Annual Report 2012

Kavli Institute for Systems Neuroscience and Centre for the Biology of Memory

Norwegian Centre of Excellence

NTNU – Trondheim
Norwegian University of Science and Technology

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The people at KI/CBM March 2013. (Photo: Matias Okawa, NTNU)

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May-Britt and Edvard Moser established the Laboratory for Memory Studies at the Norwegian University of Science and Technology (NTNU) in Trondheim in 1996.

In 2002, a ten-year-long grant from the Research Council of Norway enabled the laboratory to expand to become a Centre of Excellence (CoE). The new institution was named the Centre for the Biology of Memory (CBM).

In 2007, the Norwegian-American physicist, businessman, billionaire and philanthropist Fred Kavli selected the CBM as one of 15 prestigious Kavli Institutes worldwide. The centre accordingly changed its name to the Kavli Institute for Systems Neuroscience and the Centre for the Biology of Memory (KI/CBM).

The first CoE period expired in 2012, but the Research Council of Norway decided at the same time that the Trondheim research group should be awarded new funding. At the end of 2012-2013 the centre changed its name to the Kavli Institute for Systems Neuroscience and the Centre for Neuronal Computation (KI/CNC). KI /CNC is part of the Norwegian Brain Centre at NTNU in Trondheim, which is home to perhaps the largest infrastructure for systems neurophysiology in the world.

The centre's basic 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. The sense of location is closely linked to the hippocampus, where place cells were discovered in 1971. The researchers at KI/CNC have taken the plunge into adjacent and interacting brain structures, especially the entorhinal cortex.

Ten memorable years

"We are even more impressed and intrigued today by the sophisticated computations of the brain than we were ten years ago. And we are both proud and amazed at all the new knowledge we've accumulated over the past ten years," says Professor Edvard Moser.

The Research Council of Norway decided on 12 June 2002 that Edvard and May-Britt Moser's then-laboratory for memory studies in Trondheim should be expanded to be a Centre of Excellence (CoE), with a decade's worth of generous funding. Just a week after the award, the researchers published an article in the journal Science, reporting they had found that direct connections from the cortex were enough to form a spatial map in the hippocampus. The finding hinted that the mammalian sense of location was not confined to the hippocampus.

It's not every day that Norwegian researchers publish in international journals such as Nature and Science, but for Edvard and May-Britt Moser, this was only the beginning. In the years that followed, the two published 16 original research articles in these journals.

The discovery of grid cells and mechanisms the sense of location

Perhaps the duo's most widely recognized finding was in 2005 with the discovery of the so-called grid cells in the entorhinal cortex, a 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.

In 2006 came the news that the entorhinal cortex also contains neurons that encode how fast a rat is moving and in which direction. The brain, in other words, has a GPS, a speedometer and compass, the researchers reported.

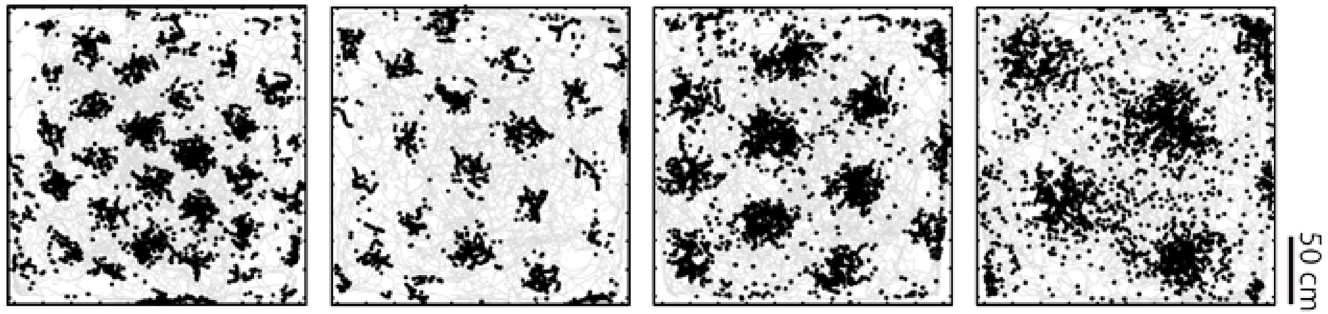
In 2007, the Moser group showed that grid cells form universal maps that are applicable to any environment visited by the rat. The internal metrics of the map are preserved from one environment to the other. Two cells will also fire in the same place in one room will fire at the same places in another room. This differs radically from the maps of place cells in the hippocampus, where different combinations of active cells are recruited for every environment. The grid map is like a ruler, which should stay the same no matter the location, whereas the place cells are part of the memory system, where every memory should be as distinct as possible.

In 2008, the Mosers and their students created another stir with the discovery of so-called border cells in the entorhinal cortex, which "fire" electrical signals in laboratory rats when the animals approach a wall, a fence or a drop.

From single cells to complex networks

Brain waves are generated when billions of neurons communicate with each other by means of tiny electrical impulses. In 2009, KI/CBM researchers discovered that the brain uses gamma brain waves to filter incoming messages to the place map in the hippocampus. When place cells in the CA1 area oscillate at low gamma frequencies, they are tuned to inputs from the CA3 area. When they oscillate at higher frequencies, they are primarily sensitive to inputs from the grid cell area in the entorhinal cortex. Thus the hippocampal system is similar to a radio station that broadcasts information about location on one frequency and archive material from memory on a different frequency.

In 2010 we learned that rats come into the world with a rudimentary sense of location. In 2011 we learned that various memories are stored as indivisible packets or "quanta" in the brain, without being mixed with each other. In 2011, researchers at KI/CBM found a protein that controls a kind of zoom function in the rat brain navigation system, and in 2012 came the sensational news that researchers in Trondheim had proved that the sense of direction in the mammalian brain is organized into independent modules (see separate article). The discovery of modules provides strong evidence of how the most elevated parts of the cortex are organized and was thus a great end to the first CoE decade. And now the work will continue for at least another ten years.



Grid cells fire electrical signals at spatial points that together form a triangular, Chinese-checkers-like grid.

Grid cells were the biggest find

"If I have to rank the findings, the discovery of grid cells would be the most important up to now. It actually defined a whole new research area. But it is also important to recognize that grid cells coexist with several other cell types that are important for the sense of direction, such as border cells and direction cells. Our research has shown how these cell types are organized in complex networks. The discovery of grid cell modules illustrates a new way to organize the cortex, and will probably eventually prove to be almost as important as the discovery of grid cells," says Edvard Moser.

"There is more and more evidence that neural wiring is 'hard-wired' from birth, and that the brain uses hardwired space networks as a framework to save memory. We see that the sense of location and memory are closely linked. If you remember an important experience, you also remember the location," he adds.

June 2002: Announcement of the 13 first Centres of Excellence, including the CBM. (Photo: Rune Petter Ness, NTNU Info)

Edvard and May-Britt Moser have come much farther than they could have dreamed of ten years ago.

"There has been rapid development on two fronts. Firstly, we have been able to record the activity of many more neurons simultaneously, from anywhere in the brain simultaneously, and we have the technology to control the activity of specific groups of cells while measuring the activity of the other groups. Secondly, we have been involved in a major conceptual development, in the

CBM was considerably smaller in 2003 than today. (Photo: Bjarne Røsjø)

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sense that we have concepts, ideas and models of how the brain works. Method development and model development must take place simultaneously if we are to continue to make progress," Moser says.

The brain is much better than the computer

In the research group's annual report from 2002, Edvard Moser drew a number of comparisons between the brain and the computer. Ten years later, he emphasizes how much better the brain is than the computer. Computers must still pretty much do things sequentially, or in one step after another, and even the best have only a small number of parallel processors that operate independently.

"In comparison, the brain runs hundreds of thousands of processes interactively and in parallel, and therefore is very good at drawing conclusions on the basis of unclear or ambiguous information. That is why the European Commision provided the KI/CNC with funding for a research initiative that aims to use the knowledge of how the brain functions to develop better computers. It's going to be very exciting," Edvard Moser says.

Edvard and May-Britt Moser emphasize that they got a good start in their career during their studies with the legendary Professor Per Andersen at the University of Oslo. "It has also been very important that we have had a group of seven visiting professors who come here not just to give lectures, but also to do research with us. Our good friends and partners deserve a great deal of the credit for our efforts having gone as well as they have," says Edvard Moser.

Of particular importance is the collaboration with Menno Witter, which started in 2000, 2 years before CBM was established. Witter became the third professor of the Kavli Institute in 2007. His move to Trondheim intensified the collaboration and many of the key findings of the Centre are true products of this effort.

Edvard and May-Britt Moser have been Directors of the CBM over its entire lifetime. (Photo: Matias Okawa, NTNU)

From research group to institute

When CBM was established in 2002, the centre consisted of May-Britt and Edvard Moser and their research group of approximately 10 people, including PhD students and technical staff. During the next 10 years, the number of coworkers increased and an increasing percentage of the staff were postdoctoral fellows who came from all over the world to learn about grid cells and neural circuits in the hippocampus and entorhinal cortex.

With its recognition as a Kavli Institute, the Centre was able to recruit Menno Witter from Amsterdam in 2007 and Yasser Roudi from Stockholm in 2010. Most recently, Cliff Kentros was headhunted from the University of Oregon in 2012. The Centre is no longer a single research group but an institute composed of 5 groups and more than 100 scientists who work together towards a common goal of understanding neural computation in the cortex.

Prime Minister opens Norwegian Brain Centre

The Norwegian Prime Minister, Jens Stoltenberg, was full of praise when he officially opened NTNU's new brain research centre in early 2012. " I didn't understand everything, but I will definitely remember that this is a world-class research environment," Stoltenberg said after a tour of the new facilities.

On 28 February 2012, Jens Stoltenberg officially opened NTNU's Norwegian Brain Centre. Instead of cutting a ribbon, the Prime Minister connected two cables that illuminated a blue light under the centre's unique cornerstone, which is a crystal and contains a reconstruction of a stellate cell from the rat's entorhinal cortex. This type of cell has helped NTNU researchers unlock the secrets of spatial map formation in the brain.

Prime Minister Jens Stoltenberg connects two cables to illuminate a crystal with a grid cell to symbolize the opening of the Norwegian Brain Centre. (Photo: Matias Okawa, NTNU)

Many approaches are necessary

The Norwegian Brain Centre is already one of the world's largest brain research laboratories of its kind. As of early 2013, the centre has approximately 90 staff members (and 200 rats). NTNU's rector, Torbjørn Digernes, said at the opening that he hopes the centre will expand to closer to 150 employees over the next two to three years. The 4000 m² facility will continue the research conducted by the KI/CBM. The centre will also host select PhD candidates and researchers from Norway and abroad who need training in the latest technology focused on the brain.

"We are creating a centre that will cover a wide range of methodological approaches to understanding how the brain's networks function: everything from theoretical studies in physics to microscopic studies of connections between neurons and imaging studies of the brain in action. The brain is such a complex puzzle that many approaches are needed to crack its code," said Edvard Moser, director of the KI/CBM.

The centre will grow

The Norwegian Brain Centre will be fully built out when the research groups from NTNU and St Olavs Hospital that work with MRI technology have moved into facilities next to the KI/CBM. Over the longer term, it makes sense to bring other research groups that work with brain-related science – such as psychology, biology and physics – to the same general area. NTNU has invested NOK 42 million in the centre.

A happy minister

The new centre is a part of the Norwegian Brain Initiative (NORBRAIN), which received NOK 80 million in a grant from the Research Council of Norway in October 2011.

NORBRAIN is structured around two Centres of Excellence – the KI/CBM and the Centre for Molecular Biology and Neuroscience at the University of Oslo – as well as one Centre for Research-based Innovation – the Medical Imaging Laboratory (MI Lab) at NTNU. The aim is to build one of the best neuroscience infrastructures in the world.

Prime Minister Stoltenberg was still smiling when he left Trondheim, carrying an extra brain cell – or more precisely, a model of a brain cell from a rat. The model was given to him by Professor May-Britt Moser as a token of appreciation of the government's support for brain research.

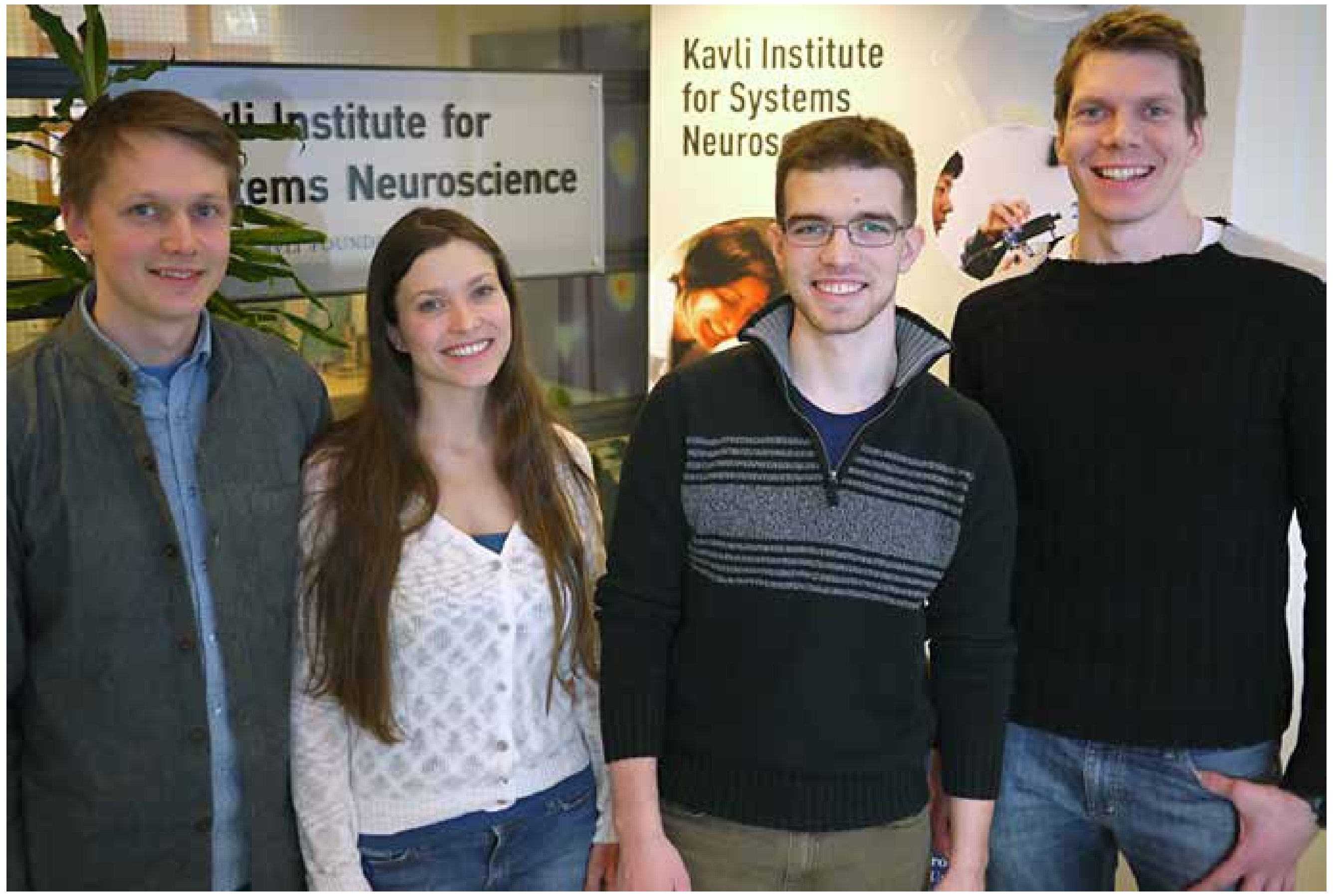
First insights into the organization of the higher cortex

Brain researchers know a great deal about how neurons are organized in the lower parts of the cortical hierarchy, in the sensory and motor systems. In 2012, scientists got a first glimpse of how the higher cortical regions are organized, when researchers at the KI/CBM showed that the sense of location in the mammalian brain consists of independent modules.

There are several different ways to describe the 2012 research findings of Hanne and Tor Stensola and their counterparts in the Moser group at the KI/CBM. The first is as pure research news, that the sense of location in the mammalian brain can be seen as consisting of four independent modules. The second is that Norwegian research results were presented in a seven-page spread in Nature, the world's most respected scientific journal. The third way to describe the news is that for the first time, scientists have gained an insight into how the higher parts of the cortex are organized.

This third description is the main reason that the discovery has been described as the most important by KI/CBM researchers since 2005, when Edvard and May-Britt Moser along with former students discovered grid cells in the entorhinal cortex (see page 2).

Scientists know that in the visual cortex and other lower parts of the cortex, neurons working with similar tasks are organized into columns and are located near each other. This applies, for example, to neurons that respond to particular aspects of vision, such as orientation or left or right eye input. But our knowledge of how neurons are organized in the higher parts of the cortex is minimal – the equivalent of a blank spot on a map.



From left: Hanne and Tor Stensola were first authors on a paper published in Nature on 6 December 2012. Their collaborators were Kristian Frøland and Trygve Solstad, as well as May-Britt and Edvard Moser (not shown). (Photo: Haagen Waade, NTNU).

A technological breakthrough

The background to the new breakthrough is that after KI/CBM researchers discovered grid cells in 2005, they immediately began to wonder how the brain stores all of its map-related information.

Does the brain store just one large, continuous map that it uses for all kinds of navigation, or does it create a number of different, modular maps for different purposes? At that time, it was only possible to "listen" to a few neurons simultaneously from the same small area of the brain, which made it difficult for scientists to find the patterns they needed to help answer the question. But a technological breakthrough in which Hanne and Tor Stensola participated made it possible to record signals from as many as 186 neurons simultaneously from multiple locations in the rat brain. This advance made it possible to detect a pattern in the brain's organization.

The brain zooms in discrete steps

When Hanne and Tor Stensola started their project, researchers knew that the grid cells in the top of the entorhinal cortex draw a map with a small grid size, and that the grid size increases deeper in the brain. But they did not know whether the grid size increased gradually, or stepwise.

To answer this question, laboratory rats ran around in special boxes in the lab to look for treats, while the researchers recorded the electrical activity of grid cells at several levels in the entorhinal cortex. "We then saw that electrical signals from the upper grid cells 'drew' a triangular grid of the laboratory boxes, with roughly 30-40 centimetres between grid line intersections. Further down in the brain, we found, as expected, grid cells that drew a grid with larger triangles. We also observed that there is no overlap in the different mesh sizes that the brain draws," says Tor Stensola.

In other words: A camera allows you to zoom continuously from the closest focusing distance to infinity, but the researchers found that the brain instead seems to "zoom" in a stepwise fashion.

"Grid cells draw a discontinuous grid. We could also conclude that the scale is on average 42 per cent larger each time the brain 'zooms out'," says Hanne Stensola.

The experiments also showed that the grid cells in the entorhinal cortex, which in practice is the seat of the brain's sense of location, are organized into independent groups or modules. The modules are independent because changes in the environment may well lead to changes in one module without affecting the others.

"We definitely found four modules, and evidence of a fifth. It is possible that the grid cells in this area form as many ten different modules, but not more," says Tor Stensola.

It's easy to explain why the researchers did not find more than four or five modules this time. "The biggest box we used in this test was a square with sides that were 2.2 metres long. If we wanted to find a tenth module, we would have had to have rats running around in an area the size of a football field. Our lab is just not big enough for that kind of experiment!" Hanne Stensola says.

Research at a new level

Ever since Santiago Ramon y Cajal proved that the brain consists of separate units – neurons – instead of fused cells in a network, brain scientists have spent a great deal of time studying different cell structures and functions. As a result, we now know a great deal about these areas. But what remains to be understood is how neurons together create complex mental functions. The door began to open on this when Hanne and Tor Stensola's article appeared in Nature.

"We have begun to describe how the different parts of the mapping system and sense of direction in the rat brain work together into a unified system. The new discovery is also a strong indication that rats – and other mammals – are born with a predisposition to use the sense of location as a basis for memory. The organization of the grid map is not primarily the result of experience and interaction with the environment," says Tor Stensola.

The new research shows that a modular organization is found in the highest parts of the cortex, far away from areas devoted to senses or motor outputs. It is not possible to locate the different modules with a microscope, because the cells that work together are intermingled with other modules in the same area.

Sense of location as mother to memory

Hanne and Tor Stensola also noticed that the navigation system in the rat brain has huge overcapacity. The rat would have managed with approximately 20 grid cells in each module, but instead has at least 1000 times that number. The result is an enormous number of possibilities for combinations, when thousands of cells in four to ten modules overlap the same area.

This excess capacity presumably reflects the fact that it is extremely important to navigate properly, for the rat and for that matter for human beings. "The sense of location is the mother to memory. The excess capacity means that the brain's navigation systems could continue to work even if the brain is weakened by ageing or injuries," the researchers said.

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Actions speak louder than space

Researchers at the KI/CBM have spent several years studying rat brain neurons that encode what the animals are doing. In 2012, Jonathan Whitlock and colleagues also found neurons that encode what the animal is planning to do. But the biggest surprise was to find parietal cells that were determined by the rat's actions instead of its location.

Jonathan Whitlock (left) was the lead author of the article in Neuron February 23, 2012, shown here with Nenitha Dagslott, the second author. The other authors were Gerit Pfuhl, May-Britt Moser and Edvard Moser. (Photo: Matias Okawa, NTNU)

When Jonathan Whitlock and four colleagues from the Moser group at the KI/CBM published an extensive paper in Neuron in February 2012, it was the result of four years of hard work training rats and studying neurons in two small but important regions of the rat brain. The posterior parietal cortex (PPC) lies behind the primary somatosensory cortex and plays an important role in producing planned movements. The entorhinal cortex is located in the medial temporal lobe and functions as a hub in a widespread network for memory and navigation. It is famous for containing the grid cells that were discovered in Trondheim in 2005.

Both the PPC and the medial entorhinal cortex (MEC) are important elements of the neural circuit for space and navigation, but nobody really knew what the navigational neurons in these areas respond to. Navigational neurons had already been found in the PPC by other scientists, but the researchers in Trondheim became the first to study how individual neurons in the PPC behave while the rats are performing different spatial tasks, with the broader goal of understanding whether PPC and MEC work together or independently.

"Let's say you have a cell in PPC that fires every time the animal makes a right hand turn when the animal runs in an open field. When we moved the animal from an open field to a hairpin maze, we found that the cells completely changed the behaviour they responded to. A cell that would fire when the animal turned right in the open field, would fire when the animal was running straight ahead in the hairpin maze, for example. We showed that the cells actually flip their preferences from one task to the next – and that was very surprising" Jonathan Whitlock explains.

Behaviour beats space

Does this mean that the neurons in the PPC respond to actions and not to locations? To find out more, the researchers decided to use two different mazes in the exact same location in the lab. The open field was in fact in the same box that was used in the hairpin maze experiment – the only difference was the insertion of walls. The next stage was even smarter:

"We took the walls out of the box and trained three rats to run in the open field as if the walls were still there. This took many weeks, of course, but the result was very interesting. We found that structuring the animals' behaviour into north-south hairpin-like sequences was sufficient to cause the cells to change their firing properties. This caused almost the same magnitude of flip as we saw between the open field and the real hairpin maze," Whitlock explains.

Jonathan Whitlock and his colleagues thus became the first researchers who were able to investigate whether space or behaviour is more important in driving parietal cells.

"It became very clear that the structure of the animals' behaviour is the primary thing that determines when the cell is going to fire. It was very unexpected to discover that actions speak louder than space in the posterior parietal cortex. This also means that there is a functional split between the parietal and entorhinal cortices in the rat," Whitlock says.

Decoding the future

Jonathan Whitlock not only observed that the parietal cells were mostly governed by actions: He also discovered that the firing properties of the parietal cells started to become very clear before the animal made their movements. In other words, the researchers were actually able not only to see what the animal was doing, but what it was planning to do.

"If the rats were making simple decisions about where to go in the open field, we could see that the forward looking 'spotlight' in the neurons appeared up to about a half a second into the future. But we hypothesize that if the animal was given a task where it had to choose between two specific goal locations, we might be able to see the spotlight extend several seconds in advance," he says.

Is Whitlock actually reading the animals' minds? "The answer is no. But we showed in principle that it is possible to do that. Other researchers have made similar observations in primates, but this is the first time that planning related signals have been seen in rats," Whitlock says.

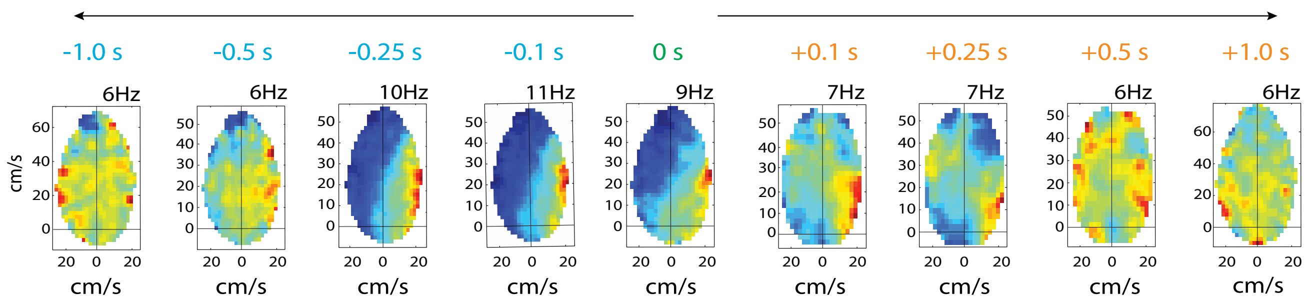
The best place in the world

Jonathan Whitlock's results make an interesting ouverture to the research that will be conducted at the Centre for Neuronal Computation during the next ten years.

"The major challenge for neuroscience in the 21st century is to understand the activity patterns and the algorithms that the brain uses for consciousness, behaviour, planning and the understanding of location. The brain's algorithm for even doing something enormously simple, like turning your head to the left or positioning yourself to grab a cup of coffee, requires computations that today look like a mountain with a sheer cliff that we must climb. It is a daunting task to negotiate this cliff, but I am sure that the next ten years will bring great advances," Whitlock says.

Jonathan Whitlock completed a doctorate in neuroscience at MIT in 2006 and came to Trondheim the following year. He is very happy to work with Edvard and May-Britt Moser.

"Their excellent science is of course the ultimate driver for young scientists who want to make a career, and in addition, they are extremely nice people who really care about their students and colleagues. Trondheim is, in my opinion, the best place in the world right now to be doing unit recordings in freely behaving animals," Whitlock says.



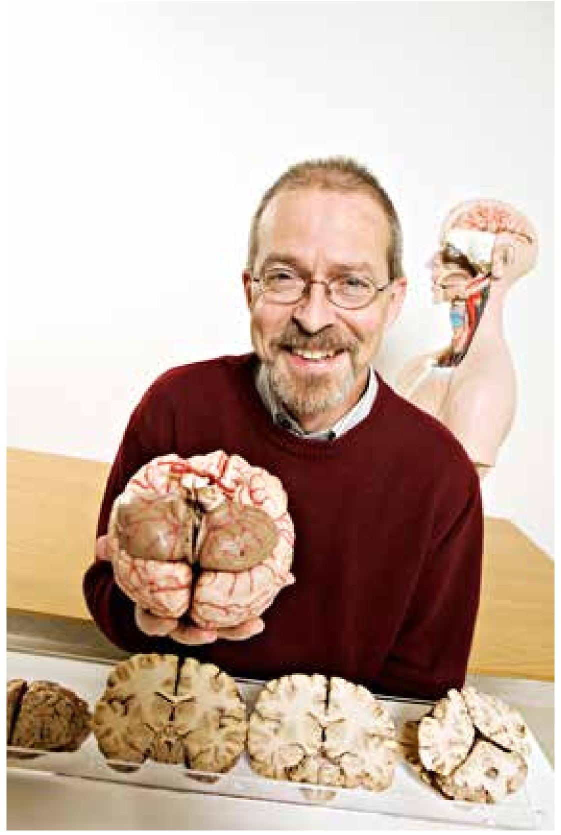
Rate maps for a PPC cell tuned to right-forward displacements; the maps were made using spiking activity and path segments traversed up to 1 s prior to and after the animal's actual position. This cell expressed clear tuning up to 250 ms before the actual displacement.

Norway gets a national Research School in Neuroscience

Four universities are joining forces to establish the Norwegian Research School in Neuroscience in 2013. The school will be coordinated from the Norwegian Brain Centre and the Kavli Institute in Trondheim, with an enthusiastic Professor Menno Witter as director and chairman of the board.

The Research Council of Norway has decided to fund ten new national research schools, and the Norwegian Research School in Neuroscience (NRSN) is going to be one of them. Professor Menno Witter is looking forward to having a school to run again, because he has very good memories from when he was the director of the Graduate School in Amsterdam for eight years. That school was – and is – both great fun and a great success, and Witter's ambition is to make the NRSN a similar success for both Norwegian neuroscience and the four participating institutions.

"The Norwegian Research School in Neuroscience, which will start its activities from 1 March 2013, will provide an important training opportunity for the next generation of Norwegian-trained neuroscientists, by combining the specific expertise of the participating institutions. I expect that it will also pave the way for more extensive collaborative neuroscience in Norway," says Witter.



Professor Menno Witter is director and chairman of the board of the newly established Norwegian Research School in Neuroscience. (Photo: Geir Mogen, NTNU)

Four neuroscience universities

Four of the eight universities in Norway – NTNU, the University of Oslo, the University of Bergen and the Norwegian University of Life Sciences in Ås – currently teach neuroscience. Between them, they have a total of approximately 100 PhD students at any given time, but none of the institutions covers the whole field of neuroscience.

"We need a school like this because neuroscience has become very multidisciplinary. If you look at the individual neuroscience institutes in Norway, they are simply too small to cover this enormous field. We are now bundling our areas of expertise, and that makes it possible to do a much better job in providing students with a good, broad educational programme from which they can make choices that can benefit their careers," Witter says.

A virtual school

The main objective of the research school is to coordinate and complement existing educational activities with the partner and affiliated institutes, thereby providing additional training to PhD candidates in genetic, molecular, and cellular neuroscience, systems neuroscience, cognitive neuroscience and neuropsychology, neurophilosophy, developmental neuroscience, computational neuroscience, and neuroinformatics.

The NRSN is a virtual school with no teachers or courses of its own. The school instead will use existing courses at the different institutions and make those available to students from the other universities. The aim of NRSN is to organize and secure a broad, diverse, and nationally coordinated neuroscience training programme for PhD students in Norway.

The research school will be based on the partners' existing PhD programmes. It will also exploit NORBRAIN, the recently established national neuroscience infrastructure programme. All courses will be available to all neuroscience PhD students in Norway. The NRSN also has an extensive international network.

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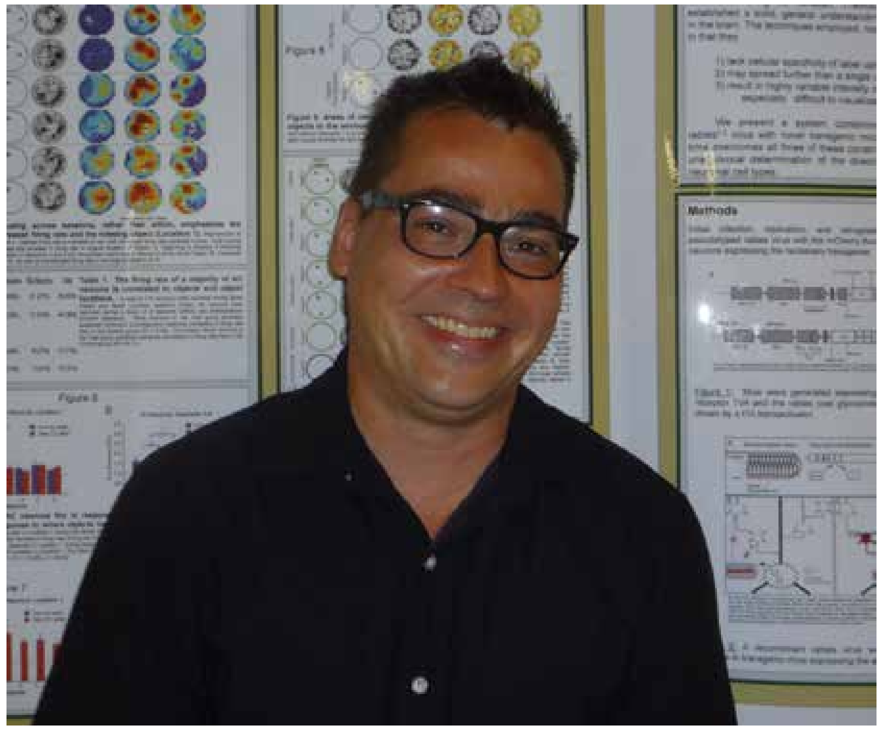
Molecular biology shines new light on the brain

In 2012, Clifford Kentros became the fourth professor at the Kavli Institute and the leader of a new research group. Kentros adds new strength to the institute with a set of molecular and genetic tools that are specially designed to unravel the wiring and functioning in the brain.

Professor Clifford Kentros describes himself as a recovering molecular biologist. He has been the leader of a research group in molecular genetics at the University of Oregon for several years, and has both admired and collaborated with Edvard and May-Britt Moser and Menno Witter. The collaboration made it increasingly clearer that Kentros could make important contributions to the Kavli Institute, so the solution became obvious: Professor Kentros is now a bi-continental scientist with one research group in Oregon and the other in Trondheim.

Kentros, like all the other Kavli Institute scientists, is intrigued by the brain structures that are necessary for memory. While Edvard and May-Britt Moser are specialists in recording and analysing electrical signals from neurons in and around the hippocampus, Kentros's forte is transgenic mice that have been developed in Oregon. A transgenic mouse is a mouse where researchers have introduced a gene from another organism.



Professor Clifford Kentros is the forth professor at the Kavli Institute. (Photo: Clifford Kentros)

The brain is an electrical circuit

The starting point for Kentros's scientific approach is that the brain consists of billions of neurons that communicate by sending electrical signals to each other via tiny wires and contact points. In short, the brain is an electrical circuit. Or more precisely, a giant network of electrical circuits.

In older days, when people would sometimes do their own car repairs, it was common to find a drawing of the car's electrical wiring right in the car's manual. Professor Kentros is drawing a similar wiring diagram, but of the part of the brain that is involved in memory. In addition, he is trying to figure out the function of the different parts of the electric circuit.

"The brain can be compared to an incredibly fancy and complicated foreign car. It is difficult to study the wiring diagram, but we have developed some very powerful tools," Kentros says.

Checking the currents

Much as you might send an electric current through a wire in a car to see what it is connected to, Kentros is sending electrical signals between neurons to trace their pathways in the brain. This is where the transgenic mice come in.

"In one of the mice we made, we started with the genetic sequence that makes a neuron into a grid cell. We then introduced another gene from a cyanobacteria, which makes grid cells sensitive to light. We are able to use genetic techniques to engineer mice with grid cells that are turned off when light shines on them, as well as mice where the grid cells become more active, and so on," Kentros says. "This corresponds to putting switches or meters on the grid cells, and they allow us to trace the electrical signals between neurons. I'm very much looking forward to using and developing these techniques further in collaboration with the excellent researchers in Trondheim."

Good news in 2012

Brain researchers in Trondheim received a continuous stream of good news in 2012. The best news came from the government and the Research Council of Norway.

Prime Minister Jens Stoltenberg's visit in February received broad coverage in the Norwegian media. The Prime Minister met Edvard and May-Britt Moser and Dean Stig Slørdahl (far right). (Photo: Haagen Waade, NTNU)

When the Norwegian Ministry of Finance in September submitted its budget proposal for 2013, the document contained two key phrases:

"The Kavli Institute for Systems Neuroscience at the Norwegian University of Science and Technology in Trondheim is one of the premier research institutions in Norway. The Government proposes that NOK 12.5 million be earmarked for the centre in the state budget for 2013."

And so it was: the Kavli Institute now has a separate line item in the state budget, in the form of a basic grant that will be used to finance infrastructure and the centre's technical staff. The grant ensures stability for the centre's operations and thus, better conditions for researchers to do excellent research in the future.

In November, the centre got even bigger news when the Research Council of Norway announced the award of a grant totaling NOK 175 million over ten years (see separate article). Faculty of Medicine Dean Stig Slørdahl was on a business trip in the US when, in the middle of the night Norwegian time, he discovered that the award had been published on the Research Council's website. He sent a text message with congratulations to Professor May-Britt Moser, who was happy to be awakened with that kind of news.

Awards for excellent science

In December, the University of North Carolina at Chapel Hill awarded the 13th Perl-UNC Neuroscience prize jointly to Edvard and May-Britt Moser. Past recipients have included four subsequent winners of the Nobel Prize for Physiology and Medicine.

Kavli researcher Lisa Giocomo received a highly competitive 'Starting Grant' from the European Research Council. She also received the Peter and Patricia Gruber International Research Award in Neuroscience from the Society for Neuroscience (SfN). Giocomo came to KI/CBM as a postdoc in 2008, and started on 1 Jan 2013 at Stanford University as an assistant professor in neurobiology.

May-Britt Moser was elected to be a member of the European Molecular Biology Organization (EMBO). The organization's membership is composed of 1500 invited scientists, whose goal is to promote excellence in European life sciences. Edvard Moser was elected to EMBO in 2011.

Media coverage

Norwegian and foreign media are still interested in research at KI / CBM. The database of the media monitoring agency Retriever lists approximately 200 articles that were published about the research group in the Norwegian media in 2012, along with a number of television and radio broadcast reports.

The most widely publicized research result was the news that the sense of location in mammals consists of four independent modules (see separate interview with Hanne and Tor Stensola). Prime Minister Jens Stoltenberg's visit in February and the news of the Research Council's Centres of Excellence grant to the CNC also received broad coverage.

"Among the top 0.1% of neuroscience centres"

The members of the Scientific Advisory Board at the KI/CBM are impressed by the results from 10 years of research in Trondheim. According to the report from their final meeting, what has been accomplished is "beyond exceptional".

Larry Squire, Edvard Moser and May-Britt Moser at Runde Lighthouse. (Photo: Mayank Mehta)

The KI/CBM has had an active Scientific Advisory Board (SAB) composed of renowned international researchers since its beginning in 2002. The board has supplied the Centre with constructive criticism and lots of good advice over the years and has provided important contributions to the centre's scientific progress.

The closing symposium of the KI/CBM, with the attendance of the SAB and the Centre's visiting professors, was held in June 2012 on the picturesque island of Runde, on the western coast of Norway, just a few kilometres from where both May-Britt and Edvard Moser were born. The four group leaders at the KI/CBM – Edvard and May-Britt Moser, Menno Witter and Yasser Roudi – gave talks about their results. The SAB wrote a report with very positive comments after the meeting.

Eighteen papers in Nature, Science and Cell

According to the SAB, it is difficult to overstate what the Centre has achieved. "Beginning with a small group of 3-4 graduate students and fellows, it has grown into a large, internationally renowned research centre involving 42 graduate students and fellows, 3 additional full-time faculty, and 7 visiting faculty from Europe and the United States who spend significant time working at the Centre," says the report.

The SAB also pointed out that the Centre's full-time members have published more than 120 scientific papers, 18 of which were published by the most important international science journals (Science, Cell and Nature). They discovered "grid cells", a new functional cell type, as well as head-direction cells and border cells intermingled with grid cells in the entorhinal cortex. Prior to this discovery, the last time a novel cell type had been described in the brain's space system was in the 1980s. The SAB described the laboratory as a national treasure, which is held in high esteem in the international community.

In the top of the group

In summary, what has been accomplished here is "beyond exceptional", says the SAB. The SAB also points out that neuroscience is a vigorous and broad field and that the discipline's North American Society for Neuroscience numbers more than 40,000 members.

"We regard the Moser laboratory in the top 0.1% of this vibrant and diverse group. The Centre in Trondheim has become a magnet for systems and computational neuroscience that attracts the best young people in the world," the report says. The top 0.1% of neuroscientists corresponds to a distinguished group of only 40. If the average size of neuroscience groups is 4, that puts the centre among the top 10 in the world.

The members of the Scientific Advisory Board in 2012 were Professor Larry Squire from the University of California, San Diego (Chairman); Professor Terrence Sejnowski from the Howard Hughes Medical Institute in Chevy Chase, Maryland and the Salk Institute for Biological Studies in La Jolla, California; and Professor Erin Schuman from the Max Planck Institute for Brain Research in Frankfurt am Main.

Visiting professors and Advisory Board members at CBM's closing symposium in June 2012 on Runde, an island known for its huge nesting seabird populations. (Photo: May-Britt Moser).

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A passion to understand the brain

There were shouts of joy all around Professor May-Britt Moser when the news came on 12 November 2012: The Research Council of Norway had awarded the Centre for Neuronal Computation NOK 175 million (US $ 31million) over the next ten years.

Then it was back to work – with a group of researchers who have stars in their eyes, driven by a passion to plumb the secret workings of the brain.

The competition was fierce in early 2012 when the Norwegian Research Council invited research groups to submit applications for a new round of funding to establish Centres of Excellence (CoE). A total of 139 different research groups applied for funding, from which the Research Council first selected 29 finalists. Only 13 were awarded support in the end, with the Centre for Neuronal Computation (CNC) – led by Professor May-Britt Moser – one of the fortunate few.

"I am overjoyed and grateful for all the support the centre and its research has received from NTNU, the Norwegian Research Council, colleagues and collaborating labs," Moser said.

The whole of NTNU also celebrated that day, because the Research Council awarded CoE funding to all four of the NTNU centres that had applied.

A clear vision

Professor May-Britt Moser has a clear view of what the Trondheim brain scientists will tackle in the next ten years.

"The vision is that we will uncover the basic mechanisms of complex brain functions. Our starting point is the network of nerve cells that forms the sense of location in the mammalian brain, and we will build on our results from our first ten years as a Centre of Excellence," she said.

"Ten years ago, we worked only with the hippocampus, and we started with being able to use a maximum of 16 electrodes simultaneously when we recorded electrical signals from neurons in the brain. We were using this equipment when we discovered both grid cells and border cells and head direction cells, and how the brain is able to tell the difference between this year's and last year's Christmas celebrations, and all the rest. Today we can use many more electrodes when we need to," says Moser.

Brain researchers in Trondheim are now using a new 'hyper drive' with more than 100 electrodes that can detect signals from hundreds of neurons simultaneously. The electrodes are becoming ever thinner and more sensitive, and the techniques for analysing signals from a large number of neurons that are all "speaking at the same time" is becoming increasingly refined. The researchers also use the signals they record to infer the connections – the networks – between neurons, with the goal of pioneering the extraction of computational algorithms from the mammalian cortex.

An on-going technological revolution

Neuroscience today is in the midst of a technological revolution that is about to give scientists a variety of new tools. This includes not only new recording technologies but also genetic approaches to activating and inactivating specific cell populations.

"And the trend is continuing" May-Britt Moser says. "It gives us hope that we will be able to deliver more exciting research results in the next ten years."

Researchers have gradually accumulated a great deal of knowledge about how individual brain cells work and how they communicate. Now researchers are focused more on understanding the neural networks in the brain better.

"Which brain cells 'talk' to each other? We are eager to find answers to this and similar questions, and now we have techniques that can help us," says Moser.

Creating neurons with little 'eyes'

CNC researchers are pioneering the fusion of optogenetics with neural ensemble physiology. Scientists can make brain cells sensitive to light in two ways, either by breeding mice with a genetic modification that means the mice are born with a light-sensitive receptor – rather like a small eye – in some brain cells, or by injecting a harmless virus that will infect cells that scientists want to activate during an experiment. The target neurons become active when researchers shine lights on them. The researchers can also use a virus that can be passed from one cell to the next, but that never spreads beyond the first new cell.

"The virus can only be transmitted through the synapses that cells use to exchange information with each other. If a brain cell becomes active when we illuminate it, we know that it must have gotten the virus from an infected neighbouring cell. Cells that are indirectly activated have longer reaction times than those directly activated. This will help the virus to reveal to us which brain cells talk to each other," May-Britt Moser says.

Professor May-Britt Moser and colleagues raised their glasses in celebration when they received the news that the Research Council of Norway had granted them status as a Norwegian Centre of Excellence. (Photo: Thor Nielsen, NTNU Info)

The 2022 annual report

"Where do you hope the centre is in ten years?"

"What I want most of all is for us to understand much more of the brain than we do today. Another thing that is also important is that the centre be a showcase for the ethical treatment of animals – and for our human researchers, too. We hope that our scientists will have stars in their eyes, because we have put everything in place for them as best we can. We're lucky that we can choose from among top-ranked students and researchers, because many of the best neuroscience research centres in the world like to send their best people to Trondheim. My job as manager is to make sure that the stars continue to twinkle in all of their eyes," says Moser.

May-Britt Moser thinks of the CNC as a nursery for talented people who will have the opportunity to learn both research and research management.

"One of our tasks will be to identify and nurture young group leaders who want to lead research groups. Several Nobel Prize winners and the Kavli Laureates have agreed to be external mentors for these up-and-coming researchers, and to give them advice on how to build a research career," says Moser.

The centre members have a number of bold ideas that they plan to test in the coming years.

"We have always carefully thought through new projects before they started, and we still do. But the long-term and good funding that we have now makes it possible to invest in riskier projects. We will be moving more in the direction of a high risk / high gain strategy. I will be very excited to share what we have found out when we write the 2022 annual report!" May-Britt Moser says.

Distinguished visitors

Many leading international brain researchers visited Trondheim in 2012, both during the annual Kavli week and for other reasons. The most well-attended arrangement was Professor Richard Morris's lecture on "The making, keeping and losing of memory."

The Kavli Public Lecture by Richard Morris from the University of Edinburgh in Scotland in September was a success, with a full house and an inquisitive audience. Richard Morris was already a neuroscience celebrity in the early 1980s, when he invented the Morris water maze. This maze later became one of the most widely used tasks in behavioural neuroscience for studying the psychological processes and neural mechanisms of spatial learning and memory.

Richard Morris is equally excellent as a lecturer and a scientist. He explained during his lecture that memory is an important aspect of human personality. Different people may have completely different memories of the same event, because the brain is biased and would prefer to remember events that match the individual's established interests and perceptions.

The Kavli Week

Professor Morris held his lecture during the Kavli Week in September, which added to a string of scientific pearls in Trondheim during the year. Two researchers held their Kavli prize lectures in Trondheim: The two neuroscience prize winners Professor Cornelia Isabelle Bargmann from Rockefeller University in New York and Winfried Denk from the Max Planck Institute for Medical Research in Heidelberg.

"We loved having the opportunity to meet and talk with these masters of the mind, and hope our guests feel the same way. Naturally we need to express our gratitude to Fred Kavli and the Kavli Foundation, as well as to the laureates. We are a happy and growing scientific family, and these Kavli events make the ties stronger every time," said Professor May-Britt Moser.

Kavli Distinguished Lecturers

In March, Nobel laureate Linda Buck from the Howard Hughes Medical Institute and the Fred Hutchinson Cancer Research Center in Seattle gave a lecture on "Deconstructing smell." In June, Professor Oscar Marín and Assistant Professor Beatriz Rico from the Institute of Neuroscience in Alicante presented "Assembly of cortical circuits."

Professor Giacomo Rizzolatti from the University of Parma, the discoverer of the mirror neurons, held a Distinguished Kavli Lecture in June on "How the actions of others are understood." Professor Charles F. Stevens at the Salk Institute in La Jolla held a lecture in September on "Maps and anti-maps in the brain."

In November, Dr. Philip Campbell, Editor-in-Chief of Nature and Editor-in-Chief of Nature-branded publications, held a lecture on "Publishing in Nature – and what happens afterwards." The timing was not just by chance: a week later, the prestigious scientific publication devoted seven pages to the Trondheim researchers' latest findings.

The Kavli Public Lecture by Richard Morris was a great success with a full house and an inquisitive audience. (Photo: Matias Okawa, NTNU)

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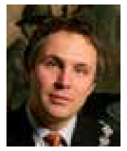
Who's who at KI/CBM

CBM, KAVLI AND ADVISORY BOARD

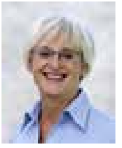
Bjørn Hafskjold
Dean Faculty of Natural Science and Technology, NTNU

Jan Morten Dyrstad
Dean of Faculty of Social Sciences and Technology Management, NTNU

Stig Slørdahl
Dean of Faculty of Medicine, NTNU



Tore O. Sandvik
County Council Chair, Sør- Trøndelag County



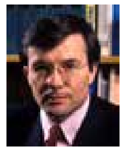
Kari Melby
Prorector, NTNU

May-Britt Moser
Professor, NTNU

Menno Witter
Professor, NTNU

Stig Slørdahl
Dean of Faculty of Medicine, NTNU

Larry Squire
Professor University of California San Diego, USA



Terry Sejnowski
Professor Howard Hughes Medical Institute, Salk Institute, USA

Erin Schuman
Professor Max Planck Institute for Brain Research, Germany

Earl Miller
Professor Massachusetts Institute of Technology, USA

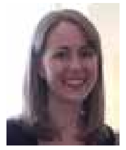
FACULTY AND JUNIOR GROUP LEADERS

Edvard Moser
Professor and Director

May-Britt Moser
Professor and Director

Menno Witter
Professor

Ayumu Tashiro
Group leader



Lisa Giocomo
Group leader

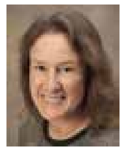
Yasser Roudi
Group leader

Sheng Jia Zhang
Group leader

VISITING PROFESSORS

Alessandro Treves
Professor II

Bruce McNaughton
Professor II



Carol Barnes
Professor II

Mayank Mehta
Professor II

Ole Paulsen
Professor II

Randolf H.R. Menzel
Professor II

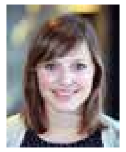
Richard Morris
Professor II

ADMINISTRATON

Elisabeth Kathleen Ofstad
Executive Officer Support group

Elise Skottene
Executive Officer Support group

Hege Tunstad
Communication Officer Support group



Ingrid Martine Håpnes
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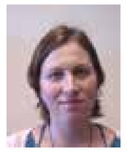
Iuliana Mariana Hussein
Head of office Support group

Jens Fredrik Andersen Senior
Executive Officer Support group

Linda Katalin Veres
Executive Officer Support group



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Unni Iversen
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Katarzyna Anna Kapusta
Master's student
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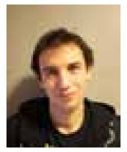
Magnus Helgheim Blystad
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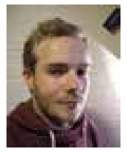
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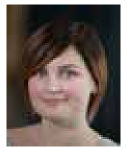
Rine Sørlie Wågan
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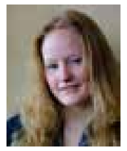
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Moser group


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Bruno Monterotti
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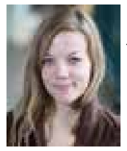
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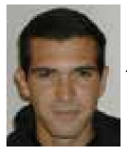
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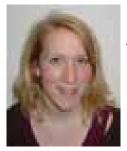
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Ingvild Hammer
Infrastructure
Support group


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Kyrre Haugen
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Merethe Andresen
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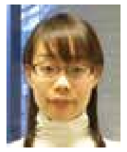
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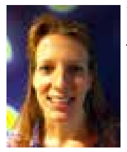
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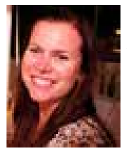
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Isabel Moser
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Moser group


Juan Wu
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Zhang group


Vanja Cnops
Research assistant
Tashiro group


Nylza Yadira Ibarguen Vargas
Research assistant
Tashiro group


Qin Zhang
Research assistant
Zhang group

Annual accounts 2012

Income

Norwegian Research Council: Centre of Excellence	10 000 000
Norwegian Research Council: other	28 139 000
International(European Commission, James McDonnel Foundation, Louis Jeantet Foundation)	12 296 000
Other Public/Private (Kavli foundation, Norwegian Health authorities)	3 143 000
Norwegian University of Science and Technology	35 508 000
Total income	89 086 000

Expenses

Net personnel costs	38 671 000
Indirect costs	23 564 000
Equipment	9 880 000
Operational expenses	16 971 000
Total expenses	89 086 000

Amounts in NOK

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Publications

May-Britt and Edvard Moser

Publications

Whitlock JR, Pfuhl G, Dagslott NC, Moser M-B and Moser EI (2012). Functional split between parietal and entorhinal cortices in the rat. Neuron, 73, 789-802

Canto CC, Koganezawa N, Beed P, Moser EI and Witter MP (2012). All layers of medial entorhinal cortex receive presubicular and parasubicular inputs. J. Neurosci. 32, 17620-17631.

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Yasser Roudi

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Annual report 2012
Kavli Institute for Systems Neuroscience and Centre for the Biology of Memory

Ten years with Norwegian Centres of Excellence

In November 2012, the Research Council of Norway awarded NOK 2 billion over 10 years to 13 research groups to establish Norwegian Centres of Excellence (NCoE) starting in 2013. NTNU was awarded four of the new centres.

The first three Centres of Excellence in Trondheim were inaugurated on 18 November 2002. From the left: Professor Peder Emstad of the Centre for Quantifiable Quality of Service in Communication Systems, Professor Edvard Moser of the CBM, Professor Torgeir Moan of the Centre for Ships and Ocean Structures, Christian Hambro, Director of the Norwegian Research Council, and Kristin Clemet, Minister of Education and Research. (Photo: Rune Petter Næss, NTNU Info).

The Centre for the Biology of Memory (CBM), led by Edvard and May-Britt Moser, was one of the initial 13 centres established in 2002, when the Research Council launched its first NCoE scheme. In 2007, eight new centres were established.

The Norwegian Minister of Education and Research, Kristin Halvorsen, extended heartily congratulations to the 13 new centres that were awarded funding in 2012. "Researchers who are seeking a role at the cutting edge of their international fields need flexible, long-term funding to give them a chance to take bolder steps," said Halvorsen.

"All our experience indicates that these 13 new centres will deliver research that makes a lasting impact for years to come. They are already well-established research groups; this long-term funding gives them the chance to make their mark at the forefront of international research," said Arvid Hallén, Director General of the Research Council.

"This is a big day for NTNU. We are very happy and proud that all four of the NTNU applicants who were finalists were also selected to be Centres of Excellence. This is an important recognition of the quality of the research that is conducted at NTNU," said Kari Melby, NTNU's Pro-Rector for Research.

The four new CoE units awarded to the NTNU in 2012 were:

• Centre for Autonomous Marine Operations and Systems (AMOS)

• Centre for Molecular Inflammation Research (CEMIR)

• Centre for Neural Computation (CNC)

• Centre for Dynamics of Biological Diversity

Illustration, frontpage:
Grid cells are organized into modules that operate at different spatial scales.

NTNU – Trondheim
Norwegian University of
Science and Technology

Annual Report for KI/CBM 2012

NTNU
The Norwegian University of Science and Technology (NTNU) is Norway's primary institution for educating the nation's future engineers and scientists. The university also has strong programmes in the social sciences, the arts and humanities, medicine, architecture and fine art. NTNU's cross-disciplinary research delivers creative innovations that have far-reaching social and economic impact.

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