distances from 15 to 12,700 kilometres.

These experiments will study the number of muon and electron neutrinos detected as a function of their energy and distance travelled. Each interaction that a neutrino undergoes in water or ice produces a flash of light, and the neutrino is judged to be muon-like or electron-like on the basis of the shape of the light pattern that is captured by thousands of photon detectors. The neutrino's energy can be determined by the size of this pattern and, by using the pattern to reconstruct the angle of the incoming neutrino, scientists can estimate the distance that it travelled after being generated in the atmosphere, including how much of its path went through Earth.

The behaviour of the neutrino as it travels is intimately tied to the fundamental properties of the particle. For example, muon neutrinos that are generated in the atmosphere with intermediate energy (1–10 GeV) are more likely to change into electron neutrinos after travelling through Earth if the lowest mass component of the neutrino is mostly electron-type. This mass ordering corresponds to what scientists refer to as 'normal' (as opposed to inverted) ordering, because the electron is the lightest of the three charged particles after which the neutrino types are named, followed by the muon and the tau.

Argüelles *et al*. estimated the sensitivity associated with the four experiments and ran computer simulations of the processes involved. Their study suggests that a combined analysis of atmospheric-neutrino data from all these detectors should, by 2030, give rise to statistically meaningful information about the ordering of neutrino masses. Particle-accelerator[5,8–10] and reactor-based[11] projects will also have key roles in this determination.

Incorporating the results of other experiments could offer even more insight. Telescopic observations of large-scale structure — the 'clumpiness' of galaxy networks — can provide a measure of the total sum of the neutrino masses[12], which is closely related to the ordering. This is because near-light-speed neutrinos tend to carry their mass away from objects that are coalescing under gravity. Observing less clustering than expected would therefore indicate a more massive neutrino. Some laboratory-based nuclear experiments are also sensitive to neutrino mass, including those involving the β decay of the hydrogen isotope tritium, and an ultra-rare process called double β decay, in which an unstable nucleus exchanges two neutrons for two protons.

The researchers' analysis confirms the enormous potential of atmospheric-neutrino studies. Despite the many approaches to understanding neutrinos all being complementary, the teams involved in these diverse experiments are in competition with each other to determine the mass order. And yet, in an amazing coincidence, their efforts are all expected to converge on current estimates for the range of neutrino masses in the next decade or so. Scientists might expect that the results will be compatible across these wildly different probes, pointing to a clear and consistent picture of neutrinos on Earth, in the atmosphere and in space. However, any kind of inconsistency between the measurements could be viewed as an exciting indication of both new particle physics and new cosmology.

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Neuroscience

Mysterious ultraslow brain activity observed in mice

Gilles Laurent

Neurons with a role in navigation fire sequentially in mice, forming patterns that repeat every minute or so — but which are neither spatially organized, nor related to any visible behaviour. **See p.338**

Brain oscillations result from the rhythmic and coordinated activity of groups of neurons. Most of the types that have been recognized so far (for example, alpha, theta and gamma oscillations) occur on timescales of less than 1 second; that is, at frequencies of 1 to around 100 cycles per second. On page 338, Gonzalo Cogno *et al*.[1] provide evidence for sequential and periodic events in the mouse medial entorhinal cortex (MEC) — a region of the brain involved in navigation — that extends these timescales to the minute range.

Advances in brain recording and analysis techniques have enabled scientists to study the activity of many neurons simultaneously[2,3]. When applied to organisms with small nervous systems, these methods have revealed ordered patterns of activity in populations of neurons, which relate to sensory inputs[4] or to the animal's behaviour[5] and cannot be detected from single-neuron recordings. Relatively ordered dynamics have also been shown to exist in larger brains; for example, in the mammalian motor cortex during preparation for movement[6].

These insights provide an overarching framework to understand the sometimes puzzling properties of single neurons, such as those in the neural circuits involved in navigation[7,8]. Moreover, they emphasize that the brain is a 'dynamical system' — a system with properties that result from interactions between its components over time — and that interesting things happen in it over a wide range of timescales. Periodic synchronization and sequential activation of neurons are examples of these kinds of dynamics.

In their experiments, Gonzalo Cogno *et al*. took measurements from the brains of awake mice, which were running or standing on a rotating wheel in the dark so that they were not influenced by their visual surroundings. The authors used two-photon calcium imaging, an optical technique that measures the increase in cytoplasmic calcium in electrically active neurons, to look at the activity of hundreds of MEC neurons simultaneously. After processing the resulting data, Gonzalo Cogno *et al*. were able to examine the calcium signals in each individual neuron. They found that the signals oscillated with periods (the duration of a full cycle) ranging from tens of seconds to minutes — producing a range of frequencies that the authors refer to as 'ultraslow'.

Having established that most simultaneously recorded neurons tended to undergo similar ultraslow oscillations, Gonzalo Cogno and colleagues observed that the neurons did not all oscillate at the same time. Instead, they were activated sequentially, forming a string

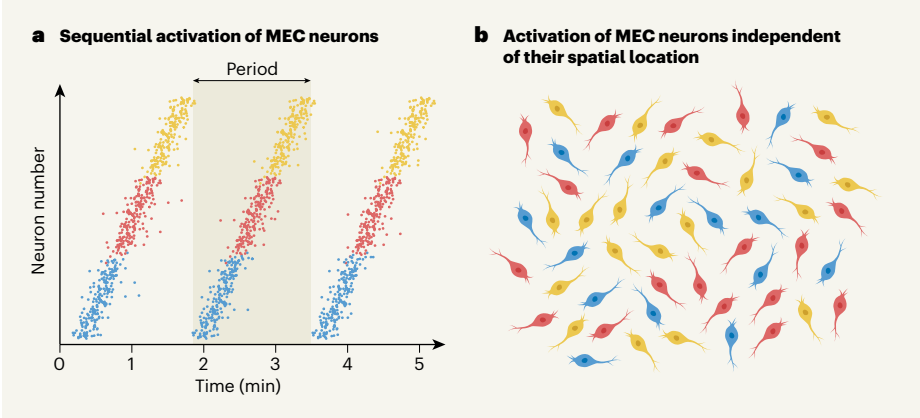

Figure 1 | Neurons involved in navigation show ultraslow sequential activation. **a**, Gonzalo Cogno *et al.*[1] report that neurons in the medial entorhinal cortex (MEC) of awake mice in the dark exhibit sequential activity, repeating spontaneously with periods (the duration of one full sequence) on a timescale of minutes. Each neuron is plotted on the *y* axis, and the dots indicate when each neuron is active. By sorting the neurons according to how synchronized they are with each other, the authors reveal that almost all of the neurons in the population are activated sequentially. The colours represent subsets of neurons that are active around the same time. **b**, Notably, this sequential activation is not the result of a travelling spatial wave of activity in the MEC. Instead, the time of activation of a neuron is independent of its spatial location in the MEC. The colours in **b** correspond to those in **a** and represent the time of activation.

of successively active neurons whose collective firing filled an entire ultraslow oscillation period (Fig. 1a). Each of these sequences repeated many times in a single recording session, typically at a similar speed and with few interruptions between sequences. Comparable results were obtained with other analytical approaches or by measuring the electrical activity of neurons directly using recording electrodes. In short, populations of (presumably) excitatory neurons in the MEC of awake mice in the dark exhibit slow sequences of activity that repeat every 40–200 seconds, and often tens of times during recording sessions of 30 or 60 minutes.

Almost all of the neurons in the MEC showed this kind of oscillatory activity. Although a sequence could start when the mouse began to move, there was no direct link between the repeating sequences and the mouse's movements, its position on the wheel or the speed at which it was moving, suggesting that these slow and repeating sequences do not correspond to any overt behaviour of the animal. The phase (or the response time relative to the period) of a given neuron in a sequence tended to remain the same throughout a recording session. In other words, if a neuron was active at the onset of one sequence, it was also active at the onset of the preceding or following sequences.

These findings did not apply everywhere. The authors also recorded the activity of cells in two other regions of the brain — the parasubiculum and the visual cortex — and found that although individual neurons in these areas sometimes showed ultraslow oscillations, only traces of the organized MEC-type sequences could be identified there. Together, these observations suggest that the dynamics of the MEC are somehow unique to this network of neurons.

The sequential recruitment of neurons is suggestive of travelling waves, in which a wave of neuronal activation propagates physically across a substrate such as a retina or a cortical area[9–11]. These travelling waves can take many forms (such as linear or spiral) and can sometimes be explained by relatively simple rules of network connectivity (for example, local feedforward excitatory connections, which push activity from neighbour to neighbour[10]) or physical principles (for example, the properties of coupled oscillators under certain conditions[10]). What is intriguing in Gonzalo Cogno and colleagues' study is that the observed sequences are apparently not the expression of travelling waves.

The authors had at first identified the coordinated sequential activity of MEC neurons using purely functional criteria (namely, a ranking of pairwise correlations) rather than by examining the physical location of the neurons in the cortex. They therefore tested whether the position of a neuron in the MEC was correlated with its phase of activation, as would be expected in a travelling wave: it was not (Fig. 1b). The sequences thus seem to be distributed in space in a manner that cannot be explained by simple neighbour-to-neighbour propagation. If the slow sequences are indeed due to cell-to-cell propagation, then one surmises that some unknown, non-topographic connectivity graph (a mathematical depiction of the network of connections between all of the neurons) links up the sequentially recruited neurons. The fact that all phases are represented in the data also indicates that if such a connection graph exists, it should operate over all distance scales.

These results raise many exciting questions. What are the mechanisms that underpin the slow distributed sequences? Can the suggested connectivity graphs be identified? Or could the sequences be inherited from other areas of the brain in which conventional travelling waves are produced, and then projected non-topographically to the MEC? Such explanations would also imply that sequences are stable over time. How stable, then, are they during long periods of time such as days or weeks?

What types of neuron are involved in these sequences? Given the high rates of participation among the neurons sampled, many physiological or functional neuronal types probably take part in ultraslow oscillatory activity. If so, is there any logic to the manner in which different types of neuron are recruited? Electrophysiological data will be needed to identify the participating neurons in freely behaving animals.

Researchers know from decades of studies that navigation circuits can generate fast brain oscillations such as theta and gamma[12,13]. Might fast oscillations be nested within the ultraslow ones? Are the phenomena reported here observed only when mice are running or standing in the dark, or do they also take place in animals performing orientation, planning or retrieval tasks, or in animals that are sleeping?

Finally, building on numerical simulations, the authors speculate that the slow sequences might serve as templates for neuronal sequences in other brain areas that receive input from the MEC. If that is correct, what do these sequences represent in the first place, and how reconfigurable would they need to be to be useful? The findings by Gonzalo Cogno *et al.* open up a vast set of avenues for future research in a fascinating region of the mammalian brain.

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