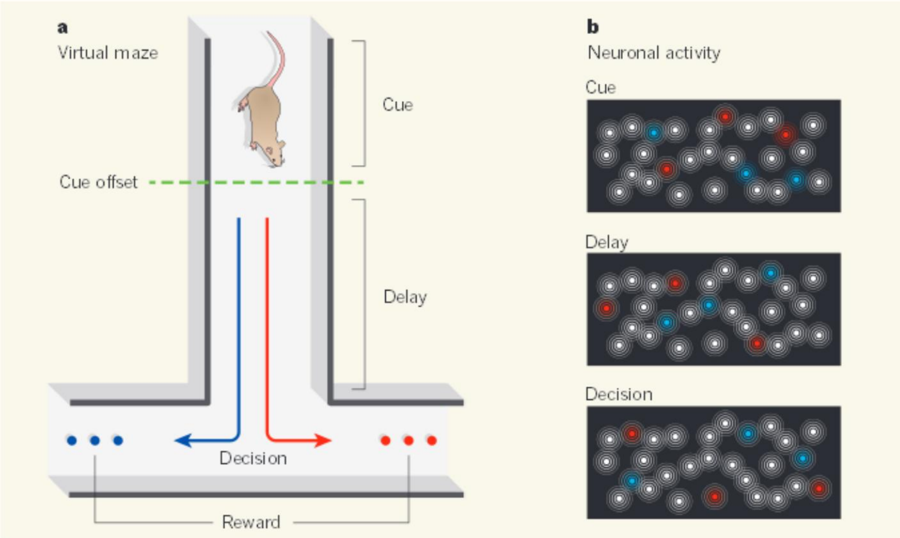

Figure 1 | Neuronal ensembles for decision-making. Memory-guided choices rely on activity in the brain's parietal cortex. **a**, Harvey *et al.*[3] set up a virtual T-maze in which mice had to choose either a left or a right turn to reach a reward, based on a previously displayed visual cue. **b**, The authors monitored neuronal activity in the mouse parietal cortex while the animals performed the task. An idealized microscopic view of the neurons is shown, in which neurons are coloured either blue or red to indicate activity when the mice took the correct turn (left or right, depending on the cue). The researchers found that the parietal cortex shows transient neuronal activity during specific periods of the task (cue, delay and decision), and that the activities of individual neurons form sequences that are choice-specific for the correctly performed trials. Although highly organized, these neuron-population dynamics emerge without apparent anatomical organization.

It has been found[7] that intermingled circuits can implement functional connectivity. In fact, Harvey *et al.*[3] provide indirect evidence that supports the emergence of functionally connected neuronal assemblies, much like those proposed by Hebb[8] in the 1940s, given that neurons that are sequentially activated during correctly performed trials have similar activity relationships during incorrectly performed trials and inter-trial intervals. This observation raises the possibility that — as has been observed in other neuronal circuits[9,10] — the sequential activation of neurons in the parietal cortex emerges from internal dynamics, probably reflecting the connectivity patterns in the circuit.

Accumulated evidence from studies in various animals — from leeches[11] to songbirds[12] and rodents[3,9] — points towards sequence-based dynamics as a common mechanism underlying action planning. The ordered progression of neuronal activity through a population of neurons suggests that indexing of information or time coordination occurs as an action is being performed. So, in real-world situations, competition between different actions might be established as competition between different paths of activity at the neural-circuit level. According to this view, particular environmental features would trigger sequences of neuronal activity that would lead to specific actions depending on the functional connectivity between sequence elements. Similarly, the presence of common elements in different sequences of neuronal activity could generate switching points ('Am I right, or am I wrong?' moments), in which the behavioural output would depend on the internal properties of the circuit and the weight of each environmental feature at that particular moment.

The parietal cortex is interconnected with other brain areas involved in, for example, sensory and motor processing, memory and decision-making. Such a strategic position, together with the neuronal-population dynamics now reported by Harvey *et al.*[3], places this brain region at the heart of the above-mentioned competition between different actions. Researchers will probably not extract a decision-making algorithm solely from decoding the parietal-cortex circuitry, but understanding the parietal orchestra will certainly shine a light on the principles of action planning. ■

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ATOMIC PHYSICS

An almost lightless laser

Lasers are often described in terms of a light field circulating in an optical resonator system. Now a laser has been demonstrated in which the field resides primarily in the atomic medium that is used to generate the light. **See Letter p.78**

VLADAN VULETIC

Atomic clocks based on optical transitions in trapped ions or atoms are the most accurate instruments ever made[1–4]. However, the best atomic clocks are limited by the frequency stability of the laser with which the optical transitions are probed. In a study that builds on previous theoretical research[5], Bohnet *et al.*[6] (page 78) describe a prototype of an unusual ultrastable laser.

Atomic transitions used for optical clocks have spectral linewidths of the order of millihertz, and standard 'free-running' lasers are not sufficiently stable in frequency to probe such ultra-narrow transitions directly. Therefore, the best atomic clocks rely on lasers whose frequency is stabilized using an external reference optical resonator — an arrangement of two highly reflective mirrors that allows light to bounce back and forth between them many times.

Currently, such reference resonators achieve a fractional frequency stability of one part in 10^{15}. This value corresponds to a change in the resonator's length (the distance between the mirrors), caused by vibrations in the mirrors, of less than the radius of a proton. Below this level, the stability of the reference resonator is limited by thermal noise in the mirrors, a fundamental process that leads to fluctuations in the resonator's effective length, and thus in the frequency of the laser. Although further progress is difficult on this front, it may be possible

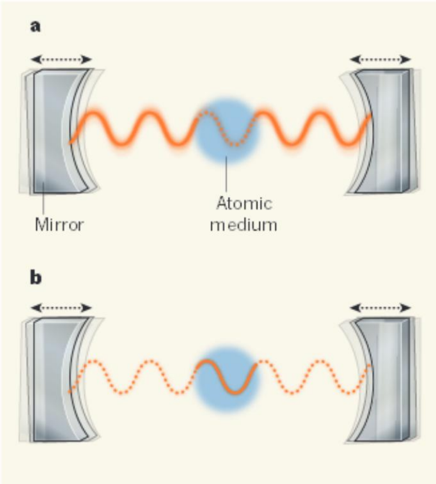

Figure 1 | Standard and superradiant lasers. **a**, In a standard laser, the amplitude and phase of the laser light are mostly stored in the light field that circulates between two reflective mirrors, rather than in the atomic medium that is used to generate the laser light. Vibrations in the mirrors, and so in the distance between them, lead to variations in the laser's frequency. **b**, In a superradiant laser such as that demonstrated by Bohnet *et al.*[6], the amplitude and phase are mostly stored in the atomic medium, and the laser frequency depends only very weakly on the distance between the mirrors.

to increase the frequency stability by operating the system at cryogenic temperatures and using mirror materials that have improved mechanical properties.

To realize an ultrastable laser that does not require an external reference resonator, theorists have proposed[5] a laser that operates in an unusual regime, in which the spectral linewidth of the atomic medium used to generate the laser light is much smaller than the linewidth of the optical resonator in which the medium is placed. In such a system, which may be termed a 'superradiant' laser after early work by the physicist Robert Dicke[7], the laser's energy is stored predominantly inside the atoms, rather than in the light field circulating inside the resonator (Fig. 1). This makes the laser frequency largely immune to changes in the resonator's length, with the extent of immunity given by the ratio of the linewidth of the atomic medium to that of the resonator.

Bohnet and colleagues[6] used an atomic medium consisting of rubidium atoms, a species that is easy to cool and trap but for which no narrow-linewidth atomic transition is readily available for lasing. To produce a superradiant laser, the authors resort to a neat trick: a narrow atomic transition can be mimicked by employing an external laser to weakly drive a transition between two long-lived atomic ground states. In this case, the emitted laser light is not absolutely stable in frequency, but only when measured relative to the frequency of the driving laser. Nevertheless, the authors were able to use their set-up to test key predictions[5] for the superradiant laser.

Although similar lasing has been observed before in a cold-atom system[8,9], Bohnet *et al.* are the first to characterize the frequency stability of the laser, and to demonstrate explicitly that the frequency of the laser depends only very weakly on the resonator's length. The authors find that the effect of changes in the resonator's length on the frequency of the laser is 10,000 times less than that observed for a standard laser.

Remarkably, the laser can be operated when the resonator contains, on average, less than one photon. Furthermore, the authors show that if the light field inside the resonator is completely turned off by switching off the driving laser, the phase of the laser light (the timing of the electromagnetic wave's peaks and troughs) can be preserved in the atoms for several milliseconds before the driving laser is turned back on. This observation demonstrates that the laser's electromagnetic waves are stored inside the atomic ensemble, as first predicted by Dicke[7].

Although further tests of the frequency stability need to be performed with a system that operates on an absolutely narrow and stable atomic-clock transition, Bohnet and colleagues' work[6] is encouraging, and paves the way towards a scheme with the potential to significantly improve the precision of atomic clocks. Ever more accurate timekeeping not only has a variety of technological applications, such as in telecommunication networks and the Global Positioning System, but will also allow unprecedented tests of some of the basic laws that govern our Universe. ■

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CANCER

Limitations of therapies exposed

Certain drugs that are used to treat cancer affect blood-vessel formation in tumours. But it seems that these antiangiogenic drugs can reduce the efficiency of other anticancer agents and increase the tumours' aggressiveness.

ORIOL CASANOVAS

Tumour growth depends on angiogenesis, the formation of new blood vessels, to ensure a continuous supply of oxygen and nutrients. That is why antiangiogenic agents are used to treat certain cancers, either alone or in combination with traditional cytotoxic drugs. However, the mechanistic details of how these combination therapies work are far from clear, and accumulating evidence is exposing their limitations. Writing in *Cancer Cell*, Van der Veldt *et al.*[1] report that angiogenesis inhibitors can decrease the delivery of cytotoxic drugs to tumours in patients, and hence hinder the drugs' therapeutic benefits. And in a paper published in *Proceedings of the National Academy of Sciences*, Conley *et al.*[2] find that tumours can adapt to antiangiogenic therapy by accumulating particularly aggressive cells.

The main target of current antiangiogenic agents is a protein called vascular endothelial growth factor (VEGF), which has a central role in angiogenesis. Although it has been known for several years that VEGF inhibitors provide additional antitumour effects when combined with cytotoxic drugs (Fig. 1a), the underlying mechanism has been a mystery since the early positive results of drug-combination trials[3]. The most widespread explanation for such a mechanism, the 'vascular normalization' theory, was proposed in 2001. According to this theory[4,5], antiangiogenic therapy induces structural and functional changes in tumour blood vessels — which have abnormal features — to make them more similar to normal vessels and, as a result, blood flow is increased and cytotoxic drugs can more easily enter the tumour.

To test the theory in a clinical setting, Van der Veldt and colleagues[1] studied the uptake and retention of a cytotoxic drug (docetaxel) in 10 patients with advanced-stage non-small-cell lung cancer (NSCLC). By using radiolabelled docetaxel together with a