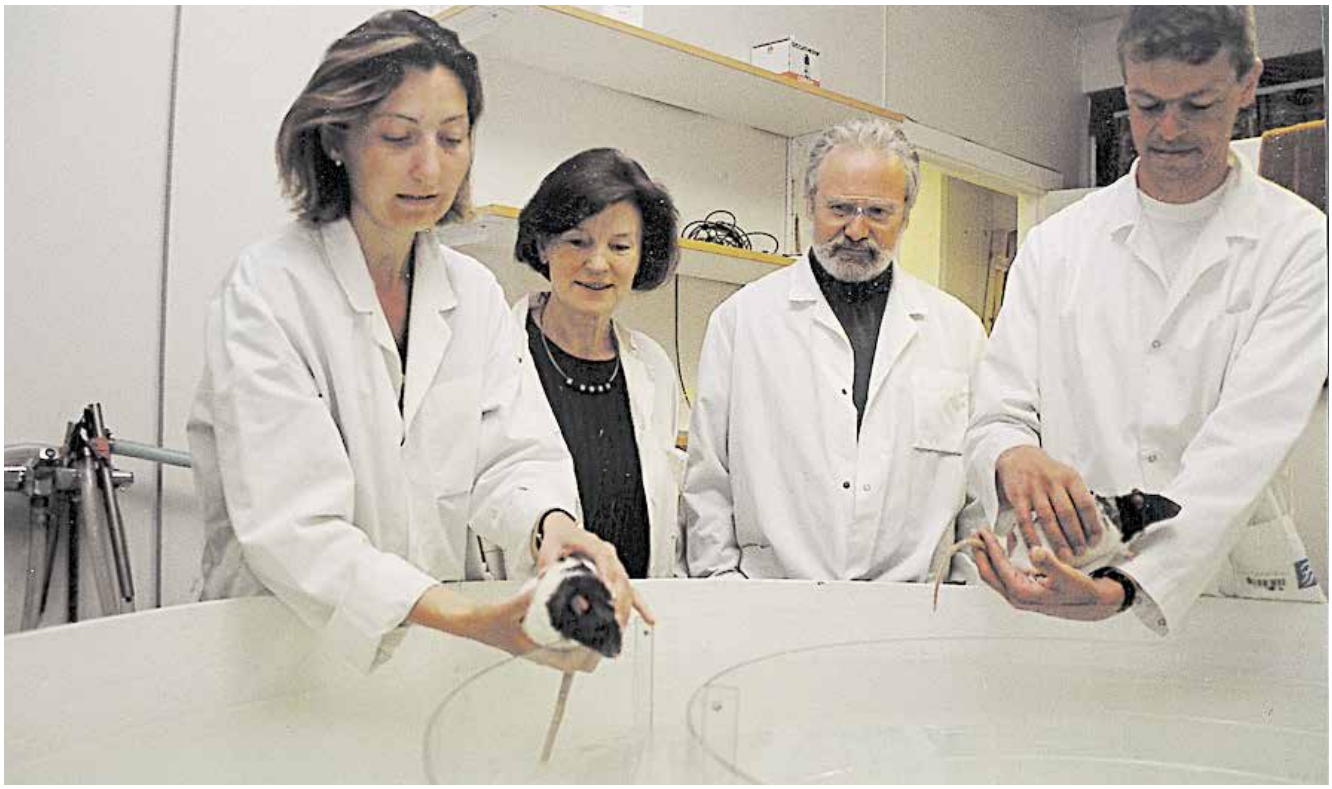


Miami, at the Society for Neuroscience annual meeting in 1999. May-Britt had insisted on pink posters. Photo: Private

if they could build a water maze laboratory after the design pioneered by University of Edinburgh neuroscientist Richard Morris.

Needless to say, the Mosers built the tank, which then allowed them to work on LTP in the hippocampus. Andersen wanted them to remove most of the hippocampus in living animals and then train them in the maze. The thought was that this training would increase the density of learning-induced synaptic changes. They hoped that with most of the hippocampus removed, the effects of learning (and thus LTP) would be concentrated in the small remaining part of the hippocampal slice. That, in turn, might make it possible to actually see LTP in the slice.

Until then, it had been assumed that the hippocampus was more or less homogeneous, but the Mosers decided to conduct their tests by removing most of the hippocampus from the dorsal side in one group of animals, and from the ventral side of the hippocampus in another group of animals as a control. This also allowed them to see if the location of the position of the remaining slice of hippocampus actually mattered. This rigorous scientific approach paid off. The experimental design allowed the Mosers to show that the dorsal hippocampus was much more important for spatial memory than the ventral hippocampus. That brought home the importance of detailed brain anatomy for understanding brain function, a lesson that would prove invaluable later in their careers.



Water maze where the Mosers studied memory in rats (in a basement room at the former Lade campus at NTNU)
From left: Associate Professor May-Britt Moser from the Department of Psychology, Professor Hanna Mustaparta from the former Department of Zoology, Professor Arne Valberg from the Department of Physics and Professor Edvard Moser, Department of Psychology.
Photo: Lars Kr. Iversen/NTNU Info.

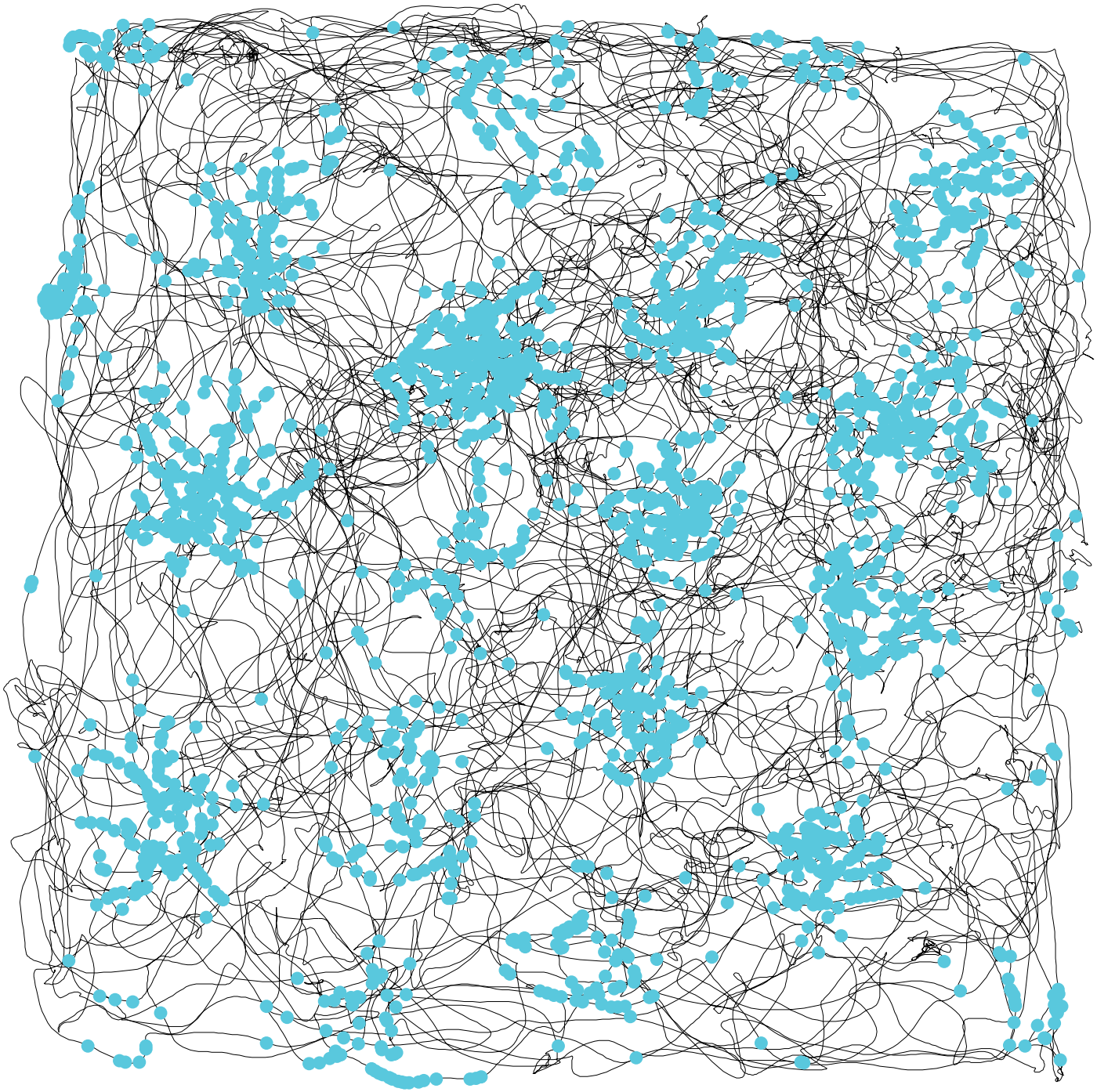
Partners and competitors

In 1991, both Mosers were awarded doctoral fellowships from the Research Council of Norway, and in 1995 they both defended their disserations at the University of Oslo. After submitting their theses but before their defence, they spent time in Edinburgh with Richard Morris, and then after their defence, they spent a few months as postdocs with John O'Keefe of University College London as their mentor. O'Keefe taught the pair how to implant electrodes in the brains of rats so that they could listen in on the brain's electrical activity in place cells in the hippocampus as the rats roamed freely in a box. This was the beginning of a rich relationship that was also characterized by friendly competition – and that would eventually result in the trio being awarded the 2014 Nobel Prize in Physiology or Medicine.

In 1996, just a few months into their postdocs, the Mosers received a surprise offer of two associate professorships at the Norwegian University of Science and Technology (NTNU) in Trondheim. The offer was simply too good to turn down, so they moved to Trondheim, by this time trailing a toddler and a baby. The first goal in Trondheim was to develop a better understanding of the origin of the place cell signals in the hippocampus. By 2000, both had been named full professors.

Their work also proved so successful that in June, 2002, the Research Council of Norway (RCN) announced that the Moser's laboratory for memory studies in Trondheim would be expanded to become a Centre of Excellence (CoE), with a decade's worth of generous funding. This marked the establishment of the Centre for the Biology of Memory (CBM).

Just a week after the RCN grant was announced, the Mosers published an article in the journal Science. This time, they reported that direct connections from the cortex were enough to form a spatial map in the hippocampus. The find hinted that the mammalian sense of direction was not only found in the hippocampus.



A perfect grid

The black line shows the path of a rat, roaming freely in a box of approximately 1.5x1.5 metres. The blue dots each show where a single spike signal from a grid cell in the rat's brain was obtained. Together the signals from one grid cell map out an hexagonal pattern like the one shown above.

Grid cells discovered

The duo's most famous result came in 2005 with the discovery of the grid cells in the entorhinal cortex, the brain structure that connects the hippocampus with the rest of the cortex. Grid cells react and send electrical signals at spatial points that combined form a triangular, Chinese-checkers-like grid. While human mapmakers draw a square grid of longitude and latitude to define points in their surroundings, the rat brain instead draws a grid consisting of equilateral triangles.

In 2006 the researchers were able to report that the entorhinal cortex also contains neurons tthat conjunctively encode where a rat is, how fast it is moving and in which direction. The brain, in other words, has a GPS, a speedometer and compass, the researchers reported.

In 2007 the couple got some of the best news they have ever received: The Kavli Foundation, which had been established by the Norwegian-American businessman and philanthropist Fred Kavli (1927-2013) to promote basic research, would finance the creation of the Kavli Institute for Systems Neuroscience at NTNU.

May 2008. Edvard Moser, Fred Kavli and May-Britt Moser at opening of the Kavli Institute for Systems Neuroscience Photo: Rune Petter Ness

Being named a Kavli Institute brought international recognition to the lab, along with membership in the community of other Kavli Institutes across the globe, and permanent financing. The newly named Kavli Institute was thus able to finance new positions. The first went to the Dutch neuroscientist Menno P. Witter, who accepted the offer to establish his own research group in Trondheim. The institute has since brought on Yasser Roudi, Clifford Kentros, Jonathan Whitlock and Emre Yaksi to establish their own research groups. Roughly 100 scientists, graduate students and staff now work at the Kavli Institute.

This is what we're looking for!
The Professors Edvard Moser and May-Britt Moser have just been appointed directors of the Centre for the Biology of Memory (CBM). They are showing recordings from a rat's brain. The tiny bumps are spikes that give off "a popcorn sound", and signify the firing of a neuron. Photo: Bjarne Røsjø

Contrasts are amplified

In early 2007, the researchers in Trondheim showed that a part of the hippocampus called the gyrus dentatus is involved in a process where the contrasts between similar memories are amplified before the memories are stored. While we as office workers might be inclined to store related documents near each other, the brain goes at this task in the exact opposite manner: it saves related memories in the most dissimilar ways possible.

The Mosers created another stir in late 2008 with their discovery of border cells in the entorhinal cortex. These cells "fire" electrical signals in laboratory rats when the animals approach borders in their environment, such as a wall, a fence or a drop.

From single cells to complex networks

Distractions are everywhere and we are bombarded by information, yet we somehow manage to focus on specific tasks, whether it's making dinner or writing scientific articles. Researchers had theorized that the brain must have a mechanism that it can use to pay attention to the body's present surroundings or its memories, perhaps as a failsafe and as a method to compare previous experience with what is happening in the here and now.

In 2009, Kavli researcher Laura Colgin and colleagues found out that the brain probably uses the frequency of gamma oscillations to route the flow of information in the hippocampus. This allows the brain to switch between paying attention to the present surroundings or to memories.

In 2010, the Mosers and colleague Rosamund Langston showed that rats come into the world with a rudimentary sense of location. We are not born with minds that are "blank slates", nor are we fully equipped with a finished functional navigational system. Our sense of location and ability to find our way needs to be developed and perfected by experience.

In 2011, the Kavli team with Lisa Giocomo as the lead author found a protein that controls a kind of zoom function in the rat brain's navigation system, comparable to what you see when you use the zoom function for Google maps.

The Kavli researchers also discovered that same year that memory is divided into discrete individual packets, analogous to the way that light is divvied up into individual bits called quanta. This allows different memories to be stored as individual packets without being mixed with each other. Lead author Karel Jezek also reported that each memory is just 125 milliseconds long – which means the brain can swap between different memories as often as eight times in one second.

In 2012, the Mosers' lab in Trondheim caused a new sensation when, led by researchers Hanne and Tor Stensola, they showed that the sense of location in the mammalian brain is organized into independent modules. The discovery of modules provides strong evidence of how the highest parts of the cortex are organized and was thus a great end to the first Centre of Excellence decade.

When the 10-year funding period for the Centre for the Biology of Memory ended in 2012, the Research Council awarded the Mosers a second Centre of Excellence, with funding to 2022. May-Britt Moser is the director of this new centre, while Edvard Moser continues as director of the Kavli Institute. The whole institution is now known as the Kavli Institute for Systems Neuroscience and Centre for Neural Computation (KI/CNC).

Congratulations are in order
May-Britt Moser with the employees at the Centre for Neural Computation, The second Centre of Excellence was awarded to the Mosers by the Research Council of Norway. Photo: Thor Nilsen

Expanding the toolbox

In January 2013, 16 scientists from three different research groups at the KI/CNC published two articles simultaneously in Nature Neuroscience – a testament to the power of cross-collaboration among the Kavli groups.

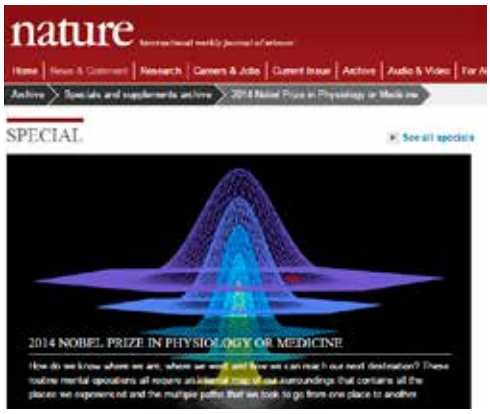
The articles described two findings. The first was about how a specific property of the network of stellate cells, the star-shaped neurons that are found in the medial entorhinal cortex, where grid cells are found, is able to generate grid-cell firing patters. The second related finding shows that the firing pattern is only formed when grid cells receive excitatory signals from neurons in the hippocampus.

Later that same year, researchers at the KI/CNC showed that a whole range of different specialized cells combine to provide place cells their information. The brain's GPS – its sense of place – is created by signals from head direction cells, border cells, cells that have no known function in creating location points and grid cells. Place cells receive both information about the rat's surroundings and landmarks, but also continuously update their own movement, which is actually independent on sensory input.

The discovery was made by using a new tool in the Kavli Institute's ever expanding toolbox: a genetically modified virus to carry a gene for developing a light-sensitive receptor into the cells that were directly connected to the place cells in the hippocampus.

Another tool in the Kavli toolbox is the ability of group leader Clifford Kentros to create a variety of special transgenic mice that give neuroscientists the ability to perceive and control specific neural activity in selected parts of the brain – for example, in the medial entorhinal cortex, the part of the brain where the Mosers found grid cells.

In addition, he designs and uses viruses, such as a "defanged" rabies virus that acts like a tracer in the brain, because it has been engineered to jump from the first neuron it infects to just one and only one other neuron. The virus carries a protein that causes the neurons it infects to glow when researchers shine a special light on them. In this way, the researchers can see which neurons are talking to which other neurons.



The Mosers love playing with the lab rats. Photo: Friedrun Reinhold

These tools allowed Kentros and David Rowland, then a PhD and now a postdoc in the Moser lab, to discover a shortcut in a key neural circuit in the hippocampus. They published their findings in the Journal of Neuroscience in 2013. Now Kentros and colleagues are trying to understand the significance of this shortcut. The article also proved the enormous potential of modern molecular neuroanatomical tools, because of their ability to determine the precise connectivity of the neuronal cell types that comprise the innate circuitry of the brain.

How the brain computes

In a feature news story in Nature after the Nobel Prize announcement, the Mosers were credited for giving traction to one of the most challenging twenty-first-century research frontiers: how the brain computes.

"Just as computers use programming languages such as Java, the brain seems to have its own operating languages — a bewildering set of codes hidden in the rates and timing with which neurons fire as well as the rhythmic electrical activities that oscillate through brain circuits. These codes allow the brain to represent features of the external world — such as sound, light, smell and position in space — in a language that it can understand and compute. With their grid-cell work, the Mosers have been the first to crack one such code deep in the brain; now the challenge for the field is to find all the rest," reporter Alison Abbott wrote in the 6 October 2014 issue.

The Mosers' basic research approach has always been to understand the sense of location as a model for developing a deeper understanding of memory and the workings of the brain. Edvard and May-Britt Moser have come much farther than they could have dreamed of when they visited Professor Per Andersen in his office in 1988. As leaders of the KI/CNC in Trondheim, they are well on their way towards unravelling how the brain generates cognitive functions from its network of connections between billions of neurons.

It's not hard to see that the coming years will continue to bring a series of exciting discoveries from the internationally leading research environment that has grown out of the efforts of two determined psychologists who would not take no for an answer.

At the Nobel Prize Award Ceremony in Stockholm, Sweden, on 10 December, presentation speeches extoll the Nobel Laureates and their discovery or work, a

fter which His Majesty the King of Sweden hands each Laureate a diploma and a medal.

The Nobel Banquet 2014

The Nobel Prize Award Ceremony is followed by the Nobel Banquet, with 1,300 guests, held at the Blue Hall of the Stockholm City Hall since 1934.

Speeches

Nobel Laureate John O'Keefe gave the speech on behalf of the Physiology or Medicine Laureates.

Divertissement

" Honour our past while nourishing the future"
Excerpts of works performed by The Royal Swedish Ballet

Menu

Cream of cauliflower soup, mosaic of red king crab, peas and lemon pickled cauliflower florets

Spiced loin of red deer, carrot terrine, salt-baked golden beets, smoked pearl onions, potato purée and game jus

Mousse and sorbet of wild dewberries from Gotland, saffron panna cotta and brown butter sponge cake

Stadshusrestauranger in collaboration with Chef Klas Lindberg and Pastry Chef Daniel Roos

Reality is distorted in brain's maps

The brain's GPS would be worthless if it simply contained maps of our surroundings that were not aligned to the real world. But we now know how this is done.

The way that the brain's internal maps are linked and anchored to the external world has been a mystery for a decade, ever since 2014 Nobel Laureates May-Britt and Edvard Moser discovered grid cells, the key reference system of our brain's spatial navigation system. Now, researchers at the Mosers' Kavli Institute for Systems Neuroscience believe they have solved this mystery. The results were published in February 2015 in Nature.

Tor and Hanne Stensola, lead authors of the Nature paper. Photo: selfie.

To understand the finding, think of regular maps and how they relate to your surroundings. When we go hiking and orient ourselves with a map and compass, we align the map using the north arrow on the compass and match it to the longitude lines on the map, to align the map with the terrain and make sure we find our way (unless we have a GPS that does the work for us).

We know our brains contain a number of internal maps, all mapped onto the surroundings, ready to be pulled up to guide us in the right direction. These grid maps come in different sizes and resolutions, but until now they have offered few clues as to how they are anchored to the surroundings.

The findings published in Nature explain the surprising twist the brain uses to align its internal maps.

Stitched to the wall?

"We recorded the activity of hundreds of grid cells," Tor Stensola, a researcher at the Kavli Institute for Systems Neuroscience says. "Looking at the information from more than 800 grid cells, we noticed that grid patterns typically were oriented in the same few directions. This was true for all the animals studied, which suggested the grid map aligns to its surroundings in a systematic way. Grid cells all seemed to be anchored to one of the local walls, but always with a specific offset of a few degrees. So we decided to investigate this."

The researchers recorded the activity of grid cells in rats as the animals foraged for cookie crumbs in a 1.5 square metre box. Now, if a map, represented by the activity of grid cells, were to represent the box it would need to look the same every time the rat ran in the box. And it would need to be aligned the same way too, independently of which way the rat ran, and where the rat was put into the box.

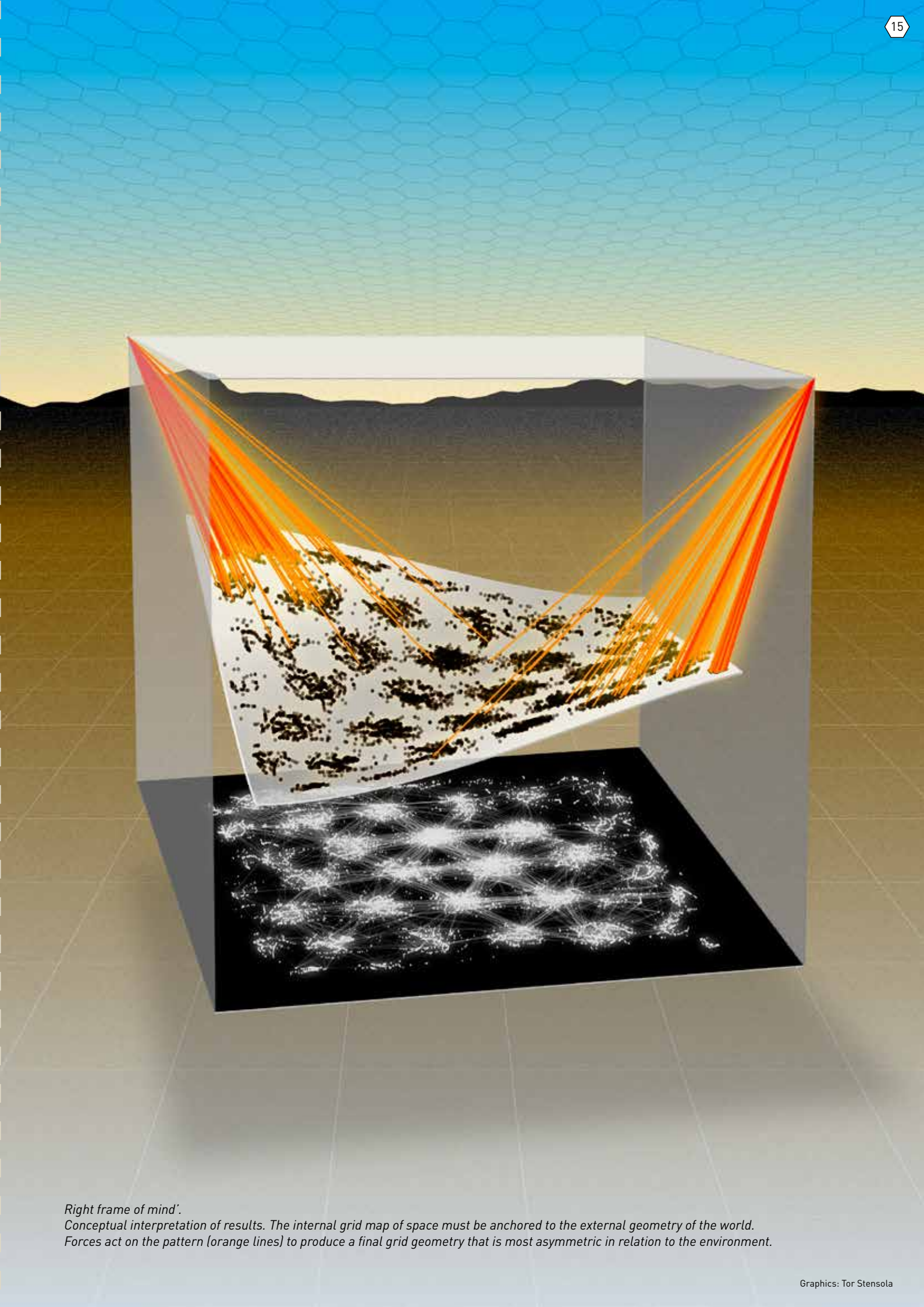
The recorded maps were indeed consistent. Each grid pattern was anchored to one of the walls. But none of the grids' axes were perfectly aligned with either wall; they were consistently askew.
"The map was rotated," Stensola says, where the angle was always approximately 7.5 degrees off of the anchored wall.

"We did some calculations and realized that there might be a very good reason for that particular angle. At 0- and 15-degree angles, the map would be symmetric. In other words, if it were perfectly aligned with the wall, that would mean it would mirror either the cardinal axis or the diagonal of the square box respectively, making it likely that places would get mixed up. The 7.5 degrees angle of rotation is the one that minimizes symmetry with axes in the environment, thereby minimizing these kinds of potential errors."

Perfectly asymmetric

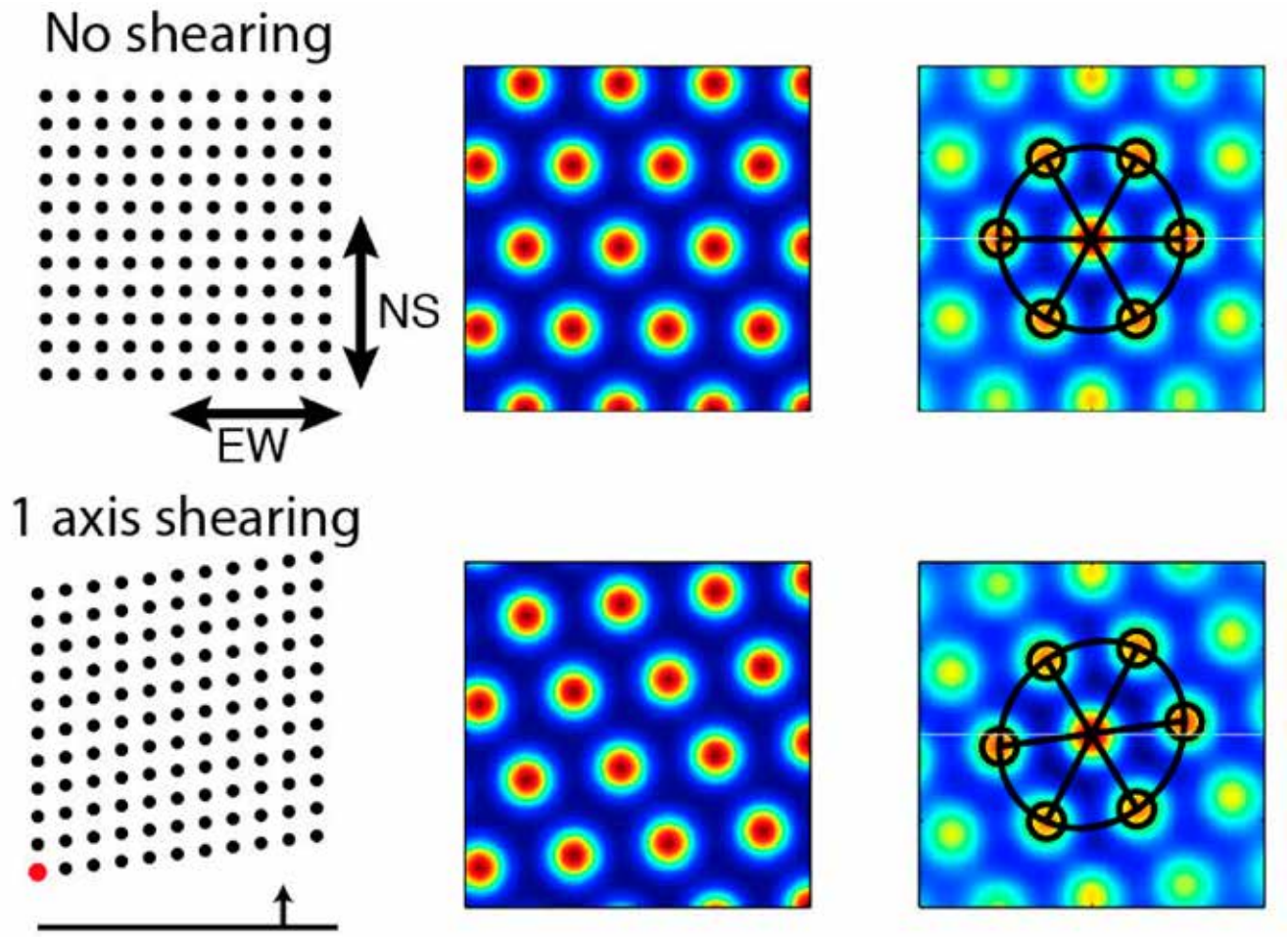
The researchers found more asymmetry in the grids. Grid patterns were not perfectly hexagonal, but instead seemed distorted such that they became asymmetric. Although this was known from before, nobody had any idea why.

"The inner six fields of the grid, the centre of the map, would lie on a perfect circle if the pattern was perfectly hexagonal," Stensola says. "The asymmetry caused these points to form an ellipse instead."



Right frame of mind'.
Conceptual interpretation of results. The internal grid map of space must be anchored to the external geometry of the world. Forces act on the pattern (orange lines) to produce a final grid geometry that is most asymmetric in relation to the environment.

Graphics: Tor Stensola



Shearing explains grid asymmetries. When a fake grid pattern is subjected to shear forces along a wall, both deformation and rotation result, exactly as seen in the recorded grids. Right panels show the effect on a square grid, middle and left panels on a hexagonal grid pattern. Both the orientation of the grid axes and the ellipse that arises from the deformation are shown with black lines.

The researchers looked into the connection between the rotation and anchoring of the grid, and the distortion of the pattern and found an almost perfect correspondence between the direction the ellipse was pointing and the direction the grid was anchored towards.
By skewing the pattern along one of the walls – a process known as shearing– the researchers could replicate both the ellipse and the 7.5-degree rotation of the grid.

Shearing forces displace parts of an object differently depending on the location of the part. To visualize how it works, think of when you push a deck of cards along the table, and the deck slides. The bottom card will stay put, the top card will be moved the most, and all the cards in between will move a distance that reflect its position in the deck. This kind of deformation has been seen in nature, where it is known to happen in trilobite fossils when external forces in the ground squeeze them into a new shape.

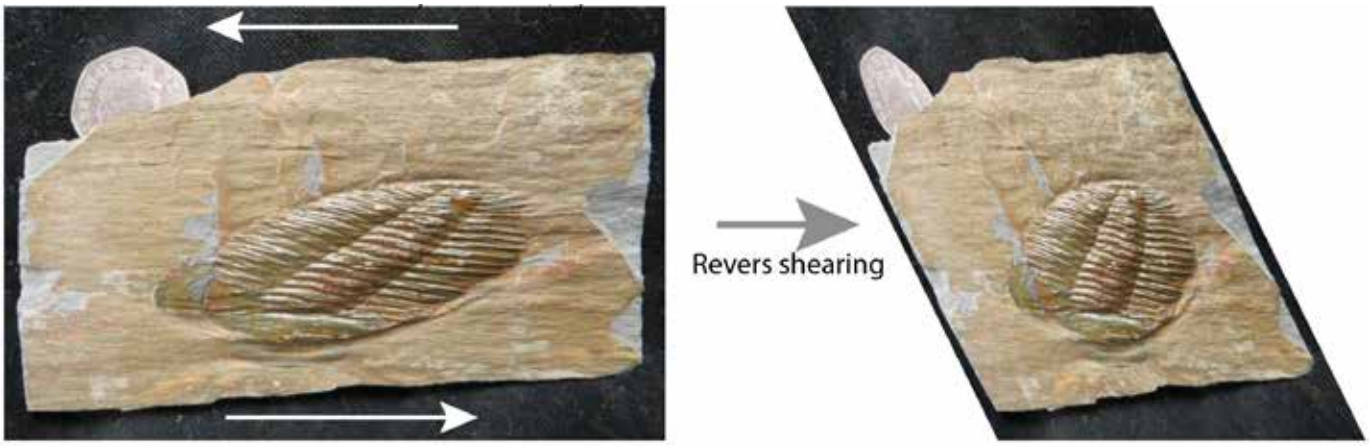
The researchers believe that once an animal experiences a novel environment it will form a map of the environment where one of the axes is perfectly aligned with a nearby wall. Gradually, shearing forces will distort and skew the map 7.5 degrees away from the anchoring wall, forming a stable and robust map with low chance of error.

Cornfields and the brain

But what happens to the internal maps when an environment is very large, like a cornfield? If local landmarks are very far apart, it may be advantageous for the brain to create several local and accurate maps rather than one inaccurate overall map. The researchers tested this by recording grids in a much bigger square box (2.2m squared). The map had the same asymmetries here as in the smaller box, but showed one crucial difference.

"As the box got bigger, some maps looked different," Stensola explains. "The maps broke in two, and became two separate local maps for the same box, anchored to opposite walls.
The grids were just as elliptical as in the smaller box. When the maps broke apart, we had to reevaluate. We knew that maps could anchor locally in complex environments. We now believe that the shearing forces can operate on not only the entire environment, but may apply locally as well."

This distortion towards asymmetry is likely what our brains use to reduce the frequency of error in self-localization, the researchers believe.



Shearing is occurs in many natural systems. Shown here is a trilobite fossil that has been deformed over time through forces operating in the earth's crust (left). By mathematically reversing the shear forces, the original shape of the fossil can be inferred (right).
Photos: Pete Lawrance, www.bigfossil.com

Edvard Moser. Photo: Geir Mogen

Physics enters the brain

Professor Edvard Moser, director of the Kavli Institute for Systems Neuroscience, believes these findings are important in connecting different fields of science.

"It is always a great feeling when we find the solution to a mystery that has puzzled us for a decade," he says. "The findings give us more clues as to how our internal maps interact with the surroundings. Now we'll have to figure out in detail how the information about the orientation of walls and boundaries in the surroundings reach the grid maps, and how this information is processed. Perhaps border cells will prove to hold the answer to this, we do not know this for sure yet."

Moser notes that they had to turn to physics to solve the puzzle of the sheared maps.

"How the laws of physics apply in the nervous system is an area full of unsolved questions," he said. "We'll just have to keep up the work to find out."

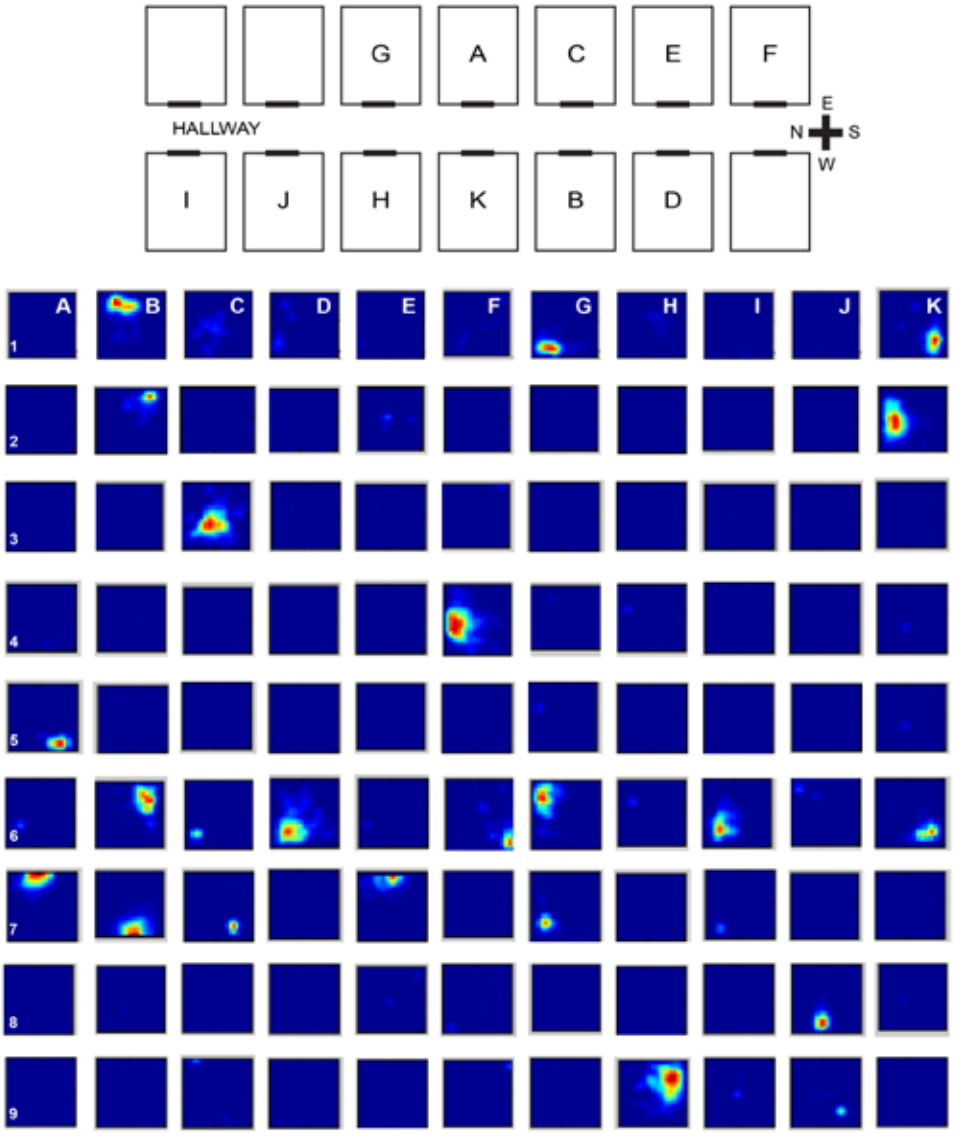
Eleven maps for eleven rooms

The brain has an enormous capacity for storing memories and keeping them from getting mixed. Kavli researchers have shown that memories are kept separate by connecting them to an environment, which then is stored in what resembles its own room in the brain.

Since the time of the Greeks, people have used a special memory trick that links memories to familiar places. You retrieve the memory by thinking of the place and calling up the associated memory. In 2014, researchers from KI/CNC published new findings on how the brain is able to store many separate but similar events, which helps explain how this trick works.

Place cells in the hippocampus

The brain creates and stores memories in small networks of brain cells, with the memories of events and places stored in the hippocampus. Researchers have long wondered if there is an upper limit to our capacity to store memories. Nor do they fully understand how we are able to remember so many events without mixing up events that are very similar.



Top: Schematic of the organization of the rooms inside the lab.
Bottom: Place cells (1-9) form maps that are independent across 11 rooms (A-K)

Charlotte Alme and her colleagues from the Kavli Institute and from the Czech Republic and Italy explored these issues by testing the ability of rats to remember a number of distinct but similar locations. Alme is a PhD candidate and first author of a paper that was published in the Proceedings of the National Academy of Sciences of the United States (PNAS).

The researchers studied seven laboratory rats as they ran around in 11 distinct yet similar rooms over the course of two days. The freely running rats wandered around the rooms in pursuit of chocolate crumbs while researchers recorded brain activity in specific cells, called CA3 place cells, in the hippocampus.

Separate and independent memories

The rooms were very alike, but the rats still managed to create a separate, independent memory, or a map for every environment, the researchers found.

The CA3 place cells the researchers recorded formed unique representations for each environment. The researchers also found that these unique representations or firing patterns were stored in the rats' memories so that when the animal was introduced to one of the rooms a second time, the spatial map from the rat's first exposure to the room was reactivated.

"We investigated whether these memories overlapped across some rooms, but all of the memories were completely independent. This indicates that the brain has an enormous capacity for storage. The ability to create a unique memory or map for every locale explains how we manage to distinguish between very similar memories and how the brain prevents us from mixing up events," Alme explains.

Professor May-Britt Moser, who is the corresponding author of the paper, mentioned the research in her Nobel Lecture on 7 December in Stockholm and said that the findings are important for understanding episodic memory, or memories that are formed from autobiographical experiences. The publication is a contribution by Professor Moser to a special series of Inaugural Articles being published by PNAS in honour of those elected to the National Academy of Sciences in the USA in 2014.

Photo: Erlend Lånke Solbu

Why your nose can be a pathfinder

In 2014, researchers at the KI/CNC discovered that the brain connects smells to memories through an associative process where neural networks are linked through synchronized brain waves of 20-40 Hz.

The discovery helps explain the process behind the phenomenon made famous by the French author Marcel Proust (1871-1922) in his novel Remembrance of things past. When an adult Marcel eats a madeleine cookie dipped in lime-blossom tea, the fragrant smell immediately transports him to memories of his childhood and his Aunt Léonie, who used to serve madeleines every Sunday before mass.

Kei Igarashi
Photo: private

"We all know that smell is connected to memories," KI/CNC researcher Kei Igarashi explains. "We know that neurons in different brain regions need to oscillate in synchrony for these regions to speak effectively to each other. Still, the relationship between interregional coupling and formation of memory traces has remained poorly understood. So we designed a task to investigate how odour-place representation evolved in the entorhinal and hippocampal region, to figure out whether learning depends on coupling of oscillatory networks."

The KI/CNC findings with Igarashi as lead author were published in Nature in June 2014.

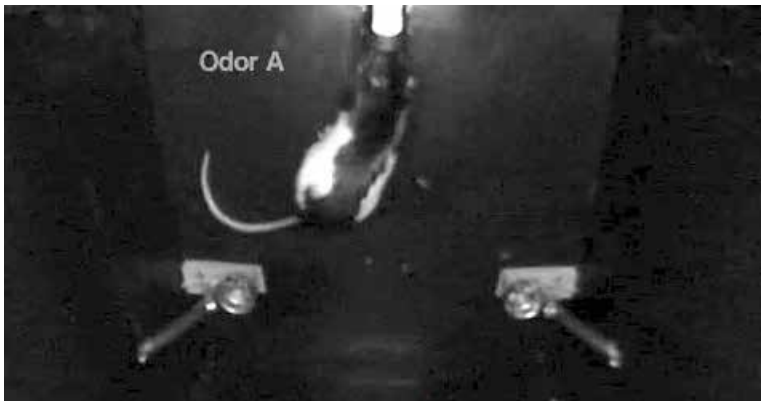
Smell guides the way in maze

The researchers designed a special maze that included a hole that a rat could poke its nose into. When the rat poked its nose into the hole, it was presented with one of two different smells. One smell told the rat that food would be found in the left food cup behind the rat. The other smell told the rat that there was food in the right cup. The rat soon learned which smell would lead to a food reward where. After three weeks of training, the rats chose correctly in more than 85% of the trials. In order to see what happened inside the brain during the task, 16–20 electrode pairs were inserted in the hippocampus and in different areas of the entorhinal cortex.

After the rat had made clear, strong associations between smells and places, the researchers could see a pattern of brain wave activity (the electrical signal from a large number of neurons) when the rat actually performed its task correctly and retrieved the food.

Coherent brain activity evolves with learning

"Immediately after the rat is exposed to the smell there is a burst in activity of 20–40 Hz waves in a specific connection between an area in the entorhinal cortex, lateral entorhinal cortex (LEC), and an area in the hippocampus, distal CA1 (dCA1),



When the rat poked its nose into the hole, it was presented with one of two different smells. One smell told the rat that food would be found in the left food cup behind the rat. The other smell told the rat that there was food in the right cup. Photo: Kavli Institute

while a similar strong response was not observed in other connections," Igarashi explains.

This coherence of 20–40 Hz activity in the LEC and dCA1 evolved in parallel with learning, with little coherence between these areas before training started. By the time the learning period was over, cells were phase locked to the oscillation and a large portion of the cells responded specifically to one or the other of the smell-odour pairs.

Long distance communication in brain mediated by waves

"This is not the first time we have observed that the brain uses synchronized wave activity to establish network connections," Edvard Moser, director of the Kavli Institute for Systems Neuroscience says. "Both during encoding and retrieval of declarative memories there is an interaction between these areas mediated through gamma and theta oscillations. However, this is the first study to relate the development of a specific band of oscillations to memory performance in the hippocampus. Together, the evidence is now piling up and pointing in the direction of cortical oscillations as a general mechanism for mediating interactions among functionally specialised neurons in distributed brain circuits."

So, there you have it – the signals from your nose translate and connect to memories in an orchestrated symphony of signals in your brain. Each of these memories connects to a location, pinpointed on your inner map. So when you feel a wave of reminiscence triggered by a fragrance, you can think about how waves created this connection in the first place.

Born with a border patrol in our brains

It has been known for a few years that grid cells in rats function in a rudimentary way as soon as the rats are born, but that they also take a while to perfect their performance. Border cells are different, however: New research shows that they are mature and able to respond to borders, edges and ledges as soon as baby rats open their eyes.

The feeling you experience as you approach the edge of a cliff is partly fear, partly excitement, and most definitely not indifference. Your senses are on alert and sharpened.

Whether or not this reaction is something you were born with has been heavily debated. It taps into the philosophical question of whether our minds are blank slates or have an inherent mental content when we are born. This is not easily tested in humans, but experiments with rodents have now brought us closer to the answer.

The brain in humans and other mammals computes its surroundings almost as if it was a GPS. In order to pinpoint your location, the brain uses signals from your senses as well as an inner calculation of how far and fast you move.

Some cells in the brain know which way your head is pointing. A specific set of cells responds exclusively to borders and edges. A different class of cells, the grid cells, does not respond to sensory input, but rather computes your movement in a system that corresponds to latitudes and longitudes. These combined calculations pinpoint where you are – projected onto an inner map of your surroundings.

All of these cells feed signals into cells in the hippocampus that give rise to what we call place fields. The signals work as identifiers of specific places.

Solving the riddle

The major riddle has been that these place fields, or place identifiers, show a maturity and specificity that the input signals do not. The place field signal is clear, but the reason why has been unclear – until now. Researchers at the Kavli Institute for Systems Neuroscience have now taken a closer look at the border cells and their role in this mystery.

"One way to figure out if some cell types need experience to become fully developed is to check how they work at a point in time when the rats have limited navigational experience, and follow changes in the cells as the animals grow older, and that is what we did," said Tale Bjerknes, lead author of the article "Representation of Geometric Borders in the Developing Rat", published in Neuron in March 2014.

Bjerknes explained that signal electrodes were inserted into the brains of rat pups before the age where they open their eyes, so that researchers could figure out their contribution to the place field. Rats open their eyes about 14 days after they are born.

Tale Bjerknes and May-Britt Moser with rat pups. Photo: Kavli Institute

Grid cells mature slower than border cells

The researchers used 9 female and 11 male rats. Electrodes recorded the activity in cells in the medial entorhinal cortex (MEC). When the young rats opened their eyes they were introduced to 70 cm x 70 cm boxes with 50 cm walls where they could roam freely, eating snacks.

From the pattern of signals, different cells were identified. Nine out of 128 cells were classified as border cells. Most of these cells responded to one wall, while some responded to two walls. Their reaction pattern did not change as the rats grew older.

But the grid cells showed only rudimentary pattern until the rats were about four weeks old. The experiment shows that grid cells function in a rudimentary way in newborn rats, but take a while to perfect their performance.

"These results point to the role of border cells as important in a local circuit mechanism that give rise to the mature place fields of the hippocampus," Bjerknes said. "Border cells, possibly with head direction cells as an additional source of modulation, could be the source of spatial information in young animals, awaiting the maturation of grid cells."

Attempt at displaying the Moser group in a grid pattern.
From back left: Juan Wu, Torgeir Wåga, Tanja Wernle, Debora Ledergerber, Maria Mørreaunet, Klaus Jenssen, Øyvind Arne Høyda
Grethe Jakobsen, Vadim Frolov, Eirin Hårstad, Alice Burøy, Li Lu,Ingvild Ulsaker Kruge,Ragnhild Irene Jacobsen, Endre Kråkvik,Hiroshi I

l, Jing Ye, Emilie Ranheim Skytøen, Kyrre Haugen, Richard Gardner, Ann Mari Amundsgård, Chenglin Miao
to, Håvard Tangvik, May-Britt Moser, Tor Grønbech, Bjarte Bye Løfaldli, Kei Igarashi, Edvard Moser. Photo: Ned Alley

Watching (fish) neurons in action

Neurobiologist Emre Yaksi brought roughly 10 000 zebrafish with him when he established his research group at the KI/CNC.

Zebrafish are small and their larvae are transparent. Yaksi's zebrafish also have an interesting modification: the neurons in their brains flash a light when they are active. The result is that you can see neural activity with a microscope.
Emre Yaksi began preparations in the autumn of 2014 to establish a new lab at the KI/CNC. The main goal of the Yaksi lab is to understand the fundamental principles underlying the function and development of neural circuits in genetically tractable model organisms.

The brain changes perception

Yaksi's special interest is how internal states of mind can modify the way an organism perceives sensory information. For example, if you smell food when you are hungry, you are likely to eat it. But if you smell food when you're not hungry, you don't care so much – even though the information entering your nose is exactly the same.

"Neuroscientists have long studied the parts of the brain where signals from the sensory organs are processed. Instead, we at the Kavli Institute are studying how 'pictures' from the sensory organs are processed during the next steps, deeper into the brain. We have known for years that brain areas like the hippocampus and the amygdala work respectively with memories/navigation and emotions such as fear, but recently we have realized that they also have the potential to modify the brain areas that process sensory information. The Kavli Institute is the best place in the world for studying these things," says Yaksi.

"It is important, of course, to ask the right questions when you are studying fish. Fish have to eat, avoid predators, reproduce and form social clusters, just like humans or other mammals. We want to understand the precise brain mechanisms that underlie these types of behaviours," he says.

A simplified version of the human brain

One advantage of looking at small zebrafish brains is that they only have 10-20 000 neurons. The human brain is far more complex and consists of about 80 billion neurons. But even though the zebrafish have simple brains, they still share several similarities with the human brain.

"You might compare the human brain to a modern computer with parallel processors, and the zebrafish brain to an old Commodore 64 from the 1980s. If you don't know how a computer works, it might be a good idea to start by studying the Commodore 64 and gradually progress to more sophisticated computers," Yaksi says.

"The big difference between zebrafish and human brains is that their cortex – which is responsible for advanced capabilities like thought, language and consciousness in humans – is much smaller than ours. Today, we have the means to look into the brains of the fish, but that is not the ultimate goal of our research.

By looking into the brains of these small fish, we are developing the tools that can make it possible to understand what we will find when neuroscience sometime in the future develops a technique to look into the human brain," he said.

Emre Yaksi

Emre Yaksi started his studies at the Middle East Technical University in Ankara, Turkey in 1996. He studied zebrafish for both his master's and PhD degrees from the Max Planck Institute for Medical Research in Heidelberg, Germany. He accepted a postdoc position in 2007 at Harvard University in the USA. From 2010, Yaksi was a group leader (and interim director) at Neuroelectronics Research Flanders in Belgium before he accepted an invitation from May-Britt and Edvard Moser in 2014 to join the KI/CNC. He has been awarded a Young Investigator's Prize from the Federation of European Neuroscience and, two generous research grants from the Norwegian Research Council and the European Research Council.

A neuroscientific toolbox

In studying zebrafish instead of rodents, Yaksi brings a radically new approach to the KI/CNC. In addition, the zebrafish larvae are so small and transparent that it is possible to see straight into their brains with the help of advanced microscopes.

The zebrafish are also genetically modified so that each neuron in their tiny brains expresses a fluorescent protein that was originally isolated from a bioluminescent algae. The fluorescent protein is embedded in each neuron's membrane and responds to variations in the concentration of calcium ions inside the neuron, which again reflects the neuronal activity.

The result is that the protein emits light each time the neuron sends a signal – an action potential – to another neuron. Yaksi and his colleagues can measure these small light flashes in the microscope and use them to study the inner workings of the brain and the connections between neurons.

"We are not really reading their minds, but you could say that we are getting closer. It is very fascinating to see how their small brains light up almost like Christmas trees when everything is in action," Yaksi said.

When Yaksi's new lab in Trondheim is completed, it will include between 90 and 100 different transgenic fish lines. The complete set of lines gives the researchers a large toolbox that can be used for many different experiments. In one of the fish lines, for example, the neurons express a special protein – channel rhodopsin – that is sensitive to blue light, and which is not so different from the rhodopsin protein in our retina that enables us to see blue light.

"When we shine a blue light into the brain of a fish from this line, the channel rhodopsin starts to let protons into the neurons. This activates the neurons and makes them fire action potentials to communicate with other neurons. This method can be used to unravel the connections between neurons," Yaksi explains.

The lab can also use some of these tools to study neurological disease. A small team of students is trying to understand what happens when a zebrafish has an epileptic seizure. If you can understand what causes the seizure, you might also be able to prevent it. Yaksi aims to expand the scope of his lab further and study neurological diseases that can cause autism and mental retardation in humans.

Yaksi group
Front row: Robbrecht Pelgrims, Ewelina Bartoszek, Nathalie Jurisch-Yaksi, Stèphanie Forè, Maximilian Hoffmann
Back row: Cecilia Brandt, Emre Yaksi. Photo: Ned Alley

Moving in 3D space

When animals decide to move, they first have to "plan" the movements they will make to get them to where they want to go. A part of the brain called the posterior parietal cortex (PPC) is deeply involved in generating these plans, but little is known about the kinds of neural computations that are made in the PPC.

Kavli group leader Jonathan Whitlock was awarded a NOK 7 million young research talents grant from the Research Council of Norway in December 2014 to fund a collaboration that will try to understand the codes the cortex uses when an animal moves in three dimensional space.

"The grant will fund a collaboration between my group, doing large-scale calcium imaging, and an expert in deep belief machine learning who will work closely with Benjamin Dunn (with the Roudi group)," Whitlock said. "The goal of this study is to deepen our knowledge of how cell populations in the PPC represent ongoing and upcoming bodily movements in their native 3D during self-guided motion though space."

The Mosers have mainly focused on spatial mapping, with grid cells and other cells in the hippocampus and the entorhinal cortex. Whitlock's work also involves navigation, but with a twist, because the parietal cortex is an area of the brain that plays an important role in visual attention, working memory, spatial processing and movement planning.

"The thing you have to realize at the outset is that navigation is not something that just the grid cells or hippocampus does, the whole animal does it," Whitlock said. "It is a composite contribution from the brain, it is complex behaviour. It's not just using your eyes or your legs, the whole animal is navigating."

And while we see the movements of an animal like a mouse as an integrated, fluid action, Whitlock explains that navigation involves serial motor planning, where the animal has to figure out a series of movements to get from point A to B.

The grant will allow Whitlock and his colleagues to track the behaviour of freely-foraging mice using both marker-based and markerless 3D motion capture – similar in many ways to the technology used by the movie industry to record actors' movements and transform them into CGI creatures, most famously used by Peter Jackson to create Gollum.

Monitoring movements

The researchers will record the relative limb positions, bodily kinematics and joint angles of the animals as they move about

Whitlock ushered the KI/CNC into the YouTube era when he gave a TEDx talk in April 2014 in Trondheim about the cellular bases of navigation and memory. Photo: screenshot from TEDx website

spontaneously. While the animals are foraging, they will conduct large-scale calcium imaging in the PPC to monitor neural activity from several hundred cells at a time.

"Our central goal will be to 'map' the activity of these neurons onto the moving body. To conduct such a massive-scale analysis we will develop powerful statistical tools, termed deep belief machine learning algorithms, which will 'learn' to discern regularities between neural activity patterns and movement features such limb motion, posture or gait," Whitlock explained.

"By imaging neural activity during a variety of natural locomotor behaviors, we aim to make a quantum leap forward in understanding the cortical representation of whole-body movements which largely comprise an animal's waking behaviour."

Whitlock also published a Perspectives article in Frontiers in Human Neuroscience in May entitled "Navigating actions through the rodent parietal cortex."

And while much of the output of the Kavli Institute takes the form of scientific publications and graduate students, Whitlock ushered the KI/CNC into the YouTube era when he gave a TEDx talk in April 2014 in Trondheim about the cellular bases of navigation and memory.

The talk described the basic concept of synaptic modifications as a memory storage mechanism, and also explained the idea of place cells and grid cells, and how spatial representation and memory are linked fundamentally at the cellular level.

"The audience was very enthusiastic about the topic," Whitlock said.

Whitlock group
Tuce Tombaz, Benjamin Dunn, Jonathan Whitlock, Bartul Mimica, Mikkel Antonsen, Qichen Cao, Tadiwos Feyissa Mergiya. Photo: Ned Alley

The Rat brain in 3D

The development of the first web-based rat brain atlas took a major step forward in 2014, when a new website opened with a standardized 3D volume of the brain.

The atlas is well on its way to achieving the goal of making information about the brain more accessible, detailed and specific for the benefit of international neuroscience.

Professor Menno Witter is leading the effort to create a detailed atlas of the hippocampus and parahippocampus in the rat brain. In 2014, these two regions were the first to become described in detail in a 3D brain atlas. The atlas will become increasingly more useful as new regions are added. Photo: Geir Mogen

"The ultimate goal of the 3D rat brain atlas is to allow researchers from anywhere in the world to enter their experimental data into the same volume and share them with other researchers," Witter says.
"Researchers don't normally present more than a few examples from all the experiments they have done in most of the papers that are published today. In contrast, the digital atlas allows researchers to enter all their data and make them available to anybody who might be interested."

The rationale for creating a digital brain atlas is similar to the rationale for creating a map of the world: It is useful to have an overview of how the world is divided into countries – and the brain into areas – with as much information as possible about each country/area and the communications between the different areas.

Eliminating duplicate efforts

"As the atlas becomes more and more complete, if you are planning an experiment in a specific region of the hippocampus, you should be able to navigate to that particular area in the atlas and find what is already known about the region," Witter said.

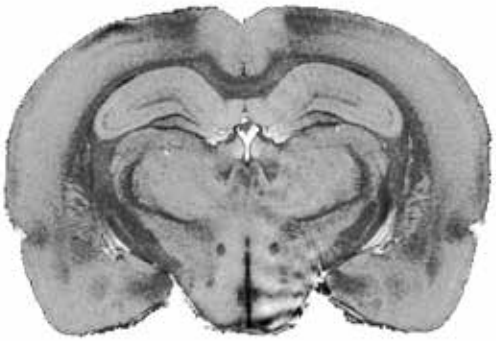
Having all of this information assembled in one place eliminates the need for scientists to put a lot of time and effort into collecting scientific papers and extracting information from them. The atlas can also give researchers information about work that needs to be replicated.

"They can also avoid doing research that is unnecessary because somebody else has already done it," Witter says. "This effort should really make neuroscience more cost effective."

Zooming in on details

The first version of the hippocampal and parahippocampal parts of the rat brain atlas consisted of two-dimensional sections through selected parts of the brain. The new version includes three planes of sections.

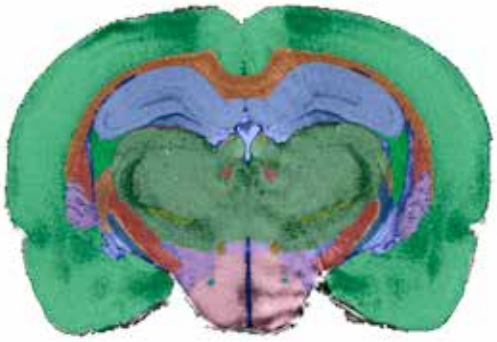
"The main delineations in the current version of the 3D atlas are based on magnetic resonance imaging (MRI). This information is then supplemented with information about the directionality of fibres inside the brain, created with a technique called diffusion tensor imaging (DTI), which also relies on the use of an MR scanner. We have also been able to enter 15 different borders that define the internal subdivisions of the hippocampus and parahippocampus," Witter explained. The detailed data from the sections will be added this coming year.



The website opened in 2014 with a detailed 3D map of the hippocampus and parahippocampus in the rat brain. More regions will be entered as quickly as resource allow it. Illustration: http://www.rbwb.org/

The atlas will allow researchers to virtually move around the brain to see what different cross sections might look like from different angles.

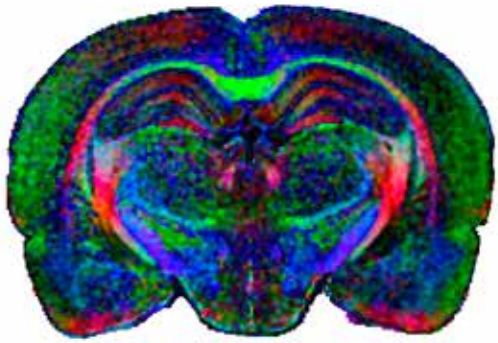
"For example, if you have an experimental brain that is cut into a coronal (frontal) plane, you can use the atlas to find out what a section at the same place would look like if you had cut it in a horizontal (transverse) plane or in a sagittal (lateral) plain instead," Witter said. "Another feature that is almost ready is that users will be able to rotate the volume and look at sections that are tilted in relation to the three original planes. This is a useful feature, because it is quite common in experimental work to cut sections that are slightly tilted."



Next step is mapping connections

The atlas contains detailed information about more than 50 parts of the brain, but the hippocampus and parahippocampus are the only parts with a great amount of detail thus far.

"If you compare the whole cortex to Europe, you could say that we now have delineated Norway and Sweden and started filling the map with information about all the places that have been studied," Witter said. "The next thing will be to map the connections inside Norway and between Norway and Europe."

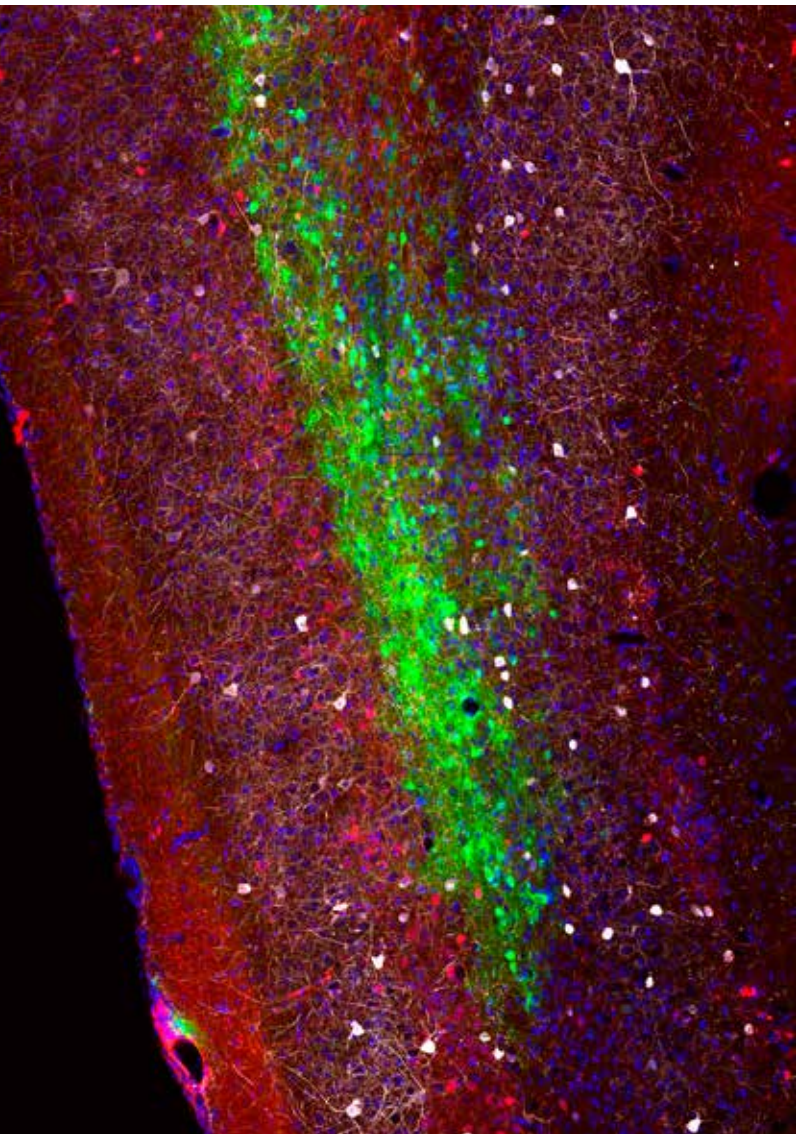


Witter is developing the atlas in close cooperation with Professor Jan G. Bjaalie, who is a specialist in neuroinformatics and heads the Institute of Basic Medical Sciences at the University of Oslo.

Witter group
Back row: Maria José Lagartos Donate, Anne Nagelhus,Belma Skender, Kang Zheng,Thanh Pierre Doan, Amy Robinson, Heidi Kleven, Eirik Stamland Nilssen, Jørgen Sugar,Bente Jacobsen, Hanne Tegnander Soligard.
Second row: Ingrid Heggland, Øyvind Wilsgård Simonsen, Asgeir Kobro-Flatmoen, Karoline Hovde, Michele Gianatti, Bruno Monterotti
Front row: Gunhild Fjeld, Grethe Mari Olsen, Pål Kvello, Menno Witter. Photo: Ned Alley

Match.com for brain cells

What does it take to find the perfect match? For humans it can be anything from chance to the careful vetting of candidates via an online algorithm that matches you with other people who have the characteristics you're after. Researchers at the KI/CNC are developing similar methods to today's online dating algorithms as they work with the brain.



Neuronal profiling:
The picture shows a section of a mouse brain that has been injected with a viral vector that cannot replicate. The viral vector transfers a construct into the genome of the cells it infects. This construct consists of one of the regulatory elements followed by a reporter gene (GFP, green). Though the viral vector infects neurons indiscriminately, the GFP gene is specifically expressed in neurons in the deep layers of the medial enthorhinal cortex. The identity of the cells can be further investigated by immunohistochemical staining using markers for specific interneurons, such as parvalbumin (red) and calretinin (white).

The Kentros group is continuously looking for better ways to label brain cells, to find the right match between regulatory elements in the genome and genetic labelling of specific neurons.

"We want to find new ways to genetically label very narrowly defined populations of neurons," group leader and Professor Cliff Kentros says. "The brain is a vast network containing a huge number of different neurons. These different neurons can be grouped in homogenous populations based on their morphology, gene expression and electrophysiological properties. But to determine the role that individual populations of neurons play in the brain, we need to manipulate them."

Kentros says that existing transgenic lines of mice allow researchers to label relatively broad populations of neurons that comprise several different subpopulations. But because of this, they are unable to label a single specific subpopulation of neurons. Instead, to investigate the role of specific neurons in the brain, Kentros and his team need to be able to label single subpopulations of neurons. To do this, they are creating special transgenic mice in collaboration with researchers at Yale University.

The group is looking for elements in the genome that regulate the expression of genes in specific cell types as a way to get access to single subpopulations of neurons, Kentros says. "This is where the matching comes in," Kentros says. "We work with our collaborators at Yale to identify regulatory elements in the genome that are specific for certain cell types. Then we make mice and viral vectors that drive expression of transgenes in these specific cell types. When we find a match between a regulatory element and the labeling of a subpopulation of neurons we can investigate the role of this specific subpopulation."

Genetically labeled mice in the making

The group's way of making mice is different from more traditional approaches. When most researchers make transgenic mice in the traditional way, the researchers try to recapitulate the expression of a specific gene. This gene labels a population of neurons that all express the gene, but they may be different from each other in their morphology, electrophysiology and function in the brain.

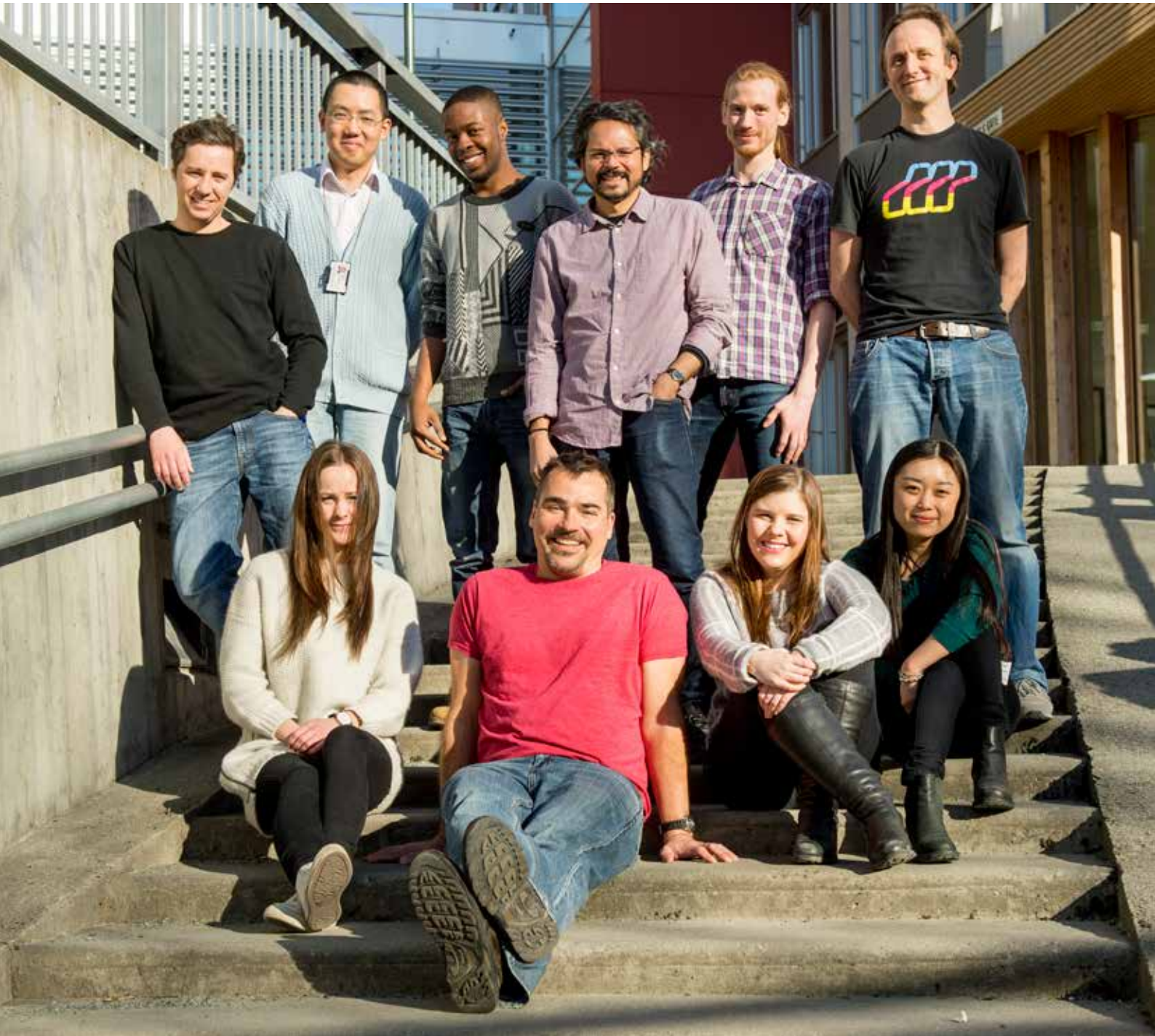
"With our technique we try to identify subpopulations that share most of the same characteristics," Kentros explained. "We're hoping for the perfect match between regulation on a molecular genetic level and the subpopulation of neurons in the brain,

which because of our transgenic mice are homogenous in all characteristics, but different from other neurons in the brain for at least one characteristic."

When the method of labelling specific neurons are in place, the hunt for connectivity and functional roles of the specific populations of neurons begins.

"We think we have found a way here to label very specific populations of neurons. By combining this with methods like rabies tracing and optogenetics, we expect we can solve questions like which neuron connects to which other neurons, and what are they doing, in the brain. We have set up the match. com regime, and now we can see who dates whom," Kentros said.

Kentros group
Back row: Thomas Doublet, Yixin Tong, Kadjita Asumbisa, Rajeevkumar Raveendran Nair, Stefan Mattias Adriaan Blankvoort , Nils Borgesius
Front row: Ida Helene Andersen Røst , Clifford Kentros, Christin H. Berndtsson , Qiangwei Zhang. Photo: Ned Alley



Revealing hidden patterns

In the hunt to decipher the brain's codes, researchers must collect an almost unimaginable amount of data. This ever-increasing amount of information makes it harder to figure out the difference between associations that reveal an underlying truth, and associations that simply arise as an artefact of having so much data.

That's where the tools used in statistics and statistical physics can be of great help. Physicist Yasser Roudi and his Kavli research group bring these tools to bear in allowing brain researchers to dig deep into the data and to extract detailed, exacting information from it.

Over the course of the last five years, Roudi has built a team that both analyses empirical data from the measurements made by other Kavli researchers and develops models based on these data. In a new paper in Current Opinion in Neurobiology ("Multi-neuronal activity and functional connectivity in cell assemblies") Roudi and his colleagues summarize how the activity of cell assemblies can be analysed using different statistical models.

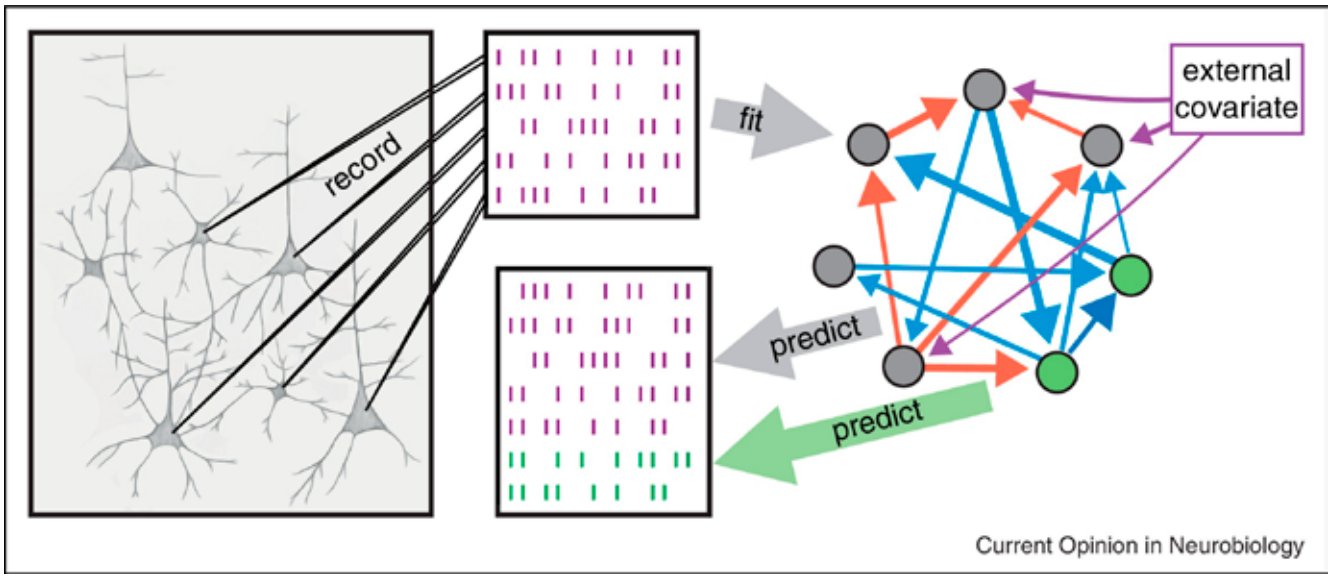
Cell assemblies are groups of neurons that share similar functions. Grid cells are an example of cells that all fire maximally at locations that form a hexagonal pattern. If we want to understand computation in the mammalian nervous system, we have to characterize the different types of cell assemblies and their relationship to each other. And we have to identify the anatomical and molecular features associated with the specific assemblies.

All of these tasks involve assembling huge amounts of data and sifting through them to find the underlying patterns, Roudi says.

"Although the theoretical concept of cell assemblies is not new, tools for analysing them have only recently emerged in systems neuroscience," Roudi says. ¬ "The researchers who do the experiments can now record the activity of many cells at the same time, with rapidly increased spatial and temporal resolution. They can also access areas that were previously inaccessible."

Roudi says that Kavli researchers have also increased their use of optogenetic and other molecular and genetic techniques that allow them to stimulate specific kinds of cells during their recordings.

"All these advances have shifted the focus of efforts to understand neural computation from single-neuron recordings to simultaneous recordings of many neurons," he says. "Data analysis must follow these advances. And that is where the power of statistical models is extremely useful."



If we use spike trains recorded from neurons (upper middle panel), we can build a statistical model and infer the functional connections between the neurons. We may also learn the functional connection between the recorded neurons and external factors that influence the spike trains. This process can also include learning and inference of hidden variables, for example, unrecorded neurons (green circle in the right panel). The functional connections do not in general correspond to actual physical connections, though in some cases they may be very informative the presence or absence of connections.

In this latest paper, Roudi and his colleagues describe how these tools can lead to new ways of thinking about information processing at the population level. They describe how to build statistical models of multi-neuronal activity and show how these models can help scientists understand the computational and physiological properties of cells assemblies, as well as the relationship between them.

Revealing functional connections

An example of this was published in PLoS Computational Biology in October, 2014. The paper, Correlations and Functional Connections in a Population of Grid Cells describes how Kavli researchers, led by Roudi's PhD candidate Benjamin Dunn, used statistical models to show how grid cells are functionally coupled together.

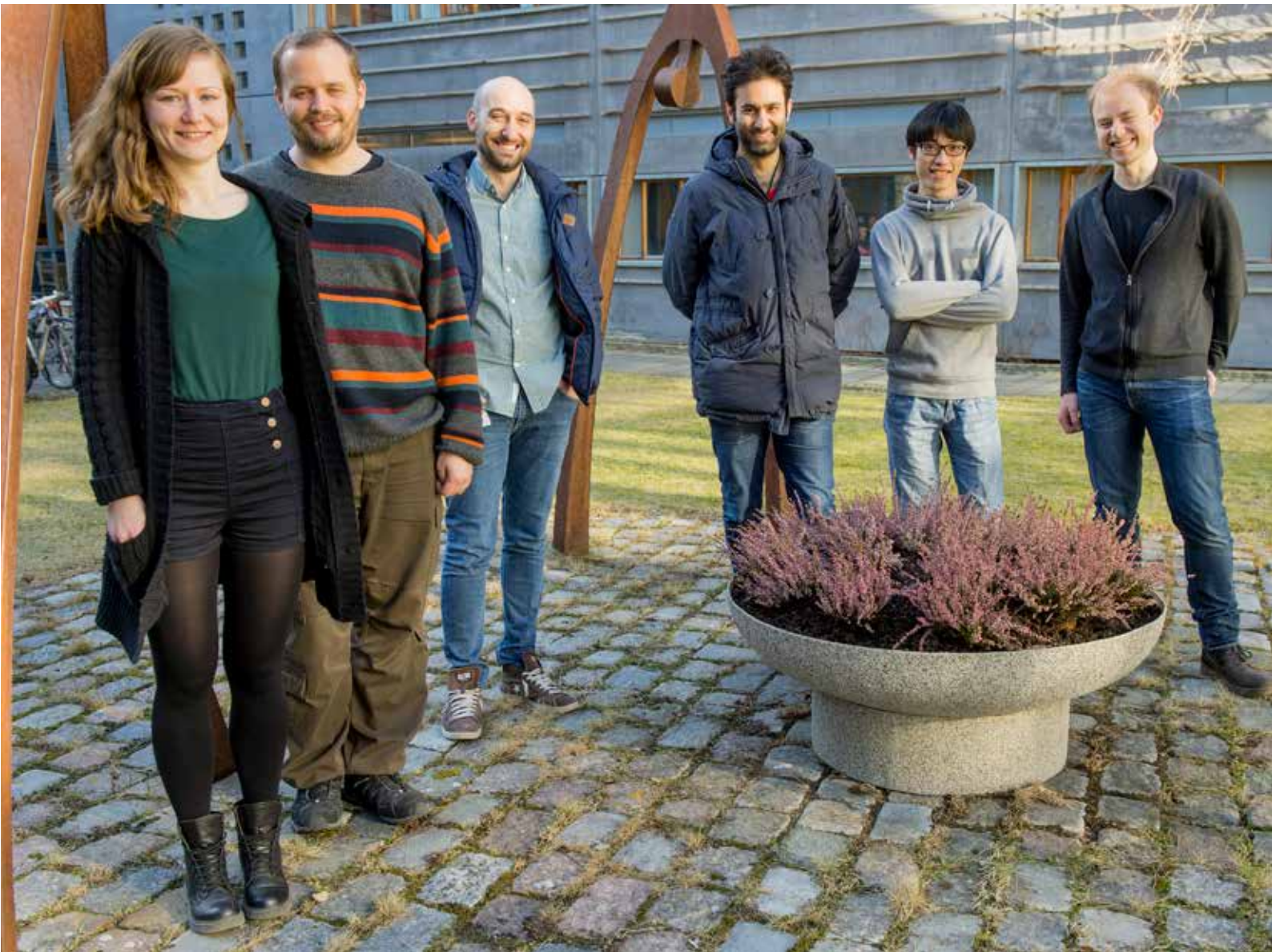
"Despite several years of work, not much is known about the correlated activity of neurons in the medial entorhinal cortex and how grid cells are functionally coupled to each other," Dunn said. "Here, we took a statistical approach to these questions and studied pairwise correlations and functional connections between simultaneously recorded grid cells."

This allowed the researchers to see that grid cells that had firing positions near each other tended to get positive responses from each other, while those further apart tended to have inhibitory or no effects. Kavli researchers have previously described this tendency of grid cells to work in groups as "modules." Dunn says that their findings show how "cells belonging to a module have stronger interactions with each other than those in different modules."

In other words, the results "support a model where the cells are organized so that they are connected more within modules and local networks, than between," he said.

Roudi group

Maria Mørreaunet, Benjamin Dunn, Nicola Bulso, Yasser Roudi, Ziwei Huang, Daniel Wennberg. Photo: Ned Alley



The supporting cast and crew

Behind every major research group lies a team of capable and enthusiastic technicians, administrators and other staffers who give their all to make sure that research can happen. That's certainly the case at the Kavli Institute.

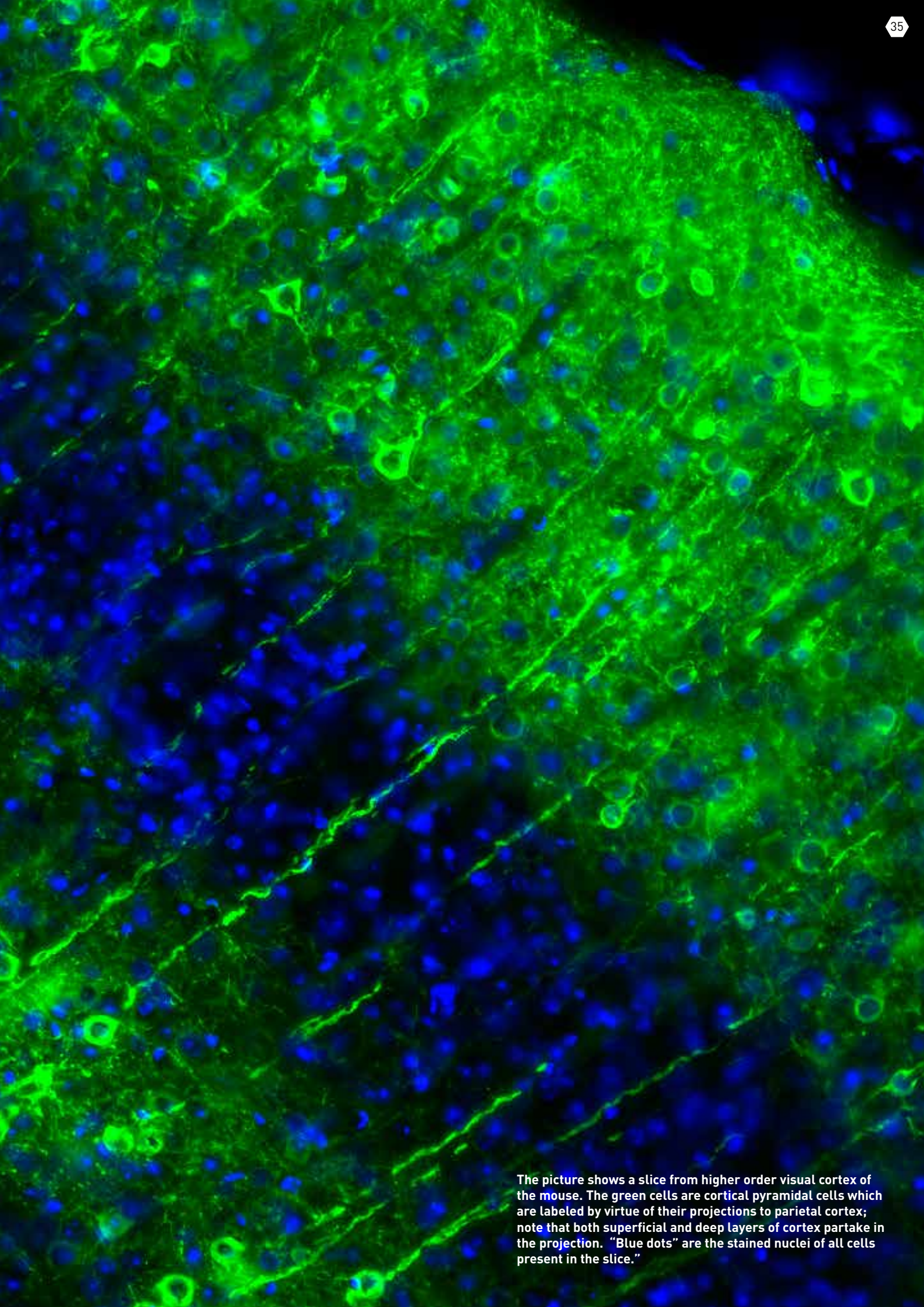
In 2014, the institute's support staff grew by two with the addition of Hege Tunstad as the KI/CNC's new Head of Communications, and Siv Eggen as our new veterinarian.

The technician's and administrators' mantra is "excellent support, so researchers can do excellent science". These are the individuals who take care of the researchers and their animals, arrange for visits and conferences, handle media requests, help new employees get settled, and help our international researchers navigate the Norwegian system.

When it is time to celebrate, it's the support group that buys the champagne and orders the flowers and cake. The institute had more than its fair share of exactly those activities in 2014, with the Spitsbergen Conference and Kavli Week and culminated by the award of the Nobel Prize.

The KI/CNC had a total of 91 employees in 2014, drawn from 24 different countries. The institute has five professors and six research groups, and 35% of all employees are women. And the tally wouldn't be complete without adding that the Kavli Institute now has two Nobel Prizes.

Support group
Grethe Jakobsen, Hege Tunstad, Haagen Waade, Merethe Andresen, Claudia Melis, Nora Gullbekkhei, Siv Eggen, Eirin Hårstad. In front: Håvard Tangvik. Photo: Ned Alley



The picture shows a slice from higher order visual cortex of the mouse. The green cells are cortical pyramidal cells which are labeled by virtue of their projections to parietal cortex; note that both superficial and deep layers of cortex partake in the projection. "Blue dots" are the stained nuclei of all cells present in the slice."

Who's who at KI/CNC

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Clifford Kentros
Professor and group leader

Jonathan Whitlock
Group leader

Yasser Roudi
Professor and group leader

Emre Yaksi
Group leader

Annual accounts 2014

Income

Norwegian Research Council: Centre of Excellence	12 500 000
Norwegian Research Council: other	30 893 000
International (European Commission, EMBO, Louis Jeantet Foundation)	13 138 000
Other Public/Private (Kavli foundation, Norwegian Health authorities)	3 448 000
Norwegian University of Science and Technology	38 776 000
Total income	98 755 000

Expenses

Payroll and indirect expenses	62 503 000
Equipment	7 861 000
Operational expenses	28 391 000
Total expenses	98 755 000

Amounts in NOK

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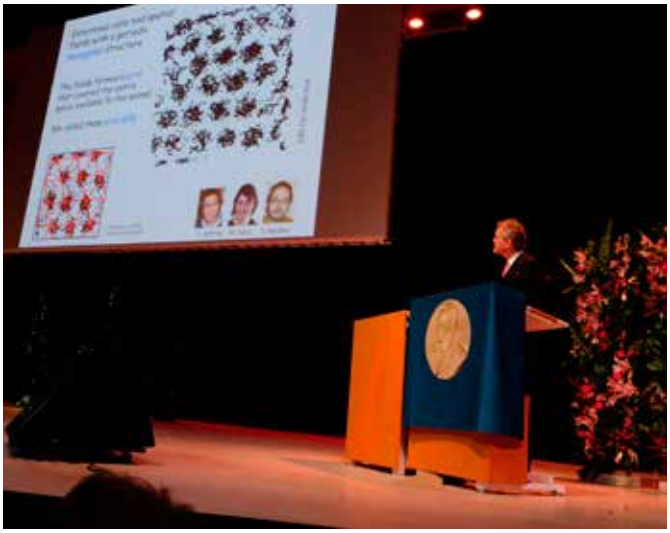
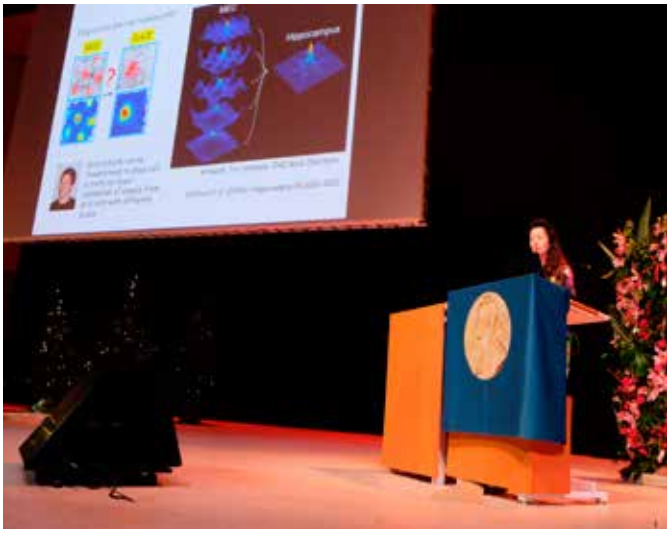

Nobel Lectures. Aula Medica. 7 December 2014. Photos: Gunnar Hansen / NTNU

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