Crystals of the brain

When we find our way in the environment, we need to integrate information about location, direction and distance into a coherent map-like representation. Our work over the last 10 years has suggested that the medial entorhinal cortex plays a central role in this process. A key component of the entorhinal network for spatial mapping is the grid cell, which we discovered, together with our colleagues, in 2005. Grid cells fire only when animals move through specific, regularly spaced positions. Their active firing positions form a hexagonal pattern that spans, for each cell, the entire local space available to the animal (Fig 1). The periodic pattern is reminiscent of the cross-points of graphic paper but the repeating units are equilateral triangles, not squares. Grid cells interact with other specialized cell types, such as head-direction cells and border cells. Head-direction cells signal orientation whereas border cells fire only near the edge of the local environment (Fig 2). Together, these entorhinal cells establish a coherent generic map of local space that is maintained across environments, independently of the animal’s speed and direction and independently of the identity of the particular landmarks of the place.

» Grid cells have attracted attention because the crystal-like structure underlying their firing fields is not, like in sensory systems, imported from the outside world, but is created within the brain itself. «

“One synapse” downstream, in the hippocampus, the map is associated with specific features and experiences, forming individualized maps that are stored in the neural networks of this brain region. Studies of grid cells may thus provide access to some of the basic computational operations of cortical circuits. In this Perspective, we shall review the work that led to the discovery of grid cells and the entorhinal spatial map, concluding with a brief look to the future.

Finding the trail

Both of us were born on remote islands on the outer west coast of Norway. Our interests in science were raised by our parents, who wanted an education themselves but did not have this opportunity. Both of us applied for studies at the University of Oslo in the early 1980s but neither of us had a clear career plan. We started out on independent paths but finally met in an undergraduate course in psychology. Psychology kindled our fascination by the brain and we jointly decided to find out how we could learn about the neural basis of behaviour.

There was no neuroscience curriculum at this time, but Carl Erik Grenness, a teacher of an undergraduate course in behaviour analysis, alerted the two of us to the pioneering work on brain-behaviour relationships that had taken place during the preceding two decades. He gave us a copy of a special issue about the brain published by Scientific American in 1979. During our wandering in wilderness, this was like manna from heaven. With a number of articles from the most prominent researchers in the field at the time, the issue communicated the enthusiasm of the field and strongly attracted us to this evolving scientific discipline. The many authors outlined the enormous progress that had been made on a number of topics, including such exciting advances as Kandel’s demonstration of learning-related synaptic modifiability in accessible invertebrate systems and Hubel and Wiesel’s characterization of the mechanism for feature analysis in the...
visual cortex. Grenness directed us to Terje Sagvolden, the only psychologist at the university with research projects in neuroscience at that time. Working on neurochemical mechanisms of attention deficit disorder for 2 years, in parallel with studies in psychology, we were taught the basics of animal behaviour and experimental design.

Terje Sagvolden’s work on animal learning turned our interest to the underlying neural mechanisms and we went to see Per Andersen, the grand neurophysiologist of Norway. Per Andersen became the PhD supervisor for both of us. May-Britt’s project concerned the anatomical basis of hippocampal learning; Edvard’s investigated the role of synaptic potentiation. Per introduced us to the mysteries of the brain. We learned to focus on basic questions with wide implications. Through Per, we came in touch with Richard Morris at the University of Edinburgh and John O’Keefe at the University College of London. During our PhD studies, we visited Richard several times to participate in work on the functions of the hippocampus and hippocampal long-term potentiation. After the PhD defense late in 1995, we spent a few very rewarding months with John to learn place-cell recording in the hippocampus. This was probably the most intense learning experience in our lives. In August 1996, we left the UK full of hippocampal baggage. We had been offered two jobs in the same department at the Norwegian University of Science and Technology in Trondheim—an offer that we could not resist. A few months of postdoctoral experience was short but with a decent start-up package we now had the opportunity to combine what we had learnt about animal behaviour and neurophysiology, fulfilling our dream from the early 1980s.

Finding the entorhinal space circuit

The start-up in Trondheim was tough but enjoyable. There were no animal housing facilities, no workshops and no technicians. We did all the work on our own; we cleaned rat cages, changed bedding, sliced brains and repaired cables. Starting from scratch gave us the opportunity to shape the lab exactly as we wanted it. Our first student started in 1998 and we received our first international collaborative grant, from the European Commission, in 1999. The two of us coordinated a consortium of seven groups aiming to perform one of the first integrated neural-network studies of hippocampal memory, which was mostly virgin territory in the late 1990s. One of the aims was to determine how the position code of the hippocampus is computed. It had been known since 1971 that the hippocampus has ‘place cells’, cells that fire if and only if an animal is in a certain place (O’Keefe & Dostrovsky, 1971); however, it was still unclear whether those place signals originate in the hippocampus itself or come from the outside. To address this question, we made lesions in the early stages of the hippocampal circuit (CA3) and recorded place cells from the latest stage (CA1) (Brun et al, 2002). The anatomical component of the work was performed in collaboration with Menno Witter from the Free University of Amsterdam, one of the key members of the EU grant. To our surprise, the disconnection from the associative circuitry of the hippocampus did not abolish place coding in CA1. This implied that the spatial signal might originate from the surrounding cortex, via connections that circumvent the intrahippocampal circuit. The observation was a major breakthrough as it turned our attention to the entorhinal cortex, a cortical region with major direct connections to the CA1 area of the hippocampus.

Through our continued collaboration with Menno Witter, it became possible, for the first time, to target electrodes to the exact part of entorhinal cortex that provides the densest input to the place cells in CA1 of the dorsal hippocampus. Two years after the hippocampal disconnection study, we provided the first evidence for strong position-related activity in this area (Fyhn et al, 2004), and 1 year after that, the work culminated in the discovery of grid cells as the principal functional cell type in the entorhinal spatial map (Hafting et al, 2005). By using extended spatial environments, we found,
together with our students, that medial entorhinal neurons have periodic spatial firing fields that cover the environment in a tessellating triangular pattern (Fig 1). The invariantly periodic structure of these cells pointed to grid cells as the metric of the brain map for space.

To understand how grid cells operate and how they are generated, we saw it as necessary to characterize the wider network in which they are embedded. In 2006, we observed that the medial entorhinal cortex also contains cells that signal the animal’s head direction, like the head direction cells of the presubiculum (Taube et al, 1990), and we found that many cells signal direction and position conjunctively (Sargolini et al, 2006). In 2008, we observed a third entorhinal cell type—border cells—which fires exclusively at edges and boundaries of the local environment (Solstad et al, 2008, Fig 2). Further work showed that grid cells determine how memory is stored downstream in the hippocampus (Fyhn et al, 2007), and gamma oscillations were found to be instrumental in routing information between grid networks in the entorhinal cortex and place and memory networks in the hippocampus (Colgin et al, 2009). Collectively, these studies have outlined the basic properties of a spatial representation system in the entorhinal cortex of the mammalian brain.

Where next?

The time has come to dig into the mechanisms lying behind the formation of dynamic representations as well as the interactions between cell types resulting in a unified representation of self-location. For this, we need to understand the wiring of the circuit and manipulate its key components, one at a time.

The intricately interlaced nature of neural circuits rules out classical approaches to functional studies such as experimental lesions and drug interventions, tools that we got so familiar with during our early training in Oslo and Edinburgh. However, a technological revolution has taken place in the meantime. With the ever-expanding knowledge of the mouse and rat genome, it has become possible to change gene expression in specific cell types without affecting their surrounding neighbours. By turning discharges in specific groups of cells on or off, using light-responsive microbial opsins such as channelrhodopsins and halorhodopsins, it is now possible, in principle, to determine how the activity of each cell type contributes to the global computations of a neural circuit (Deisseroth, 2011; Peron and Svoboda, 2011). These new tools can certainly be used to determine how the activity of individual cell groups in the entorhinal–hippocampal spatial representation circuit contributes to the performance of network.

With the help of cell-specific manipulations, the field is now finally taking the direction that we had vaguely dreamt about when we approached Professor Grenness as young students in 1984. At that time, the neural mechanisms of mammalian behaviour were still terra incognita, despite the very significant advances that we were introduced to as undergraduates. This brings us back to the Scientific American issue from 1979.

In this issue, there was one paper that differed from the others—the concluding essay by Francis Crick. Crick reflected on the limits of neuroscience, and what strategies could be followed for neuroscientists to be able, one day, to explain the most complex functions of the brain (Crick, 1979). The key limitation, according to Crick, was the fragmented nature of knowledge in neuroscience. Crick suggested that, in order to understand the workings of the brain at an integrated level, neuroscientists should develop concepts and methods for studying computation at the level of neural circuits. Today, the need for circuit analyses is widely recognized. The focus on network computations, outlined in Crick’s essay, was the starting point for our first project grant in 1999 and it is at the heart of contemporary neuroscience. Powerful tools are now available and several brain systems, such as the entorhinal–hippocampal circuit, have been described in sufficient detail to enable a mechanistic analysis. We have great hopes for the coming years.

The authors declare that they have no conflict of interest.

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