On the axonal road to circuit function and behaviour

Workshop on The Assembly and Function of Neuronal Circuits

Iris Salecker¹⁺, Michael Häusser² & Mario de Bono³

¹MRC National Institute for Medical Research, London, UK, ²University College London, London, UK, and ³MRC Laboratory of Molecular Biology, Cambridge, UK

The EMBO workshop on the 'The Assembly and Function of Neuronal Circuits' was held at the Centro Stefano Franscini in Monte Verità, Ascona, Switzerland, from 25 to 30 September 2005. The meeting was organized by S. Arber, T. Bonhoeffer, B. Dickson, P. Caroni, C. Krull and A. Lüthi. Left panel, conference poster; right panel, view from the conference centre towards Lago Maggiore (photo by M.H.).

Keywords: axon guidance; GABAergic neurons; innate behaviour; plasticity; neural coding

EMBO reports (2006) 7, 585–589. doi:10.1038/sj.embor.7400713

Introduction

In September 2005, about a hundred neurobiologists travelled to Ascona on the shores of Lago Maggiore in Switzerland to attend the EMBO Workshop on 'The Assembly and Function of Neuronal

Circuits'. The meeting was the first in a new series that intends to bring together both developmental and systems neuroscientists. The talks covered a wide range of areas in neurobiology in many model organisms from worms to primates. The organizers chose not to subdivide the meeting into themed sessions to foster communication between scientists working across the spectrum. This workshop thus highlighted the developmental logic of neuronal circuit assembly and linked it to the basis of information coding and behaviour.

Mechanisms regulating dendritogenesis and axon guidance

Y.N. Jan (San Francisco, CA, USA) opened the workshop with findings about dendritic arbor formation in sensory neurons of the peripheral nervous system of *Drosophila*. Hippo kinase, which is known to coordinate proliferation and apoptosis, controls branching, tiling and dendritic stability in these neurons. Hippo forms a signalling complex with the serine-threonine kinase Tricornered and the HEAT-domain-containing protein Furry to regulate dendritic branching and tiling, and interacts with the serine-threonine kinase Warts and the adaptor protein Salvador to control dendritic stability. These findings establish a compelling role for Hippo in regulating the formation of complex dendritic arbors.

Guidance molecules and their receptors signal to the actin and microtubule cytoskeleton to regulate growth cone motility. Previous studies have also shown that local protein synthesis in growth cones is required for responses that involve turning. C. Holt (Cambridge, UK) reported a new link between the regulation of the cytoskeleton and local protein synthesis to control growth cone motility. Exposure of cultured retinal ganglion cells to gradients of guidance cues alters the levels of *de novo* protein synthesis of cytoskeletal components and their regulators. For example, the repellent cue Slit promotes local protein synthesis of cofilin, which, as an actin-depolymerizing factor, contributes to the retraction of filopodia and the collapse of growth cones (Piper *et al.*, 2006).

Motor neuron identity and connectivity

The ability of animals to perform complex locomotion tasks depends on fine-tuned motor neuron circuits innervating different muscles along the anterior–posterior body axis. Several talks focused on analysing the mechanisms that control the wiring of motor neurons. M. Bate (Cambridge, UK) provided new insights into how Hox genes

¹Division of Molecular Neurobiology, National Institute for Medical Research, The Ridgeway, London NW7 1AA, UK

²Wolfson Institute for Biomedical Research and Department of Physiology, University College London, Gower Street, London WC1E 6BT, UK

³Laboratory of Molecular Biology, Division of Cell Biology, University of Cambridge, Hills Road, Cambridge CB2 2QH, UK

*Corresponding author. Tel: ++44 (0)208 816 2601; Fax: ++44 (0)208 816 2109; E-mail: isaleck@nimr.mrc.ac.uk

Submitted 22 February 2006; accepted 21 April 2006; published online 26 May 2006

in *Drosophila* shape the segment-specific diversification of locomotor circuits as the neuronal basis for peristaltic crawling. His analysis revealed that Hox genes elicit distinct cell-specific responses in the same set of motor neurons across segments. Hox genes cell-autonomously regulate the dendritic branching patterns of motor neurons in anterior segments and promote programmed cell death of the equivalent cell type in posterior segments.

T. Jessell (New York, NY, USA) reported that Hox genes form a regulatory intrinsic network in the vertebrate spinal cord to establish specific motor neuron identities and patterns of muscle innervation. Remarkably, the sequential and combinatorial expression, as well as cross-repressive interactions of Hox genes control neuronal fates not only in motor columns but also in motor pools (Dasen *et al*, 2005). *Hoxc6* and *Hoxc9* initially specify somatic and visceral motor neuron subtypes in the brachial lateral motor column (LMC) and in thoracic columns. In the LMC, *Hox5* and *Hoxc8* assign different rostro-caudal identities to motor neuron pools, whereas combinations of *Hox4*, *Hoxc6* and *Hox7* cell-autonomously define intrasegmental motor neuron subtypes. The Hox network in conjunction with specific downstream transcription factors determines the expression of guidance systems and, thus, the selection of axonal trajectories to specific muscles. In addition, extrinsic signals, such as glial-cell-line-derived neurotrophic factor (GDNF), retrogradely influence the expression of specific transcription factors and survival of some motor neurons. R. Klein (Munich, Germany) identified a new role for GDNF and Ret kinase—the regulation of motor neuron pathfinding in cooperation with ephrin A/EphA4 signalling to establish the dorsal trajectory in the limb (Kramer *et al*, 2006).

When motor neurons reach their target muscles, each muscle fibre is innervated initially by many motor neurons. During post-natal development, this pattern becomes refined through activity-dependent mechanisms so that the number of muscle fibres contacted by an axon is reduced sharply and only one motor axon retains synaptic contacts with each muscle fibre. J. Lichtman (Cambridge, MA, USA) reported that fine-tuning of synaptic connections relies on subtle local competition between axonal branches of the same neuron, leading to the progressive expansion of some synaptic contacts and the elimination of others. Ultimately, to untangle ‘the connectome’—the end product of these fine-tuning steps—Lichtman emphasized the power of sophisticated genetics to create improved live-imaging tools. This includes, for example, a set of new transgenic mouse strains called ‘rainbow’, in which Cre–Lox-mediated recombination of four fluorescent reporter genes will make it possible to visualize the maturation and interactions of individual neurons in their respective complex neuronal circuits *in vivo* (Fig 1).

Development and function of the visual pathway

Visual information is processed by many interconnected neuronal circuits, each encoding distinct aspects of a stimulus. In the vertebrate retina, the inner plexiform layer (IPL) contains the projections of local interneurons, amacrine cells and bipolar cells, which form connections with dendrites of retinal ganglion cells (RGCs) in two sublayers. Highlighting the importance of live imaging, R. Wong (St Louis, MO, USA) reported that RGCs and amacrine cells in the intact zebrafish retina target to their respective sublayers by different mechanisms. Amacrine cells direct the outgrowth of lateral branches specifically to their prospective sublayers. By contrast,

Fig 1 | Adult cerebellum from a ‘rainbow’ mouse that has been genetically modified to express several fluorescent proteins. Mossy fibre axons innervate the internal granular layer and form rosettes (presynaptic terminals) on cerebellar granule cells. The first patch-clamp recordings from mossy fibre boutons were reported at the meeting by M. Häusser. The mouse was generated by J. Livet in the laboratories of J. Lichtman and J. Sanes (Cambridge, MA, USA). The image was taken by T. Weissman.

the dendrites of RGCs initially extend processes throughout the IPL, and subsequently undergo extensive pruning and remodeling until branches become refined to the correct sublayer (Godinho *et al*, 2005).

Detecting the differential motion of objects in a visual scene is a highly complex task. Surprisingly, the processing of such information in the visual pathway begins in the neuronal circuitry of the retina. M. Meister (Cambridge, MA, USA) showed that a subtype of RGCs remain silent when the entire image moves as a result of eye movements, but fire when a part of the image moves with respect to the surroundings. These properties in the response of RGCs depend on the input of specialized poly-axonal amacrine cells. The firing of RGCs in response to an unchanging scene is suppressed by the inhibitory synapses of these amacrine cells if they are activated synchronously by the same visual stimulus. By contrast, if the activity of amacrine cells is uncorrelated with that of their postsynaptic RGCs, the responsiveness of the RGCs to new differential motion is enhanced (Ölveczky *et al*, 2003).

Activity-dependent mechanisms contribute to the refinement of retinotopic maps in the developing and mature visual pathway. Using *in vivo* time-lapse imaging in the optic tectum of tadpoles, H. Cline (Cold Spring Harbor, NY, USA) linked the formation of morphologically detectable synapses with the refinement of retinotopic maps during development. Analysing branch dynamics in parallel with synaptic strength (reflected by fluorescent-protein-tagged synaptophysin accumulation) in RGC axons revealed a strong correlation between synaptic maturation and stabilization of branches

(Ruthazer *et al*, 2006). M.M. Poo (Berkeley, CA, USA) focused on retrograde signalling as a target-dependent mechanism to refine synaptic inputs dynamically. In the intact retinotectal system, retrograde transfer of long-term potentiation from axonal terminals to the dendrite of retinal ganglion cells depends on the neurotrophin brain-derived neurotrophic factor (BDNF) and is associated with an increase in α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors at the dendrite (Du & Poo, 2004).

In the mammalian neocortex, visual experience from both eyes during the critical period is essential for the formation of ocular dominance columns in the primary visual cortex V1. However, the basic columnar architecture of this cortical area is laid down before the critical period. Using an elegant optical-fibre-based approach in combination with *in vivo* Ca^{2+} imaging, A. Konnerth (Munich, Germany) detected spontaneous large-scale Ca^{2+} waves in cortical neurons of new-born rodents (Adelsberger *et al*, 2005). Neuronal activity later switches to an anaesthesia-resistant form of Ca^{2+} waves in cortical layers 2/3, which depends on the function of *N*-methyl D-aspartate (NMDA) receptors and persists throughout life. The onset of the critical period in the visual cortex is elicited by the activity of distinct γ -aminobutyric acid (GABA)ergic connections. T. Hensch (Wako-shi, Japan) proposed an unexpected mechanism that involves trans-neuronal transfer of the paired homeodomain transcription factor Otx2 to mediate the maturation of parvalbumin-positive GABAergic neurons and the onset of the critical period.

Olfactory circuit function and behaviour

Coding of odour information in both insects and vertebrates relies on the precise wiring logic of neurons in their primary olfactory centres, the antennal lobe and the olfactory bulb: first, olfactory receptor neurons (ORNs) express mainly one subtype of odorant receptors; second, axons of ORNs expressing the same receptor type converge into common spherical synaptic modules, called glomeruli; third, in glomeruli, ORNs connect with projection neurons in insects or their equivalent cells in vertebrates called mitral cells; and finally, interneurons form inhibitory connections between glomeruli. During development, genetically hardwired guidance mechanisms lead to the formation of a discrete chemotopic map (Komiyama & Luo, 2006).

How does the mature olfactory system encode odour information using the glomerular map that is laid down during development? In both vertebrates and insects, odour molecules activate a range of odorant receptor types and thus evoke patterns of activity not just in one but also across defined sets of glomeruli. The talks of R. Friedrich (Heidelberg, Germany) and G. Laurent (Pasadena, CA, USA) pinpointed important features of neuronal computations performed in the olfactory system. Information about the identity and category of odour molecules is encoded as a spatial and temporal dynamic activity pattern. Odours induce fast oscillations of electrical activity that can be measured as local field potential (LFP). Using zebrafish as a model, Friedrich showed that the spatial distribution of active mitral cells changes during the initial phase of a response to a given odour and that the overall pattern becomes informative about odour identity. Concomitantly, subsets of mitral cells phase-lock to the LFP and convey information about odour category. Results from high-resolution activity imaging and computer modelling indicate that these computations rely on inhibitory feedback circuits formed by local interneurons. Laurent compared the firing patterns of an ensemble of about a hundred projection neurons relative to the activity of

higher-order neurons (Kenyon cells) in response to short pulses of specific odours in locusts. This showed that dynamic aspects of the firing patterns of projection neurons indeed support odour discrimination. Sets of Kenyon cells, which generally respond to odours with rare spike events, react selectively during the transient on and off phases of projection neuron activity, but not when the highest steady-state firing rate has been reached (Mazor & Laurent, 2005).

Activation of the olfactory system elicits defined changes in animal behaviour. In vertebrates, the longstanding view has been that olfactory information is processed in two separate hardwired neuronal circuits, the main olfactory system and the vomeronasal system. The former is thought to convey information about general odours, whereas the latter represents a specialized pathway dedicated to pheromone perception. C. Dulac (Cambridge, MA, USA) challenged this view with her recent findings that the main olfactory system can also process pheromone responses relevant for innate reproductive and social behaviour. A subpopulation of endocrine neurons that express luteinizing-hormone-releasing hormone (LHRH) in the hypothalamus and the basal forebrain has a central role in controlling such behavioural responses. A novel retrograde transneuronal tracing method uncovered major afferent connections from the main olfactory system to LHRH neurons instead of the predicted input from the vomeronasal pathway (Yoon *et al*, 2005). Furthermore, inactivation of the main olfactory epithelium using chemical treatment severely affected mating behaviour, showing that the connections from the main olfactory system to LHRH neurons are indeed functionally relevant.

Neuronal basis of innate behaviour

D. Anderson (Pasadena, CA, USA), C. Bargmann (New York, NY, USA) and M. de Bono (Cambridge, UK) provided examples of how the experimental tractability and relative simplicity of flies and worms offer exciting opportunities to deduce the logic underlying behavioural responses at the molecular, cellular and circuitry levels. Anderson described experiments establishing avoidance of CO_2 as a new behavioural paradigm in the fly. CO_2 is one of a bouquet of aversive stress odours released by flies (Suh *et al*, 2004). Remarkably, puffing CO_2 onto flies that pan-neuronally express the Ca^{2+} -sensitive green fluorescent protein G-CaMP reproducibly activated a single specific glomerulus. Selectively inactivating the sensory neurons innervating this glomerulus disrupted the CO_2 -avoidance response—closing the loop between stimulus, activation of a single glomerulus and behavioural response. Bargmann described how previous contact with pathogenic bacteria modified the olfactory response of *Caenorhabditis elegans*, allowing it to avoid the pathogen and to seek more palatable bacterial food (Zhang *et al*, 2005). Interestingly, avoidance was associated with increased production of serotonin in a single neuron, providing a cellular and molecular correlate of the learned behaviour. As in the fly, the ease of manipulating the worm allowed direct intervention to show a causal relationship between altered serotonin signalling in this neuron and learning. de Bono described examples of how evolution and experience can reprogramme behavioural responses. Natural variation of a broadly expressed neuropeptide receptor reconfigured several neural circuits, changing the salient environmental features to which different *C. elegans* strains respond. Such reconfiguration could underlie the rapid evolution of behaviour across closely related species.

Coding in hippocampal and cerebellar microcircuits

The hippocampus has long attracted neuroscientists interested in linking microcircuit function with the behaviours that underlie spatial learning and episodic memory formation. The mammalian cortex is characterized by the global rhythmic activity of neural networks. One rhythm, consisting of theta oscillations (4–10 Hz), is particularly prominent in the hippocampus. These have been associated with many behaviours, although their precise function is not well understood. P. Somogyi (Oxford, UK) described the functional properties of inhibitory microcircuits in the hippocampus. These comprise 18 distinct interneuron subtypes, which innervate specific domains of pyramidal cells. Using a combination of extracellular recording and labelling *in vivo*, followed by morphological and immunohistochemical identification, he showed that interneuron subtypes make differential contributions to hippocampal network oscillations (Klausberger *et al*, 2005). H. Möhler (Zurich, Switzerland) highlighted that these interneuron types are a part of distinct synaptic circuits with pyramidal cells that express specific GABA_A receptor subtypes. Selective targeting of these receptors with drugs or mutations can thus be used to determine their function. For instance, $\alpha 5$ -containing GABA_A receptors are preferentially located at extrasynaptic sites at the base of dendritic spines of pyramidal cells in the hippocampus. Interfering with their function revealed their role in modulating NMDA-receptor-mediated associative learning (Rudolph & Möhler, 2006).

In the hippocampus, CA1 pyramidal cells can behave as ‘place cells’, encoding information about the location of an animal in its surroundings. In a freely moving rat, these place cells reproducibly fire bursts of action potentials when the animal visits a particular spot—the ‘place field’—in its environment. When a rat is exposed to a new environment, the activity of place cells changes and ‘re-mapping’ occurs. Recording the spike activity of single place cells in relation to the location of animals in a square-shaped and then a circular arena, J. O’Keefe (London, UK) reported that this process is accelerated when additional parameters in the environment, such as the material of the arena, have been altered. Exposing rats to intermediate-shaped surroundings (such as an octagon series), after they had become familiar with circular and square-shaped arenas, revealed that place cells do not respond with intermediate new states of activity but instead all switch between square-shaped and circular patterns (Wills *et al*, 2005). This suggests that the activity of place cells, which take part in the representation of a given map, is coordinated—a feature that might help an animal to connect learned and new features efficiently in changing surroundings.

When a rat moves through the place field of a given place cell, it fires action potentials during several cycles of theta oscillations. Spikes occur progressively earlier relative to the theta oscillation cycle. G. Buzsáki (Rutgers, NJ, USA) provided new insights into the mechanisms underlying this phenomenon, called ‘phase precession’. When all network activity in the hippocampus was experimentally silenced for a period corresponding to two theta oscillation cycles, phase precession was nevertheless preserved, and the phase advancement observed after recovery corresponded roughly to the expected shift in two cycles. This supports a model in which neuronal activity in the hippocampus is updated continuously by extrinsic networks (Zugaro *et al*, 2005).

Finally, firing patterns in hippocampal neurons recorded during spatial navigation have been shown to be ‘replayed’ in a sequential manner during sleep—a process that might be related to memory

consolidation. M. Wilson (Cambridge, MA, USA) reported that sequential replay also occurs during awake states immediately after a rat had carried out a spatial task. The replay, however, is in reverse order when compared with the behavioural sequence. This suggests that, in the hippocampus, recently experienced events are evaluated in precise temporal relation to a current event. This is reminiscent of the mechanisms that underlie reinforcement learning models (Foster & Wilson, 2006).

Both the hippocampus and cerebellar cortex have a highly regular organization, which has been a strong lure for scientists investigating neural coding. The cerebellar cortex offers the distinct advantage that inputs and outputs are well defined. The main excitatory input is provided by the mossy fibres, which excite the small and extremely numerous granule cells. M. Häusser (London, UK) described the first patch-clamp recordings from cerebellar granule cells *in vivo*. Although ongoing firing rates are low, sensory stimulation evokes bursts of mossy fibre excitatory postsynaptic currents, which in turn trigger bursts of spikes (Chadderton *et al*, 2004). The results are consistent with a sparse coding scheme in which granule cells maximize the signal-to-noise ratio of sensory information transfer. Surprisingly, it was also possible to record from presynaptic mossy fibre boutons *in vivo*, which produced rapid spike bursts in response to sensory stimulation. This suggests that as few as one active presynaptic mossy fibre could drive the sensory-evoked burst of excitatory postsynaptic currents in granule cells.

Neural coding of complex behaviours

How does the brain carry out highly complex tasks such as learning to recognize a new object or to make decisions? C. Gilbert (New York, NY, USA) provided compelling evidence that information about learned objects is processed both in higher-order brain areas of the visual pathway and in the retinotopically organized primary visual cortex. V1 neurons are known to encode basic features such as orientation or contours of visual stimuli. Intriguingly, their functional properties can be modified by learning, context and attention. Training in shape-recognition tasks alters the activity of neurons in V1 in a way that can be related to the properties of learned objects. These properties are only seen when the animal performs the trained task and not when it views the same visual stimulus in a different context. These data imply that V1 acts as an ‘adaptive processor’ that integrates visual information both from the retina and about internal presentations of previously learned objects through reciprocal interactions with other cortical areas (Sigman *et al*, 2005).

Animals must constantly judge the cost–benefit ratio of competing options to make adaptive choices. W. Newsome (Stanford, CA, USA) tackled this decision-making process in the primate brain. He described an elegant behavioural model in which monkeys indicate their choice of one of two visual cues with directed eye movements to get rewards, such as fruit juice. The visual cue that is more rewarding varies with time so that monkeys constantly re-evaluate the best strategy to optimize success. The probability of choosing one cue over another best fits a mathematical model, in which the ‘local fractional income’—that is, the proportion of reward associated with one cue relative to the total rewards received over time—is estimated on the basis of recent experience. Can neurons be identified whose firing properties suggest they might be involved in decision-making? Remarkably, the answer is yes: firing of cells in the lateral intraparietal area co-varied with the final response of the animal (Sugrue *et al*, 2004).

Concluding remarks

This workshop left us with the optimistic view that different areas in neurobiology are converging in their mutual attempts to understand how functional neuronal circuits mediating innate and complex behaviours are formed. We are undoubtedly only beginning to understand the neuronal basis of many brain functions. However, unravelling the genetic and molecular principles that underlie the development of subsets of neuronal networks in both invertebrates and vertebrates with an eye on their function, and elucidating the functional significance of neuronal connections in adults with an eye on the developmental rules that shaped them, will clearly lead the way.

ACKNOWLEDGEMENTS

We thank the European Molecular Biology Organization and the organizers S. Arber, T. Bonhoeffer, B. Dickson, P. Caroni, C. Krull and A. Lüthi for this inspiring and timely workshop. We thank the speakers who allowed us to cover their unpublished work and for their helpful suggestions, and apologize to those whose exciting presentations could not be described in our short report.

REFERENCES

- Adelsberger H, Garaschuk O, Konnerth A (2005) Cortical calcium waves in resting newborn mice. *Nat Neurosci* **8**: 988–990
- Chadderton P, Margrie T, Häusser M (2004) Integration of quanta in cerebellar granule cells during sensory processing. *Nature* **428**: 856–860
- Dasen JS, Tice BC, Bronner-Morton S, Jessell TM (2005) A Hox regulatory network establishes motor neuron pool identity and target muscle connectivity. *Cell* **123**: 477–491
- Du JL, Poo MM (2004) Rapid BDNF-induced retrograde synaptic modification in a developing retinotectal system. *Nature* **429**: 878–883
- Foster DJ, Wilson MA (2006) Reverse replay of behavioural sequences in hippocampal place cells during the awake state. *Nature* **440**: 680–683
- Godinho L, Mumm JS, Williams PR, Schroeter EH, Koerber A, Park SW, Leach SD, Wong ROL (2005) Targeting of amacrine cell neurites to appropriate synaptic laminae in the developing zebrafish retina. *Development* **132**: 5069–5079
- Klausberger T *et al* (2005) Complementary roles of cholecystokinin- and parvalbumin-expressing GABAergic neurons in hippocampal network oscillations. *J Neurosci* **25**: 9782–9793
- Komiyama T, Luo L (2006) Development of wiring specificity in the olfactory system. *Curr Opin Neurobiol* **16**: 67–73
- Kramer ER, Knott L, Su F, Dessaud E, Krull CE, Helmbacher F, Klein R (2006) Cooperation between GDNF/Ret and ephrinA/EphA4 signals for motor-axon pathway selection in the limb. *Neuron* **50**: 35–47
- Mazor O, Laurent G (2005) Transient dynamics versus fixed points in odor representations by locust antennal lobe projection neurons. *Neuron* **48**: 661–673
- Ölveczky BP, Baccus SA, Meister M (2003) Segregation of object and background motion in the retina. *Nature* **423**: 401–408
- Piper M, Anderson R, Dwivedy A, Weinl C, van Horck F, Leung KM, Cogill E, Holt C (2006) Signaling mechanisms underlying slit2-induced collapse of *Xenopus* retinal growth cones. *Neuron* **49**: 215–228
- Rudolph U, Mohler H (2006) GABA-based therapeutic approaches: GABA(A) receptor subtype functions. *Curr Opin Pharmacol* **6**: 18–23
- Ruthazer ES, Li J, Cline HT (2006) Stabilization of axon branch dynamics by synaptic maturation. *J Neurosci* **26**: 3594–3603
- Sigman M, Pan H, Yang Y, Stern E, Silbersweig D, Gilbert CD (2005) Top-down reorganization of activity in the visual pathway after learning a shape identification task. *Neuron* **46**: 823–835
- Sugrue LP, Corrado GS, Newsome WT (2004) Matching behavior and the representation of value in the parietal cortex. *Science* **304**: 1782–1787
- Suh GS, Wong AM, Hergarden AC, Wang JW, Simon AF, Benzer S, Axel R, Anderson DJ (2004) A single population of olfactory sensory neurons mediates an innate avoidance behaviour in *Drosophila*. *Nature* **431**: 854–859
- Wills TJ, Lever C, Cacucci F, Burgess N, O'Keefe J (2005) Attractor dynamics in the hippocampal representation of the local environment. *Science* **308**: 873–876
- Yoon H, Enquist LW, Dulac C (2005) Olfactory inputs to hypothalamic neurons controlling reproduction and fertility. *Cell* **123**: 669–682
- Zhang Y, Lu H, Bargmann CI (2005) Pathogenic bacteria induce aversive olfactory learning in *Caenorhabditis elegans*. *Nature* **438**: 179–184
- Zugaro MB, Monconduit L, Buzsaki G (2005) Spike phase precession persists after transient intrahippocampal perturbation. *Nat Neurosci* **8**: 67–71