EDVARD MOSER AND THE GRID CELLS
MICROSTRUCTURE OF A SPATIAL MAP IN THE ENTORHINAL CORTEX

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EDVARD I. MOSER is a professor of neuroscience and a director of the Norwegian Centre for Biology of Memory in Trondheim. Moser`s research group has provided some of the most groundbreaking insights so far concerning the computation of spatial location and spatial memory in the brain. The most remarkable insight has been the discovery of a neuronal spatial map in the medial dorsocaudal entorhinal cortex. The key unit of the map is the grid cell, which is activated whenever the position of the animal coincides with any of the vertex of a regular grid of equilateral triangles spanning the surface of the environment. The map is anchored by external landmarks, but persists in their absence, suggesting that grid cells may be part of a generalized, path-integration-based map of the spatial environment. The discovery of the grid cells has led to an immediate revision of well-established views of the brain mechanisms implied in the calculation of position in the space. These results may represent an ultimate benefit for the development of tools for diagnostic and treatment of Alzheimer`s disease, in which the entorhinal cortex is one of the first brain regions to be affected and spatial and navigational problems are among the earliest symptoms to appear before a reliable diagnosis can be made.

Key words: *Edvard I. Moser, grid cells, entorhinal cortex, hippocampus, spatial memory, Alzheimer`s disease*

INTRODUCTION

EDVARD I. MOSER is born on 27th of April, 1962, in Alesund, Norway. He is a professor of neuroscience and a director of the Norwegian Centre for Biology of Memory in Trondheim **(7)**. Moser`s research interests are centred on the neuronal expression of memory processes, especially those related to spatial navigation and location.

Spatial navigation and memory in mammals depends on a distributed, modularly organized brain network which computes and represents positional and directional information, as indicated by the existence of 'place cells' in the hippocampus **(4)** and 'head direction cells' **(5)** in the parahippocampal cortices.

The hippocampus is essential for encoding and storage of new episodic memories, but has a more limited role in remote memory, which is thought to be stored primarily in the neocortex.

Memory consolidation in the neocortex appears to be a slow and gradual process based on repeated interactions with the hippocampus. These interactions are mediated by the entorhinal cortex (EC), which interconnects the hippocampus with nearly all other association cortices.

Understanding how information is processed in the EC is thus essential to resolving the interactions between the hippocampus and the neocortex during encoding, storage, and retrieval of memory. Since recently, little has been known about how sensory input is represented in the EC. Examining the neuronal activity in the layer II of the EC in freely moving rats, Moser and his research group have provided an important insight of how information is represented in the EC. They have reported the existence of a neuronal spatial map in the medial dorsocaudal entorhinal cortex (dMEC) **(2)**. The key unit of the map is *the grid cell*, which is activated whenever the position of the animal coincides with any of the vertex of a regular grid of equilateral triangles spanning the surface of the environment. The map is anchored by external landmarks, but persists in their absence, suggesting that grid cells may be part of a generalized, path-integration-based map of the spatial environment.

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The EC is one of the first brain regions to be affected in Alzeheimer`s disease (AD) **(8)**, which is a progressive neurodegenerative brain disorder. Neurons in layer II of the EC are severely damaged in patients with AD and spatial and navigational problems are among the earliest symptoms to appear before a reliable diagnosis can be made **(3)**.

Moser`s research work may represent an ultimate benefit for the development of tools for early diagnosis and eventually treatment of AD.

Here I am going to present you the life and the career of Edvard Moser, his research group, the methods they usually use for the study of memory and their scientific achievements.

LIFE AND CAREER.

While pursuing his psychology degree at the University of Oslo, Moser got interested in brain functions. He was especially intrigued by the synaptic expression of events and by the way brain treatment influences on cognitive phenomena as memory.

In the 1980s, the application of neuroscience to understanding the biological bases of memory was emerging and ‘it was as a huge and exciting challenge,’ says Moser. Before finishing his undergraduate degree, he had made up his mind to go into neuroscience research.

In 1991, Moser started his Ph.D. in the laboratory of Per Andersen at the University of Oslo. The group was investigating long-term memory at a neurophysiological level. Moser demonstrated a number of changes in the strength of connections between nerve cells-a phenomenon called synaptic plasticity-in the hippocampus of rats. Moser`s approach-risky at the time-merged psychology with physiology, investigating synaptic plasticity by recording neural signals from intact mammalian brains. ‘It was a great place to start: there was a lot of international collaboration and important discoveries were made,’ says Moser.

In 1994, Moser and his wife May-Britt Moser **(pic.1a, b)**, who did her Ph.D. in the same laboratory, moved to the University of Edinburgh, Scotland, to take postdoctoral positions. They worked in the group of Richard Morris at the Centre for Neuroscience studying the role of long-term potentialisation in the hippocampus during the learning of a spatial task.

In 1996, the couple moved to the University College of London where they joined the research team of John O`Keefe. Moser says that there he expanded his knowledge by learning to record electrical signals from individual neurons in the hippocampus. Upon finishing their postdoctoral contracts, the duo was offered second postdoctoral position at Bruce McNaughton and Carol Barne`s memory and hippocampus group at the University of Arizona in Tucson.
The Mosers never took up these positions because at the same time they were both offered associate professorships in psychobiology at the Norwegian University of Science and Technology (NTNU) in Trondheim. Although Moser thinks it was pity to cut short their postdoctoral time abroad, this career opportunity was so extraordinary that they return to Norway to take up their faculty positions.

Moser`s career has gone from strength to strength. **In 1998**, he was offered a full professorship in neuroscience at NTNU. In 2002, he became director of the Centre for the Biology of Memory (CBM) **(pic.2)** at NTNU, one of the 13 prestigious 'Centres of Excellence' funded by the Norwegian Research Council. The Centre for the Biology of Memory has a budget of 35 million euros over 10 years. Moser`s wife is co-director of the centre and together they run a laboratory of 25-30 staff **(6, 7)**.

Pic.1a: the Mosers

Pic.1b: the duo enjoys working together

Though many researchers think being part in a dual-research-career couple could force one of the partners to compromise, in Mosers' case their research interests have been an incomparable advantage. 'Being two we can have a broader research focus,' explains Moser.

Pic.2: the research group at CBM

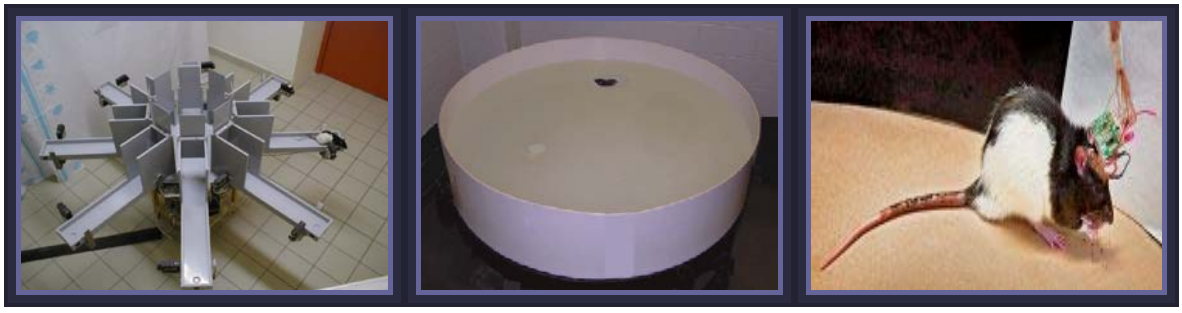
The scientific goal of the Centre is to understand the biological processes responsible for memory .This ambitious aim requires a multi-disciplinary and multi-level approach which can be accomplished by close collaboration between experts in each discipline. The Centre brings together internationally leading neuroscientists who share an interest in memory and contribute complementary expertise. The activity of the Centre includes theoretical work, experiments, and training of students, all related to the scientific goal of the Centre.

Concerning his publishing activity, Moser has regular requests for *Science, Nature, Cell, Neuron, Journal of Neuroscience, European Journal of Neuroscience, Neuroscience, Behavioural Neuroscience, Hippocampus* and in addition- requests for 15 other scientific journals.

In 2004, Edvard Moser was honoured member of the Norwegian Academy of Science and Letters. Edvard Moser is a member of the Chair Program Committee of the Federation of European Neuroscience Societies (FENS), member of the board of reviewing editors of *Science, Journal of European Neuroscience, Neuroscience and Hippocampus*.

RESEARCH METHODS

In Moser`s centre, memory is explored by using either a top-down or a bottom-up strategy. The top-down approach starts by studying cognitive or behavioural memory followed by an identification of the brain regions involved, the individual cells and molecules responsible. The bottom-up strategy begins by studying the basic molecular mechanisms of synaptic modification, and thence upwards to a coherent view of behavioural tests of memory. Neither approach has alone been successful in establishing firm links between molecules and behaviour.
So, using a combination of behavioural **(pic.3a, b)** and neurophysiological **(pic.3c)** methods, the Centre tries to determine how neuronal ensembles in the hippocampus and the neocortex give rise to specific memory operations as encoding, storage, consolidation and retrieval.

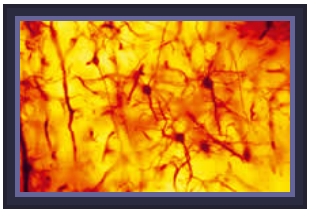


Pic.3a: Radial cross-maze **Pic.3b: Morris water maze** **Pic.3c: Microdrive implantation in-vivo**

Grid cells were discovered using a microdrive implantation containing four tetrodes, so cell activity in the medial dorsocaudal entorhinal cortex was recorded *in-vivo,* in 14 male Long Evans rats **(pic.3c)** while they were chasing pellets in enclosures of four different size and shape.

RESEARH WORK AND ACHIEVEMENTS

Spatial navigation in mammals depends on a distributed, modularly organized brain network. The network computes and represents positional and directional information, as indicated by the existence of ‘place cells’ in the hippocampus and ‘head direction cells’ in the parahippocampal cortices. Hippocampal place cells **(pic.4), (4)** are selectively active when a rat occupies restricted locations in an environment, and head direction cells **(5)** fire selectively when the rat's head is pointed in a particular direction in allocentric space. Both place cells and head direction cells are usually coupled, and they are controlled by a complex interaction between external landmarks and idiothetic cues.

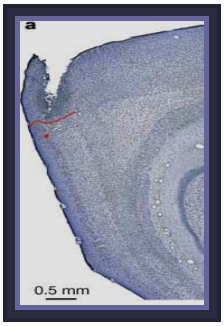


Pic.4: place cell

In 2004, in an article issued in Science **(1)**, E.Moser and his collegues demonstrated the existence of ‘place cells’ in the EC. Entorhinal neurons have stable and discrete multipeaked place fields, predicting the location of the rat as accurately as ‘place cells’ in the hippocampus, suggesting that sensory input is transformed into durable allocentric spatial representation internally in the dorsocaudal medial entorhinal cortex (dMEC).

In 2005, again in an article published in Science **(2)**, E. Moser and his research group reported the existence of a directionally oriented, topographically organized neuronal map of the spatial environment in the dMEC **(fig.1a)**. Its key unit is the grid cell **(fig.1b)**, which has a specific geometric structure. The firing field of every isolated grid cell forms a grid of regularly tessellating triangles spanning the whole recording surface. The grid unit is composed by six equidistant peaks forming the vertices of a regular hexagon. The grid cell is activated whenever the position of the animal coincides with any of the vertex of its regular grid of equilateral triangles. Grids of neighbouring cells share a common orientation (direction) and spacing (the distance from the central peak to the vertices of the inner hexagon), but their vertex locations (their phases) differ.

Grids are anchored to external cues, but persist in their absence (spike activity is recorded in total darkness for 30 min, after an initial period of 10 min, with lights on), suggesting that grid cells may be part of a generalized, path-integration-based map of the spatial environment.



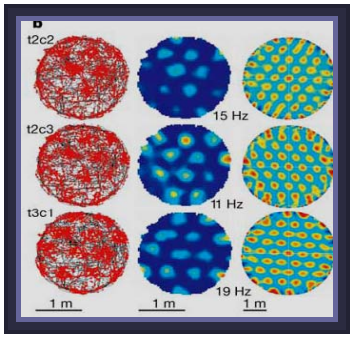


Fig.1a: recording location (red dot) in layer II of dMEC

Fig.1b: firing fields of 3 simultaneously recorded cells at the dot in a during 30min.

Alzheimer`s disease (3, 8) is a progressive brain disorder that gradually destroys memory and all superior cognitive functions as language, reasoning, communication, judgement, learning. As the disease progresses individuals may also experience changes in personality, behaviour, such as anxiety, suspiciousness or agitation, as well as, delusions or hallucinations.
Currently, there is no cure for Alzheimer`s disease. Average duration of the disease is approximately 7–10 years, although cases are known where reaching the final stage occurs within 4–5 years, or up to 15 years.

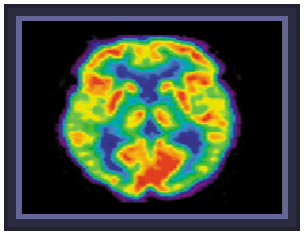


Fig.2a: PET scan of normal brain

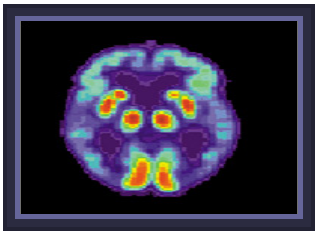


Fig.2b: PET scan of AD`s brain

The entorhinal cortex is one of the first brain regions to be affected in Alzheimer`s disease (fig.2b). An important loss of neurons is observed in layer II of the dMEC in patients with AD and spatial and navigational problems are among the earliest symptoms to appear before a reliable diagnosis can be made (3).
The discovery of the grid cells may represent an ultimate benefit for the development of neuropsychological tools for early diagnosis and eventually treatment of Alzheimer`s.

REFERENCES

1. M. Fyhn, E. I. Moser & al.: Spatial representation in the entorhinal cortex, *Science*, vol.305: 1258-1264, August 2004
2. T.Haftig, E. I. Moser & al.: Microstructure of a spatial map in the entorhinal cortex, *Nature*, vol.436: 801-806, August 2005
3. T. Gomez-Isla &al: Profound loss of layer II Entorhinal cortex neurons occurs in very mild Alzheimer`s disease, *J.Neurosci.* 16 (14): 4491-4500, July 1996
4. J. O`Keefe & I. Nadel: The hippocampus as a cognitive map, *Oxford, Calendron press*, 1978
5. J.S. Taube, R.U. Muller, J.B. Ranck: Head direction cells recorded from the postsubiculum of freely moving rats, *J.Neurosci* 10: 420-447
6. http://www.cbm.ntnu.no/people
7. http://sciencecareers.sciencemag.org/career_development/previous_issues/articles/2005_11_04/the_biology_of_memory
8. http://www.alz.org/AboutAD/whatis Ad.asp/