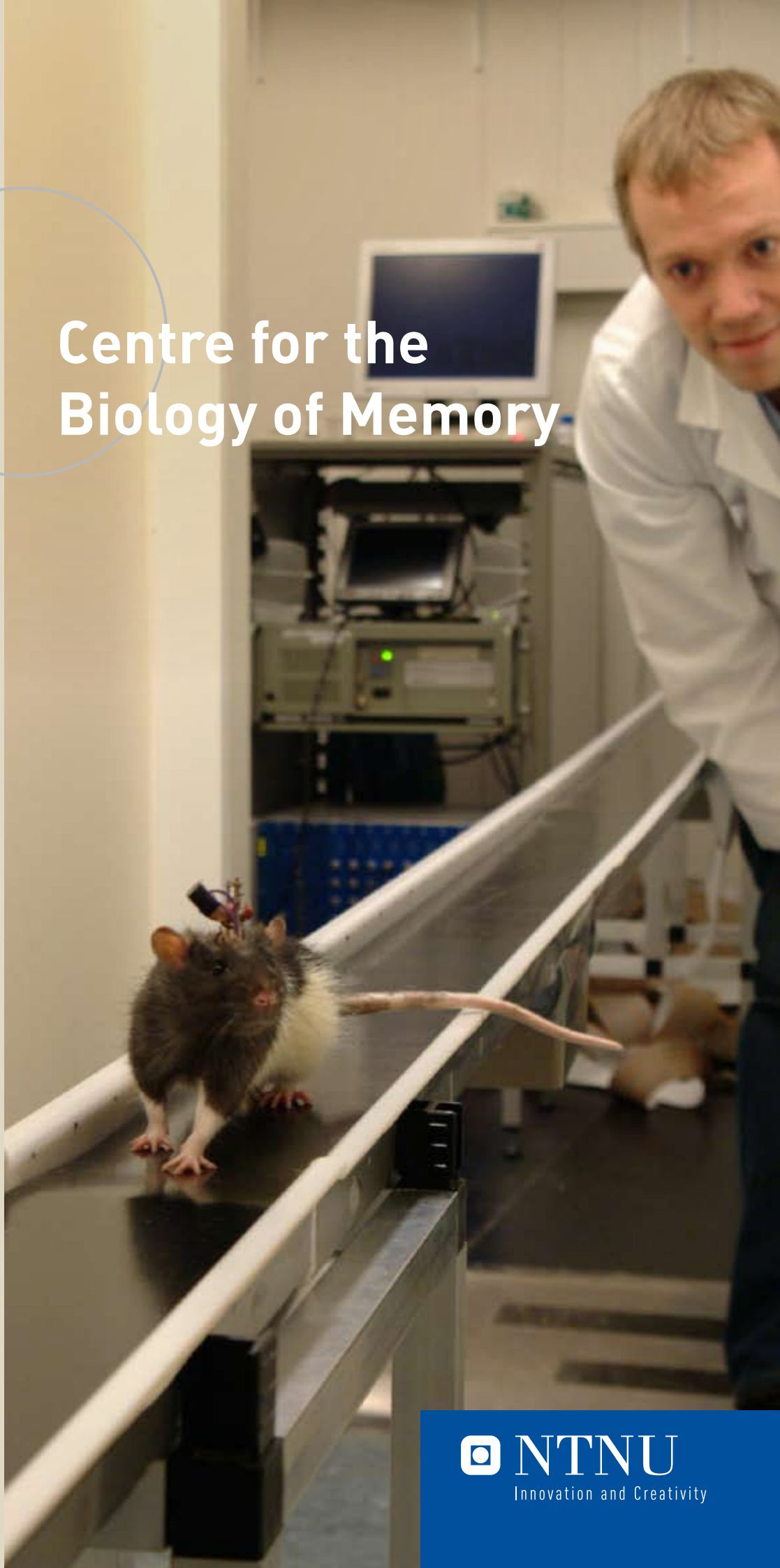
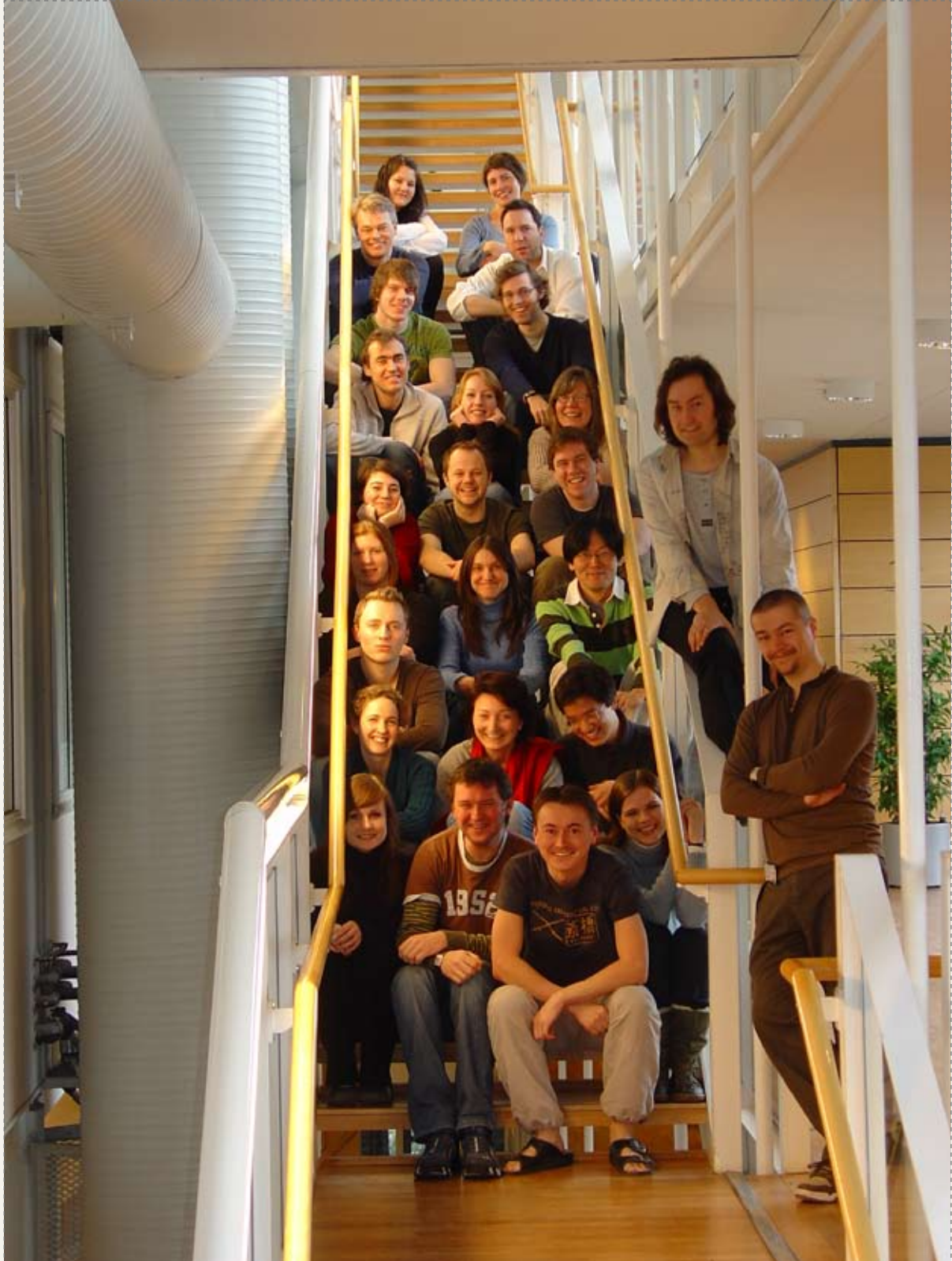
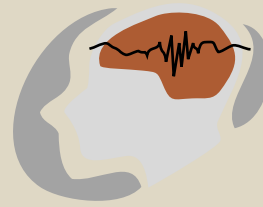


Annual Report 2006

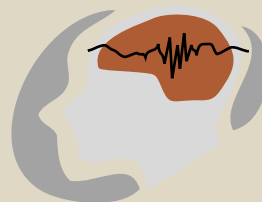
Centre for the Biology of Memory





Members of the Centre 12 March 2007

Table of Contents



Centre for the
Biology of Memory

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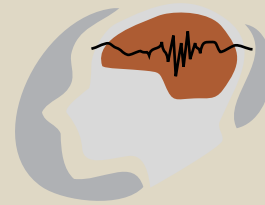
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A year with maps and memories	4
The world's best PhD thesis in 2005	5
The differential amplifier in the brain	6
"I've been here before, but something's changed"	8
The entorhinal cortex has a map, a compass and a speedometer	10
Prizes to May-Britt and Edvard Moser	12
An exceptionally succesful first period	13
Dutch professor attracts international researchers	14
The silencing of the hippocampal formation	15
Who's Who at CBM	16
Annual accounts	18
Seminars, Media and Doctoral defenses	19
Publications	20



Brain slices stained with antibodies



The brainchild is now four years old. Since the Centre for the Biology of Memory (CBM) was inaugurated in December 2002, it has provided some of the most important insights so far into how spatial location and spatial memory are computed in the brain.

While the first years at the CBM were used to test and expand hypotheses outlined in the original research plan, the agenda was soon overtaken by the exciting discovery of grid cells in the entorhinal cortex. As we prepare for the second half of the Centre's lifetime, the ultimate goals remain unaltered, but priorities have changed and a number of new questions and techniques have emerged. It is becoming clear that a deeper understanding of the workings of cortical microcircuits requires a cross-disciplinary experimental-theoretical approach using some of the latest tools for selective intervention with specific elements of the neuronal circuits.

Computation in the hippocampus

The discovery of grid cells is the result of a 10-year-long research programme aimed at determining how the brain computes location and how information about location is stored in memory. The hippocampus consists of several serially organised subfields with different inputs and outputs. The structural differences between the subfields laid the foundation for hypotheses about how each subfield contributes to spatial representation. In several papers published between 2004 and 2007, Jill and Stefan Leutgeb showed, together with colleagues, that certain cell assemblies in the CA3 area of the hippocampus perform pattern completion and pattern separation, and that pattern separation is supported by processes that enhance differences between input signals. These processes are located upstream at the entrance of the hippocampus, in the dentate gyrus.

The discovery of grid cells

While our insights into internal hippocampal computational processes were considerably enhanced by these studies,

other experiments drew our attention to the cortical input and output regions of the hippocampus. The first important step in this direction was taken when Vegard Brun and colleagues showed in 2002 that direct inputs from the entorhinal cortex are sufficient for place representation in the CA1 cells of the hippocampus. His observations led Marianne Fyhn and others to record electrical activity directly from the entorhinal cortex, and in 2004 she reported that the entorhinal cortex contains an accurate, topographically arranged spatial map of the animal's environment.

In 2005, Torkel Hafting and colleagues, recording from the same area, discovered the grid cell – a cell type different from any other functional cell category in the nervous system. These cells fire electrical signals with remarkable periodicity and this, together with the representation of direction and distance in the same network, as discovered by Sargolini and colleagues in 2006, pointed to a possible role for the entorhinal cortex in the computation of self-location based on movement.

Finally, at the beginning of 2007, Marianne Fyhn and others found that coordinate changes in grid cells predict pattern separation processes downstream in the hippocampus, which linked the entorhinal studies directly to the previously published studies of hippocampal computational functions.

An understanding of how the brain computes

This body of work has resulted in eight original papers, which were published in *Nature* and *Science* from 2002 to 2007. The grid-cell data, characterised by *Science* as the most important discovery in the field for more than two decades (*Science*, 5 May 2006), have brought us closer to understanding how the brain computes where we are and how we get from one place to another.

I would like to use this opportunity to thank every member of the Centre – visiting professors, post-docs, graduate students, master's students and technical and administrative staff – for their important contributions to these achievements. Likewise, I am grateful to the Board of CBM, the Advisory Board, the Institute of Neuromedicine, the

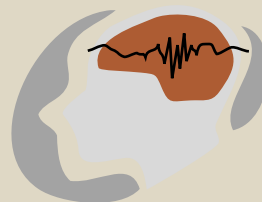
Faculty of Medicine and the rectorship of NTNU for their enthusiastic support.

The next five years

Where will we be going during the next five years? While we will continue pursuing the original aim of understanding the computational functions of hippocampal networks, and the interaction between the hippocampus and the rest of the cortex, we will use the grid cells as an experimental model for understanding computation in neuronal circuits in general. Spatial representation is beginning to be one of the best understood non-sensory brain functions, and studies of mechanisms by which neuronal circuits keep track of an animal's location are likely to uncover computational mechanisms applied by neuronal networks across the entire cortex. The structural symmetry of the grid cells is unique in that it is generated by the nervous system rather than derived from sensory input. Understanding its origins thus offers a direct window into some of the most fundamental operational principles of neuronal assemblies and microcircuits. To understand neuronal computation at the network level, we will use a combination of modelling and experimental testing. One of the most important developments will be the introduction of new technologies for cell-type-specific gene silencing, which in my view could provide us with a unique opportunity for determining the functions of the many diverse cell classes in the network.

Edvard Moser
Director, CBM

The world's best PhD thesis in 2005



Centre for the
Biology of Memory



Marianne Fyhn was awarded the American Society for Neuroscience's Donald B. Lindsley Prize for the most outstanding PhD thesis delivered in 2005. The prize was presented by the chair of the selection committee, Dr Thomas Carew, University of California. (Foto: SFN)

In October 2006 post-doctoral researcher Marianne Hafting Fyhn was awarded the Donald B. Lindsley Prize in Behavioural Neuroscience for the most outstanding PhD thesis in neurobiology in 2005, which demonstrated the existence of grid cells in the mammalian brain. Grid cells are nerve cells that contain a map with grid lines that is extraordinarily similar to the maps you can buy in your local bookshop.

Fyhn and four other researchers at the CBM caused a sensation when they published an Article in Nature in May 2005 reporting the existence of a complete mapping system in the rat brain. It is highly probable that the same system is to be found in the brains of other mammals and humans. The system is located in the grid cells in the entorhinal

cortex, which fire an electrical signal each time the rat passes the same place in the environment. But what attracted most attention was that the electrical signals fired by the grid cells at different spatial points collectively form a grid. While cartographers use a square grid in which the squares are marked by lines of longitude and latitude, in rats the grid is composed of equilateral triangles.

The Article in Nature was the third scientific publication in Fyhn's thesis: "Spatial maps in the hippocampus and entorhinal cortex". The first two were published in *Science* (2005) and *Neuron* (2002) respectively. Fyhn received her PhD in spring 2005. Her supervisors were May-Britt and Edvard Moser, and her research was partly supported by the Research Council of Norway.

Textbooks must be revised

The Donald B. Lindsley Prize is awarded for the most outstanding PhD thesis in the

general area of behavioural neuroscience submitted and approved during the previous calendar year. The jury stated that Fyhn's thesis breaks new ground in the efforts to understand the functions of the different parts of the temporal lobe, and how information about the spatial environment is represented in the brain. According to the jury, leading researchers have said that the new findings make it necessary to revise textbooks in the field.

The Donald B. Lindsley Prize is awarded by the Society for Neuroscience, which is the world's largest organisation for researchers studying the functions of the brain, spine and nervous system. The prize is presented at the Society's annual meeting, which in 2006 was held in Atlanta, Georgia.

"I am very proud to receive this prize. The award is a profound acknowledgement of my work," says Fyhn. "It is inspiring and rewarding to know that my findings have attracted the attention of researchers in so many different fields, and that our results are promoting cross-disciplinary research in subjects like mathematics, physics and biology. This will hopefully generate new knowledge and provide greater understanding of how the brain processes information and how it is able to create new memories," she says.

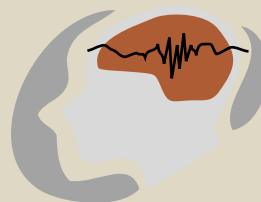
The CBM – a centre of excellence

Fyhn has been doing research at the CBM since 2000. The prize is seldom awarded to a researcher who is not from the US, and Fyhn is the first Norwegian to receive it.

"In addition to being a recognition of my PhD thesis, the prize is a feather in the cap for the CBM and May-Britt and Edvard Moser," comments Fyhn.

Based on their findings, Fyhn and Torkel Hafting have monitored the activity of place-selective grid cells in both the entorhinal cortex and the hippocampus simultaneously. The new results indicate that the entorhinal cortex possesses a universal map that can be used in all spatial environments, and that the details specific to each environment are probably aligned with the map in the hippocampus. See the separate article on this subject in the Annual Report.

The differential amplifier in the brain



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Stefan Leutgeb and Jill Leutgeb, Research Scientists

In an office's filing system, related documents are normally placed close to one another. The brain, on the other hand, files related documents in as many different ways as possible. This is done by enhancing the differences between memories. This "differential amplifier" is located in a small structure called the dentate gyrus.

Researchers at the Centre for the Biology of Memory (CBM) are now able to draw a surprisingly detailed picture of the way the mammalian brain functions. In general one can say that the brain structure called the hippocampus receives and processes sense impressions and sends them in the form of electrical signals called action potentials to different areas of the cerebral cortex. Auditory impressions are stored in one area of the cortex, smells in another, visual impressions in a third, and so on. The sum of the stored impressions forms a memory that can later be retrieved.

The memories are stored in the form of physical changes in the synapses, which are the junctions between the different nerve cells, or neurons, in the cerebral cortex.

Previous studies have shown that storage in a synapse takes place through the formation of proteins that can enhance or reduce the ability of the synapse to send electrical signals to other nerve cells in the brain.

The brain's differential amplifier

In order to understand how memory works, however, we need to know many more details. The brain contains an enormous number of neurons, and each neuron can have a large number of synapses, so the brain's storage capacity is huge.

Jill Leutgeb at the CBM has studied the way the brain manages to distinguish between memories that resemble each other, such as this year's Christmas as opposed to last year's.

"The brain solves the problem by exaggerating the differences between the external signals. You could say that it enhances the differences between different memories," explains Leutgeb.

The theory has been put forward that the brain's differential amplifier is located in a small area of the hippocampus called the dentate gyrus, and this has been substantially supported by Jill

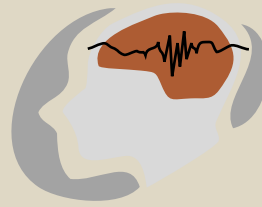
Leutgeb and her colleagues Stefan Leutgeb and Edvard and May-Britt Moser in a recently published article in *Science*.

Leutgeb's study shows that the dentate gyrus cooperates with another part of the hippocampus called CA3. The dentate gyrus and CA3 receive the same signals from the sensory organs and the cerebral cortex, but because they are anatomically different, they treat the signals in very different ways.

"In CA3 each nerve cell is joined by synapses to an extremely large number of other cells in this area, so that the nerve cells



Recording positions in dentate gyrus and CA3



of CA3 'talk to each other' all the time. The dentate gyrus, on the other hand, consists of an extremely large number of small (granule) nerve cells that are mainly silent," explains Leutgeb.

Many of the cells in the dentate gyrus are not active. There are about 1 million granule cells in the dentate gyrus of rats, and about 300,000 neurons in CA3. Each dentate cell only has about 15 synapses in CA3. There are approximately three times as many dentate cells as CA3 cells, so each CA3 cell receives close to 50 inputs. Since only 2 per cent of the dentate cells are active, on average only one of these 50 will be active.

A dual mechanism

Leutgeb and colleagues placed rats in specially designed enclosures, where they roamed about searching for food, and monitored the activity in their brains by means of microelectrodes that register electrical signals from individual cells. In a previous study, also published in *Science*, Jill and Stefan Leutgeb showed that the hippocampus contains a detailed map, in which different groups of cells recognise specific spatial locations and link them to events occurring at the place in question. Every time the rat passed the same place in the enclosure, the same group of nerve cells would fire an electrical signal.

Leutgeb and colleagues wished to test the theory that it is the dentate gyrus that distinguishes between memories, a process known as pattern separation. They placed rats in enclosures with flexible walls that gradually changed shape from a square to a circle or vice versa, and recorded the electrical activity in selected cells in both the dentate gyrus and CA3 simultaneously. Few experiments recording dentate gyrus cells had been performed previously, which was one reason why *Science* accepted the article for publication.

"This is a difficult place for recording cellular activity," says Jill Leutgeb. "The cells are very small and only about 2 per cent of them are active. This makes it difficult to place electrodes close to an active cell."

An exciting discovery

The main reason why *Science* was interested in publishing the study was of course that the results were sensational. The findings by Leutgeb's group point to the existence of a dual mechanism for distinguishing between similar memories, where both the dentate gyrus and the CA3 play a role. "Our results seem to confirm the hypothesis that the dentate gyrus enhances small differences. On the other hand the dentate gyrus also cooperates with CA3, which behaves more like the office filing system and places related memories close to each other. These two structures work together to control related memories," explains Jill Leutgeb.

The authors found that the gradual changes in the shape of the morph box resulted in progressive changes in the electrical activity in the neurons in both the dentate gyrus and CA3. In CA3 the same cells were active all the time but the firing intensity varied in line with the changing shape of the enclosure. In the dentate gyrus, on the other hand, the firing activity changed in a seemingly random way. Some dentate cells were active in the initial part of the experiment, while others were active halfway through and still others in the final shape.

"The entire cell does not shut off, but each cell gradually becomes silent at one location and gains activity at a different

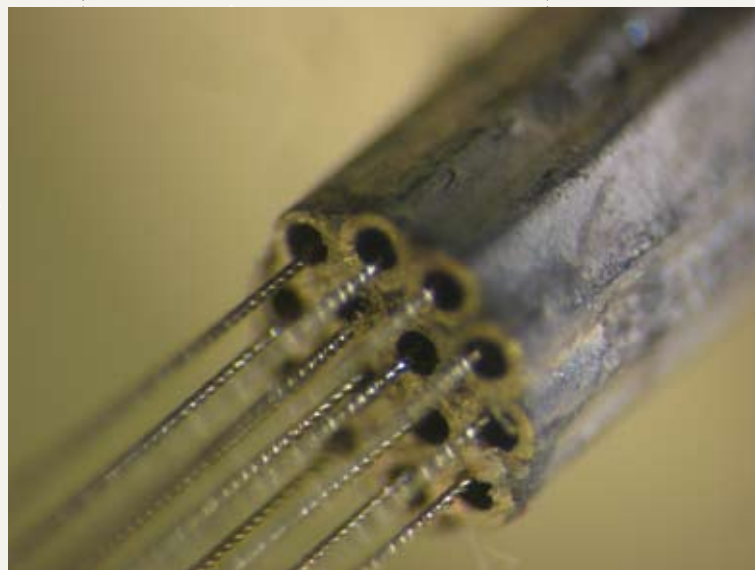
location. There may be three or four of these potentially active locations, and the firing at each changes at a different pace, and sometimes also in a different direction," explains Leutgeb.

The authors believe that this shows that the dentate cells exaggerate the differences, as predicted by the theoretical model, but that the mechanism involved is one that was previously unknown. The dentate gyrus tells the brain when similar experiences are in fact different by generating very different patterns based on very small differences.

Research into Alzheimer's disease

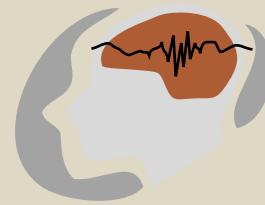
The dentate gyrus is one of the very few areas of the brain where new cells develop throughout life; the number of neurons in the rest of the brain is given at birth and does not alter during later life. The dentate gyrus is also one of the first structures to be weakened in Alzheimer's disease in humans, together with the entorhinal cortex. One of the aims of research in this field is to acquire knowledge that makes it possible to intervene in the development of the disease and either restore memory or halt the process of memory loss.

The most surprising finding in the study was the fact that the same cells in the dentate gyrus were active all the time. "The same cell population continued to be active even when we placed the rats in completely different environments. This raises the question of what the other 98 per cent of dentate cells do, but it could be that they are activated when the rats engage in activities other than searching for food in enclosures. Investigating this will certainly be exciting," says Leutgeb.



Tetrode bundle

“I’ve been here before, but something’s changed”



The mammalian brain has two structures that are essential to memory: the entorhinal cortex and the hippocampus. CBM researchers Marianne Hafting Fyhn and Torkel Hafting have recently studied these two structures in detail in the rat brain, and discovered that their interactions are more important than scientists have realised. Their findings were so groundbreaking that they were published in Nature. The study was a collaboration with Alessandro Treves and May-Britt and Edvard Moser.

ment.

The discovery came about when Fyhn and Hafting and colleagues studied how grid cells in the entorhinal cortex cooperated with place-selective cells in the hippocampus. Grid cells were discovered by Fyhn and colleagues at the CBM in 2005 to form a universal system of coordinates that are used for local navigation.

Memory and the hippocampus

Although the hippocampus has been known ever since the 1950s to play a decisive role in memory, little attention has been paid to the neighbouring entorhinal cortex. However, in the last few years research at the CBM has promoted interest in this structure, which

only fired when the rat passed particular places, which suggested that these cells have as much place-specific information as the corresponding cells in the hippocampus. This means that since information concerning the rat’s position has already been registered in the entorhinal cortex, the hippocampus can concentrate on associating place with other details, so that a memory can be formed.

The researchers concentrated on the rats’ sense of place, since memories of place are an important element of episodic memory: it is difficult to remember an event without attaching it to a particular place. The ability to recognise places is extremely important for all mammals, whether they are humans



Post-doctoral researchers Marianne Hafting Fyhn and Torkel Hafting.

The hippocampus receives information from almost all parts of the brain and puts it together in complex memory representations. All sensory information goes first through the entorhinal cortex, and Fyhn and Hafting’s new findings suggest that this part of the cortex computes the rat’s location in distances and angles, while the hippocampus associates the position coordinates with the unique details of each spatial environ-

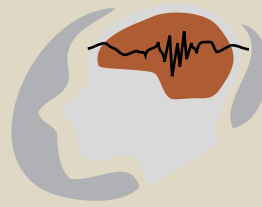
acts as a gateway into the hippocampus.

For over 30 years it was believed that brain cells with place-specific activity were only present in the hippocampus. However, Fyhn and Hafting discovered position-modulated cells in the entorhinal cortex and monitored activity in the place-selective cells in the hippocampus and the entorhinal cortex simultaneously. They found that a given place-selective cell in the entorhinal cortex

on their way to work or squirrels searching for their stores of nuts. The rat brain has so many features in common with the brains of other mammals, including humans, that the results can be generalised to a considerable extent.

The brain draws a map

Fyhn and Hafting studied brain function by implanting microelectrodes in the brain of



rats. Electrodes register electric signals from individual cells, and the researchers can monitor the activity on a computer screen that tells them which neurons are activated, in other words which cells are firing electrical signals at any given time.

The rats were first trained to find food in enclosures of different shapes, for example round or square, or with walls of different colours. Previous experiments had shown that rats placed in a new enclosure seem to develop a map in their brains as they become familiar with their surroundings. For every place in the enclosure, a specific group of neurons in the hippocampus fire an electric signal as the rat passes it. Since each cell fires at the same place each time the rat revisits the same place in the same enclosure, recording the firing provides a window into the memory, and it can be assumed that the rat recognises places it has visited before. The researchers were also able to conclude the whereabouts of the rat in the enclosure by seeing which cells were firing.

"It isn't possible to see from the rats' behaviour whether they recognise places, since they don't really do anything except run around looking for biscuits. So the most accurate way we can measure whether they recognise a place is to record the activity of the brain cells," says Fyhn.

The entorhinal cortex – the brain's global positioning system

Previous studies mapping the electrical activity of brain cells have shown that the firing pattern in the hippocampus coincided closely with the rat's position. This supported the theory that the hippocampus is able to recognise previously visited places. However, it is not enough for the rat to know whether it has been there before, it also needs to know whether anything has changed since the previous visit.

"If the rat arrives at a place that has changed since its previous visit, for example because the experimenter has exchanged the white walls for black ones, the place is recognised as being the same by the entorhinal cortex, while the hippocampus registers that there are some differences compared with the previous

time," explains Fyhn. In other words, the entorhinal cortex recognises places and says "I've been here before", and the hippocampus receives this message and comments, "Yes, but something has changed since then."

Grid cells and representations of place

"The group of place-selective cells that are active in one room create a map, and if you go into another room the hippocampus draws a new map by activating a different subset of cells. In the Nature article we conclude that if the environments are so different that the entorhinal cortex has a different set of map coordinates for each of them, this will cause the hippocampus to draw a new map. This indicates that the hippocampus uses spatial information from the entorhinal cortex to determine whether the place where you are standing is the same or completely different. If the grid cells in the entorhinal cortex do not change their firing pattern, the group of activated cells in the hippocampus remains the same but the firing intensity changes. Thus you know you're in the same place but the map has changed colour, showing you that something has happened since you were last there," explains Fyhn.

There is every reason to believe that the

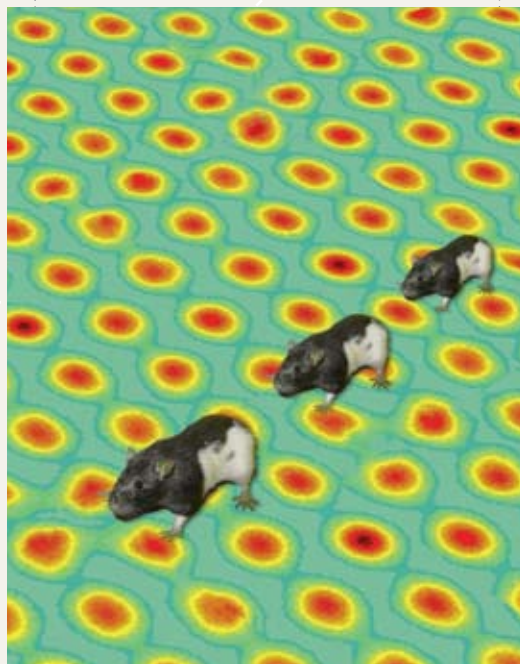
rat's experience of familiarity with a place resembles that of a human. "If for example you enter a room where you have been before, you can retrieve the memory of what the room looks like. If someone has altered minor details in the room, you are likely to notice this at once but you will continue to believe that it is the same room. You now have two memory representations of the same room. The hippocampus enables you to distinguish between the original and the new appearance of the room," says Fyhn.

Building on her PhD thesis

The letter in Nature is largely built on work in Fyhn's PhD thesis of 2005, which is described in a separate article in the Annual Report.

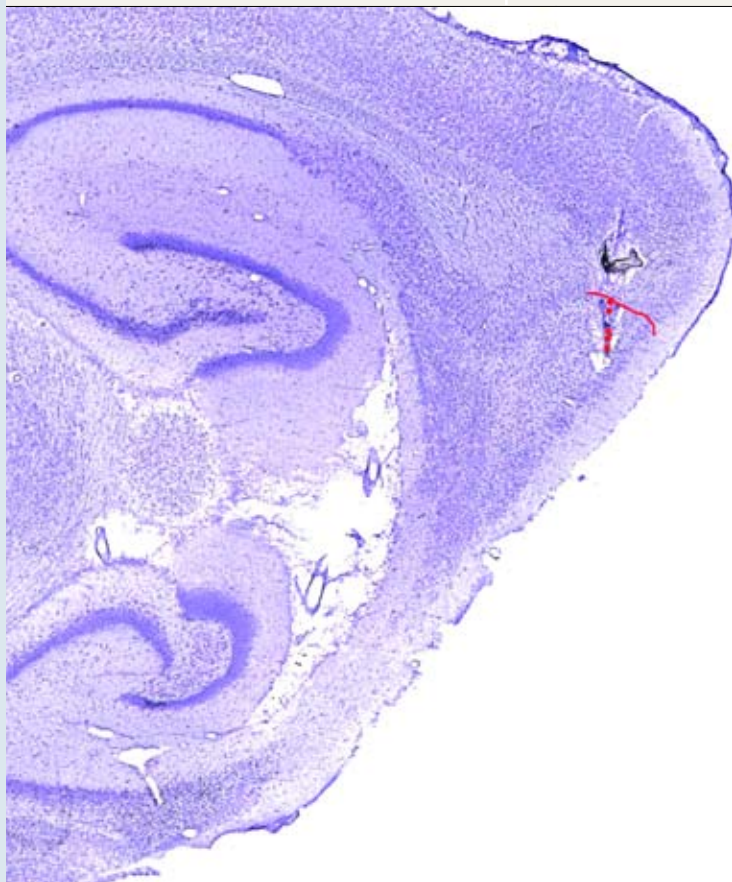
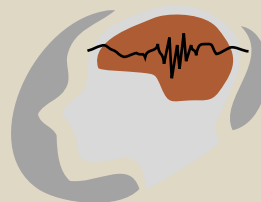
The new results show that the CBM researchers have taken a new and important step forward in the efforts to map the different functions of the brain. Fyhn says: "We are beginning to understand more about the different roles of the hippocampus and the entorhinal cortex. Since the hippocampus is one of the most widely studied structures of the brain, there are many different theories as to how it functions. Our study of the entorhinal cortex has confirmed some and refuted others, which makes it possible to put forward new theories that can be tested."

Fyhn's next project is concerned with an exciting phenomenon called "phase precession". Thus the place-selective cells in the hippocampus can not only tell where the rat is at any given time, they can also predict where it will be in the near future. Fyhn will now investigate whether the cells in the entorhinal cortex can do the same. Studies will also be carried out to determine how the network of grid cells in the entorhinal cortex functions and to what extent the place-specific information in the hippocampus and the entorhinal cortex depend on each other. This is because the electrical signals do not just pass from the entorhinal cortex to the hippocampus, they also go the other way; so that the two structures form a kind of loop. Fyhn will inactivate the hippocampus in order to study how this affects the representation of place in the entorhinal cortex.



Using grid cells for navigation

The entorhinal cortex has a map, a compass and a speedometer



Recording positions in entorhinal cortex

In 2005 researchers at the CBM found that there are special nerve cells in the mammalian brain that contain a map with grid lines that is extraordinarily like the maps you can buy in a bookshop. Now Francesca Sargolini and other CBM researchers have shown that the brain is equipped with a compass and a speedometer as well. Thus it has all the tools it needs for navigation.

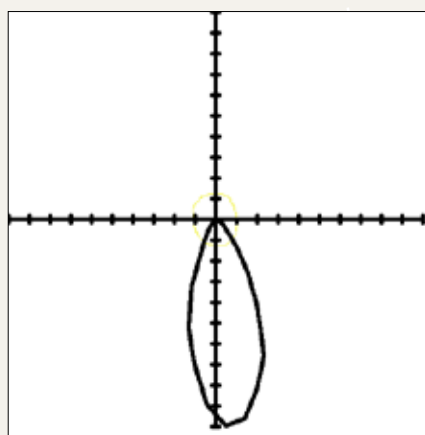
It is not easy to decide which of the discoveries made at the CBM has attracted the most international attention, but the letter to Nature from Torkel Hafting, Marianne Fyhn, Sturla Molden and May-Britt and Edvard Moser in May 2005 is unquestionably one of them. The authors have discovered that there is a mapping system in the rat brain, and probably in the brains

of humans and all other mammals as well.

The authors' first noteworthy finding was that the mapping system is located in the entorhinal cortex and not the hippocampus, which was what theoretical models had indicated. Even more amazing was the fact that the mapping system is very like that used for maps in general, although there are important differences. For example, cartographers use the lines of longitude and latitude in a grid system based on squares, while the grid lines in the rat brain form equilateral triangles. Furthermore the brain map covers in principle the whole world, in other words it is more of a globe than a two-dimensional map.

The next breakthrough

The mapping system in the entorhinal cortex consists of grid cells. These fire an electrical signal every time the rat passes specific places in the environment. Each grid cell can fire at many different points, but the interesting feature of the system is that each cell fires a signal at distinct spatial points



Polar plot of a head-direction cell

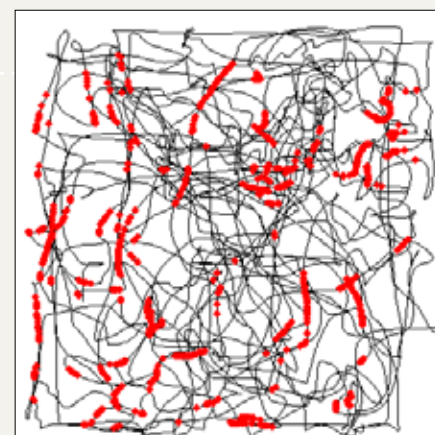
that form a triangular grid. The system is so precise that researchers can determine the rat's whereabouts accurately to within a few centimetres just by looking at the signals fired by a few cells.

The mapping system described in 2005 was found in two of the six layers of the entorhinal cortex: layers II and III. The next breakthrough from the CBM came in 2006. Building on the 2005 results, Francesca Sargolini and six co-authors published an article in Science in May 2006, in which they describe neurons in the entorhinal cortex that encode not only where a rat is, but also how fast it is moving and in what direction. Theoreticians believe that grid cells and their connections to other neurons may finally clarify ideas about how the brain performs spatial navigation.

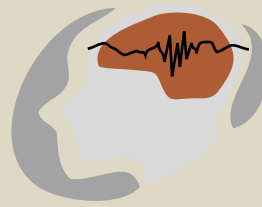
Two main differences

"There are two main differences between the article in 2005 and that in 2006. The first is that in the latter case we studied electrical activity in all the active layers of the entorhinal cortex, while the 2005 article only reports measurements in layers II and III, mainly layer II. The 2005 results seemed to indicate that grid cells are only found in layers II and III, but we have now established that these cells are present throughout the entorhinal cortex. This means that the outer and inner layers of the entorhinal cortex probably do not perform different functions, but that the entire cortex functions as a whole," explains Sargolini.

The entorhinal cortex consists of six layers, but only four of them contain neurons.



Head-direction cell: Spikes and trajectory



The other two consist of fibres running through to the other layers.

The other main difference between the two articles is that in the 2006 article Sargolini and colleagues show that the entorhinal cortex has even more functions than the grid cells that process spatial information. "The cortex also contains head-direction cells, in layers III to VI, which provide information on the direction in which the rat's head is pointing. In addition it contains

the cortex and from there to the hippocampus, which in turn passes it on to the deeper layers of the entorhinal cortex. The CBM researchers now have a very detailed impression of how information from the sensory organs is processed during this loop.

The instrument panel in the rat brain

These findings increasingly suggest that the rat brain resembles the instrument panel in an airplane or ship, which is equipped with

separate instruments showing direction, position and speed. "But I must emphasise that this does not mean that there are three different types of brain cells. We have found grid cells that modulate speed as well, we have found head-direction cells that modulate speed as well, and we have found cells that modulate direction, GPS and speed. Thus all three functions may be performed by the same cells. This is a system that makes it possible to navigate very efficiently in a spatial environment," says Sargolini.

The researchers are not quite sure which sensory information is the most impor-

tant for navigation, but it has been shown that rats are able to navigate in complete darkness. "The conjunction of positional, directional and translational information in a single cell type may enable grid coordinates to be updated during self-motion-based navigation," suggests Sargolini.

International attention

The research carried out at the CBM has been highly praised by many prominent international brain researchers. "It's amazing to see the interaction between theory and experiment that has come together in the Mosers' work," the neuroscientist David Redish of the University of Minnesota in Minneapolis has told Science. James Knierin of the University of Texas Medical School in Houston has described the results as "the most important discovery in our field in over 20 years", and John O'Keefe of University College London is "over the moon about this discovery". O'Keefe is an authority in the field and discovered the place cells in the hippocampus as early as the 1970s. Even then O'Keefe realised that there was a missing factor, since an animal needs more than place cells for navigation. "We predicted right from the beginning that there would also have to be information about direction and distance to tie together the place cells into something like a map formation," O'Keefe told Science in May 2006.

Theory and practice

Sargolini, who is originally from Rome and came to Trondheim and the CBM as a post-doctoral researcher in 2005, is now doing research at the University of Marseilles. She will be continuing her research on the navigation system of mammals, with special emphasis on how the rat's consciousness of its goal is coded into the mapping system, allowing it to plan its movements in space.

Sargolini admits that she has lost her way in Trondheim several times owing to her poor sense of direction, but there is obviously nothing wrong with her theoretical understanding of the rat's navigation system.

"Being involved in the research at the CBM has been very interesting, and I hope to be able to continue my cooperation with the researchers in Trondheim even though I have moved to Marseilles", says Sargolini.

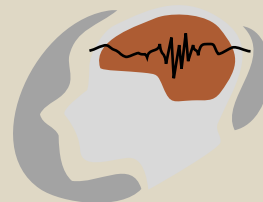


Francesca Sargolini, Associate Professor at University of Marseille

cells that register the speed at which the rat is moving in relation to its surroundings," says Sargolini.

The entorhinal cortex and the hippocampus are in close contact with each other. All information from the sensory organs passes through the two uppermost layers in

Prizes to May-Britt and Edvard Moser



Centre for the
Biology of Memory

May-Britt and Edvard Moser received the 2006 Liliane Bettencourt Life Sciences Award for their research and administrative contributions to building up the Centre for the Biology of Memory (CBM). This prestigious prize of EUR 250,000 is awarded to younger European researchers with an international reputation.

The Liliane Bettencourt Life Sciences Award is given every year by the Bettencourt Schueller Foundation, which was established in 1987 by Mrs. Liliane Bettencourt in memory of her father, the late Eugene Schueller. The prize is intended to support the work of a top-level European researcher under the age of 45, along with his or her team, in the field of biology or medicine. The prize confers considerable prestige and is worth a substantial amount of money. The Mosers will use the prize money to hire a new postdoctoral fellow.

The jury stated: "By combining neuro-anatomical, neurophysiological, behavioural and mathematical concepts and methods, the group headed by Edvard and May-Britt Moser has provided insights into how spatial location and spatial memory are com-

puted in the brain. Their most important contribution was perhaps the discovery of grid cells in the entorhinal cortex, which immediately pointed to the entorhinal cortex as a hub for the brain network that makes us find our way through the environment." The jury was chaired by Pierre Corvol, Professor of Experimental Medicine at the Collège de France and member of the French Academy of Sciences.

Seven million euros awarded every year

The jury also attached importance to the fact that the ultimate goal of the research group is to understand how information is encoded, stored and used in cortical systems and microcircuits and, implicitly, how a disruption of these processes leads to various forms of neurological disease or psychopathology.

The Liliane Bettencourt Life Sciences Award of EUR 250,000 is an important part of the Bettencourt Schueller Foundation's commitment to medical research. The Foundation's mission is to encourage entrepreneurship in the arts, sciences and social commitment. In 2006, the Foundation awarded over EUR 7 million in grants and prizes, 62 per cent of which was allocated to medical research and health programmes.

Cosmetics and beauty products

In 1907, a young French chemist called Eugene Schueller developed a new hair-colour formula, which he called Auréole, and in 1909 he registered the company that was to become L'Oréal. Its guiding principle was to use research and innovation in the cause of beauty. Liliane Bettencourt inherited the L'Oréal fortune from her father in 1957 and is still the largest shareholder. According to Forbes Magazine she is the world's richest woman, with assets worth about USD 16 billion in 2006. L'Oréal is the world's largest group in cosmetics and beauty products.

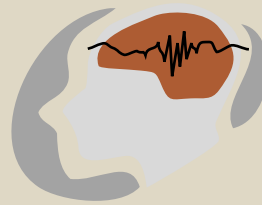
The Koetser Prize

In the same year the Mosers also received the memorial award from the Betty and David Koetser Foundation for Brain Research. The foundation was established in 1993 to support basic and clinical research in neurology and in the neurosciences, and the award is given every year to outstanding scientists who have made major contributions to neuroscience. The Mosers received the prize, worth CHF 20,000 (EUR 12,500), in Zürich on 20 October. Previous laureates include James Randi (1993) and Professors Pat Wall (1994), Anders Björklund (1995), Semir Zeki (1997), Laurence R. Young (1998), Wolf Singer (2003) and Rodolfo Llinas (2004).



Liliane Bettencourt presented the Life Sciences Award to May-Britt and Edvard Moser at a ceremony in Paris on 12 December 2006. (Photo: Bettencourt Schueller Foundation).

An exceptionally successful first period



Centre for the
Biology of Memory

The Centre for the Biology of Memory (CBM) has by all standards been exceptionally successful during the first period of operation, according to the Research Council of Norway's Midway Evaluation of the Norwegian Centres of Excellence in 2006. This means that the Centre is ensured financial support up to 2013.

and the quality is exceptionally high and the quantity clearly satisfactory", according to the evaluation.

"We are naturally very happy to receive such a positive evaluation, which is highly motivating for the whole staff of the centre. It gives us a sound basis for our work in the period up to 2013, and we will do our best to maintain a scientific standard that is at the very least as high as this," comments the director of the CBM, Edvard Moser.

The evaluation process

The Norwegian Centres of excellence scheme is designed to encourage Norwegian research groups to establish centres dedicated to long-term basic research. The intention is to raise the quality of Norwegian research and bring more researchers and research groups up to a high international standard. The purpose of the midway evaluation was to assess the scientific quality and performance of the individual centres both in absolute terms and relative to their original research plans.

The midway evaluation involved putting together extensive background material, an assessment of each centre by three international experts, and an overall evaluation by an interdisciplinary international evaluation committee chaired by Professor Sten Grillner at the Nobel Institute for Neurophysiology, Karolinska Institutet, Stockholm, Sweden. The overall impression of the evaluation committee is that the CoEs have had a very positive effect on the research environment in which they were formed.



An efficient organisation

The report commented that the centre is being managed very efficiently by the two directors. The evaluation committee stated that the relations between the centre and the NTNU appeared to be excellent, and that the interaction had clearly enriched the overall research environment. "The two directors have thus made an excellent contribution, both as coordinators of the centre and as researchers. The Mosers and their colleagues have established themselves as one of the leading research centres in memory research, which is one of the 'hottest' areas of brain research. Their overall plan is ambitious but realistic," according to the evaluation.

The evaluation committee also praised the PhD and post-doctoral training programmes, and stated that the CBM is now attracting foreign PhD students and post-doctoral researchers. They also concluded that there is clearly a need for more space for the centre.

The Midway Evaluation, which was published in October 2006, praised the quality of research and administration of the CBM. The centre is one of the 13 research groups that were given the status "centre of excellence" when the Research Council established the scheme in 2002, and in the midway evaluation the CBM was one of nine centres awarded the highest distinction, "exceptionally good".

The main conclusion with regard to the CBM was that the centre has had a major impact on studies of the biology of memory and has developed into a major international centre in this field. "The centre has a remarkable series of high-profile articles published in *Nature*, *Science*, *Neuron* and *Proceedings of the National Academy of Science*. The articles of the centre have a very high impact

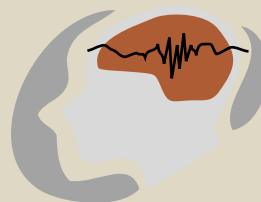
The evaluation report also points out that the centre's international collaboration has been a very important aspect with regard to both methodology and concepts. The structure of the centre is somewhat unusual in that except for the two directors, the principal investigators have been recruited from other European countries and North America. They are leading international scientists in the various fields covered by the centre, according to the report.

The evaluation also reports that the centre has followed the original plan and not only achieved its goals, but also discovered the existence of grid cells – a major new finding that was not even conceived of when the experiments in this field were first started.

Then Minister of Education and Research Kristin Clemet attended the inauguration of the three centres of excellence at the Norwegian University of Science and Technology in 2002.

(Photo: Rune Petter Ness)

Dutch professor attracts international researchers



Centre for the
Biology of Memory

Professor Menno Witter of the Netherlands has been cooperating with the CBM since 2000, and on 1 January 2007 he was appointed head of the CBM's new neuro-anatomy research group.

Menno Witter was Professor of Anatomy and Embryology at the Department of Anatomy and Neurosciences, VU University medical center, where he conducted basic research that included the use of magnetic resonance imaging (MRI) and other medical imaging technology. He has also been scientific director at a number of institutes of the VUmc and director of the graduate school for Neurosciences in Amsterdam.

"I accepted the CBM's offer because it gives me an opportunity to do full-time research again. In addition the research environment is extremely interesting and stimulating, and the cooperation we established in 2000 has been very productive," says Witter.

"We are very pleased to have managed to recruit Menno P. Witter, who will make an important contribution to research at both the CBM and the NTNU as a whole," says Dean Stig Slørdahl of the Medical Faculty at the Norwegian University of Science and Technology (NTNU). "He has already attracted other renowned international researchers," says Slørdahl.

An innovative recruitment strategy

Witter is internationally renowned in his field, and the leadership of the Medical Faculty adopted a fresh approach when recruiting him. "We can't compete with foreign universities in terms of salary, but salary is not always the only thing that counts. In this case we put together a package that consisted, in addition to the salary, of an extremely good research environment, state-of-the-art equipment and premises, which competed favourably with what other universities could offer. This was a new approach for us, but it has already had spillover effects; for example a number of prominent international scientists have applied for other positions at the faculty," says

Slørdahl.

Slørdahl adds that the recruitment of Witter is fully in line with the NTNU's new strategy, which is to ensure that the university occupies a leading position



Professor Menno P. Witter is head of the Neuroanatomy Group at the CBM and will also be cooperating with MI Lab, a Centre for Research-based Innovation at the NTNU.

internationally by 2020. He says: "Witter's contribution will help us exploit the CBM's potential even more fully. He will also function as a bridge-builder between the CBM and MI Lab, which is NTNU's new Centre for Research-based Innovation in imaging therapy."

Developing imaging tools

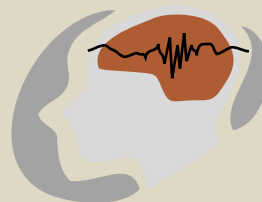
Witter confirms that it was the combination of salary, a good research environment and state-of-the-art equipment that decided him to move to Trondheim. "I am happy to have the opportunity to build up a laboratory with state-of-the-art equipment that Trondheim has not previously possessed. My research is concerned with describing the architecture of the brain that is involved in learning and memory, and the new equipment will include several different types of microscopic equipment at the very high end of current technology. The Medical Faculty already has access to an electron microscope, but we will also be acquiring a confocal laser scanning microscope (CLSM), which will

enable us to produce images almost as far down as the synaptic level. Another particularly important piece of equipment will be a system for voltage-sensitive dye imaging, which makes it possible to study the electri-

cal activity in sections of living brain tissue," says Witter.

Witter is also looking forward to intensifying cooperation with the MI Lab and its head, Olav Haraldseth. "MI Lab works with innovation aimed at the health service, while we at the CBM primarily study the rat brain. But we all want to know more about the functioning of the human brain and central nervous system, and one of our aims is to test the hypotheses we form on the basis of rat brain findings by using functional imaging in humans," adds Witter.

The silencing of the hippocampal formation



Centre for the
Biology of Memory

Most Alzheimer researchers have characterised the disease as a biochemical disturbance leading to the formation of plaques and cell death in the cerebral cortex. Stefan Leutgeb has taken an entirely new approach and investigated local loss of function in the hippocampus region and its effect on the brain's ability to store memories in the cerebral cortex.

The construction of the mammalian brain can be compared to that of a computer, with an internal memory that processes incoming information and a hard disk where the memory of the information is stored. It is difficult to use the hard disk if important parts of the internal memory are damaged. This has many parallels with what happens in a brain affected by Alzheimer's disease,

of the new research group at the Centre for the Biology of Memory that is studying the silencing of the hippocampal formation. The group's name reflects its new approach: "Memory consolidation and Alzheimer's disease".

Complete silence even in the early phase

Leutgeb explains: "The entorhinal cortex and the dentate gyrus are closely linked with the hippocampus, and play a central role in the ability of the mammalian brain to store and retrieve memories. These two structures are the first to be affected in people who are developing Alzheimer's disease, but the effects are most serious in the dentate gyrus. There is already complete silence in this area in the early phase of the disease."



Assembling a hyperdrive

on the computer's hard disk.

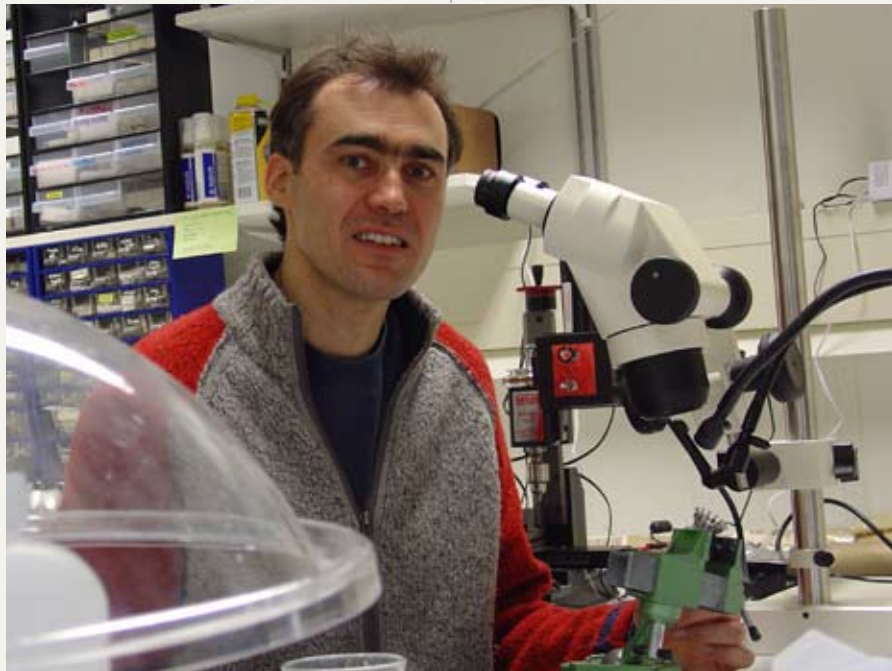
One of the triggers of Alzheimer's disease is that the brain produces too much of a protein called amyloid. Amyloid then accumulates in the brain in the form of plaques and causes cell death and cerebral degeneration. When such plaques are experimentally induced in mice, it has been found that the mice develop memory loss long before the amyloid is deposited as plaques. The problems begin when the mice are only five months old, when the amyloid in the brain is still in a soluble form. Leutgeb believes that this process may also apply to people.

Good prospects for drugs against Alzheimer's

The first experiment the new group will perform will be to inject soluble amyloid into the hippocampus region of laboratory rats in order to investigate the local effects in the entorhinal cortex and dentate gyrus. The rats' behaviour will also be monitored with a view to identifying signs of memory loss.

"I am trying to establish whether the effects of amyloid on the hippocampus really can result in problems for the brain as a whole. So far only a few researchers have studied the influence of amyloid on the circuitry of the brain in the early phase of the disease," explains Leutgeb.

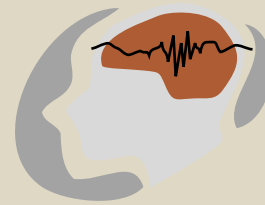
The long-term goal is to contribute to the development of drugs that can prevent or slow down the development of Alzheimer's disease. "A lot of international research is being done in this field, and I am fairly certain that one or more drugs against Alzheimer's will be developed in the next 10 years," says Leutgeb.



Stefan Leutgeb is head of the research group on "Memory consolidation and Alzheimer's disease", which is studying Alzheimer's disease from a new angle.

since the hippocampus is a very important part of the "internal memory" of the mammalian brain, and the hippocampus formation is the first part of the brain to be affected in this disease. Leutgeb is head

Leutgeb's research is based on the theory that the function loss in the hippocampus probably undermines the consolidation of memories in the mammalian brain, which is a process comparable to the storage of data



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Research scientists



Stefan Leutgeb,
Research Scientist



Jill Leutgeb,
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Ayumu Tashiro,
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Paul Ganter,
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Francesca Sargolini,
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Vegard Heimly Brun,
Post doc



Marianne Fyhn,
Post-doc



Torkel Hafting Fyhn,
Post-doc



Laura Colgin,
Post-doc



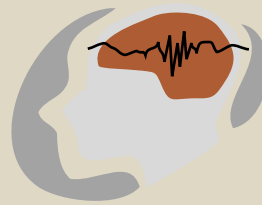
Karel Jezek,
Post-doc



Dori Derdikman,
Post-doc



Alessandro Sale,
Post-doc



Graduate students



Cathrin Barbara Canto,
Ph.D. student



Kirsten Brun Kjelstrup,
Ph.D. student



Paulo Girão,
Ph.D. student



Trygve Solstad,
Ph.D. student



Espen Joakim Henriksen,
Ph.D. student



Charlotte Boccara,
Ph.D. student



Mona Kolstø Otnæss,
Ph.D.

Project students



Tora Bonnevie,
Project student



Adam Johnson,
Project student

Master students



Kamilla Medås,
Master



Amela Felic,
Master



Beathe Christin Haatveit,
Master



Ingrid Funderud,
Master



Karoline Einarsen,
Master

Technical team



Ingvild Hammer,
Bioengineer



Kyrre Haugen,
Histology technician



Klaus Jensen,
Electronics engineer



Raymond Skjerpeng,
Programmer



Haagen Waade,
Computer engineer



Ingunn E. Bakken,
Senior executive officer



Ann Mari Amundsgård,
Histology and animal care



Espen Sjulstad,
Histology and electrode wiring



Knut S. Grøn,
*Animal technician
(part-time)*



Ingolf Hanssen,
Veterinary (part-time)



Bjørn Håvard Solem,
Electronics technician (part-time)

Associated members



Gerit Pfuhl,
Ph.D. student



Hanna Mustaparta,
*Professor NTNU,
Norway*



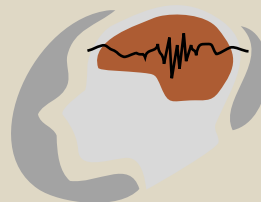
Hanne Lehn,
Ph.D. student



Hill-Aina Steffenach,
Ph.D.



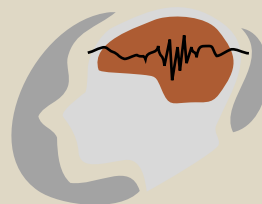
Robert Biegler,
*Associate professor
NTNU (Psychology),
Norway*



Income (<i>Inntekter</i>)	Accounts (<i>Regnskap</i>)	Budget (<i>Budsjett</i>)
Grants (<i>Bevilgninger</i>)		
Norwegian Centre for Excellence (<i>SFF</i>)		10 800 000
Other External projects (<i>Andre eksterne prosjekt</i>)		2 417 000
Contribution from the Norwegian University of Science and Technology (<i>Bevilgning fra NTNU</i>)		
Transferred from 2005 (<i>Overført fra 2005</i>)		2 109 000
S/O funding (<i>S/O-midler</i>)		1 450 000
Operational grants (<i>Driftsbevilgning</i>)		5 876 000
Scientific equipment (<i>Vitenskapelig utstyr</i>)		
Salaries (<i>Lønnsmidler</i>)		1 723 000
Other benefits (<i>Naturalytelse</i>) Note 1		2 530 000
Total Income (<i>Sum inntekter</i>)		26 905 000
Expenses (<i>Utgifter</i>)		
Net personnel costs (including social benefits) (<i>Netto faste lønnsmidler inkl sosiale kostnader</i>)	10 975 000	
Scientific equipment (<i>Vitenskapelig utstyr</i>)	1 538 000	
Laboratory consumables (<i>Drift av laboratoriet</i>)	9 823 000	
Other expenses (<i>Naturalytelse</i>)	4 253 000	
Transferred to 2007 for new equipment in expanded lab areas (<i>Resultat overført til 2007</i>)	316 000	
Total expenses (<i>Sum utgifter</i>)	26 905 000	

Note 1 - Other benefits

Server operations and backup, rooms and general operation, compensation for the use of administrative services.
Drift og backup av server, areal og drift, bruk av sentrale tjenester.



1. Seminars

23. – 24. jan

Professor Glen Tomas Prusky, Canadian Centre for Behavioural Neuroscience, University of Lethbridge.
Experience-dependent plasticity of motion vision.

23. – 24. jan

Professor Rob Sutherland, Department of Psychology and Neuroscience, University of Lethbridge.
Hippocampal retrograde amnesia: Retroactive reorganization of long-term memories.

19. – 21. feb

Professor John Lisman, Brandeis University, Boston.
Function of theta/gamma oscillations.

30. mar – 1 apr

Professor Fritjof Helmchen, Department of Neurophysiology, Brain Research Institute, University of Zurich.
Fiber-optic two-photon fluorescence microscopy.

17. – 21. jun

Professor James Knierim, University of Texas Medical School, Houston.
Multiregion analyses of memory processing in the hippocampal formation.

26. – 29. jun

PhD Jonathan R. Whitlock, Department of brain and cognitive sciences, MIT, USA.
Learning induces LTP in the hippocampus.

26. – 29. jun

PhD Gowan Tervo, Watson School of Biological Sciences – Neuroscience, Cold Spring Harbour Laboratory.
Dissection the function of complex neural circuits by manipulating neurotransmission in genetically defined neurons.

7. – 21. aug

Matt Jones, Department of Physiology, University of Bristol.
An accidental knockout: dentate gyrus NMDA receptors enable contextual and episodic separation.

11. – 14. sep

Mayank Mehta, Brown University.
Resonance learning: Relationship between brain rhythms, synaptic plasticity and place cell plasticity.

12. – 15. nov

Hannah Monyer/Alexei Ponomarenko, University of Heidelberg.
GABAergic interneurons and their role in synchronous network activity.

16. – 18. nov

Tad Blair, UCLA.
More interference between grid fields produces scale-invariant memory representations.

7. – 10. des

David Redish, University of Minnesota.
Learning and attention in the hippocampus: sharp-waves and multiple-maps.

12. – 16. des

Francesca Caccuci, University College London.
Hippocampal place cell plasticity in normal rats and mutant Mice

14. – 16. des

Professor John O'Keefe, University College London.
Hippocampal place cell plasticity in normal rats and mutant Mice

2. Doctoral defenses

04 April

Mona Kolstø Otnæss
Spatial and non-spatial learning in the hippocampus.
External Committee:
Senior Lecturer Paul Dudchenko
Professor Clive Bramham

3. Media

ScienceDaily 14 November

Speak, Memory: Research Challenges Theory Of Memory Storage

NormaleNews 04 August

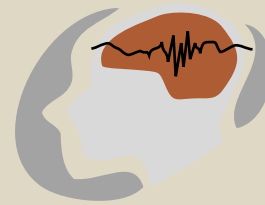
I meccanismi neuronali alla base della memoria spaziale degli animali

derStandard 10 July

Kranke Nerven

ANSA.it 04 May

CERVELLO: C'E' UN 'NAVIGATORE' CHE AIUTA AD ORIENTARCI



1. Scientific journals: Work performed at the Centre

Colgin, L.L., and Moser, E.I. (2006). Rewinding the memory record. *Nature*, **440**, 615-617.

Sargolini, F., Fyhn, M., Hafting, T., McNaughton, B.L., Witter, M.P., Moser, M.-B., and Moser, E.I. (2006). Conjunctive representation of position, direction and velocity in entorhinal cortex. *Science*, **312**, 754-758.

McNaughton, B.L., Battaglia, F.P., Jensen, O., Moser, E.I., and Moser, M.-B. (2006). Path-integration and the neural basis of the 'cognitive map'. *Nature Reviews Neuroscience*, **7**, 663-678.

Leutgeb, S., Leutgeb, J.K., Moser, E.I., and Moser, M.-B. (2006). Fast rate coding in hippocampal CA3 cell assemblies. *Hippocampus*, **16**, 765-774.

Solstad, T., Moser, E.I., and Einevoll, G.T. (2006). From grid cells to place cells: a mathematical model. *Hippocampus*, **16**, 1026-1031.

Witter, M.P. and Moser, E.I. (2006). Spatial representation and the architecture of the entorhinal cortex. *Trends in Neurosciences*, **29**, 671-678.

Leutgeb, J.K., Leutgeb, S., Moser, M.-B., and Moser, E.I. (2007). Pattern separation in dentate gyrus and CA3 of the hippocampus. *Science*, **315**, 961-966.

Fyhn, M., Hafting, T., Treves, A., Moser, E.I., and Moser, M.-B. (2007). Hippocampal remapping and grid realignment in entorhinal cortex. *Nature*, **446**, 190-194.

2. Conference abstracts: Work performed at the Centre

Bonnevie, T., Moser, E.I., Moser, M.-B. (2006). Differential response to input patterns in interneurone subtypes of hippocampal area CA1. *Federation of European Neurosciences*, R11656.

Colgin, L.L., Jensen, O., Moser, M.B., Moser E.I. (2006) Gamma frequency and CA3-CA1 synchrony are modulated by theta phase. *Federation of European Neurosciences*, R12055.

Fyhn, M., Hafting, T., Moser M.B., Moser, E.I. (2006) Theta modulation and phase precession in grid cells in the medial entorhinal cortex, *Federation of European Neurosciences*, R11630.

Hafting, T., Fyhn, M., Treves, A., Moser, E.I., Moser M.B., (2006) Coherent realignment of entorhinal grid cells coincides global remapping in the hippocampus, *Federation of European Neurosciences*, R11641.

Haarveit B.C., Funderud I., Tuvnes, F. A., Witter M.P., Moser, E.I., Moser M.B. (2006). Disrupted retrieval of contextual fear after lesions of the medial entorhinal cortex, *Federation of European Neurosciences*, R11587.

Henriksen, E.J., Felic, A., Tuvnes, F., Steffenach, H. A., Witter M.P., Moser, M.B., Moser E.I., (2006). Impaired spatial navigation in rats with minimal lesions in the dorsocaudal medial entorhinal cortex, *Federation of European Neurosciences*, R11573.

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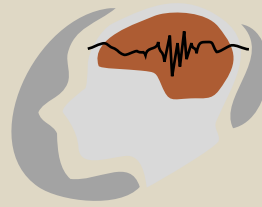
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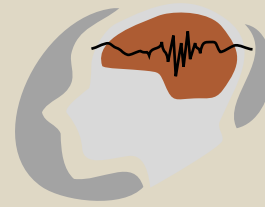
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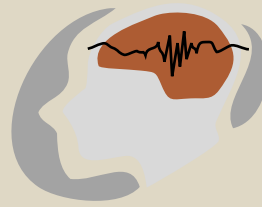
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