

Internal brain states in motion

Ethan Scott

The brain fluctuates between different internal states, each of which drives particular behaviours. Brain-wide imaging reveals the internal states that help zebrafish larvae to choose between exploring and hunting. **See p.239**

Internal brain states modulate how we perceive, feel about and respond to the stimuli around us. The neurons and networks that encode these various states remain mysterious, owing to the brain's enormous complexity. As a result, researchers have only a vague sense of how animals, including humans, use recent experience and context to select appropriate behaviours. On page 239, Marques *et al.*¹ perform a first-of-its-kind exploration of brain-wide activity in zebrafish larvae as the animals encounter a classic state-driven behavioural choice: whether to explore their environment or to exploit resources in the local area. By monitoring individual neurons across the brain as these decisions play out, the authors open a window onto the neural underpinnings of internal states and how they can influence behaviour.

Advanced microscopy is revolutionizing the ways in which we observe the functioning brain. Historically, neural activity has been monitored either using brain-wide methods that cannot resolve individual neurons, or with electrophysiology, which records individual neurons or small localized populations. Neither approach can address activity across vast assemblies of individual neurons – which is exactly what our brains are.

Genetically encoded calcium indicators (GECIs) offer a possible solution to this problem. These proteins provide a pulse of fluorescence when a neuron is active. When expressed throughout the brain and combined with the right microscope, they produce a blinking light field that can reveal the activity of thousands of individual neurons simultaneously.

Zebrafish larvae are small and transparent, making it possible to image GECIs across their entire brains at cellular resolution^{2,3}. However, microscopy techniques have typically required that the animals are stationary, either paralysed or with their heads embedded in agarose, hampering our ability to analyse how sensory processing relates to natural behaviour.

Brain-wide GECI imaging during free-swimming behaviour became possible when the group behind the current study introduced a tracking fluorescence microscope⁴.

“The authors have delivered a satisfying scheme for how exploration and exploitation behaviours are controlled by internal brain states.”

This machine constantly monitors and predicts the movements of a free-swimming larva, and moves the imaging platform to compensate for the animal's movement, keeping the brain in the microscope's field of

view. Meanwhile, it uses brief pulses of light to record fluorescence signals from GECIs in the brain. After spatial alignment of the images across the experiment, the approach produces brain-wide, cell-level data on neural activity, complemented by behavioural information on the animal's position, speed and movements.

In the current study, Marques and colleagues used this platform to explore the neural underpinnings of two larval behaviours that involve free swimming: exploration (efficient swimming over distance) and exploitation (localized predation). Exploration and exploitation place opposing pulls on diverse animals^{5,6} – the former offers the possibility of resource discovery, but at a metabolic cost, and the latter is an effective approach for predatory feeding, but only if prey are present. These behavioural modes are influenced by external inputs and hunger level, but also alternate spontaneously, suggesting that internal brain states have a role in which behaviours are chosen.

The authors recorded videos of free-swimming larvae, and categorized each of the animals' movements to generate thorough descriptions of behaviours during exploration and exploitation phases. They showed that movements such as forward swimming and routine turns tend to occur at a similar time and indicate that the larva is in an exploratory phase. Other movements, including targeting turns and predatory strikes typical of hunting, identify exploitative phases.

Marques *et al.* next performed GECI

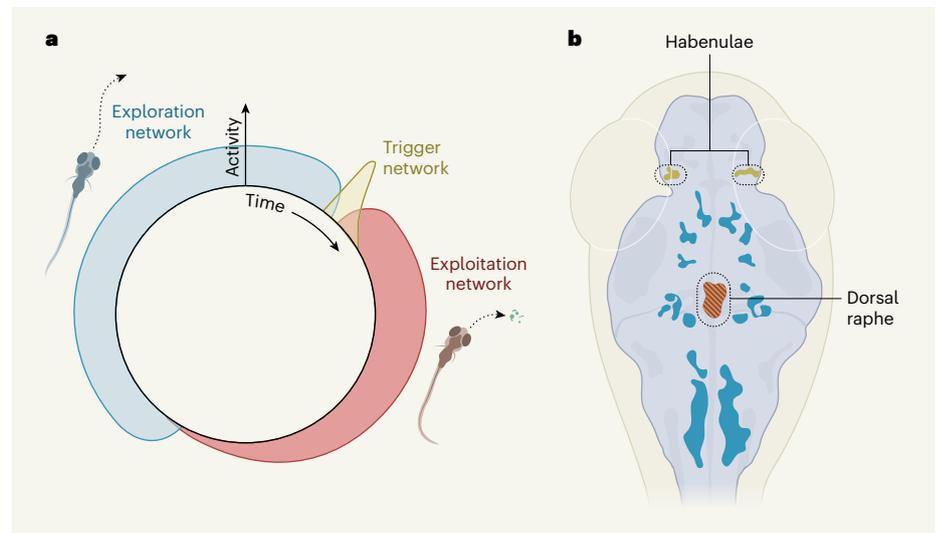


Figure 1 | Mapping exploration and exploitation. **a**, Using whole-brain imaging of neuronal activity in free-swimming zebrafish larvae, Marques *et al.*¹ have identified distinct categories of neuron that are active during phases of larval behaviour involving exploration (blue larva) and exploitation (hunting; red). As this cyclical graph shows, a network of neurons (blue) is steadily active throughout exploration. This activity is replaced by a peak in a 'trigger network' of neurons (yellow), which then drives the activity of exploitation-network neurons (red). Exploitation-network activity tails off over time, reaching a baseline as the exploration network becomes active once more and the cycle begins again. **b**, The exploration network is distributed throughout pre-motor regions of the zebrafish hindbrain. The exploitation network is found mainly in the dorsal raphe. The trigger network is also found in this region, and in the habenulae.

imaging to analyse which brain networks encode the corresponding internal states, and what changes occur during the transitions between phases of behaviour. They extracted activity data from tens of thousands of individual neurons per animal, seeking neurons with activity that correlated with specific swimming manoeuvres, with exploration or exploitation phases, or with transitions between exploration and exploitation. This analysis revealed three notable categories of neuron (Fig. 1).

First, there are neurons dispersed across the brain that are active during exploration. Because they are broadly distributed and their activity does not show obvious peaks, they are probably involved in executing exploratory manoeuvres, rather than encoding or triggering the state itself.

Second, there is a neuronal population that is present in high numbers in a structure called the dorsal raphe. These neurons are powerfully active at the beginning of an exploitation phase. Their activity gradually weakens over time, settling to a baseline during the phase transition back to exploration.

Third, there is a 'trigger network' of neurons, located in multiple localized regions across the brain. The activity of these neurons peaks sharply when the larva is transitioning from exploration to exploitation. The strength of the peak from the trigger network predicts the strength of the subsequent activation in the dorsal raphe's exploitation-network neurons. This, in turn, predicts the duration of the ensuing exploitation phase.

How does this arrangement help to deliver appropriate behaviours at appropriate times? The expectation is that exploration and exploitation phases are influenced both by hunger and by the local availability of prey. A hungry larva should stay where it is and exploit prey when they are present, and should look for prey if they are absent locally. In agreement with this theory, the authors found that exposing larvae to light after a period of dark – revealing the presence of local prey to the larvae, whose predation is largely visual – caused increased trigger-network activity, activation of exploitation neurons in the dorsal raphe, and predation. By contrast, however, they found only a weak trend towards exploitation in hungry animals presented with prey. These mixed results provide a strong incentive to study the combinations of environmental stimuli and internal cues that spur trigger-network activity, and therefore feeding.

In summary, Marques *et al.* have delivered a plausible and satisfying scheme for how exploration and exploitation behaviours are controlled by internal brain states. Rather than being a conclusion, this is a departure point for further exploration of the underlying networks. Although whole-brain GECI imaging is a powerful tool, it provides little information

on neuronal connectivity, and reveals only correlations between neurons' activity rather than the causal relationships among them.

Going forward, ablations or light-based optogenetic manipulations of targeted neurons could help to reveal exactly how activity patterns or network-level properties drive transitions between exploration and exploitation states. Furthermore, mapping out neurons' functional properties against their physical architecture (as described in a recent atlas of cell morphologies in zebrafish⁷) or connectivity (as inferred from brain-wide electron-microscopy data⁸) would provide an anatomical framework for the flow of information through the system. Such functional and anatomical information will allow researchers both to test Marques and colleagues' model of

internal states, and to identify the fine details of how exploration, exploitation and trigger networks interact to control behaviour.

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Astronomy

Not all fast radio bursts are created equal

Matthew Bailes

Astronomical signals called fast radio bursts remain enigmatic, but a key discovery has now been made. A second repeating fast radio burst has been traced to its host galaxy, and its home bears little resemblance to that of the first. **See p.190**

Millisecond-duration, extragalactic radio flashes called fast radio bursts^{1,2} (FRBs) present many puzzles that are strikingly similar to past mysteries concerning phenomena now known as quasars and γ -ray bursts. Like FRBs, these phenomena seemed to be uniformly distributed in the sky, but of almost impossible luminosity if cosmological in origin. Ultimately, it was revealed that quasars are associated with supermassive black holes, and γ -ray bursts with the formation of black holes after supernovae (stellar explosions) or with mergers of stellar remnants called neutron stars. Repeating FRBs provide the opportunity to identify the homes and possible progenitors of FRB sources. The first known repeater was localized to a star-forming region in a tiny, metal-poor galaxy³. On page 190, Marcote *et al.*⁴ pinpoint the home of a second repeater and find it to be very different.

As an FRB travels through the ionized intergalactic medium, its radio waves interact with free electrons and are slowed. High-frequency waves are less affected than low-frequency ones, so the former arrive at an FRB detector slightly sooner than the latter. This time difference is proportional to the total number of electrons between the FRB source and the detector, and can therefore be used to

estimate the enormous distance to the source. Early FRB detectors could not unambiguously identify an FRB host galaxy because their localization resolutions spanned hundreds or even thousands of potential host galaxies. But now, multi-element radio telescopes such as the Australian Square Kilometre Array Pathfinder (ASKAP) and the Deep Synoptic Array ten-antenna prototype (DSA-10) in California

“The host galaxy is about 200 times farther from Earth than is our nearest neighbour, the Andromeda galaxy.”

have high enough resolution that host galaxies can be easily identified.

At the same time, a radio telescope known as the Canadian Hydrogen Intensity Mapping Experiment⁵ (CHIME) is revealing that many FRBs repeat. The individual bursts of a repeater tend to be clustered in time, which means that the probability of catching a burst is higher when a repeater is active. Because CHIME surveys the sky daily, it is in an ideal position to trigger other telescopes to carry