Comparative chemosensation from receptors to ecology

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Odour perception is initiated by specific interactions between odorants and a large repertoire of receptors in olfactory neurons. During the past few years, considerable progress has been made in tracing olfactory perception from the odorant receptor protein to the activity of olfactory neurons to higher processing centres and, ultimately, to behaviour. The most complete picture is emerging for the simplest olfactory system studied — that of the fruitfly *Drosophila melanogaster*. Comparison of rodent, insect and nematode olfaction reveals surprising differences and unexpected similarities among chemosensory systems.

All living organisms detect chemicals in their environments. Animal olfactory systems are impressively complex, and can detect almost all airborne molecules and distinguish between them with great precision. The odorant receptor genes that permit chemosensation were discovered in 1991 through insightful use of molecular biology[1]. Fifteen years later, the process of receptor-gene discovery continues in a new form: because the large gene families involved in odour detection are highly diverse in different animals, new receptor genes are identified daily by genome sequencing projects.

Olfaction begins with the detection of odours by G-protein-coupled receptors (GPCRs), which are encoded by up to 5–10% of an animal's genes. Biochemistry, genetics and physiology have been used to probe the functions of a few of these many receptors, giving a first view of the relationship between odours and their molecular detectors. Although odour recognition is sometimes presented as a chemical problem of the carbon-chain lengths and functional groups the odour contains, it is fundamentally a biochemical process in which a complete chemical is matched with potential receptors. Odours are beginning to be understood as ligands for these receptors, and not just as chemical structures.

The matching of odours with receptors results in activation of olfactory receptor neurons. In mammals and insects, each of these expresses only one or a few receptor genes. These neurons convey odour information to second-order neurons, in which information is integrated and refined. The mapping of odours onto the full array of receptor proteins, receptor neurons and second-order neurons is best understood in the simple olfactory system of *Drosophila*. Because olfactory research in *Drosophila* has progressed rapidly in recent years, it is a focus of this review.

Higher-order mapping in the brain couples odours to innate or learned behaviours. The olfactory system can sense an astonishing array of chemicals, but most odours are produced by living organisms, and each animal specializes in detecting biologically relevant features of its own environment. A view of olfaction that incorporates evolutionary constraints explains non-intuitive features of olfactory recognition and processing.

Chemosensory receptor proteins are diverse

Mammalian olfactory receptors are G-protein-coupled receptors

Olfaction in the mammalian olfactory epithelium is mediated by a large family of GPCRs from the rhodopsin-related receptor superfamily. These are known collectively as odorant receptors (Ors)[1] (Fig. 1a). Receptors from two additional GPCR families mediate olfaction in the specialized vomeronasal organ (see page 308); and two smaller GPCR families mediate sweet and bitter taste (see page 288). The total number of odorant receptor genes varies widely across species; mice have about 900 functional odorant receptor genes (and ~1,200 chemoreceptor genes in all), whereas humans have about 350 functional odorant receptor genes and have lost the vomeronasal receptors during evolution[2]. These differences result both from duplication of genes in the mouse lineage and from extensive loss of genes in the human lineage [3]. Odorant receptor genes also diversify quickly in comparison with other genes, so it can be challenging to recognize orthologous gene pairs even between humans and mice[2]. The odorant receptor family exists from fish through to mammals, but is not present in the simple chordate ancestor *Ciona*.

Invertebrate olfactory receptors have distinct origins

Like other gene families, odorant receptor families have expanded over time by gene duplication and divergence. In addition, however, new odorant receptor families have been recruited several times during evolution (Fig. 1b). Invertebrate olfaction is mediated by receptor families that are evolutionarily distinct from vertebrate receptors. The genome of the nematode worm *Caenorhabditis elegans* encodes more than 1,500 predicted GPCRs in nematode-specific families of the rhodopsin-related GPCR superfamily[4]. These genes subserve both taste and smell, and perhaps other functions; most are expressed in chemosensory neurons, but ~20% are expressed in other tissues[5–8]. There may be more than 1,000 functional chemosensory receptors in nematodes, a surprisingly large number for a small animal. *C. elegans* also uses non-GPCRs for chemosensation — it senses environmental oxygen levels using soluble guanylate cyclase homologues that bind directly to molecular oxygen through a haem group[9,10]. Receptor-like guanylate cyclases may also function as nematode chemoreceptors[11]. The diversity of nematode receptors highlights the opportunistic nature of chemosensation, and its ability to recruit many receptor types to a common task.

The genome of the fruitfly *Drosophila melanogaster* has only 62 odorant receptors encoded by 60 genes, and 68 gustatory receptors (GRs) encoded by another 60 genes[12,13]. The malaria-carrying mosquito *Anopheles* has a similar molecular complement of 85 odorant receptors and 76 gustatory receptors, suggesting that small numbers of receptors may be the norm in insects (see page 302). The insect receptor genes

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are molecularly unrelated to any other known gene, and seem to be of different evolutionary origin from canonical GPCRs (Fig. 1b). Indeed, it is questionable whether these molecules are GPCRs at all. Antibody-tagging experiments suggest that the membrane topology of at least two of the *Drosophila* odorant receptors is altered with respect to classical GPCRs, which have extracellular amino termini — the N termini of fly odorant receptors are cytoplasmic[14] (Fig. 1a). This experimental evidence is bolstered by computational analysis of GPCR sequences — hidden Markov models suggest that *Drosophila* odorant receptor membrane topology differs from that of known GPCRs[15]. Expression of *Drosophila* odorant receptors in heterologous cells can result in signalling pathway activation[16]; whether this is a G-protein-mediated action of the odorant receptor is an interesting question.

The small complement of *Drosophila* odorant receptors simplifies the mapping of odorant specificity by an order of magnitude compared with mice or *C. elegans*. The near-complete set of *Drosophila* odorant receptors has been analysed at the level of peripheral expression, functional response and anatomical mapping to the antennal lobe. This is unlikely to be equalled in other animals in the near future.

Odour–receptor interactions in the olfactory system

A GPCR-based view of odour-receptor recognition

A few dozen mammalian odorant receptors have known odour ligands[17–24]. With respect to ligand binding, odorant receptor properties are consistent with those of rhodopsin and related GPCRs that have been the subject of extensive biochemical and structural analysis[25,26]. Rhodopsin-like GPCRs exist in one of two main conformations: an inactive conformation, and an active conformation that interacts productively with an intracellular heterotrimeric G protein. The transition between these conformations occurs through the movement of various membrane-spanning domains. This movement is nucleated around a small molecule or peptide that interacts with several domains simultaneously[25,26]. Although a subset of membrane-spanning regions are most frequently associated with ligand binding, different agonists of the same GPCR need not bind to the same site within the receptor[27]. GPCR agonists stabilize the active form of the receptor, whereas antagonists can block agonist binding and inverse agonists stabilize the inactive conformation. Partial GPCR agonists can stabilize subconformations of the active state, allowing different ligands to have different effects. Thus the efficacy of a GPCR agonist does not depend on a single functional group or feature of the chemical, or even on its affinity for receptor binding, but rather on its ability to stabilize the active functional GPCR state and destabilize the inactive state.

The properties of odorant receptors are likely to follow the rules described above for rhodopsin and related GPCRs. For example, the functional properties of the known odorant receptor ligands are distributed throughout the entire structure of the chemical, not in individual features such as functional groups, and many regions of the receptor contribute to binding[28]. Flexible long-chain aliphatic molecules can adopt many conformations, so odorant receptors that sense aliphatic molecules can also recognize families of related molecules[19]. Rigid ring structures can mediate more selective odorant receptor activation[20]. In addition, specific antagonists can block receptor activation by odour agonists[23,24,29].

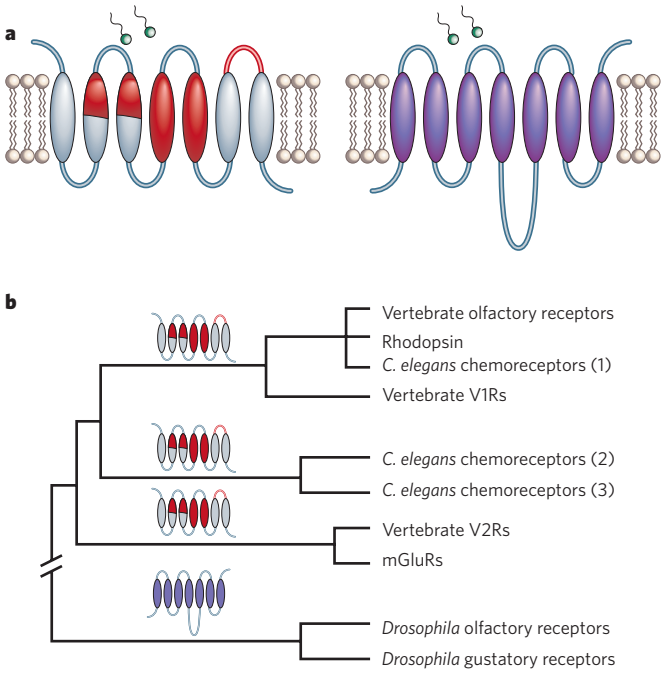

Figure 1 | Olfactory receptor diversity. a, Vertebrate olfactory receptors and *C. elegans* chemoreceptors are classical GPCRs with extracellular N termini (left), whereas *Drosophila* receptors have an inverted topology (right). Red regions denote regions of the vertebrate olfactory receptors that are highly diverse between different receptors, suggesting a role in ligand recognition. Small odour molecules reach the receptor from the extracellular environment (top). (Data from ref. 15.) **b**, Vertebrate olfactory receptors and some nematode chemoreceptors derive from the rhodopsin family of GPCRs; other nematode chemoreceptors and vertebrate vomeronasal V1R and V2R receptors derive from more distant branches of the GPCR tree. *Drosophila* gustatory and olfactory receptors are distant from GPCRs in evolutionary origin, and are possibly more closely related to 6-transmembrane-domain ion channels. mGluR, metabotropic glutamate receptor. 1, 2 and 3 represent different families of putative chemoreceptor genes.

Broadly and narrowly tuned receptors contribute to olfaction

In *Drosophila*, the properties of 31 classes of olfactory neurons have been recorded directly by electrophysiology or calcium imaging[30–34]. In addition, 35 of the 62 odorant receptor genes have been systematically expressed in a single 'host' class of olfactory neuron and characterized by extracellular recording after exposure to up to 110 odorants[35–37]. This work shows that fruitflies detect many odorants with a small number of odorant receptors and a combination of strategies. Some such receptors are highly selective: Or82a responded strongly to only one of 110 chemicals and weakly to five additional chemicals. Others were broadly activated by up to 30% of the odorants presented, including odorants with little structural similarity. Some odorant receptors were found have intermediate properties. Fruit odours activate about two-thirds of the receptors, highlighting the fly's ecological speciality. Odour-independent basal activity is prominent, and the basal activity of receptors can be inhibited by up to 30% of odorants[37]. Different odours can generate distinct temporal responses from the same receptor, perhaps by acting as partial agonists.

Thus, the first step of *Drosophila* odour perception incorporates activation and inhibition, as well as generalist, intermediate and specialist receptors. Comparisons among the broadly tuned receptors that recognize aliphatic fruit odours may be important for food identification, and more specific information may be provided by the highly tuned receptors.

Little is known about the recognition specificity of *C. elegans* chemoreceptors. Forward genetic screens for olfactory mutants identified one GPCR, ODR-10, as the receptor for the volatile odorant diacetyl[38]. *odr-10* mutants have a 100-fold reduced sensitivity to diacetyl but are sensitive to all other tested odorants[38]. As mentioned above, soluble guanylate cyclases seem to function as oxygen sensors[9,10]. These results suggest that at least some of the many *C. elegans* receptors are narrowly tuned to specific chemicals.

Expression strategies for chemosensory receptors

Like the receptor genes themselves, expression strategies for olfactory receptor genes differ among animals. The 10 million vertebrate olfactory neurons follow an apparently strict expression pattern of one odorant receptor gene being expressed per cell[39,40] (Fig. 2a). Transcriptional elements limit receptor expression to a broad zone of the olfactory epithelium but do not explain the precise single-cell pattern[41–43]. After one

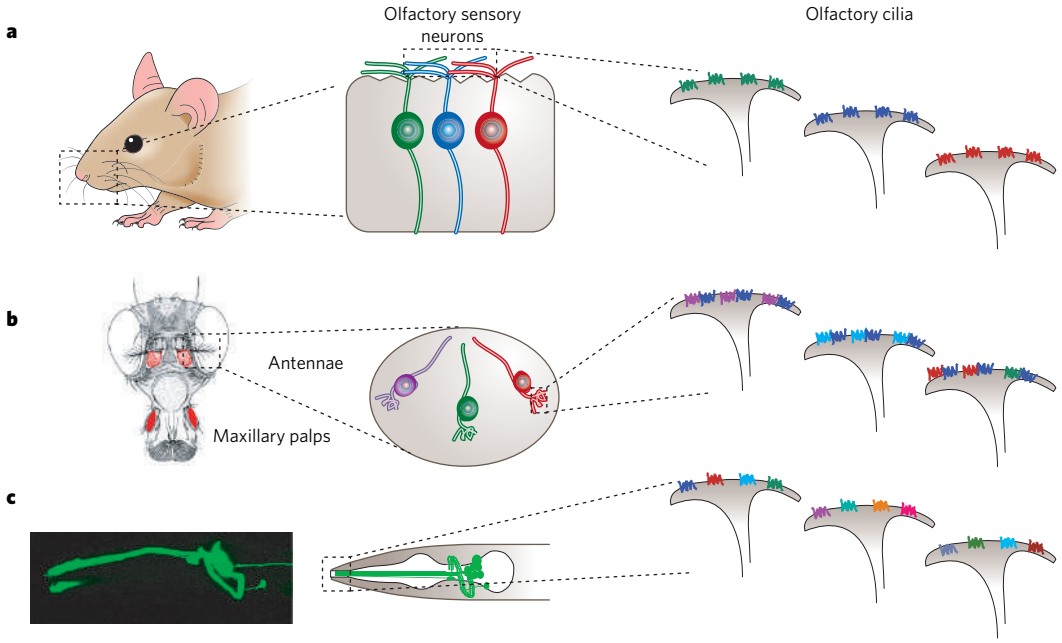

Figure 2 | Different receptor expression strategies in different animals. The locations of the main olfactory tissues in the mouse (**a**), *Drosophila* (**b**) and *C. elegans* (**c**) are shown. The odorant detection machinery is localized to the olfactory cilia, which are specializations of the olfactory neurons that come into direct contact with the environment (centre). The cilia of three representative olfactory neurons in each species are illustrated in the right-hand panel. Colours denote different odorant receptor proteins in the cilia. **a**, In mammals, olfactory neurons reside in the nasal epithelium. Each olfactory neuron expresses one type of odorant receptor, a GPCR. **b**, In *Drosophila,* olfactory neurons are localized to antennae and maxillary palps. Most olfactory neurons express one specific olfactory receptor and one ubiquitous one, Or83b (dark blue). Occasionally, neurons express two specific olfactory receptors in addition to Or83b (far right). The orientation of fly olfactory receptors is inverted with respect to classical GPCRs (Fig. 1a). (Fly head image modified, with permission, from Kyotofly Kit, Kyoto Institute of Technology, Japan.) **c**, In *C. elegans,* each olfactory neuron expresses several different GPCRs. The cell body is in the head and the cilia are at the tip of the nose. (Image courtesy of Jason Kennerdell, Rockefeller University, New York, USA.)

functional receptor is chosen, it seems to prevent expression of other receptor genes through feedback mechanisms[40,44,45].

Most of the ~2,600 *Drosophila* olfactory neurons express two receptor genes — one specific to the cell type, and a second, ubiquitous gene known as *Or83b*, whose protein product dimerizes with the specific receptor and mediates its transport to olfactory cilia[13,16,46] (Fig. 2b). This arrangement can be thought of as functionally equivalent to the one receptor gene per cell pattern of vertebrates, but *Drosophila* allows more flexibility in expression patterns. For example, six to eight classes of olfactory neuron associated with the antennae express two odorant receptor genes in addition to *Or83b*[32,47–50]. Unlike the stochastic vertebrate odorant receptor gene-expression pattern, expression in *Drosophila* is established by a deterministic developmental pathway, so that neurons in a particular sensillum always express the same receptor gene. Feedback is unlikely to have a role in *Drosophila* receptor expression, as transgenes can be used to misexpress an odorant receptor gene in a cell containing a second, endogenous one[32,49].

A radically different expression pattern is seen in *C. elegans,* which has hundreds of chemoreceptor genes but only 32 chemosensory neurons. In *C. elegans,* a single neuron expresses many different chemoreceptor genes (Fig. 2c); for example, at least nine different genes are strongly expressed in ADL neurons[5,7]. Most chemoreceptor genes are strongly expressed in a single left–right pair of chemosensory neurons, although some receptors are expressed in only one cell or in many cell types[5–8,11]. These complex gene-expression patterns are established mainly through cell-type-specific transcription factors and micro RNAs[51–53]. One case of stochastic receptor expression is known[54].

Despite the different gene-expression strategies, a common theme in all these animals is the great diversity of receptor cell types. Further diversity comes from regulated odorant receptor expression. The expression of certain chemoreceptor genes in *C. elegans* is regulated by pheromones and food, allowing the animal to adjust its chemical sensitivity to the environment[55,56]. In the malaria mosquito, the expression of certain receptor genes is downregulated after a blood meal[57], suggesting that insects, like nematodes, may use gene-expression changes at the periphery to alter behavioural sensitivity to odours. *Drosophila* larvae express odorant receptor genes that are largely non-overlapping with those expressed in adults[36,58], and fish odorant receptors are also induced at different times during development[59]. Regulated receptor expression has not yet been described in mammals.

Second-order coding of olfactory information

Convergence of sensory inputs onto glomeruli

A common feature of olfactory coding in *Drosophila* and vertebrates is the convergence of olfactory neurons expressing the same receptor to glomeruli in the second processing station, the antennal lobe or olfactory bulb (Fig. 3). In glomeruli, neurons expressing the same receptor converge on target neurons known as projection neurons in flies and as mitral or tufted cells in mice. Mapping of olfactory neurons to glomeruli is precise and invariant in flies; in mammals, the map is fairly precise but has small variations from one individual to another[13,60–62]. The development of the mouse glomerular map is controlled by the odorant receptors themselves[63]. The nematode *C. elegans* is unusual among animals in lacking a glomerular structure in its olfactory processing centres[64].

Although convergence on glomeruli is a common feature of olfaction, the mapping of odour sensation across the glomerular sheet varies in different animals. A complete map of the odorant receptor projection patterns to the antennal lobe has been generated for *Drosophila*, so the olfactory receptor inputs to each of the 43 glomeruli are known[13,47,48]. There is no clear chemotopic map of odour features or structures in the fly antennal lobe; almost any odour can be detected by neurons projecting to almost any glomerulus[37,47,48]. By contrast, in the mammalian olfactory bulb, adjacent glomeruli often recognize similar odours[65]. The most extensive studies in mammals have been performed using intrinsic signal imaging, a method for mapping an animal's response to dozens of odours across about 200 glomeruli[66]. The intrinsic signal reports presynaptic activity, and therefore the sensitivity of peripheral olfactory receptors[67]. Intrinsic signal imaging has revealed clusters of glomeruli with

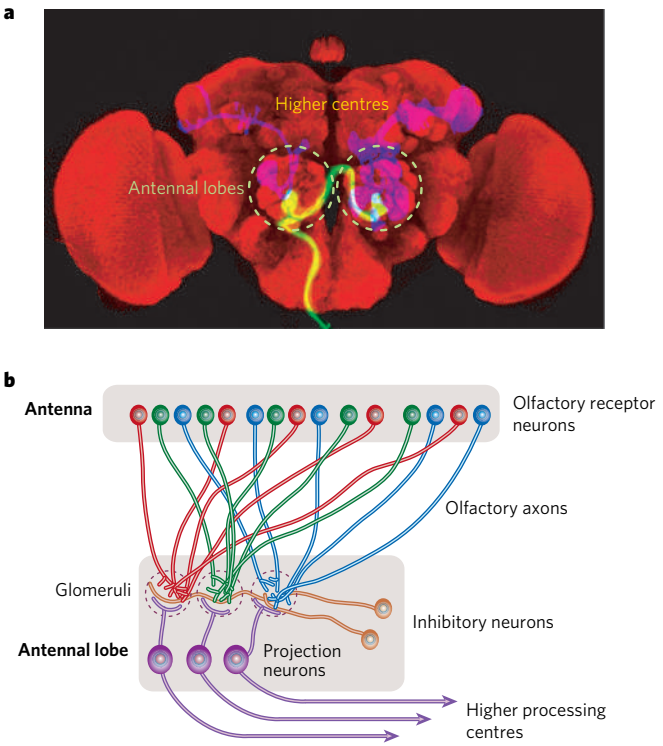

Figure 3 | Transition from the first to the second stage of olfactory processing. **a**, Superimposed images of antibody-stained *Drosophila* brains. In the *Drosophila* brain, olfactory receptor axons project from sensory organs to the antennal lobes, where they connect to projection neurons. A few olfactory receptor axons are labelled in yellow. Projection neurons (purple) in the antennal lobes (dashed green circles) project to higher brain centres, including the mushroom bodies and the lateral protocerebrum. (Image courtesy of Liqun Luo, Stanford University.) **b**, Schematic illustration of the glomerular organization of the *Drosophila* antennal lobe. The axons of neurons expressing the same type of odorant receptor converge on glomeruli in the antennal lobe. Blue, green and red are used to denote olfactory neurons expressing a common odorant receptor. Glomeruli are outlined in purple. In *Drosophila*, each excitatory projection neuron sends its dendrites to a single glomerulus, where it receives extensive input from a single class of olfactory receptor neuron, and sends an axon to higher brain centres (purple). The inhibitory (lateral) neurons (orange) in *Drosophila* project to multiple glomeruli. A similar organization of olfactory receptor axons and mitral cells (which are analogous to projection neurons) is found in the vertebrate olfactory bulb, the first processing station after the nose. Vertebrate interneurons, however, are more numerous and complex.

similar properties, and in some cases has shown a graded mapping of odour features across groups of adjacent glomeruli[65]. A different pattern seems to exist in zebrafish, in which the olfactory bulb is divided into two distinct regions, one with large, well-separated glomeruli, and one with a clustered plexus of glomeruli that sense amino-acid odorants[68,69].

The transformation between sensory and second-order neurons

In flies and mice, a single projection neuron or mitral cell receives most of its sensory input from a single glomerulus, suggesting that the projection neuron or mitral cell will be activated primarily by the odorants recognized by one type of receptor[13,47,48,60,61]. This can be tested in the fly olfactory system, because the odour specificity of the peripheral neurons is known and the odour specificity of defined projection neurons can be determined electrophysiologically. One such study has been conducted using the DM2 glomerulus, which is innervated by Or22a, one of the most broadly tuned odorant receptors. The projection neuron response in DM2 approximately matched the Or22a input for about half of the tested odorants[70]. For most odorants, the projection neuron response was amplified and accelerated compared with the peripheral response, a result expected on the basis of the ability of projection neurons to extract accurate information from correlated sensory inputs. Three odorants seemed to activate the projection neuron strongly without activating Or22a: octan-3-ol, phenyl acetaldehyde and butan-1-ol. However, in another study butan-1-ol was reported to activate Or22a — this mismatch may be the result of variations in sensitivity[37]. The responses to phenyl acetaldehyde and octan-3-ol suggest that the projection neuron can respond to odours not sensed by the odorant receptor. The only odorant receptor known to sense phenyl acetaldehyde projects to the glomerulus adjacent to DM2, providing a possible nearby source of the novel odour information.

Less complete comparisons can be made for three other glomeruli for which the peripheral odorant receptors and projection neurons have been characterized by different groups. In two cases (VA3/Or67b and VM3/Or9a), the projection neuron was well matched to the odorant receptor for all tested odorants; in the third case (DM5/Or85a), the projection neuron response was very different from the response of the input neuron[36,37,70,71]. Together, these results suggest that the projection neuron can function as a site of integration and transformation, not just as a collector of peripheral inputs.

In apparent contrast to the electrophysiology, calcium imaging studies of olfactory terminals and projection neuron dendrites seem to show a close match between the sensory input and the projection neuron output[32,72] (Fig. 4). Discrepancies between the results of calcium imaging and electrophysiological studies can probably be partly explained by the bias of calcium imaging towards strong excitatory responses, which are likely to represent the primary odour quality but would not reflect subtle shaping of the odour response. Another contributory factor might be the differences between the olfactory dendrite and its axon terminals; odorant receptor axon terminals might be modulated by other inputs in the antennal lobe, and there are notable differences between reported dendrite responses and axon terminal responses for some olfactory receptor neurons[32,37].

In the antennal lobe, olfactory information is shaped by inhibitory γ-aminobutyric acid (GABA)-mediated interneurons of the antennal lobe known as local neurons. Local neurons modulate projection neuron properties and might also affect presynaptic olfactory receptor neuron terminals. Most inhibitory local neurons in *Drosophila* project widely, but not ubiquitously, across the antennal lobe, suggesting that they have a broad modulatory role[71]. Projection neurons have a substantial basal firing rate, and therefore the potential to be regulated by inhibitory inputs. Inhibitory episodes are prominent features in the response of projection neurons to odours, and much of this inhibition is blocked by a GABA type B antagonist that disrupts slow local-neuron signalling[71]. Complex local computations in and between glomeruli are also important contributors to mammalian olfaction, and these are the subject of ongoing research.

The tentative conclusion that can be drawn from this initial analysis is that the antennal lobe uses various processing strategies. Some odorant receptors and projection neurons are broadly tuned, whereas others are narrowly tuned. Projection neurons report many sensory inputs fairly faithfully, with an enhanced signal-to-noise ratio due to convergence and inhibition, and, with the assistance of local neurons, can transform sensory information to generate new messages. A subset of odorants activate projection neurons at frequencies of more than 100 Hz within milliseconds of odour presentation; most of these odorants strongly activate the input odorant receptor. Many odorants cause more subtle shifts in projection neuron behaviour, and a large number can inhibit the projection neuron for at least part of the time after presentation or removal of an odour; these are more likely to represent effects of antennal lobe processing.

Other insects — locusts, honeybees and moths — have long been studied at the electrophysiological level but have lacked the genetic and genomic resources available for research in *Drosophila*. Nonetheless, enough information is available to suggest that certain common principles apply to the coding strategies of different insects. Sphinx moth olfactory neurons are a mixture of narrowly tuned and broadly tuned

cells, with distinct aromatic and aliphatic classes, similar to fly olfactory neurons[73]. Honeybee antennal lobes have glomeruli that respond broadly to aliphatic compounds, with little specificity for functional groups, similarly to fly glomeruli[74]. Possible differences between insects arise in the patterns of projection and local neuron projections. In moths, some projection neurons collect information from a number of glomeruli[75,76], and some local neurons project only to a few glomeruli, whereas others project broadly, like the local neurons of *Drosophila*[77]. A broader view of insect olfaction is provided in the review on page 302.

The detection of natural odours may be sparse

Pure chemicals are rare in nature. Real odours are mixtures of volatiles, and human odour perception is not always dominated by the most abundant organic molecule in a mixture. A deeper understanding of olfaction requires analysis of the complex odours found in the real world. The most extensive study of natural odours so far has been conducted in the mouse, using intrinsic signal imaging of the olfactory bulb. These experiments show that natural concentrations of complex odours, such as that of peanut butter, activate only a small number of glomeruli[66,78]. Sixty natural food odours, including those of onions, mushrooms, nutmeg and coffee, were mapped; most odours activated less than five glomeruli of the 200 that were investigated[78]. These results suggest that natural odour representations are sparse in the olfactory bulb.

To map the chemical features of complex odours, the individual volatile compounds in coffee and cloves were fractionated by gas chromatography and then tested for activity in mice using intrinsic olfactory imaging. The glomeruli activated by the complex natural odours could be predicted from their responses to about ten individual chemical fractions identified by the gas chromatograph. A mixture of the purified fractions in the correct ratio recapitulated almost all of the olfactory bulb activity observed in response to the complex odour[78]. This analysis suggests that the mouse olfactory system identifies a mixture by responding strongly and specifically to a small number of its constituent chemicals.

From flavour to behaviour

C. elegans has been particularly useful in establishing the link between odour and behaviour. A single *C. elegans* sensory neuron recognizes various chemicals, which is consistent with the expression of multiple receptor genes, but each cell seems to be specialized at the behavioural level[79]. Certain chemosensory neurons recognize attractive tastes or odours; others recognize repulsive tastes or odours; and a third group strongly affect development[79]. These rules are not absolute, but suggest that individual chemosensory cell types are wired into characteristic behavioural responses. Direct support for this hypothesis has been provided by targeted misexpression of chemosensory receptor genes in inappropriate cell types. The odour diacetyl is attractive to wild-type *C. elegans,* but transgenic misexpression of the diacetyl receptor ODR-10 in AWB neurons, which normally sense repellents, produces animals that avoid diacetyl instead of approaching it[80]. This idea was extended to the expression of a heterologous ion channel, the mammalian transient receptor potential channel TRPV1, in sensory neurons that normally mediate rapid escape behaviours in response to noxious stimuli. Expression of TRPV1 in these neurons caused *C. elegans* to avoid capsaicin, the chilli pepper irritant that causes TRPV1 channels to open[81].

The taste systems of mice and *Drosophila* recapitulate the idea that some chemoreceptor neurons are hard-wired to behavioural responses. In the mouse, bitter receptors and sweet receptors are expressed in non-overlapping epithelial taste cells of the tongue. When a RASSL, a mutated GPCR sensitive to a synthetic opiate, is expressed in the taste cells that normally express bitter receptors, mice reject water flavoured with the opiate[82]. When the same RASSL is expressed in the taste cells that normally express sweet receptors, mice preferentially drink opiate-spiked water[83]. Similarly, *Drosophila* taste cells for sweet and bitter substances can be activated by capsaicin after transgenic expression of mammalian TRPV1 (ref. 84). If expressed in the sweet-sensing neurons, TRPV1 mediates capsaicin preference; if expressed in the bitter-sensing neurons, TRPV1 mediates capsaicin rejection. These results support the existence of a hard-wired labelled line linking fundamental taste qualities to behavioural outputs.

The results of several studies suggest that at least some olfactory responses are hard-wired and innate. In the fly olfactory system, for example, certain neurons are highly selective for carbon dioxide[31,32,85]. Stressed flies release carbon dioxide, which acts as an alarm substance to other flies to elicit a strong avoidance response[85]. Carbon-dioxide-sensing neurons are excellent candidates for hard wiring into behavioural responses. The behaviour varies according to species: in mosquitoes, carbon dioxide released by mammalian hosts acts as a strong attractant; the same is true for sphinx moths, which are attracted to carbon-dioxide-producing flowers[86]. Sex-specific olfactory behaviours are also hard-wired into the fly olfactory system[75,87].

Mammals, too, have innate responses to certain odours. Predator odours elicit innate defensive freezing or flight responses in mice, even in laboratory mice that have not experienced predation in hundreds of generations[88]. Olfactory neurons that sense predator odours thus seem to be hard-wired into defensive responses. Conversely, odours from potential mates elicit innate sexual responses in mice, largely through the main olfactory system[89]. These olfactory neurons also seem to be hard-wired into behavioural circuits.

Are all olfactory preferences hard-wired? This is unlikely, as even flies and nematodes exhibit olfactory learning[90,91]. Like the receptors themselves, the behavioural responses to odours are likely to involve many strategies, with hard-wired sexual responses at one end and flexible learned responses at the other extreme.

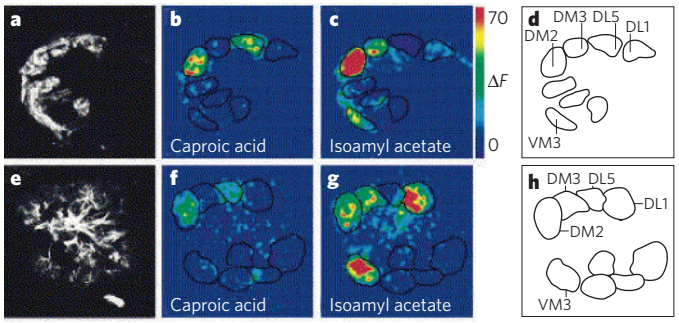

Figure 4 | Odorant sensitivity of olfactory sensory neurons and projection neurons. In antennal lobes, the axons of olfactory sensory neurons and the dendrites of projection neurons can be visualized. **a**–**d**, Expression of a genetically encoded calcium indicator in a subset of olfactory sensory neurons. **e**–**h**, Expression of a genetically encoded calcium indicator in a subset of projection neurons. There is considerable overlap in the glomeruli visualized in the upper and lower panels. Odours activate similar sets of sensory neurons and projection neurons. **a** and **e** show the expression patterns of the indicators; **b**, **c**, **f** and **g** show calcium responses after exposure to odours (caproic acid and isoamyl acetate); **d** and **h** provide a glomerular map of the relevant part of the antennal lobe. (Image modified, with permission, from ref. 32.)

An evolutionary view of olfaction

A behavioural and ecological view of the olfactory system provides explanations for features that at first seem puzzling. For example, chemosensation is a primitive sense recognizable in unicellular organisms, yet the olfactory system relies on completely independent families of receptor genes in nematodes, insects and vertebrates. This seems a surprising violation of evolutionary conservation, but a rapidly changing olfactory system can be understood as an adaptation to the requirements of a dynamic odour landscape.

About 400 million years ago, nematodes, insects and vertebrates came on land independently and encountered new volatile odours. Departure from the aquatic environment correlates with a massive expansion of odorant receptor genes in vertebrate olfactory systems[92] — genes almost certainly selected to detect airborne odours. Terrestrial vertebrate odorant receptor genes expanded preferentially from a subset of the fish

odorant receptor repertoire[93], and the water-to-air transition can still be detected in the sensory anatomy of amphibians. The 'water nose' that frogs use when swimming preferentially expresses genes similar to those found in fish, whereas the 'air nose' used on land preferentially expresses genes similar to those seen in other terrestrial animals[94].

At a more specific level, the odours of interest differ among species. Dipteran insects are descended from a common ancestor that lived less than 200 million years ago; each insect species has since evolved its own olfactory preferences and receptor genes. As a result, dipteran fruitflies, mosquitoes, and flesh flies can seek food by tracking volatile metabolites of live plants, live animals or bacterial decomposition, respectively.

Moreover, odours themselves change during evolution. Angiosperms (flowering plants) are the natural source of fruit and flower odours. Angiosperms and insects form the two largest groups of multicellular organisms on Earth. Their diversification about 100 million years ago is thought to have been triggered, on the one hand, by insect pollination, and, on the other, by an arms race between herbivorous insects and the plants they consumed[95,96]. Thus the many odours produced by fruits and flowers are evolutionarily recent — perhaps 100 million years old. New receptors were needed in insects, vertebrates and nematodes to identify and distinguish these new and informative odours.

The visual system and auditory system are stable because light and sound are immutable physical entities. By contrast, the olfactory system, like the immune system, tracks a moving world of cues generated by other organisms, and must constantly generate, test and discard receptor genes and coding strategies over evolutionary time.

Conclusions and prospects

Much remains to be understood about the nature of odour perception. At the peripheral level, the odour specificity of most mammalian receptors is still unknown. A major opportunity to link biochemistry to perception is provided by human olfaction, in which the manageable number of receptor genes could perhaps be matched to odours. An advantage of working with humans is that they can directly communicate their perception of odour intensity and quality. It is possible that the genetic variation that exists between receptors in different people might someday be matched to individual differences in olfactory perception and preference.

In terms of the molecular biology of mammalian olfaction, each neuron's stochastic choice of a single odorant receptor gene from a large repertoire remains an unsolved mystery. Recent results suggest an unconventional cross-chromosome communication[97]; more will surely be discovered.

The greatest challenge facing the field at present is that of the higher brain levels, where neuronal activity must be assembled into a perception of odour quality. How the combinatorial encoding of odour quality occurs is an important and so far elusive question, and the subject of much ongoing research. Studies of olfaction in *Drosophila* larvae show that the activation of pairs of olfactory neurons triggers behavioural responses that cannot be predicted from the behavioural response observed upon activation of either single neuron[58]. Both flies and mammals reorganize olfactory information considerably at levels above the olfactory bulb or antennal lobe, providing potential anatomical substrates for integration[98–100].

Finally, a richer view of olfaction will arise — and perhaps better questions will be asked — as the links between odour, behaviour and ecology are considered and explored. ■

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