NEUROSCIENCE

Decrypting a brain enigma

The combined neuronal activity of two seemingly opposite types of Purkinje cell in the brain's cerebellum has been found to be required to control the jerky eye movements known as saccades in monkeys. SEE LETTER P.439

KAMRAN KHODAKHAH

The brain has tremendous information-processing power and computational capacity. Neuroscientists have made great efforts to unravel how the brain encodes, decodes and processes information, but deconstructing these computations is a difficult task. On page 439 of this issue, Herzfeld *et al.*[1] use monkeys to masterfully unearth how one of the brain's most intriguing structures, the cerebellum, efficiently encodes — and perhaps subsequently decodes — the information needed to control the quick, jerky eye movements known as saccades, which occur as the eye explores a scene.

Deciphering how the brain computes is exceptionally difficult, because it requires a reverse-engineering approach. Without any prior knowledge of how the brain's circuits are designed, neuroscientists need to dissect these circuits to understand their function and computational principles. Consider the heroic efforts needed to reverse-engineer the Enigma machine, which was used during the Second World War to encrypt and decrypt military messages. By analogy, each of the brain's different computational units (neurons or neuronal circuits that process the information contained in their inputs to determine appropriate outputs) can be considered to be like an Enigma machine, with its own algorithm and code. Although Enigma's purpose was to encrypt and subsequently decrypt the same message, brain circuits process the information that they receive and often completely transform it to generate a new message. Furthermore, we do not fully understand the different types of information processing that occur in different brain regions.

However, this problem can be made more manageable by the thoughtful selection of specific brain regions to study. The more information there is about the inputs and outputs of a brain region, the details of its neuronal circuitry, the nature of the information it processes, and how and why it transforms the information, the better the chance of cracking its codes and understanding the purpose of its computations. Fortunately, because different brain regions often use the same or similar principles, understanding the code that underlies one brain circuit can shed light on similar computations in other regions.

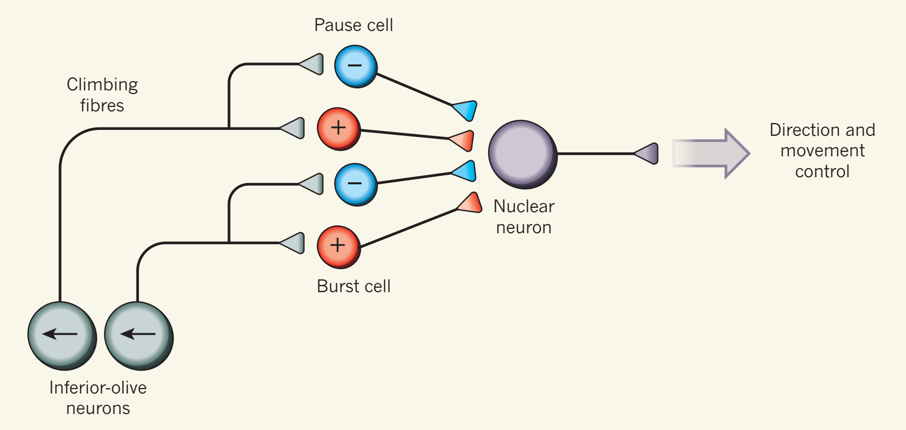


Figure 1 | Wiring up saccades. Neuronal projections called climbing fibres that originate in a brain region called the inferior olive encode the direction of saccades (quick, jerky eye movements that occur when exploring a scene; directional tuning indicated by arrows). Climbing fibres send input to Purkinje cells in the brain's cerebellum (although note that the activity of the Purkinje cells is primarily driven by projections called mossy fibres, which are not shown). The activity of one type of Purkinje cell, called burst cells, transiently increases with saccades (indicated by a + symbol), whereas the activity of another type, pause cells, ceases when saccades begin (indicated by a – symbol). Herzfeld *et al.*[1] suggest that, in monkeys, pause- and burst-cell signals are integrated by the nuclear neurons to which they signal to coordinate the movement of the eye during saccades. In addition, the authors used computer simulations to show that Purkinje cells that have climbing-fibre inputs with the same saccade directional tuning may target the same nuclear neuron. In this way, a simple neuronal circuit controls both the direction and movement of the eye during saccades. (Figure adapted from ref. 1.)

One region that has great potential for helping us to understand the brain is the cerebellum, which has a fairly simple anatomy. The cerebellum is mainly composed of repeats of the same computational circuit, at the core of which is a type of neuron called a Purkinje cell. Among other roles, the cerebellum controls and coordinates movements, and the anatomical connections involved in these functions are reasonably well delineated. These features, along with the ease with which the cerebellum's motor outputs can be quantitatively monitored, make it an ideal structure for deciphering the computational principles of some of the brain's Enigma machines (neuronal circuits).

The cerebellum is essential for the accurate control of saccades[2], the jerky eye movements that endow us with high-resolution vision by ensuring that the high-acuity region of the retina is exposed to the most important components of an image. Electrical recordings from Purkinje cells have long since revealed that the activity of some of these neurons changes with saccades[3–5]. But the individual activity of each saccade-related Purkinje cell is a poor predictor of saccade kinematics[3–6] — the moment-to-moment speed of the eye during saccades. This is in stark contrast to the cerebellar control of smooth eye pursuit, in which the activity of individual Purkinje cells reliably predicts, in real time, the movement of the eye as it follows a moving object[7,8].

The failure of individual Purkinje cells to accurately predict saccade kinematics has led to speculation that the combined population-wide activity of Purkinje cells might more effectively encode the required information[6,9]. Two types of saccade-related Purkinje cell have been identified: burst cells, whose activity transiently increases with saccades, and pause cells, whose spontaneous pre-saccade activity ceases when saccades begin. Although the activity of pause cells has been largely ignored, the population-wide activity of burst cells has been examined and found not to be predictive of saccade kinematics[6]. By analysing the activity of Purkinje cells in monkeys as the animals made saccades, Herzfeld *et al.* made a breakthrough. They found that although neither the pause cells nor the burst cells predicted saccades as an individual population, their combined activity accurately predicted saccadic eye movements.

How might the brain decode the information encoded by the activity of the Purkinje-cell population? Herzfeld and colleagues suggest a plausible mechanism based on the anatomical organization of the cerebellum. Most of the cerebellar output is from clusters of neurons compacted into structures called cerebellar nuclei. Each nuclear neuron receives converging information from about 50 Purkinje cells. This organization[9], combined with the speed at which Purkinje cells transfer information[10], might enable nuclear neurons to faithfully integrate the population-wide activity of Purkinje cells in real time while preserving its temporal profile (Fig. 1). This possible decoding mechanism warrants careful experimental and theoretical scrutiny.

How the cerebellum encodes the direction of saccades is another long-standing puzzle, and Herzfeld and colleagues again offer a solution. Each Purkinje cell receives an input from a climbing fibre — the output projection of neurons in the inferior olive, a brain region outside the cerebellum. The activity of climbing fibres is tuned to the direction of saccades[11]. The authors used computer simulations to explore the possibility that climbing fibres dictate the functional organization of the cerebellar circuitry. They postulated that Purkinje cells that receive inputs from climbing fibres with the same directional tuning converge on the same nuclear neurons (Fig. 1). Remarkably, they found that when this organization is modelled, the activity of the Purkinje-cell population encodes both the real-time motion of the eye and the direction of the saccade, through a gain field — a multiplicative encoding mechanism found in the brain's cortex. Although purely speculative, this is a graceful solution to a difficult puzzle and is well worth experimental validation.

In addition to its role in motor control, the cerebellum has also been implicated in cognitive tasks. It is likely that many of the computational principles that the cerebellum uses for motor coordination are also implemented in its cognitive functions. It is equally likely that there are more, perhaps specialized, algorithms dedicated to its non-motor tasks. Some of the brain's toughest and most elegant Enigma machines remain to be cracked, and the cerebellum might offer unique advantages for tackling them. ■

Kamran Khodakhah *is at the Dominik P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, New York, New York 10461, USA.*
e-mail: k.khodakhah@einstein.yu.edu

1. Herzfeld, D. J., Kojima, Y., Soetedjo, R. & Shadmehr, R. *Nature* **526,** 439–442 (2015).
2. Barash, S. *et al. J. Neurosci.* **19,** 10931–10939 (1999).
3. Helmchen, C. & Büttner, U. *Exp. Brain Res.* **103,** 198–208 (1995).
4. Ohtsuka, K. & Noda, H. *J. Neurophysiol.* **74,** 1828–1840 (1995).
5. Kase, M., Miller, D. C. & Noda, H. *J. Physiol. (Lond.)* **300,** 539–555 (1980).
6. Thier, P., Dicke, P. W., Haas, R. & Barash, S. *Nature* **405,** 72–76 (2000).
7. Shidara, M., Kawano, K., Gomi, H. & Kawato, M. *Nature* **365,** 50–52 (1993).
8. Medina, J. F. & Lisberger, S. G. *J. Neurosci.* **27,** 6832–6842 (2007).
9. Gad, Y. P. & Anastasio, T. J. *Neural Networks* **23,** 789–804 (2010).
10. Person, A. L. & Raman, I. M. *Nature* **481,** 502–505 (2012).
11. Soetedjo, R., Kojima, Y. & Fuchs, A. F. *J. Neurophysiol.* **100,** 1949–1966 (2008).

CLIMATE SCIENCE

The long future of Antarctic melting

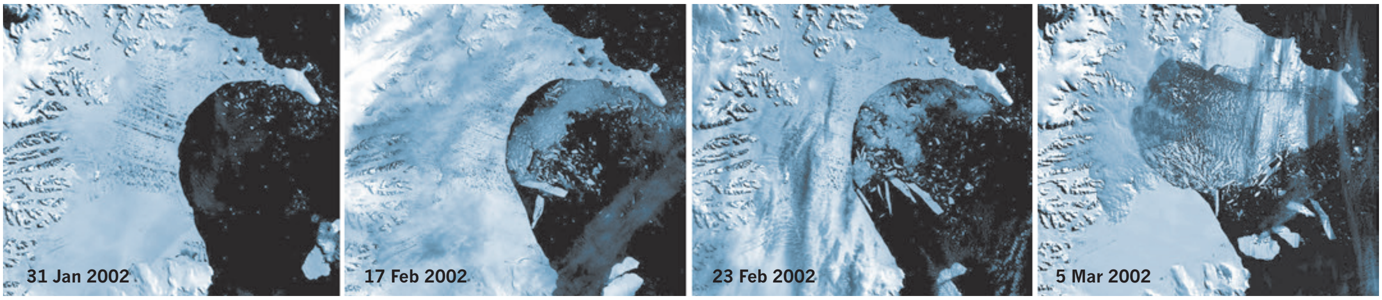
Simulations show that melting of the Antarctic ice sheet in response to climate change could raise the global sea level by up to 3 metres by the year 2300 and continue for thousands of years thereafter. SEE LETTER P.421

ALEXANDER ROBEL

Most projections of Antarctic ice melting in response to climate change extend a maximum of a few centuries into the future, a timescale that has clear relevance to immediate human affairs. But to capture the total Antarctic contribution to sea-level rise caused by climate change, it is necessary to consider the possibility that ice-sheet mass loss will continue for thousands of years. On page 421 of this issue, Golledge and colleagues[1] present multi-millennial ice-sheet simulations in which Antarctica continues to contribute significantly to global mean sea-level rise for more than 1,000 years, long after ocean and air temperatures have stopped increasing. The authors' simulations also show that ice-shelf melting driven by ocean warming over the next 100–300 years is a critical factor in determining the total future rise in global sea level.

The spectre of the imminent and rapid loss of ice from the West Antarctic Ice Sheet has been raised by dramatic events such as the collapse of the Larsen B ice shelf in 2002 (Fig. 1). Nevertheless, the contribution of the Antarctic ice sheet to global sea-level rise is currently small in comparison with that of other sources, although it is increasing at an accelerating rate[2].

The glaciologist John Mercer was the first to suggest that past recessions of the West Antarctic Ice Sheet were driven by fluctuations in climate that increased air temperatures over ice shelves to above freezing point[3]. He proposed that ice-shelf melting causes an increase in the flow of ice from land that occurs through other processes. In many coastal



TED SCAMBOS, NATIONAL SNOW AND ICE DATA CENTRE

Figure 1 | Ice-shelf collapse. These satellite images show the rapid break-up of 3,250 square kilometres of the Larsen B ice shelf in Antarctica in 2002. Golledge *et al.*[1] have simulated the retreat of the Antarctic ice sheet in response to climate change over the next few millennia.