A boon in studies of cognitive functions: brain and grid cells

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Brain that serves as the centre of the nervous system performs various neuronal activities. The sense of knowledge, position, memory, etc. that we ought to know and functioning of brain to perform these actions was difficult to understand four decades ago. In 2014, the Nobel Prize for Physiology or Medicine went to John O'Keefe, May-Britt Moser and Edvard I. Moser. May-Britt Moser had discovered cells that constitute a positioning system in the brain. She discovered an 'inner GPS' in the brain that makes it possible to orient ourselves in space, demonstrating a cellular basis for higher cognitive function.

The very neuronal signals sent by brain to different parts of the organ which were difficult to know previously, can now be easily understood by the positioning system in the brain. These discoveries led to the understanding of the hippocampus part of the brain, which shows signs of damage in Alzheimer's patients at first[1].

Scientific journey that led to Nobel

John O'Keefe, 76, currently Director of the Sainsbury Welcome Centre in Neural Circuits and Behaviour, at the University College London received his doctoral degree in physiological psychology from McGill University, Canada in 1967 (ref. 2). May-Britt Moser, 51, is currently Director at the Centre for Neural Computation in Trondheim. She studied psychology at the University of Oslo together with her co-Nobel Laureate and husband Edvard I. 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 the University College, London before moving to the Norwegian University of Science and Technology in Trondheim in 1996 (ref. 3). Edvard I. Moser, 52, currently Director of the Kavli Institute for Systems Neuroscience in Trondheim 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[4].

Elucidation of their Nobel work

Contribution of O'Keefe: Finding the place cells

Influenced by Sturmwasser's[5] micro wire implantation work, i.e. recording the free movement of animals in the environment, O'Keefe discovered the place cells. The key function of the place cells is to create a map of the environment[6].

O'Keefe recorded the cellular activity during natural behaviour, which allowed him to observe the unique place fields and relate the neural activity in the place cells to represent the sense of place.

He started working on rats with Dostrovsky, found CA1, dorsal portion of hippocampus by recording the neurons in rats moving freely in a bounded area. The firing pattern of these cells was completely unexpected. When animals are in a particular place in the environment called place fields, some individual cells only were found active. This way of information was not found for any cells in the brain. O'Keefe systematically started experimenting in different environments, tested different theoretical possibilities to create place fields. During this experiment, he observed that place cell firing did not merely reflect activity in sensory neurons, but it represented a complex gestalt of the environment. Different place cells could be active in different places and the combination of activity in many place cells created an internal neural map representing a particular environment[7,8]. He concluded together with Nadel, that place cells provide the brain with a spatial reference map system, or a sense of place[9]. He showed that the hippocampus can contain multiple maps represented by combinations of activity in different place cells that were active at different times in different environments. A specific serial combination of active place cells, may therefore represent a unique environment, while other combinations represent other environments. Through O'Keefe's discoveries, the cognitive map theory had found its representation in the brain.

No sensory activities in sensory neurons were marked under place cell firing. Rather it depicted a shaped environment.

Later in subsequent experiments, it was found that place cells may perform memory functions which may provide a cellular substrate for memory processes, where a memory of an environment can be stored as specific combinations of place cells[10].

A cellular substrate was furnished for memory processes by place cells, where a memory of an environment can be preserved as distinct amalgamation of place cells.

Contribution of Moser Couple: From hippocampus to grid cells in the entorhinal cortex

May-Britt Moser and Edvard I. Moser carried out their Ph D work studying the hippocampus, in Per Andersen's laboratory in Oslo and afterwards both as visiting scientists in Richard Morris' laboratory in Edinburgh and John O'Keefe's laboratory in London. They started working to understand whether place cell firing can be generated from cellular activity outside hippocampus. The major input to the hippocampus comes from a structure on the dorsal edge of rat's brain[11], the entorhinal cortex (Figure 1). A large part of the output from the cortex projects to the dentate gyrus in hippocampus (thought to contribute to the formation of new episodic memories, the spontaneous exploration of novel environments and other functions), which in turn connect to the region in the hippocampus called CA3, and further to CA1 in the dorsal hippocampus.

In 2002, Mosers found that disconnecting projections from the entorhinal cortex through CA3 did not abolish the CA1 place fields[12]. The idea and the findings were that medial entorhinal cortex is directly and reciprocally connected to the CA1 region, which suggested to May-Britt Moser and Edvard Moser to look in the medial entorhinal cortex for place coding cells. Initially, it was established that the medial entorhinal cortex contained cells that shared characteristics with the place cells in hippocampus[13]. However, in a study using larger encounter for animals to move in, a novel cell type was discovered, the grid cells, with amazing properties[14].

Impressive fire patterns were shown by the grid cells, which were active in multiple locations in the open box which constitutes the nodes of an extended hexagonal grid (Figure 2), like a beehive.

Firing with similar spacing and grid orientation, but different phasing was observed for grid cells in similar area of the medial entorhinal cortex. Mosers found that the distance of the grid fields changes in the medial entorhinal cortex with the largest fields in the ventral part of the cortex. Also, it was shown that the grid formation did not arise out of a simple transformation of sensory or motor signals, but out of complex network activity.

The never seen grid patterns in brain cells were surprising. Mosers stated that the grid cells were part of a navigation or path-integration system. Thus a solution to measure the movement distance was possible through the grid system and enhanced the spatial maps in hippocampus.

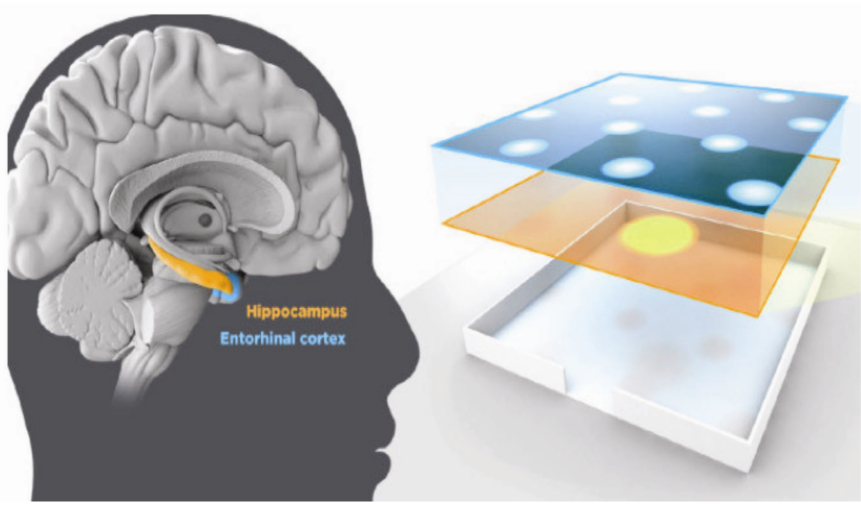

Figure 1. Grid cells, together with other cells in the entorhinal cortex that recognize the direction of the head of the animal and the border of the room, form networks with the place cells in the hippocampus. This circuitry constitutes a comprehensive positioning system, an inner GPS, in the brain. The positioning system in the human brain appears to have similar components as those of the rat brain. [Credits: Illustration and layout by Mattias Karlén/© 2014 The Nobel Committee for Physiology or Medicine.]

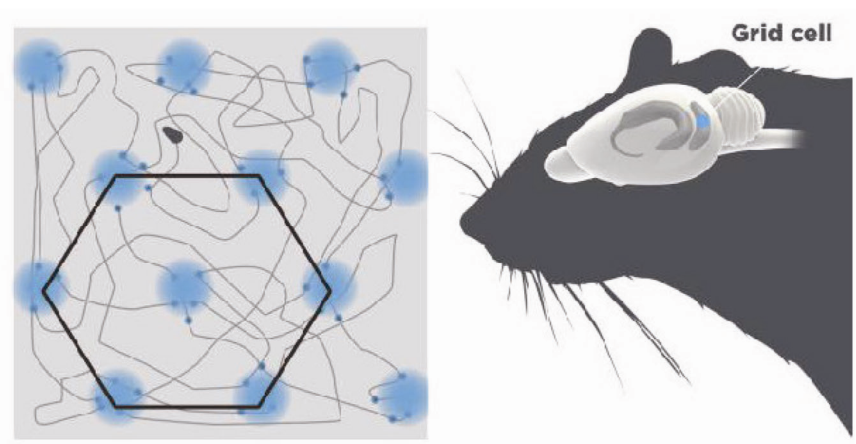

Figure 2. The grid cells are located in the entorhinal cortex depicted in blue. A single grid cell fires when the animal reaches particular locations in the arena. These locations are arranged in a hexagonal pattern. [Credits: Illustration and layout by Mattias Karlén/© 2014 The Nobel Committee for Physiology or Medicine.]

Later, Mosers showed that grid cells were embedded in a network in the medial entorhinal cortex of head direction and border cells, and in many cases, cells with a combined function[15]. Head-direction cells were first described by James Ranck (1985) in another part of the brain, the subiculum, which was acting like a compass and were active when the head of an animal points in a particular direction. Border cells are active in reference to walls that the animal encounters when moving in a closed environment[16,17]. Theoretically their existence was forecasted earlier by modelling by O'Keefe and colleagues[18]. Mosers showed that the grid, the head direction and the border cells, all are projected to hippocampal place cells[19]. They also showed that the grid cells are organized in functional modules with different grid spacing, ranging in distance from a few centimetres to metres, with the help of recordings from multiple grid cells in different parts of the entorhinal cortex, hence covering small to large environments.

Further conjunctions were explored by Mosers between the grid cells and place cells in theoretical models[20], lesion experiments[21,22] and in remapping experiments[23]. Several other studies by Mosers and O'Keefe along with the above and others, concluded that there exists a reciprocal influence between grid cells in the medial entorhinal cortex and place cells in the hippocampus and that other spatially tuned cells in the entorhinal cortex, especially the border cells (Figure 3), which may take part in the generation of the firing pattern of the place cells[24–26]. The Mosers' discovery of the grid cells, a spatial metric coordination system, and their identification of the medial entorhinal cortex as a computational centre for spatial representation, proved to be major advancement that paved path for new avenues to understand the perception of the neural mechanisms underlying spatial cognitive functions.

Future prospective of this discovery

According to exploratory studies on brain, imaging techniques and studies on neurosurgical patients, the place cells and grids also exist in humans. Studies show that the hippocampus and entorhinal cortex are frequently affected at an

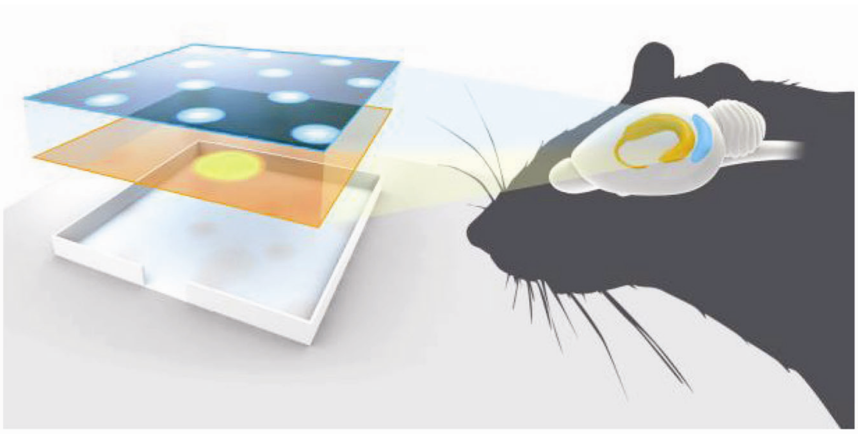

Figure 3. A schematic diagram showing grid cells (blue) and place cells (yellow) in the entorhinal cortex and hippocampus respectively. [Credits: Illustration and layout by Mattias Karlén/© 2014 The Nobel Committee for Physiology or Medicine.]

early stage, in the patients with Alzheimer's disease. These individuals recurrently lose their way and are unable to perceive the ambiance. This finding proved as a boon in understanding brains positioning system and enables us to understand the supporting mechanisms of mortifying spatial memory loss in diseased individuals. The discovery is a revolutionary step in understanding how aggregation of particular cells work together to bring to fruition of higher cognitive functions. This paved the way for several possibilities in perception of other intellectual processes[27].

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