as therapeutic approaches. If promising evidence emerges from preclinical studies, such investigations could set the stage for clinical trials.

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In retrospect

Fifty years of the brain's sense of space

Isabel I. C. Low & Lisa M. Giocomo

Neurons in a brain region called the hippocampus were found to be selectively active when rats are in a specific spatial location during natural navigation. The discovery launched research efforts into how the brain supports spatial memory.

Nearly all of our conscious experiences incorporate a sense of space: the restaurant where we ate, our route home, where we found our teacup, navigating to our favourite chair. This sense of space is how we know where we are, remember where we have been and plan where we want to go. But how the brain generates this sense and uses it for memory or navigation remained a mystery for many years. A landmark paper in 1971 by John O'Keefe and Jonathan Dostrovsky, published in *Brain Research*, offered the first glimpse into how neurons in the mammalian brain compute an animal's sense of space[1].

In their short communication, O'Keefe and Dostrovsky used microelectrodes that had been developed a few years previously to record the electrical signals, known as action potentials, from neurons in the brains of rats. Studying animals exploring a raised platform, the authors targeted the microelectrodes to a region nestled below the brain's surface called the hippocampus, because work in humans and rodents had demonstrated that damage to the hippocampus impaired memory and navigation[2,3]. There was no particular task at hand — the rats spontaneously ate, groomed, drank, slept and moved around naturally. Strikingly, the activity of some hippocampal neurons was tightly correlated with the animal's location in physical space. These neurons were silent as the rat moved through much of the environment but became active when the animal reached one small portion of the platform (Fig. 1). Because each neuron often fired action potentials while the animal was in just one position, O'Keefe and Dostrovsky called these neurons place cells and dubbed the location in the animal's environment where the neuron showed the most activity the neuron's place field.

Before O'Keefe and Dostrovsky's seminal study, researchers had proposed that animals, through exploration, could learn associations between environmental features (such as landmarks) and their own position to build an internal model — or 'cognitive map' — of the external world[4,5]. This cognitive map would allow animals to flexibly navigate their environment. It seemed possible that place cells might support such a cognitive map. If so, then, rather than these cells simply responding to a specific sensory cue (such as a visual feature visible only when in one portion of the environment), place-cell activity should represent a more abstract calculation of the animal's position. Further experiments supported this possibility, showing that some place cells remained active in the dark[6] and that place-cell activity was largely consistent, regardless of the direction in which the animal was heading[7].

The memory and navigation research field ignited, ultimately extending the role of place cells from signalling an animal's spatial position to functioning as a potential substrate for spatial memory. The electrode-recording approaches used by O'Keefe and Dostrovsky became the workhorse for studying the electrical signals of hippocampal neurons for decades, supporting stable and robust recordings of place-cell activity across a vast repertoire of environments and behavioural tasks. Using environments that differed in shape or landmark features, studies revealed that place cells 'learn' about and respond to changes to an environment[8,9]. For example, when rats explore a square box and then a circular arena,

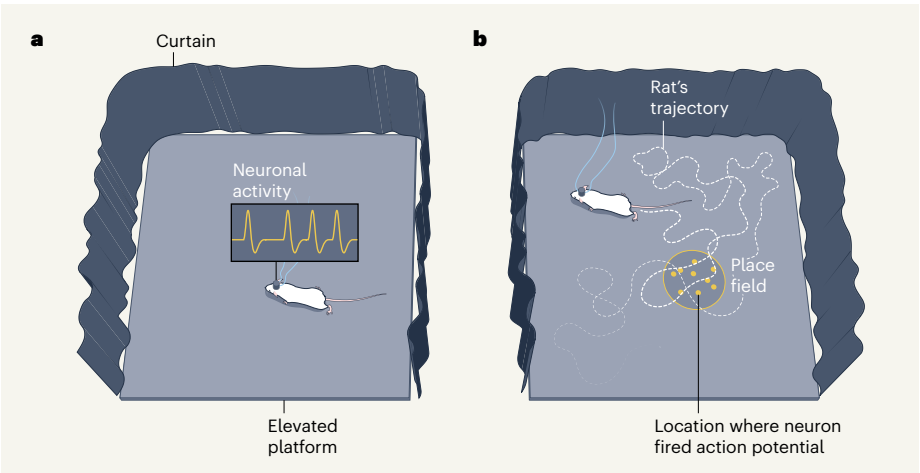

Figure 1 | The discovery of place cells representing a rat's position in space. a, In their 1971 paper, O'Keefe and Dostrovsky[1] recorded the electrical activity (including signals called action potentials) of neurons in a part of the brain called the hippocampus in rats exploring an elevated platform with a curtain around three sides. **b**, The authors found that some neurons showed activity only when the rat was in a particular region of the environment. The authors dubbed these neurons place cells and the region in which they became active, their place fields. A schematic illustration of an example place cell's place field, defined by the occurrence of action potentials when the animal was in that region, is shown here.

the place fields of some place cells turn off, turn on or move to a new spatial location. These activity changes result in a unique set of place cells that are active in each environment that an animal explores; this could allow the animal to identify its current surroundings and later remember which environment it visited.

O'Keefe and Dostrovsky's original work presented data from eight place cells. Technological advances over the past 50 years have allowed researchers to record simultaneously from tens to thousands of place cells, providing insight into how many such cells can work together to support navigation and memory. For example, a population of place cells can together maintain a stable position estimate over many days, even as individual cells change their activity patterns[10]. The techniques used have also revealed a rich diversity of place-cell responses. In 1971, O'Keefe and Dostrovsky saw hints that not all place cells were responsive to an animal's spatial position, and later work has since revealed that place-cell signals can also correspond to (non-spatial) variables such as specific odours[11], auditory frequencies[12] and social partners[13]. That place-cell signals can represent not only spatial position but also other unique aspects of an experience strongly suggests that hippocampal neurons provide the basis for generating and storing memories for specific experiences.

In the past few decades, versions of place cells have been discovered in primates, mice, bats and birds[14,15], pointing to these cells as underlying an evolutionarily conserved mechanism supporting memory and navigation. Moreover, O'Keefe and Dostrovsky's discovery of place cells in the hippocampus inspired researchers to explore the surrounding brain regions. This led to the discovery of neurons in the entorhinal cortices (regions adjacent to the hippocampus) that represent the position, orientation and running speed of an animal[16], as well as the position of objects[17] and the passage of time[18]. Neuronal responses to orientations, similar to those in mice and rats, have also been found in fruit flies, suggesting that the neuronal systems underlying navigation probably have evolutionarily ancient origins[19]. Together, the hippocampus and entorhinal cortices in mammals contain the conceptual elements needed to build a cognitive map with which mammals can flexibly navigate, remember and plan their way through the world.

So far, most studies have described correlations between place-cell activity and an animal's behaviour. Now, researchers can manipulate this activity in behaving animals[20], revealing potential causal links between place-cell activity, memory and navigation. For example, artificially switching on place cells that are usually active near a water reward can evoke licking behaviour in an unrewarded location[20]. Advances in genetic, molecular and cellular tools will undoubtedly continue to take the field of memory and navigation in new directions, all originating from the discovery of the place cell.

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Physiology

A mediator of metabolic signals influences puberty

Alejandro Lomniczi

Variants of the melanocortin 3 receptor are associated with delayed puberty and reduced growth, suggesting that this receptor might integrate signals of metabolic status that affect body growth and sexual maturation. **See p.436**

Body growth and the onset of puberty are regulated by neurons located in a part of the brain called the hypothalamus. In the central hypothalamus, signalling by hormones called melanocortins relays metabolic information to downstream growth and reproductive centres. However, the molecular and cellular targets of these signals have not been completely elucidated. On page 436, Lam *et al.*[1] describe previously unreported mutations in the gene encoding the human melanocortin 3 receptor (MC3R) protein that seem to disrupt the receptor's function. They found that these mutations are associated with a delay in the onset of puberty as well as with reduced childhood growth, adult height and lean body mass.

Early studies[2,3] showed that the timing of pubertal onset is related more to body weight than to chronological age. These studies suggested that the body's state of growth is reported to the hypothalamus by metabolic cues that act as a signal to initiate puberty. Indeed, we now know that the increases in the hormone leptin and in the levels of glucose and insulin that occur in response to energy excess are detected by a group of hypothalamic neurons that express the melanocortin precursor peptide, pro-opiomelanocortin (POMC). It is these POMC neurons that convey information about the body's metabolic status to other hypothalamic neurons that control growth and sexual maturation[4]. However, the cellular targets and receptors involved in the melanocortin-mediated control of pubertal timing and body growth have remained unclear.

MC3R and MC4R are the two main melanocortin receptor proteins in the brain that are activated by melanocortin peptides. Humans and mice that lack functional MC4R are obese and eat excessively[5,6], but show overall normal growth and pubertal development[7]. Therefore, Lam and colleagues proposed that, if the melanocortin system influences pubertal development, a melanocortin receptor other than MC4R is probably involved. MC3R is the only other melanocortin receptor known to be expressed in the brain, and the authors therefore screened the Avon Longitudinal Study of Parents and Children (ALSPAC) data set for variations in the gene sequence of *MC3R*. (ALSPAC comprises biological, environmental, body-growth and body-development data for multiple generations of people from birth to adulthood.)

The screen identified seven rare variants of the *MC3R* gene that are predicted to render the encoded receptor non-functional. In line with