COGNITIVE NEUROSCIENCE

Time, space and memory

The brain's hippocampus contains place cells, which encode an animal's specific location. The finding that hippocampal neurons may also respond to time could provide information on the coding of episodic memories.

GYÖRGY BUZSÁKI

The philosopher Immanuel Kant made life difficult for neuroscientists by posing the following dilemma: does the brain represent time and space, which are themselves actual entities, or does it produce time and space and impose these categories on the world with which we interact? A more mundane, yet important, practical issue is whether there is a dedicated time-keeping mechanism in the brain, similar to the clock of a computer. The hippocampal region of the brain has long been suspected to represent Kantian space[1]. Now, in work published in *Neuron*, Kraus and colleagues[2] attempt to address the hard problem of time by describing 'time cells' — guess where, in the hippocampus. The implications of these findings are potentially far reaching.

The authors trained thirsty rats to run on a treadmill for tens of seconds for a reward of water, while recording the activity of groups of pyramidal cells in the animals' hippocampi. The aim was to distinguish neurons that 'track' elapsed time from those that track the distance run on the treadmill. Distance is, of course, a simple product of time and running speed. But the researchers manipulated these three variables by changing the speed of the treadmill from trial to trial, and requiring the rats to run for either a constant distance or a constant time on alternate days.

Members of the hippocampal-cell population that Kraus *et al.* recorded were active transiently and sequentially, so that the entire duration of the run was evenly represented by neuronal activity within this population. Using exemplary statistical and computational-modelling methods, the authors then evaluated the contribution of elapsed time and the distance run to the activity patterns of each recorded neuron.

In agreement with previous studies[3,4], most of the recorded cells responded to an inseparable combination of time and distance. However, a minority of cells (still members of the broad distribution in the time–distance dimension) was mainly under the control of time spent on the treadmill, and the activity of an equally small fraction was distinctly correlated with distance. Kraus and co-authors acknowledge that "it is impossible to completely separate time and distance". Nonetheless, they interpret their results in favour of a dedicated mechanism in which this small population of 'time cells' specifically keeps track of time. This mechanism is distinct from that of path integration, by which distances and directions the animal takes are integrated with the help of the evolving cell assemblies.

The activity of time cells and path integration during navigation are only part of the hippocampus's story. This structure is also our resident 'search engine', which allows us to navigate in 'mental space' when recalling memories or planning future actions[5]. Kraus *et al.* suggest that the time cells they have identified are a key missing piece of episodic memory, the long-term memory that enables us to recall specific events and experiences, because such memories are embedded in a spatio-temporal context. To scrutinize this interpretation, it is useful to consider the operations of the brain in a wider context.

Brains are predictive devices and exploit the fact that recurrence is a fundamental property of the world around us. Experience and memory allow the recall of similar situations and the deployment of previously effective actions. In simple neuronal circuits, such as those of invertebrates, signals from the environment or the body can trigger appropriate (learned) responses within a relatively short time window (Fig. 1). With increasing organismal complexity, ever-increasing loops of neuronal networks are added to the basic circuit to improve prediction of more complex events and those with longer temporal separation between the input signals and the responses. After sufficient training, the long loops of larger brains can dispense with the reliance on external cues by internally processing the probabilities of outside events and their most likely outcomes. This disengagement is a necessary condition for cognition[6].

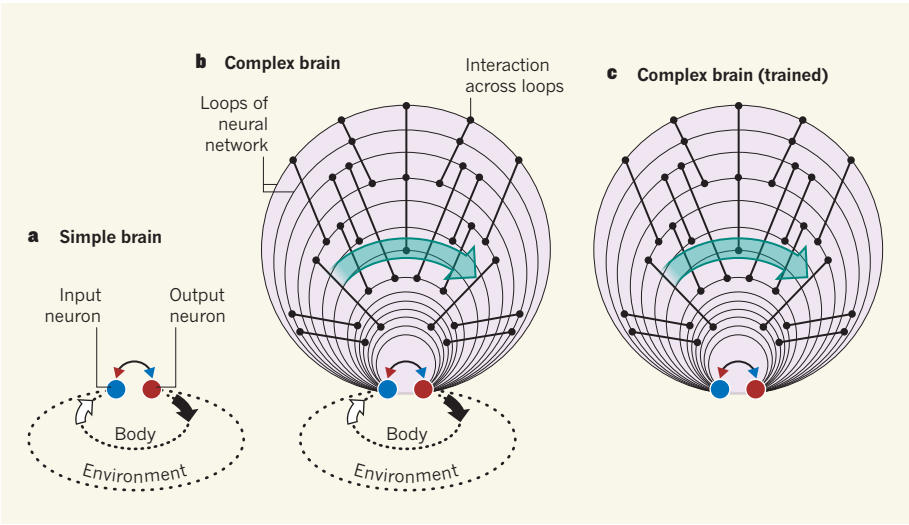

Figure 1 | Externally driven and self-organized cell assemblies track time. **a**, Evolutionarily simple brains contain simple neural networks. Sensory input from the body and the environment activates input neurons, which interact with output neurons to generate appropriate reflex actions in a short time window. **b**, In more complex brains, multiple interacting loops of increasing length improve prediction of more elaborate events that occur at longer timescales. **c**, After extensive training, the loops can sustain self-organized, long-lasting neuronal sequences without reliance on external cues and can, therefore, support cognitive operations such as memory, planning and imagination. Progression of neuronal operations correlates with elapsed time (green arrows) irrespective of whether the operations are driven externally or internally.

Returning to the findings of Kraus and colleagues, these suggest that progression of neuronal information within cell assemblies in the hippocampus during spatial navigation can be controlled by environmental or body cues (for path integration) and by a time-tracking mechanism. Alternatively, episode-specific activity sequences of cell assemblies may roll forward as a result of self-organization in the absence of changing external cues, always progressing along the path of the highest-probability events[3]. This latter perspective suggests that the qualitative distinction between the causes of sequential neuronal activity is along the dimension of external dependence versus internal self-organization, rather than being related to time or distance.

Brains, like clocks, do not produce time per se. So despite our intuition of separate time and space, it may be that the brain generates no such things. Instead, variations in the strength of synaptic communication between neurons may simply determine the direction of activity flow across neurons under all conditions. The temporal flow of activity is a framework for recalling thousands of episodic memories or planning multiple possible consequences of actions. The evolving neuronal-assembly sequences that support these cognitive operations may activate all hippocampal neurons at some point, including those that may sometimes appear in the disguise of 'time-tracking-only' cells.

Many brain regions can generate sequential activity paced for their own needs[3,7–9] — ranging from the subsecond scale in the service of perception and motor control to much longer timescales in memory, planning and imagination. These operations progress along a time line but do not need appointed time cells. Admittedly, the questions Kraus and colleagues address are among the most complex in science, and the authors should be commended for tackling a hard problem at the intersection of philosophy and neuroscience. As is always the case with good science, their findings raise as many questions as they tried to answer. I have addressed only a few, and leave the rest to the Kant scholars. ■

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GENOMICS

A spruce sequence

The first published whole-genome draft sequence of a gymnosperm, the Norway spruce, provides a powerful platform for studying the unique development, adaptation and evolution of this major group of plants. SEE ARTICLE P.579

RONALD SEDEROFF

Within the gymnosperm subgroup of seed plants are the iconic conifers, which dominate many forest ecosystems of the cold-temperate and subtropical regions of the Northern Hemisphere. Among the conifers are Earth's oldest living individual plants, the bristlecone pines; its largest trees, the giant sequoias; and its tallest, the coast redwoods. Conifers also include the pine and spruce genera that supply much of the world's wood for pulp, paper and solid-wood products. Genetic analysis is the key to understanding the biology of these trees, but gymnosperms typically have very large genomes, of up to 37 gigabases[1], and an abundance of repetitive DNA, making their sequences difficult to assemble. So the sequence of the Norway spruce genome, reported by Nystedt *et al.*[2] on page 579 of this issue, represents a major technical, as well as an information-rich, achievement*.

Gymnosperms, of which there are around 1,026 species[3], are vascular plants, meaning that they contain a tubular tissue network that transports water and nutrients, and provides mechanical support. The gymnosperms are one of two subgroups of seed-forming vascular plants, the other being the angiosperms, the flowering plants. There are some 350,000 species of angiosperm, some woody and others herbaceous, and this subgroup includes all our major food crops.

The seeds of angiosperms are enclosed in an ovary, whereas those of gymnosperms are in an open state. The two subgroups also differ in terms of their mechanisms of growth, development, metabolism, adaptation and evolution[4] — in factors including wood microanatomy, water transport, mechanical support, reproduction, development and ability to adapt to environmental change. The vascular system of conifers depends on long, thin cells with lateral pits called tracheids, a primitive system also found in early progymnosperm fossils. Angiosperms typically have more complex wood-cell anatomy, in which vessels with much larger diameters facilitate water transport and more-specialized fibre cells give mechanical support. The phenolic polymer lignin contributes to mechanical support and provides a hydrophobic surface for water transport in both angiosperms and gymnosperms, but the composition of the polymer differs markedly between the two groups of plants.

Identifying the genes that underlie these differences is of interest for both basic and applied research, but the long reproductive

*This article and the paper under discussion[2] were published online on 22 May 2013.

JOSEPH STRAUCH/GETTY

Figure 1 | Gymnosperm genes. Trees of the gymnosperm subgroup make up much of the forests of the Northern Hemisphere and provide a large fraction of the world's wood. Nystedt *et al.*[2] have presented the first draft whole-genome sequence of a gymnosperm, the Norway spruce (*Picea abies*).