PNAS PROFILE

Profile of May-Britt and Edvard Moser

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When May-Britt and Edvard Moser entered the neuroscience field in the mid-1990s, the entorhinal cortex (EC) was an uncharted brain region. Since then, their discoveries of cells and mechanisms underlying a spatial representation system in the EC have helped make this brain region a hotspot for studies of cortical network computation and brain disorders, such as Alzheimer's disease. The Mosers were elected as international members of the National Academy of Sciences in 2014, the year they received, along with neuroscientist John O'Keefe, the Nobel Prize in Physiology or Medicine. The Mosers continue to uncover how brain physiology gives rise to cognitive functions, with a focus on dynamic representations of space and memory in the hippocampal-entorhinal system. Edvard's recently published Inaugural Article (1), coauthored with May-Britt and colleagues, provides an analysis of the full functional topography of the space circuit in the medial EC (MEC). The achievement showcases a miniaturized two-photon microscope that the Mosers helped develop and that provides large-scale, high-throughput imaging of more than 1,000 neurons at a time in freely moving mice.

Edvard Moser. Image credit: Bård Ivar Basmo, Kavli Institute for Systems Neuroscience, New Haven, CT.

Kindred Upbringing

"My success as a scientist went against the odds," says Edvard while contemplating his life's journey from the isolated Norwegian islands of Haramsøya and Hareidlandet, where he was raised, to receiving the Nobel Prize in Stockholm. His parents moved to the islands after immigrating from Germany following World War II. "Both of my parents wanted an education, but it was not possible for them to study in Germany at that difficult time," he says. The son of a Lutheran pastor, Edvard's father was a skilled musician who, in lieu of a formal education, learned to build church organs and cofounded a workshop in Norway. He and Edvard's mother, who worked as a secretary, encouraged the academic interests of their three children. "By the time I started school at age 7, I had already read a lot about geology, meteorology, paleontology, astronomy, and other sciences," says Moser, who enjoyed exploring nature.

May-Britt also was raised in a scenic, sparsely populated area: the town of Fosnavåg on the Norwegian island Bergsøya. Her parents were well-read and industrious but not formally educated. With May-Britt and her four siblings, they lived on a farm, where her father also worked as a carpenter. "My mum had a dream to become a doctor," she says. "While my dad was skilled in mathematics and practical work, my mum read her medicine books thoroughly and to the extent that she knew every disease by heart, and like my dad, she was also very handy."

May-Britt was fascinated by the region's animals and aquatic life; she was nicknamed "the professor" by her friends and family because of her intense curiosity about the natural world. From an early age, she was curious about what makes animals, including humans, behave as they do. She says, "When I started school, I felt as if I had come to an El Dorado; I learned and I asked."

Edvard and May-Britt met at the Ulstein Vidaregåande Skule, a prestigious high school where they were in the same physics and chemistry classes. "I remember him as the brightest in the class but shy," May-Britt says of Edvard. They reconnected in Oslo after Edvard's compulsory year-and-a-half of military service following graduation in 1981. They married 4 years later when both studied psychology at the University of Oslo, where they initially focused on mathematics, statistics, and programming. Both were interested in behaviorism, now more commonly known as behavioral psychology, and its systematic approaches. Although they appreciated that behavior could be broken down into

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May-Britt Moser. Image credit: Torgrim Melhuus, Kavli Institute for Systems Neuroscience New Haven, CT.

elementary laws, they sought explanations that involved underlying neural mechanisms.

Mentors

As undergraduates they worked in the laboratory of behavioral neuroscientist Terje Sagvolden on the neurochemical mechanisms of attention deficit disorder in a rodent model. The research led to their first published papers, including a study on the effects of the drug methylphenidate on exploratory behavior (2), and shaped their knowledge of behavioral analysis and statistics as well as their ability to design experiments.

Inspired by pioneering research conducted by neurophysiologists David Hubel and Torsten Wiesel on neural pathways in the visual system, the couple desired to work with University of Oslo neuroscientist Per Andersen on the neural mechanisms of memory. Andersen accepted them and became a primary mentor. Their joint Master's thesis concerning differences between the dorsal and ventral hippocampus during spatial learning was the first behavioral study from Andersen's laboratory (3). Edvard says, "He was insightful and opened doors for us and others." May-Britt adds, "We learned from Per Andersen that science is not only about data, but also that the story you can tell based on your data is what matters."

While they worked on their doctoral degrees in neuroscience at the University of Oslo from 1990 to 1995, the Mosers—with their two daughters in tow—made several research visits to the University of Edinburgh, where they worked with neuroscientist Richard Morris. As doctoral students and subsequently postdoctoral researchers, they observed rodents engaged in various exploration tasks and theorized that different populations of interneurons may focus and amplify incoming signals from the EC (4). This area of the brain serves as the main gateway for information entering and leaving the hippocampal formation and is affected by early-stage Alzheimer's disease.

The Mosers did a second postdoctoral stint with O'Keefe at the University of London. "The 3 months I trained with John were the most intense learning experience of my life," Edvard says. In 1971 O'Keefe discovered place cells, which are hippocampal neurons that are activated when an individual visits specific locations in its environment. O'Keefe taught the Mosers how to make single-cell recordings and provided career guidance.

Discovery and Characterization of Grid Cells

Upon returning to Norway in 1996, the Mosers received associate professorships in the department of psychology at the Norwegian University of Science and Technology. They established a laboratory and 2 years later were promoted to full professorships in neuroscience. In 2002, the Research Council of Norway awarded their research group "center of excellence" status and a decade of funding.

One research focus concerned the hippocampal origins of place cell signals. The Mosers suspected they emerged from the EC. Recordings of neurons from this part of the medial temporal lobe helped identify cells with precise multipeaked spatial firing fields in the MEC (5). The recordings suggested that the cells exhibited a hexagonal firing pattern.

Additional recordings of neurons were made from rodents in different environments. "Within a few weeks, on several occasions, we had multiple Eureka experiences, where it became clearer and clearer that the hexagonal pattern was neither a coincidence nor a technical artefact," Edvard later wrote in a biographical piece (6). "The firing fields tiled the entire space available to the rat, in a pattern reminiscent of the holes of a beehive. We had several names for our baby, but because of the grid-like nature of the firing pattern, we suggested to call them grid cells. It was a simple and descriptive term." The discovery of grid cells and the spatial map they help form in the entorhinal cortex was reported in *Nature* (7). A subsequent study found that grid cells coexist with head-direction cells as well as conjunctive cells that display mixed grid and head-direction tuning (8).

In a conceptual article, the Mosers and colleagues theorized that grid cell patterns arise from continuous attractor networks in which recurrent synaptic connectivity constrains the joint activity of cells to a continuous, low-dimensional repertoire of possible coactivation patterns in the presence of a wide range of external inputs (9). Their team later reported evidence for a modular organization of grid cells, confirming a major prediction of the attractor model (10). The researchers clarified that grid cells operate on a low-dimensional manifold (11) and are subject to shearing forces that underly distortions of the cells' hexagonal symmetry (12).

Border, Speed, and Object-Vector Cells

In 2007 the Moser research group became the Kavli Institute for Systems Neuroscience, thanks to funding from the Kavli Foundation that enabled a transition from a single-group center to a multidivision institute. The following year, the Mosers and colleagues discovered border cells in the MEC (13). Edvard says, "Border cells fire exclusively along geometric borders of the local environment and maintain this preference across environments."

For their discovery and characterization of grid cells, the Mosers were awarded the 2014 Nobel Prize in Physiology or Medicine, which was shared with O'Keefe for his discovery of place cells and contributions to the understanding of neural processes involved in the mental representation of spatial environments. The Mosers additionally received the 2011 Louis-Jeantet Prize for Medicine from the Louis-Jeantet Foundation, Columbia University's Louisa Gross Horwitz Prize for Biology or Biochemistry in 2013, the American Philosophical Society's Karl Spencer Lashley Award in 2014, and the Koerber Foundation's Koerber European Science Prize in 2014.

May-Britt's Inaugural Article (14), published in 2014, addressed whether or not place cells in the CA3 region of the hippocampus can distinguish and encode many similar environments after only a single exposure. She says, "The rats were tested in identical square boxes in 11 different rooms that were so similar that we ourselves could not distinguish them." Despite the similarities, the rodents formed completely different mental maps for each room, leading the Mosers to theorize that the CA3 network must actively decorrelate the maps it forms, possibly based on preformed circuits within the hippocampus. May-Britt says, "The study suggests that the capacity of the CA3 place cell population must be enormous, as we would expect for cells that also encode episodic memory. We still do not know the limits of the system."

The following year, the Mosers and colleagues discovered speed cells, which are another key component of the dynamic representation of self-location in the MEC (15). The cells were shown to have a linear response to running speed, which is translated along with other information between grid cells.

Although the Mosers divorced in 2016, they continue to share time with their daughters, who are both pursuing careers in medicine. May-Britt and Edvard's collaboration remains highly productive and includes the training and mentoring of 41 postdoctoral associates and 35 doctoral students during the 1998 to 2022 period, as well as the 2019 discovery of yet another distinct functional cell type: object-vector cells (16). As abundant as grid cells in the MEC, these neurons tuned equally to a spectrum of discrete objects as well as to a broad range of dimensions and shapes in experiments.

May-Britt says, "Edvard and I really enjoy working together, and we are blessed with fantastic and skilled people working with us. Our slogan is that we want excellent science through happy people and happy animals. We work hard to achieve that."

Mechanisms of Memory

The pair have maintained their interest in the neural mechanisms of memory. With colleagues, they showed that γ-wave neural oscillations in the CA1 of the hippocampus alternate between low frequencies, linked to the CA3 of the hippocampus, and high frequencies, linked to the MEC (17). The findings suggest that a function of frequency variations is routing information between internal circuits of the hippocampal formation. Additional research supported the theory, finding that 20- to 40-Hz neuronal network oscillations in these brain areas are a mechanism for synchronizing representations in dispersed memory circuits (18). The synchronization occurs, in part, as the hippocampus receives projections from multiple functional cell types in the EC (19).

The Mosers showed that a prefrontal-thalamic-hippocampal circuit through the nucleus reuniens is crucial for representation of an individual's future path during goal-directed navigation (20). Neurons in a circuit mature in the order in which information flows. The team determined that MEC stellate cells provide an instructive signal that drives this maturation sequentially and unidirectionally through the entorhinal-hippocampal circuit (21). The discovery of a neural code for episodic time in the lateral EC reveals that passage of time is robustly encoded in an experience-dependent manner in the collective activity of neurons in this brain area (22).

Fight Against Alzheimer's Disease

In 2020 the Mosers were selected to lead the K. G. Jebsen Centre for Alzheimer's Disease at the Norwegian University of Science and Technology. The center was established following a grant worth 22.5 million Norwegian kroner from the Foundation Stiftelsen Kristian Gerhard Jebsen with the goal of translating Nobel Prize-winning brain research from the laboratory to patients. Norway's National Association for Public Health and St. Olavs Hospital work closely with the center, permitting access to state-of-the-art brain imaging systems.

Working at the interface between computational and experimental neuroscience, Mosers' collaborators are pursuing the etiology of Alzheimer's disease. Edvard says, "If we are to understand what causes Alzheimer's, we need to identify the early mechanisms of the disease, which we can use to develop an early diagnosis. Knowledge about the very first route the disease makes may enable us to intervene in the process and stop the disease before cells die and brain functions start to unravel."

Technological Advances in Recording Neurons

Leaders in the development of neuronal recording technologies, the Mosers are members of a consortium that continues to advance Neuropixels electrodes for large-scale neural population recording. Using a Neuropixels hardware system, the Mosers captured the first visualization of a continuous attractor network for grid cells (23). Based on the joint activity of hundreds to thousands of simultaneously recorded neurons, it provided evidence at the neural population level that grid cells operate rigidly and independent of experience on a toroidal manifold.

In 2022 the Mosers, their postdoctoral associate Weijian Zong, and colleagues reported the development of a miniaturized two-photon microscope weighing less than a tenth of an ounce (24). It enables fast, high-resolution calcium imaging of more than 1,000 neurons across multiple imaging planes during unrestrained behavior in freely moving mice. In his Inaugural Article (1) Edvard describes the application of the miniscope to analyze the full functional topography of the space circuit in the MEC. He says, "The paper reports that grid cells are anatomically segregated from other spatial types, which are more intermingled. The findings are consistent with the notion that grid cells form dense attractor networks with strong intrinsic connectivity."

Considering the advances in his field, Edvard says, "It is an exciting time to be in neuroscience. There is a high demand for computational approaches and mathematics in order to make sense of the data that we just can't see by eye anymore. I'm glad I studied mathematics in my early years because I certainly need it now." May-Britt adds, "Even if a lot of my bucket list already has been ticked off, I know that I have a very bright future in front of me. My wish and goal for the rest of my career is to, hopefully together with Edvard, learn more and to understand more about how the brain is generating our intellectual activities."

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