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NEUROMODULATION

On the alert

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We are all familiar with the dramatic and lasting changes in brain state that occur when we transition from sleep to wakefulness. However, brain states such as alertness also vary from moment to moment through the actions of poorly defined neuromodulatory mechanisms. In their new paper, Deisseroth and colleagues describe a method (termed MultiMAP) for the brain-wide analysis of neural activity in individual, molecularly identified cells in the larval zebrafish brain during behaviour and its application to the identification of the neuromodulatory cell types that regulate alertness.

The authors used a behavioural task in which the heads of larval zebrafish were restrained and the 'escape' tail movements that occurred in response to a visual looming dot stimulus were recorded. Their reaction times provided a measure of alertness, which fluctuated throughout the recording session. A genetically encoded fluorescent calcium indicator that was expressed in all neurons reported neural activity. As zebrafish larvae are small and transparent, the authors could use a two-photon microscope to record the activity of individual neurons throughout the brain during the behaviour.

To determine the molecular identity of neurons with activity patterns that corresponded to the fluctuating alertness, the authors fixed the larvae after live imaging, used fluorophore-linked antibodies to label specific neuromodulatory cell types and then re-imaged the brain. In the MultiMAP procedure, volume registration was used to align the live and fixed images with each other and with an anatomical brain atlas, enabling the authors to assign each active neuron a location- and molecular marker-based identity. They showed that the pre-stimulus activity of six discrete populations of neuromodulatory cells was positively correlated with alertness in the behavioural task. These included noradrenergic neurons in the locus coeruleus and several populations of neurons in the tegmentum and arcuate nucleus of the hypothalamus.

Next, the authors asked whether the association of these neuromodulatory populations with alertness is conserved in other species. They used deep-brain fibre photometry in head-fixed mice to record the activity of populations of neurons expressing cell type-specific calcium indicators during an auditory reaction time task. As in zebrafish, several populations of neuromodulatory neurons exhibited activity that correlated with alertness. Indeed, there was substantial overlap between the alertness-related neuronal populations identified in the two species.

To assess the contribution of these cell populations to the regulation of alertness, the authors used an optogenetic approach in mice to boost their activity just before stimulus onset. Activation of noradrenergic neurons in the locus coeruleus, cholinergic neurons in the lateral dorsal tegmentum and cocaine- and amphetamine-related transcript peptide (CART)-expressing neurons in the Edinger–Westphal nucleus reduced reaction times, suggesting that these cells directly modulate alertness. Activation of other populations, including those in the hypothalamus, did not influence alertness, suggesting that they may instead use the alertness information for their own computations and/or 'report' the state of alertness to their respective downstream circuitry.

These findings broaden the set of neuromodulatory cell populations thought to contribute to the regulation of alertness. It will be important to understand how downstream circuits interpret the signalling of these cells to mediate state-dependent changes in neural processing and behaviour.

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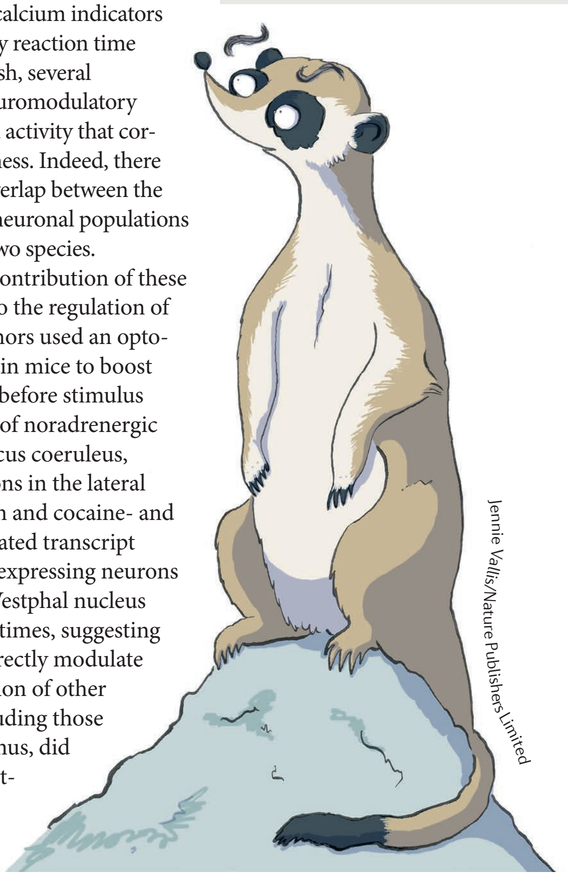

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