## Primer

# Place, space and memory cells

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Self-localization and navigation are critical functions for the survival of mobile animals. By processing sensory information such as landmarks and environmental features, as well as keeping track of the path they have taken, animals are able to remain oriented as they explore the world, learning what resources are where and planning how to reach them. This ancient capacity for self-orientation has, through evolution, become intimately entwined with the ability to remember the events of daily life — an ability known as *episodic memory*. Spatial and episodic memory involve the interaction of many cognitive faculties and brain circuits, and so are fascinating subjects for study that reveal much about how the brain works.

Spatial cognition requires an internal representation of the outside world, an idea that dates back to Tolman, who in the 1940s proposed the existence of such a representation — which he called a *cognitive map* — to explain the flexible navigation behaviour he observed in rats. Evidence for the neural basis of this cognitive map came with the discovery, made using the single-neuron recording technique shown in Figure 1A, that neurons in the hippocampus of rats (Figure 1B) display spatially localised firing (Figure 2A). These cells behave very much as though they are markers for location and were thus termed *place cells*. Since the discovery of place cells, other spatially sensitive neurons in related structures have been discovered, including head-direction cells, which support the sense of direction; grid cells, whose periodic firing patterns provide odometric (distance) information; and border cells, which mark out environmental boundaries. Below, we explore how these cell types interact to form a cognitive map, and how they may cooperate in service of both spatial and episodic memory.

## Place cells and the encoding of 'place'

The firing patterns of place cells have a number of intriguing characteristics. In small environments, most cells have only one or sometimes two (rarely more) firing locations (*place fields*). Unlike visual or other primary sensory cortices, there is no topographic arrangement of place cells in the brain — adjacent cells do not necessarily have adjacent place fields. If the animal is placed in a different environment, about 50% of the cells still express place fields but the location of these new fields is unrelated to their previous locations, as if a whole new map had been generated afresh with random resampling from the same pool of neurons — the process is thus known as *remapping*. Remapping seems to reflect a decision by the neurons that an environment is novel.

How does a place cell fire reliably in a particular location within an environment? To begin with, various different sensory modalities project to the place cell system. Visual information is important, because when a prominent landmark is rotated then the place fields rotate by the same amount, and alteration of visual but non-directional characteristics such as color induces remapping. Other sensory modalities such as tactile and olfactory input also play a part. Although many sensory systems input to place cells, they converge upstream of the hippocampus and are combined into *supramodal* (of no particular modality) representations, such as landmarks, compass cues, boundaries, linear speed, angular speed and so on, which are then passed to the place cells to exert different effects. Grouping types of supramodal information together, they fall into three broad classes. The first is external positional information, such as landmarks and boundaries, which can be used for self-localization. In rats, at least, the boundaries of an environment are extremely important for place cell firing, with experimenters being able to stretch or squash place fields by lengthening or shortening walls. The second information class comprises diffuse non-positional cues pertaining to context, such as the color or odor of the environment, or even non-physical cues like what task is to be performed. Context cues select the incoming spatial signals and help the cell disambiguate environments. The final information class consists
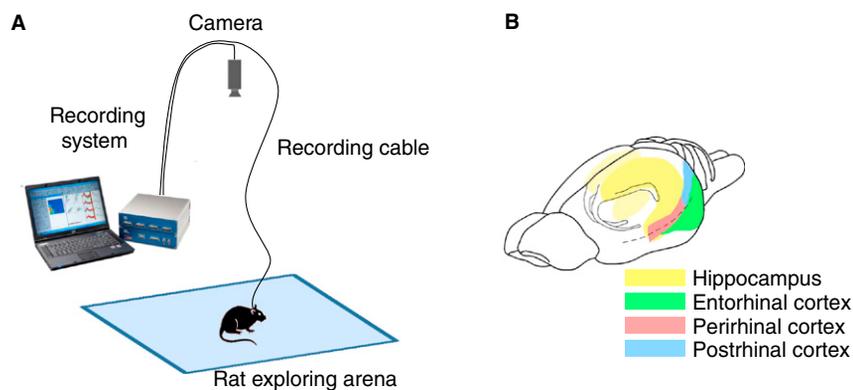


Figure 1. Recording of single neurons in the rodent hippocampal system.
(A) A typical laboratory experimental setup for recording spatially sensitive neurons in exploring animals. The animals are implanted with moveable microelectrodes that are situated in the brain region of interest. The electrodes are attached to a tiny drive mechanism that allows the experimenter to advance the electrodes through the brain in small steps of a few tens of microns. The implant can be attached to recording equipment via a headstage (not shown), which stabilizes and boosts the signal and allows it to be transmitted through a long, thin, lightweight cable without loss of signal or gain of electrical noise. Meanwhile, an overhead camera monitors the position of the animal, usually via an LED attached to the headstage. In a typical experiment the animal will forage for food over the surface of the arena while the ongoing activity of the neurons is recorded: sometimes it may perform a navigation task. (B) Schematic of the rat brain, showing the hippocampus and surrounding cortices. (Adapted from Furtak *et al.* (2007).)

A                     B                          C                    D

Place cell        Head direction cell        Grid cell          Border cell



20 Hz

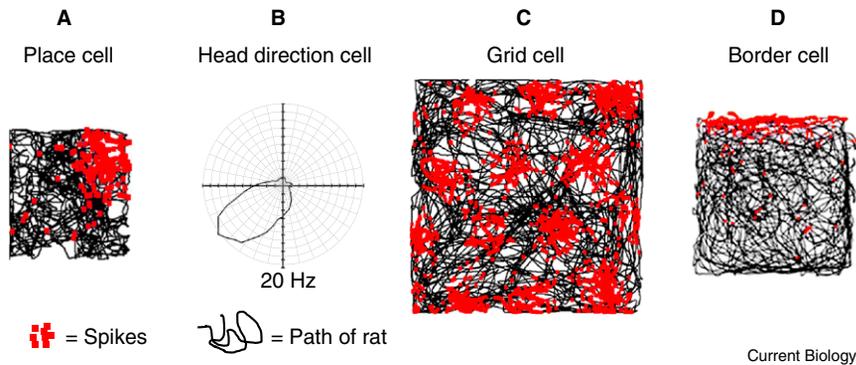= Spikes        = Path of rat

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Figure 2. Typical firing patterns of the major cell types in the cognitive map.
(A) A place cell, recorded by Elizabeth Marozzi (EM), which concentrated its firing in the Northeast corner of the enclosure. (B) A head direction cell, courtesy of Rebecca Knight, with a preferred firing direction to the Southwest of the enclosure. (C) A grid cell, recorded by EM, with firing fields evenly spaced in a close-packed hexagonal array across the surface of the arena. (D) A border cell, courtesy of Lin Lin Ginzberg, which only fired when the rat was in very close proximity to the North wall of the enclosure. For the spike plots (A, C and D), the neuronal action potentials (red squares) are superimposed on the path of the rat (black line) at the place where the rat was when the cell fired. These plots are not to scale, but the environment for the place cells was 60 x 60 cm, for the grid cell 120 x 120 cm, and for the border cell 100 x 100 cm. For the head direction cell (B), which fires everywhere in an environment, the firing is instead shown in the form of firing rate (distance from origin) as a function of head direction.

of information generated from an animal's own movements, which can update the positional calculation by a process known as *path integration.* Such information includes vestibular signals, proprioceptive signals, optic and other forms of sensory flow, and information about commanded movements (motor efference copy), and is sometimes known as 'idiothetic'.

One of the most intriguing characteristics of the place cell map of space is how it responds to environmental alteration. Animals are constantly bombarded with change — leaves grow, snow falls, objects appear and disappear — and the cognitive map would be of little use if it responded to every small change. Place cells thus have the capacity to make decisions about whether an environmental change is sufficiently great to warrant remapping — and indeed this may be one of the *functions* of the hippocampal system: to process incoming sensory information, compare it with its stored memory traces and decide if the environment is familiar, familiar but changed a little, or completely novel. This decision process is thought to be mediated by *attractor dynamics*, in which the interconnections of the hippocampal network allow neurons to regulate each others' responses to the incoming sensory information and collectively gravitate towards

a stable state, which may be either a stored state (a memory) or a new state, which will then itself be added to the store. These processes occur constantly, which may at least partly account for why hippocampal synapses are so plastic.

As well as space, there is also evidence that there is a temporal aspect to the place cell code, with firing occurring in relation to specific phases of the hippocampal activity pattern known as *theta*: the 'clock' of the hippocampus (Figure 3A). Theta is a rhythmical 6–12 Hz sinusoidal oscillation in the local field potential that is observed in awake, freely behaving rats, primarily during movements or translation through space such as walking, running, or swimming as well as during states of arousal and attention. It is thought to represent the membrane oscillations of large populations of neurons in the hippocampus synchronized by networks of inhibitory interneurons. Place cells fire rhythmically in bursts at what appears to be the same frequency as theta, but which on close inspection turns out to be very slightly faster. Thus, as a rat runs through its place field, the phase of theta at which the place cell fires occurs progressively earlier in successive theta cycles. This temporal shift or *phase precession* in place cell firing is highly correlated with an animal's location within

its place field and may allow finer-grained encoding of place.

### Head-direction cells and the sense of direction

While place cells provide an animal with a sense of location, the head-direction cells provide it with a sense of direction. A given head-direction cell fires only when the rat's head is turned towards a particular horizontal direction (*azimuth*) in the environment (Figure 2B), with firing falling off on either side of this direction almost linearly, to produce a triangular response profile (*tuning curve*) with a typical angular span of around 90–120 degrees. Within a population of cells, all directions are equally represented and the system appears to work as a coherent whole: when one head-direction cell rotates its tuning curve, other cells recorded at the same time rotate theirs by the same amount too, thus preserving their relative directions. This high degree of coherence has led to speculation that the cells are mutually interconnected in an attractor network, and that their function is to stably represent directional heading even across intervals when the animal has lost perception of or attention to landmarks.

Head-direction cells, then, collectively act like a neural compass. Unlike a real compass, however, the cells are not affected by the Earth's geomagnetic field, and firing directions are tied to a local reference frame, which is — as with place cells — defined by contextual cues and oriented by landmarks. The fact that head direction cell firing can be maintained in complete darkness (although tuning curves slightly drift over time) shows that self-motion information is also sufficient for generating and updating the head direction signal: an important part of the path integration process.

Since the initial discovery of head-direction cells in postsubiculum, they have been found in multiple brain regions, many of which comprise the classic Papez circuit, long known to be critical for memory. The adaptive significance of having head-direction cells in so many brain areas is not well understood, and nor is their relationship to memory. In different brain areas, there are subtle differences in firing rates and tuning curve widths. Additionally, the firing

of head-direction cells in subcortical structures tends to anticipate the rat's actual head direction by about 25 milliseconds, while cells in cortical areas correspond to current head direction. These findings, together with anatomical location and patterns of connectivity, have led to the proposal that cells in the cortical regions process incoming landmark information while those in subcortical regions process information about self-motion, including motor commands that carry advance warning of an impending head direction change.

Although head-direction cells are ideal candidates for the origin of the directional signal that orients place fields, there are no direct connections from the head direction areas to the hippocampus. It is now believed that before reaching the place cells, the directional information is combined with distance information to form a conjunctive signal of direction *and* distance. This conjunctive signal resides in the grid cell system.

**Grid cells and neural odometry**
The discovery of grid cells provided a great leap forward in our understanding of spatial processing. In contrast to place cells, which usually produce only one or sometimes a small number of firing fields, grid cells have multiple circular fields which tile the floor of an environment in a close-packed hexagonal array that extends horizontally in all directions (Figure 2C). Grid cells seem to represent space at different scales, with the spacing between fields increasing from approximately 25 cm for cells located dorsally to several meters for cells at the most ventral extent. Grid cells recorded at the same dorsoventral position have similar receptive field spacings and grid orientations, but are offset relative to each other. This means that only a small subset of grid cells are needed to cover an environment entirely.

Like place and head direction cells, grid cells use both environmental and self-motion information to localize their fields. Grid cell grids appear as soon as a rat first enters an environment, and their spacing is therefore initially intrinsic and self-motion-determined. Thereafter, environmental cues acquire an influence: for example, in a familiar
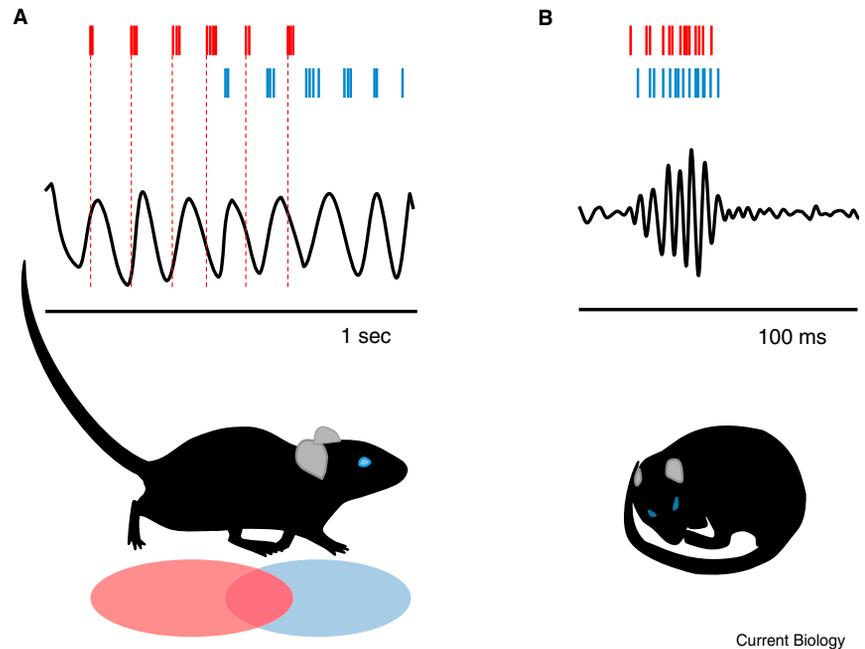


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Figure 3. Two major classes of oscillation in the hippocampal spatial system, and patterns of associated cell firing.
(A) Theta rhythm, a sinusoidal field potential oscillation which is prominent when an animal runs through space. In the schematic example shown, a rat is running successively through the place fields of two place cells, shown in red and blue, respectively. The actual spike patterns of the two cells are shown in the raster plots at the top, with each spike shown as a vertical line. The dotted lines show how the first spike in each burst corresponds to the phase of the ongoing theta rhythm — note that this line intersects the theta wave at earlier and earlier phases of the cycle with each burst — this is *phase precession*. The consequence is that the spikes occurring at the entry to the place field occur later in the cycle than spikes as the rat exits the place field. The second cell, shown in blue, has a place field that overlaps — when the rat enters this field it is exiting the field of the red cell and so its spikes occur at a different (later) phase of theta. Thus, even within one theta cycle, by knowing the phase of theta the brain can determine the relative locations of the two fields, which could help with self-localization. (B) A sharp-wave ripple (SWR), occurring as a result of neuronal bursting when the rat rests or sleeps. Note the different timescale — SWRs occur in very short time-windows. Nevertheless, the sequence of spikes in the burst is similar to the sequence of the same cells that had fired during the previous run. This *replay* may have a role in consolidating memory of the waking experience.

environment, rotation of a polarizing landmark causes grids to rotate, and — as with place cells — stretching and squashing of the environment causes (slight) stretching and squashing of grids. However, grid cells continue to maintain the same firing pattern in complete darkness, confirming an ongoing input from self-motion cues. This capacity to mediate between environment-based and intrinsic self-motion-based information is one of the strongest arguments for the grid cells being part of the path integration system.

How do grid cells pass their information on to place cells? Grid cells are one synapse upstream from place cells and so a logical assumption is that they directly inform the place cells about where to fire, perhaps by summing grids of different scales to produce focal hotspots

of activity. However, as well as the feedforward connections from the entorhinal cortex to the hippocampus, there are also feedback connections from hippocampus to entorhinal cortex, and so it is possible that this relationship is bidirectional, with grid cells providing path integration information to place cells, and place cells feeding landmark-based place information (arriving by a different route) back to grid cells. The question of how grid and place cells interact is thus an open one at present.

**Place cells and memory**
This hippocampus has long been associated with episodic memory, and much research into place cells has explored whether aspects of the physiology of spatial encoding might also serve to encode memory. In support of a possible memory

function, hippocampal synapses show a high degree of plasticity, particularly when stimulation occurs at theta frequency.

As well as theta, another important network state in the hippocampus is large irregular amplitude activity (LIA). This non-rhythmical activity, made up of sharp waves and associated with intermittent bursts of synchronous activity known as *ripples* (Figure 3B), occurs predominantly during slow wave sleep and during periods of immobility such as when a rat is sitting, eating, drinking or grooming. During these sharp-wave/ripple (SWR) events, sequences of place cell activation occur that are highly correlated with the same sequences that occurred during wakefulness, leading to the proposal that they constitute 'replay' of waking memories, possibly as part of a consolidation process that transfers, or copies, these memories to neocortex. However, it has been reported that such sequences can be observed *prior* to a rat's first-ever experience of an environment, suggesting the alternative hypothesis that the correlation arises from a common cause — something about the intrinsic wiring of the network predisposes a group of place cells to fire sequentially, both in waking (leading to the place field configuration) and in sleep. Replay events representing the space ahead of the rat (*preplay*) have also been observed when rats are making decisions at the choice point in a T-maze, and replay/preplay can occur forwards or backwards. Thus, SWR-associated replay is a complex phenomenon whose function (if there is one) is still a matter of investigation.

Another issue of interest with regard to place cells and memory is the question of time. Time has long been considered a critical component of episodic memory: as a result, researchers have been intrigued by the question of whether place cells encode time as well as space. In support of time encoding, it was reported recently that place cells respond at a particular temporal 'place' in a task, independent of space. It has also been proposed that granule cells in the dentate gyrus region in hippocampus, which (unusually in the adult brain) are constantly being generated, might serve as a 'time stamp' for memories occurring at different times during life. However, the question of whether either of these are true temporal coding mechanisms, and of whether they are involved in the temporal aspects of memory, is open at present.

## Border cells and the boundaries of space

The natural world is not a continuous open space but is parcellated into smaller regions by boundaries such as walls, rocks, ridges and so on, and as mentioned earlier, place cells are extremely interested in boundaries. This is evident from the observation that re-locating boundaries causes the cells to adjust their fields accordingly, and that placing new boundaries into an environment causes new fields to form. Boundaries also appear important for grid cells because, as we also saw above, grids can be deformed by re-scaling the environment.

Based on the observation of place field deformation in deformed environments, Burgess and colleagues proposed that place fields form at the intersection between inputs from different boundaries, and postulated the existence of *boundary vector cells*, projecting to place cells, that signal the distance and direction of the rat from a boundary. Boundary vector cells have been since reported in subiculum, and a variant, *border cells*, which fire *at* the boundary (Figure 2D), have been found in parasubiculum. Boundaries can include ordinary walls but they can also include other discontinuities such as steps, or gaps. Exactly how border cells and boundary vector cells interact with place, head direction and grid cells remains unknown. Intuitively it seems likely that they somehow attach, as it were, the grid sheet to the environment, but this straightforward account does not explain why grid and place cells remap to environmental change when border cells do not. The high importance of boundaries in the cognitive map suggests that the structure of the map is perhaps somewhat mosaic-like.

## Conclusion and future prospects

Our understanding of how the brain represents and encodes space has made great strides with the discovery of numerous spatially sensitive cell types that provide the building blocks of a cognitive map, including direction, distance, and boundaries. Despite these advances, study of the cognitive map is only just beginning, and many questions remain. Place cell encoding appears anchored to local environmental features, so is there a 'master map' somewhere that relates these local fragments together? If so, where is it? If not, how do animals navigate across large-scale, complex spaces? Where are goals encoded, and how is this information retrieved in navigation? Is the cognitive map three-dimensional? Are cognitive maps the same in humans and other animals, and if not, what are the differences, and why are they there? How does the spatial system develop in infancy? Is it hard-wired or is spatial experience necessary? What is the role of time in all of this?

The most outstanding unanswered question concerning this gallimaufry of spatial cell types is their role in memory. Why would nature have used the same structures for both space and memory, which seem so very different? An intriguing possibility is that the cognitive map provides, in a manner of speaking, the stage upon which the drama of recollected life events is played out. By this account, it serves as the 'mind's eye' not only for remembering spaces, but also the events that happened there and even — according to recent human neuroimaging evidence — imagination.

### Further reading

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