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The Nobel Assembly at Karolinska Institutet has today decided to award

The 2014 Nobel Prize in Physiology or Medicine

with one half to

John O´Keefe

and the other half jointly to

May-Britt Moser and Edvard I. Moser

for their discoveries of cells that constitute a positioning system in the brain

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How do we know where we are? How can we find the way from one place to another? And how can we store this information in such a way that we can immediately find the way the next time we trace the same path? This year´s Nobel Laureates have discovered a positioning system, an "inner GPS" in the brain that makes it possible to orient ourselves in space, demonstrating a cellular basis for higher cognitive function.

In 1971, John O´Keefe discovered the first component of this positioning system. He found that a type of nerve cell in an area of the brain called the hippocampus that was always activated when a rat was at a certain place in a room. Other nerve cells were activated when the rat was at other places. O´Keefe concluded that these "place cells" formed a map of the room.

More than three decades later, in 2005, May-Britt and Edvard Moser discovered another key component of the brain's positioning system. They identified another type of nerve cell, which they called "grid cells", that generate a coordinate system and allow for precise positioning and pathfinding. Their subsequent research showed how place and grid cells make it possible to determine position and to navigate.

The discoveries of John O´Keefe, May-Britt Moser and Edvard Moser have solved a problem that has occupied philosophers and scientists for centuries – how does the brain create a map of the space surrounding us and how can we navigate our way through a complex environment?

How do we experience our environment?

The sense of place and the ability to navigate are fundamental to our existence. The sense of place gives a perception of position in the environment. During navigation, it is interlinked with a sense of distance that is based on motion and knowledge of previous positions.

Questions about place and navigation have engaged philosophers and scientists for a long time. More than 200 years ago, the German philosopher Immanuel Kant argued that some mental abilities exist as *a priori* knowledge, independent of experience. He considered the concept of space as an inbuilt principle of the mind, one through which the world is and must be perceived. With the advent of behavioural psychology in the mid-20th century, these questions could be addressed experimentally. When Edward Tolman examined rats moving through labyrinths, he found that they could learn how to navigate, and proposed that a "cognitive map" formed in the brain allowed them to find their way. But questions still lingered - how would such a map be represented in the brain?

John O´Keefe and the place in space

John O´Keefe was fascinated by the problem of how the brain controls behaviour and decided, in the late 1960s, to attack this question with neurophysiological methods. When recording signals from individual nerve cells in a part of the brain called the hippocampus, in rats moving freely in a room, O'Keefe discovered that certain nerve cells were activated when the animal assumed a particular place in the environment (Figure 1). He could demonstrate that these "place cells" were not merely registering visual input, but were building up an inner map of the environment. O'Keefe concluded that the hippocampus generates numerous maps, represented by the collective activity of place cells that are activated in different environments. Therefore, the memory of an environment can be stored as a specific combination of place cell activities in the hippocampus.

May-Britt and Edvard Moser find the coordinates

May-Britt and Edvard Moser were mapping the connections to the hippocampus in rats moving in a room when they discovered an astonishing pattern of activity in a nearby part of the brain called the entorhinal cortex. Here, certain cells were activated when the rat passed multiple locations arranged in a hexagonal grid (Figure 2). Each of these cells was activated in a unique spatial pattern and collectively these “grid cells” constitute a coordinate system that allows for spatial navigation. Together with other cells of the entorhinal cortex that recognize the direction of the head and the border of the room, they form circuits with the place cells in the hippocampus. This circuitry constitutes a comprehensive positioning system, an inner GPS, in the brain (Figure 3).

A place for maps in the human brain

Recent investigations with brain imaging techniques, as well as studies of patients undergoing neurosurgery, have provided evidence that place and grid cells exist also in humans. In patients with Alzheimer´s disease, the hippocampus and entorhinal cortex are frequently affected at an early stage, and these individuals often lose their way and cannot recognize the environment. Knowledge about the brain´s positioning system may, therefore, help us understand the mechanism underpinning the devastating spatial memory loss that affects people with this disease.

The discovery of the brain’s positioning system represents a paradigm shift in our understanding of how ensembles of specialized cells work together to execute higher cognitive functions. It has opened new avenues for understanding other cognitive processes, such as memory, thinking and planning.

Key references:

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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 the entorhinal cortex. Science *312*, 758-762.

The Laureates

John O'Keefe was born in 1939 in New York City, USA, and holds both American and British citizenships. He received his doctoral degree in physiological psychology from McGill University, Canada in 1967. After that, he moved to England for postdoctoral training at University College London. He has remained at University College and was appointed Professor of Cognitive Neuroscience in 1987. John O´Keefe is currently Director of the Sainsbury Wellcome Centre in Neural Circuits and Behaviour at University College London.

May-Britt Moser was born in Fosnavåg, Norway in 1963 and is a Norwegian citizen. She studied psychology at the University of Oslo together with her future husband and co-Laureate Edvard Moser. She received her Ph.D. in neurophysiology in 1995. She was a postdoctoral fellow at the University of Edinburgh and subsequently a visiting scientist at University College London before moving to the Norwegian University of Science and Technology in Trondheim in 1996. May-Britt Moser was appointed Professor of Neuroscience in 2000 and is currently Director of the Centre for Neural Computation in Trondheim.

Edvard I. Moser was born in born 1962 in Ålesund, Norway and has Norwegian citizenship. He obtained his Ph.D. in neurophysiology from the University of Oslo in 1995. He was a postdoctoral fellow together with his wife and co-Laureate May-Britt Moser, first at the University of Edinburgh and later a visiting scientist in John O´Keefe´s laboratory in London. In 1996 they moved to the Norwegian University of Science and Technology in Trondheim, where Edvard Moser became Professor in 1998. He is currently Director of the Kavli Institute for Systems Neuroscience in Trondheim.

The Nobel Prize in Physiology or Medicine 2014

Fig. 1

John O'Keefe

John O'Keefe discovered, in 1971, that certain nerve cells in the brain were activated when a rat assumed a particular place in the environment. Other nerve cells were activated at other places. He proposed that these "place cells" build up an inner map of the environment. Place cells are located in a part of the brain called the hippocampus.

May-Britt Moser and Edvard I. Moser

May-Britt och Edvard I. Moser discovered in 2005 that other nerve cells in a nearby part of the brain, the entorhinal cortex, were activated when the rat passed certain locations. Together, these locations formed a hexagonal grid, each "grid cell" reacting in a unique spatial pattern. Collectively, these grid cells form a coordinate system that allows for spatial navigation.

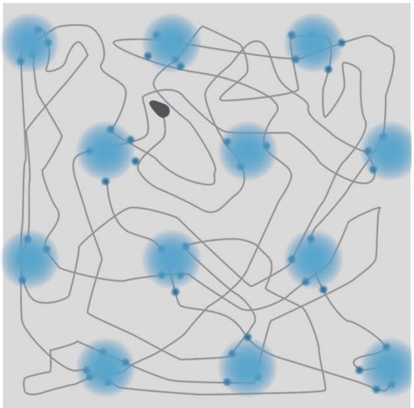
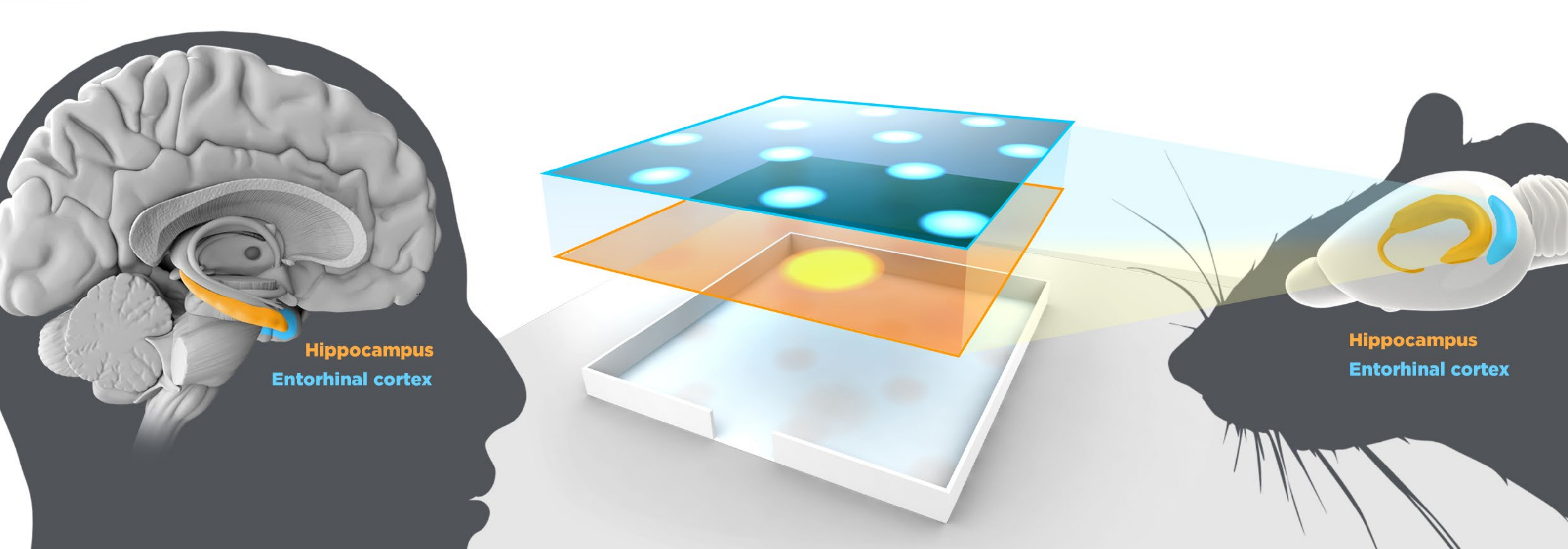


Fig. 2



Grid cells, together with other cells in the entorhinal cortex that recognize the direction of the head of the animal and the border of the room, form networks with the place cells in the hippocampus. This circuitry constitutes a comprehensive positioning system, an inner GPS, in the brain. The positioning system in the human brain appears to have similar components as those of the rat brain.

Fig. 3

Illustration and layout: Mattias Karlén