Drosophila as a Focus in Olfactory Research: Mapping of Olfactory Sensilla by Fine Structure, Odor Specificity, Odorant Receptor Expression, and Central Connectivity

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ABSTRACT  This review intends to integrate recent data from the Drosophila olfactory system into an up-to-date account of the neuronal basis of olfaction. It focuses on (1) an electron microscopic study that mapped a large proportion of fruitfly olfactory sensilla, (2) large-scale electrophysiological recordings that allowed the classification of the odor response spectra of a complete set of sensilla, (3) the identification and expression patterns of candidate odorant receptors in the olfactory tissues, (4) central projections of neurons expressing a given odorant receptor, (5) an improved glomerular map of the olfactory center, and (6) attempts to exploit the larval olfactory system as a model of reduced cellular complexity. These studies find surprising parallels between the olfactory systems of flies and mammals, and thus underline the usefulness of the fruitfly as an olfactory model system. Both in Drosophila and in mammals, odorant receptor neurons appear to express only one type of receptor. Neurons expressing a given receptor are scattered in the olfactory tissues but their afferents converge onto a few target glomeruli only. This suggests that in both phyla, the periphery is represented in the brain as a chemotopic map. The major difference between mammals and fruitflies refers to the numbers of receptors, neurons, and glomeruli, which are largely reduced in the latter, and particularly in larvae. Yet, if activated in a combinatorial fashion, even this small set of elements could allow discrimination between a vast array of odorants. Microsc. Res. Tech. 55:284–296, 2001. © 2001 Wiley-Liss, Inc.

INTRODUCTION  Understanding how animals distinguish among thousands of odorants and myriads of odor combinations has remained a puzzle for long time. Yet, the detection of a family of odorant receptors (ORs) in rodents by Buck and Axel (1991) has provoked a genuine revolution in this field of neuroscience. It has allowed the formulation of theories of olfactory coding based on the connectivity of odorant receptor neurons (ORNs) (Buck, 1996; Ressler et al., 1994). Briefly, mammalian ORNs appear to express a single OR type each. Given that every OR is able to bind multiple volatile molecules and that a given molecule can bind to multiple ORs, specific odorants should activate specific combinations of ORNs (Malnic et al., 1999; Rubin and Katz, 1999). Neurons expressing the same OR are scattered in the olfactory epithelium, but their axons converge onto one or a few glomeruli in the olfactory bulb. This suggests that odorants may be encoded by distinct combinatorial patterns of activated glomeruli.

Despite the merits of studying the rodent olfactory system, with an estimated $10^7$ types of ORs and $10^6$ – $10^7$ ORNs projecting to $10^5$ glomeruli, its analysis is clearly limited in terms of cellular identification, and combinatorial glomerular codes are hard to decipher. The olfactory system of the fruitfly, Drosophila melanogaster, represents a valuable alternative, since there is emerging evidence of common principles between insect and vertebrate olfaction (Hildebrand and Shepherd, 1997). The fruitfly olfactory system seems to be organized much like the mammalian system, though with greatly reduced cell numbers. A total of only 1,200 ORNs on the antenna and another 120 ORNs on the maxillary palp send their axons to fewer than 50 target glomeruli in the antennal lobe (AL), all of which can be individually identified (Laissue et al., 1999; Stocker, 1994). Apart from that, the fruitfly holds a 90-year record as a model system in classical and molecular genetics. A remarkable recent step was the establishment of methods for the expression of transgenes in selected cell types, by creating cell-specifically expressing P-element insertion lines (Brand and Perrimon, 1993). This technology allows in vivo dissection of the nervous system at the cellular level, both for functional and developmental approaches (see reviews by Brand and Dormand, 1995; Phelps and Brand, 1998; Sentry et al., 1993). The purpose of the present review is to report about a series of recent studies on the fruitfly olfactory system that have exploited the potential offered by this species.

On the structural level, a systematic electron microscopic study of olfactory sense organs has identified and mapped the sensory substrate of smell detection...
Large-scale electrophysiological recordings then allowed for the classification of the odor response spectra of an entire set of olfactory sensilla (de Bruyne et al., 1999, 2001). A remarkable breakthrough was the identification and mapping of candidate ORs on the Drosophila antenna and maxillary palp (Clyne et al., 1999b; Gao and Chess, 1999; Scott et al., 2001; Vosshall et al., 1999). At the central level, a three-dimensional glomerular map of the AL was recently established (Laissue et al., 1999). It facilitated tracing of the central projections of ORNs expressing a given OR (Gao et al., 2000; Scott et al., 2001; Vosshall et al., 2000) and proved useful in dissecting the output of the AL toward higher brain centers, by focussing on the glomerular arborizations of individual output neurons (Jefferis et al., 2001). Last but not least, the importance of Drosophila as an olfactory model derives also from the even further reduced cellular complexity of its larval olfactory system, containing no more than 21 pairs of ORNs (see Heinbeck et al., 1999). Another well-known invertebrate olfactory model, the nematode Caenorhabditis elegans, is attractive for its extremely reduced number of $2 \times 16$ chemosensory neurons. However, each of its ORNs expresses multiple ORs (Troemel et al., 1995), and glomerular-like target structures are lacking, suggesting that odor processing might follow a different logic than in mammals or fruitflies.

This review intends to integrate these novel findings in Drosophila and to present an up-to-date picture of the neuronal basis of fruitfly olfaction. For a more detailed account on olfactory system structure, see Stocker (1994). Genetic, biochemical, and pharmacological aspects of olfaction in Drosophila have been reviewed recently by Carlson (1996), Lessing and Carlson (1999), Smith (1996), Stocker and Rodrigues (1999), and Vosshall (2000).

ADULT OLFAC'TORY SYSTEM

Types, Fine Structure, and Innervation of Olfactory Sensilla

The olfactory sensilla of adult Drosophila melanogaster are situated at two locations: on the third antennal segment, termed funiculus (Fig. 1), and on the maxillary palp, a club-shaped appendage at the base of the proboscis. The surface of the funiculus bears three major types of sensilla: the conspicuous, sharp-tipped trichoid sensilla, the translucent, club-shaped basiconic sensilla, and the tiny, coeloconic sensilla with prominent sockets (Fig. 1) (Link, 1983; Mindek, 1968; Riesgo-Escovar et al., 1997b; Venkatesh and Singh, 1984). Electrophysiological recordings have assigned an olfactory function to all of them (Clyne et al., 1997; de Bruyne et al., 2001; Siddiqi, 1983, 1991; see below). A three-chambered pit on the posterior side of the funiculus, the sacculus (Fig. 1), comprises a modified kind of coeloconic sensilla and two additional types of sensilla (Itoh et al., 1991; Shanbhag et al., 1995). The latter ones are the only funicular sensilla that, according to their fine structure, are not olfactory, but probably have a thermo-/hygrosensitive function. The sacculus may mediate a mixed olfactory and thermoreceptive function. In fact, olfactory responses have been recorded from the sacculus (Siddiqi, 1983). The feather-like appendix of the funiculus, the arista (Fig. 1), contains three sensilla. They are composed of two neurons each, one of which may be a small basiconic sensilla (Link, 1983; Mindek, 1968; Riesgo-Escovar et al., 1997b; Venkatesh and Singh, 1984). Electrophysiological recordings have assigned an olfactory function to all of them (Clyne et al., 1997; de Bruyne et al., 2001; Siddiqi, 1983, 1991; see below).

Fig. 1. Third antennal segment (funiculus) of a male Drosophila melanogaster; posterior aspect of left antenna. The three principal types of olfactory sensilla are sharp-tipped trichoid sensilla (asterisks), translucent, club-shaped basiconic sensilla (arrowheads), and tiny, conical coeloconic sensilla with prominent sockets (arrows). Each type falls into different morphological subtypes (see Table 1). Sensilla are interspersed with numerous non-innervated spinules (trichomes). Sensillar types and subtypes are distributed on the funiculus in a peculiar, non-homogeneous pattern (see Fig. 3). Ar, basis of the arista; S, sacculus. Bar $= 20 \mu m$. 

## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AL</td>
<td>antennal lobe</td>
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<tr>
<td>EAG</td>
<td>electroantennogram</td>
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<tr>
<td>EPG</td>
<td>electropalpogram</td>
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<tr>
<td>LB</td>
<td>large basiconic sensilla</td>
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<tr>
<td>OR</td>
<td>odorant receptor</td>
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<td>ORN</td>
<td>odorant receptor neuron</td>
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<td>PB</td>
<td>maxillary palp basiconic sensilla</td>
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<td>PN</td>
<td>projection neuron</td>
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<td>SB</td>
<td>small basiconic sensilla</td>
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<tr>
<td>SOG</td>
<td>suboesophageal ganglion</td>
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<td>TB</td>
<td>thin basiconic sensilla</td>
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TABLE 1. Types, numbers, and innervation of sensilla on the antenna and maxillary palp of D. melanogaster

| Sensillum type (no. of neurons) | Function | Males | | | Females | | |
|-------------------------------|----------|-------|---|---|-------|---|
| **Antenna**                   |          |        |       |     |         |         |        |       |       |         |         | sensilla/neurons |
|                               |          |        |       |     |         |         |        |       |       |         |         |                |
| Trichoid (Funiculus)          |          | 147 (4)| 152 (4)| 166 (7)| 310      | 0       | 111 (4)| 121 (4)| 144 (9)| 262      | 0       | m > f       |
|                               | T1 [1]   | Olfactory | 53     | 78     | 0        | 60      | 77     | 0        | 0       | No        |
|                               | T2 [2]   | Olfactory | 22     | 62     | 0        | 14      | 36     | 0        | 0       | m > f     |
|                               | T3 [3]   | Olfactory | 40     | 170    | 0        | 39      | 149    | 0        | 0       | m > f     |
| Basiconic                     |          | 191 (4)| 217 (4)| 240 (2)| 606      | 0       | 236 (4)| 244 (4)| 280 (1)| 714      | 0       | f > m     |
|                               | LB-I [2] | Olfactory | 19     | 45     | 0        | 33      | 77     | 0        | 0       | f > m     |
|                               | LB-II2 [2]| Olfactory | 24     | 56     | 0        | 23      | 54     | 0        | 0       | No        |
|                               | LB-II4 [2]| Olfactory | 47     | 221    | 0        | 48      | 224    | 0        | 0       | No        |
|                               | SB [2]   | Olfactory | 49     | 113    | 0        | 71      | 166    | 0        | 0       | f > m     |
|                               | TB-2 [2] | Olfactory | 47     | 111    | 0        | 47      | 117    | 0        | 0       | No        |
|                               | TB-4 [4] | Olfactory | 2      | 9      | 0        | 2       | 9      | 0        | 0       | No        |
|                               | TB* [2 or 4]| Olfactory | 5      | 18     | 0        | 5       | 17     | 0        | 0       | No        |
|                               | J-2 [2]  | Olfactory | 8      | 19     | 0        | 14      | 33     | 0        | 0       | f > m     |
|                               | J-3 [3]  | Olfactory | 4      | 14     | 0        | 7       | 24     | 0        | 0       | f > m     |
| Coeloconic                    |          | 63 (6) | 69 (2)| 86 (1)| 206      | 0       | 68 (4)| 65 (4)| 83 (1)| 201      | 0       | No        |
|                               | C2 [2]   | Olfactory | 24     | 67     | 0        | 32      | 99     | 0        | 0       | m > f     |
|                               | C3 [3]   | Olfactory | 33     | 139    | 0        | 22      | 102    | 0        | 0       | m > f     |
| Saccus                        |          | 48 (4) | 45 (4)| 35     | 23       | 56      | 45 (4)| 51 (4)| 35     | 23       | 56      | No        |
|                               | No-pore s. I [2]| Thermo/hygro | 6     | 0      | 15      | 6       | 0      | 15      | No     |
|                               | No-pore s. II [3]| Thermo/hygro | 6   | 0      | 18      | 6       | 0      | 18      | No     |
|                               | Coeloconic I [2]| Olfact./ thermo | 12   | 12     | 12      | 12      | 12     | 12      | No     |
|                               | Aristae [2]| Thermo/hygro | 3     | 3      | 3       | 0       | 6      | 3       | 3       | 0       | 6      | No        |
| **Max. Palp**                 |          | 452 (4)| 479 (4)| 524    | 1,145    | 62      | 463 (4)| 484 (4)| 545    | 1,290    | 62      | ~ f > m?  |
| Basiconic                     |          | 57 (10)| 114    | 0      | 64 (10) | 128     | 0      | 64 (10) | 128     | 0       | f > m    |
|                               | PB-I [2] | Olfactory | 20     | 20     | 0        | 20      | 20     | 0        | 20      | No       |
|                               | PB-II [2]| Olfactory | 20     | 20     | 0        | 20      | 20     | 0        | 20      | No       |
|                               | PB-III [2]| Olfactory | 10     | 20     | 0        | 10      | 20     | 0        | 20      | No       |
|                               | Bristles [1]| Mechanosens. | 20     | 20     | 0        | 20      | 20     | 0        | 20      | No       |
| **Total**                     |          | 77 (10)| 114    | 20     | 84 (10) | 128     | 20     | 84 (10) | 128     | 20      | ~ f > m? |

1 Data in the wild-type strains Oregon and Sevelen are from Stocker and Gendre (1988), those on antennal and saccular sensilla in the Canton-S strain from Shanbhag et al. (1995, 1999), on the aristal sensillum from Foelix et al. (1989) and R. Stocker (unpublished), and on maxillary sensilla from Singh and Nayak (1985). Numbers of analyzed light microscopic preparations are indicated in brackets. The ratios of the different subtypes of sensilla (in italics) from the transmission EM map of Shanbhag et al. (1999). They are overestimates (see Fig. 2), but were used here as proportions for extrapolation of the total neuron numbers in the Canton-S strain. These calculations are in general agreement with axon counts made in the same study in EM sections through the funicular nerves (male: 1,306; female: 1,200). Numbers of certain types/subtypes of sensilla and their neurons are sexually dimorphic (last column: f, female; m, male). The overall dimorphism observed in trichoid and basiconic antennal sensilla is due to specific subtypes only. In coeloconic sensilla, the sexually dimorphic numbers of subtypes C2 and C3 compensate each other. Also, the elevated number of antennal basiconic neurons in females is largely (though not completely) compensated by higher numbers of trichoid neurons in males.

bhag et al., 1999; Singh and Nayak, 1985). Whether the three sets of olfactory sensilla—on the surface of the funiculus, on the maxillary palps, and in the sacculum—fulfill different functions is not known. Yet, the hidden location of the pit sensilla suggests that they may perceive longer-term changes in the chemical environment, in contrast to surface sensilla that may respond to short-term fluctuations.

In a series of fine structural studies, the anatomy and innervation of antennal and palpal sensilla were recently re-examined, and a new, more detailed classification was proposed (Table 1) (Shanbhag et al., 1995, 1999, 2000). Trichoid, basiconic and coeloconic sensilla all have wall pores, allowing access of volatiles (Fig. 2). However, the first two possess a single wall with a smooth surface, whereas the latter are double-walled and exhibit longitudinal cuticular fingers on the outside. Trichoid sensilla of the subtypes T-1, T-2, and T-3 are innervated by 1, 2, or 3 ORNs, respectively, whose dendrites extend unbranched into the sensillum lumen. Anatomically, trichoid sensilla are a homogeneous group. In contrast, six morphological subtypes have been proposed for basiconic sensilla (LB-I, LB-II2, LB-II4, SB, TB, TB*: Table 1), depending on shaft size and diameter, wall thickness, pore structure, and dendritic branching pattern. Yet, frequently observed intermediate characters suggest that the subtypes may represent steps in a morphological continuum rather than clearly separated classes. Irrespective of the subtype, basiconic sensilla have 2 or 4 ORNs. Within the sensillum shaft, their dendrites split into few (5) to many (150) parallel terminal branches. A few intermediate sensilla with 2 or 3 neurons combine the wall structure of trichoid sensilla with the dendritic branching pattern of basiconic sensilla. Coeloconic sensilla are structurally homogeneous except that they may be innervated by 2 or 3 neurons (subtypes C-2 and C-3). Their dendritic segments extend unbranched into the sensillum lumen. Monoclonal antibodies have been isolated that recognize proteins related to basiconic and/or coeloconic sensilla (Störtkuhl et al., 1994).

Basiconic sensilla on the maxillary palps (PB) correspond to the TB type on the antenna, but can be further classified as subtypes PB-I, PB-II, and PB-III, according to the dendritic branching pattern (Shanbhag et al., 1999). All of them are innervated by two ORNs. The aristal sense organ and the putative thermo/hygroreceptive types of sensilla in the antennal sacculus are distinct from all the others by their lack of wall pores (Foelix et al., 1989; Shanbhag et al., 1995).
Sexual Dimorphism, Numbers, and Patterns of Olfactory Sensilla

Funicular and maxillary palp sensilla have been counted in different wild-type strains (Table 1) (Shanbhag et al., 1999; Stocker and Gendre, 1988; Stocker et al., 1993; Stocker, 1994). It was shown that trichoid and basiconic sensilla, though not coeloconic sensilla, are sexually dimorphic in numbers. Depending on the strain, males possess 15–32% more trichoid sensilla than females, while females have about 12–24% more basiconic sensilla than males. The recent revision of funicular sensilla (Shanbhag et al., 1999) assigns the difference in trichoid numbers to T2 and T3 subtypes, but not to T1, which is present in equal numbers in both sexes. Also, dimorphic numbers of basiconic sensilla seem to be due to subtypes LB-I and SB (and intermediate sensilla), but not LB-II and TB. Interestingly, the numbers of the coeloconic subtypes C2 and C3 differ reciprocally in the two sexes, but are compensated for coeloconic sensilla as a whole. Regarding the maxillary palps, females possess slightly more PB-III than males, whereas the numbers of PB-I and PB-II are the same in both sexes (Shanbhag et al., 1999).

In three independent ultrastructural studies (see later in text), the total numbers of afferents from the funiculus were determined. These counts include approximately 80 afferents from the sacculus (Shanbhag et al., 1995) and six from the arista (Foelix et al., 1989). Removal of the funiculus in males of the Sevelen strain led on average to a loss of 1,150 axons in the antennal nerve (range 920–1,180; n = 6; Stocker, 1979). In a cross-section through the two nerves at the funicular base of a Canton-S male, Venkatesh and Singh (1984) counted a total of 1,260 axons. At the same level, Shanbhag et al. (1999) determined 1,306 axons in a Canton-S male and 1,316 in a Canton-S female. These data are in general agreement with estimates of the total number of neurons in the funiculus. Such a calculation, which is based on the expected numbers of sensilla of each subtype and their observed innervation (Shanbhag et al., 1995, 1999), amounts to 1,207 in a male and 1,262 in a female (Table 1). Judged by the sensillum type, about 95% of the funicular neurons may be olfactory, and only 5% may mediate other modalities, such as hygro- or thermoreception (Table 1).

In the maxillary palp nerve of Canton-S flies, 120–134 axons were counted, with slightly higher values in females (Singh and Nayak, 1985; Shanbhag et al., 1999). These figures are in good agreement with an expected 114/128 (male/female) ORNs in basiconic sensilla and 20 mechanosensory neurons in the bristles (Table 1).

A peculiarity of the antennal system is the non-homogeneous pattern of sensilla on the surface of the funiculus (Link, 1983; Mindek, 1968; Venkatesh and Singh, 1984). The recent re-classification of funicular sensilla (Shanbhag et al., 1999; see above) has allowed the improvement of the previous sensillar maps (Fig. 3). Accordingly, trichoid sensilla are located distally and laterally on the funiculus, in a mirror-symmetric fashion on the anterior and posterior surface. The T-3 subtype is located most distally and laterally, and the T-2 and T-1 subtypes follow more proximally. The trichoid region includes also the few intermediate sensilla. The large basiconic sensilla LB-I, LB-II, and LB-IV occupy a peculiarly shaped region of the proximal funiculus extending along its median edge and continuing toward lateral as two stripes. One stripe is on the anterior surface distal to the opening of the sacculus, while the second occupies the funicular base on the posterior surface. The thin basiconic subtypes TB-2 and TB-4 reside in a diagonal stripe on the anterior and posterior surface, distal to the LB-region. Further toward the tip of the funiculus follows a second diagonal stripe consisting of small basiconic sensilla (SB). In contrast, coeloconic sensilla are intermingled irregularly with other sensilla on both the anterior and posterior surface, except for a few isolated sensilla at the very base of the funiculus, between the opening of the sacculus and the arista. Whether this characteris-
tic sensillar pattern on the funiculus bears any functional significance, e.g., allowing recognition of spatial aspects of the chemical environment, remains an open question. The tiny dimensions of the *Drosophila* antenna argue against such an idea, although the symmetric pattern in the left and right antenna could be of some importance. In contrast to the antenna, the sensillar subtypes PB-I, PB-II, and PB-III on the maxillary palps seem to be randomly distributed within the sensillum field (Shanbhag et al., 1999).

The recent revision of funicular sensilla (Shanbhag et al., 1999) does not provide any clues about the variability in sensillum position. The isolated coeloconic sensilla on the funicular base were previously shown to vary considerably in numbers (6–10) and position, independent of the strain studied (Stocker, 1994). Other types of sensilla also exhibit a certain level of variation in number and location (Stocker and Gendre, 1988; Stocker et al., 1993; Stocker, unpublished data). This indicates that funicular sensilla as a rule may not be identifiable by position. Yet, both structural and functional maps of LB sensilla show a restriction of certain types to specific spatial domains (Fig. 3) (de Bruyne et al., 2001; Shanbhag et al., 1999; see below). For PB sensilla, functional mapping clearly argued against rigid locations (de Bruyne et al., 1999; see below).

Mutations have proven useful genetic tools for modifying the patterns of olfactory sensilla. For example, a *variety of lozenge* mutants reduce or eliminate antennal basiconic sensilla and increase the numbers of trichoid sensilla (Stocker and Gendre, 1988; Stocker et al., 1993), while PB sensilla are less affected (Riesgo-Escovar et al., 1997a). In contrast, *atonal* mutants lack PB sensilla, coeloconic and sacculus sensilla, but leave antennal basiconic and trichoid sensilla intact (Gupta and Rodrigues, 1997). More extreme effects are obtained by homeotic mutant expression, leading to structural and functional transformation of antennal into leg sensilla (Deak, 1976; Stocker et al. 1976; Stocker, 1977).

**Functional Mapping of Olfactory Sensilla**

Odor-induced responses have been recorded on the funiculus and the maxillary palp by electroantennograms (EAGs; Venard and Pichon, 1984) and electropalpograms (EPGs; Ayer and Carlson, 1992), respectively. EAGs and EPGs are graded responses reflecting the sum of the sensory receptor potentials of the entire appendage. These recordings were very useful for determining relevant odors and odorant acceptor sites (Siddiqi, 1983) and for dissecting olfactory function by mutant analysis (Ayer and Carlson, 1991, 1992; Deshpande et al., 2000; Dubin et al., 1995, 1998; Riesgo-Escovar et al., 1997a,b; Störtkuhl et al., 1999; Venard and Pichon, 1984; Venard and Stocker, 1991), but did not permit an analysis at the cellular level. Despite the small size of the olfactory sensilla in *Drosophila*, extracellular recordings from individual sensilla are feasible (Siddiqi, 1983, 1991). Different response amplitudes and different levels of spontaneous activity even allow one to distinguish among different ORNs within the same sensillum. Using this approach in antennal basiconic sensilla, ORNs were shown to fall into different functional types. Different types respond to different subsets of odors and are distributed in different subre-

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![Figure 3](https://example.com/figure3.png)

**Fig. 3.** Distribution of the different types and subtypes of sensilla on the surface of the male funiculus. The sensillar distribution in the female is similar. The numbers of sensilla shown in this map are underestimates by 17% to 54%, depending on the subtype. A–C: Anterior surface of funiculus; A'–C': Posterior surface showing base of arista (Ar) and sacculus (S). The dashed line indicates a flattened surface at the medial side. A,A': Trichoid sensilla (light triangles, subtype T-1; split triangles, T-2; dark triangles, T-3). B,B': Basiconic and intermediate sensilla (squares, LB subtypes; diamonds, TB; circles, SB; triangles, intermediate sensilla). C,C': Coeloconic sensilla (light stars, subtype C-2; dark stars, C-3). For subtypes, see Table 1. Reproduced from Shanbhag et al., 1999, with permission of the publisher. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
regions of the funiculus (Clyne et al., 1997; Siddiqi, 1983, 1991).

Recently, the entire set of ORNs of a particular sensillum type were functionally characterized and mapped in the olfactory tissue (de Bruyne et al., 1999), an approach hardly possible in mammals. Using single-unit recordings, the response profiles of all basiconic sensilla on the maxillary palps were characterized against a panel of test chemicals (Fig. 4). From an initial set of 16 odorants representing different chemical groups, and known as strong stimulants in Drosophila or related dipterans, seven were selected for systematically studying all PB sensilla. Different response types to odor stimulation were observed: (1) excitatory responses that terminated abruptly after the end of the stimulation period, (2) excitation continuing past the end of stimulation, and (3) inhibition, i.e., a decrease from the spontaneous firing frequency. Often a neuron is excited by one odor and inhibited by others, or exhibits different termination kinetics when stimulated with different odors. Also, ORNs residing in the same sensillum often respond differently to the same chemical. In total, three sensillum types were identified electrophysiologically: pb1, pb2, and pb3. Each type contains two neurons (A and B), in agreement with the structural studies (Shanbhag et al., 1999; Singh and Nayak, 1985), yielding a total of six ORN classes (pb1A through pb3B) (Fig. 4). Response profiles of the six classes are distinct yet overlapping. ORNs appear to be either broadly tuned to many chemicals, or narrowly tuned to one or few of the seven odorants. However, this difference may at least partially depend on odorant dosage. Interestingly, specific ORN classes are paired in each of the three sensillum types. While individual ORNs show adaptation to subsequent stimulation with the same odor or cross-adaptation to certain other odors, these forms of adaptation were not observed to extend to paired neurons. Thus, the question whether multineuronal olfactory sensilla represent functional units is only partially answered: although specific ORNs are paired, the significance of pairing remains elusive, and there is so far no evidence of ORN cross-talk. Still, a complete functional independence of paired ORNs would be surprising, given the intimate structural pairing. Perhaps the identification of the primary ligands of paired ORNs will reveal yet hidden functional relationships (see de Bruyne et al., 2001 for a discussion).

Mutations in the acj6 gene, encoding a POU-domain transcription factor, were shown to selectively affect the response properties of specific ORN types (Clyne et al., 1999a). The changes ranged from a complete block of responses to a novel response profile or to the transformation of an A neuron to a second B neuron, leading to sensilla with two identical ORNs.

Remarkably, the three sensillum types do not reveal any obvious topographic distribution on of the maxillary palps. With the exception of a small proximalateral region that is occupied only by pb1 and pb3 sensilla, the three types are intermingled. Also, the precise positions of individual sensilla are not fixed and their functional identity is not strictly determined by topography. These data argue against a chemotopic layout on the surface of the palp. The functional data are reminiscent of the random distribution of the structural subtypes PB-I, PB-II, and PB-III (see above). On the other hand, none of the functional types shows any kind of sexual dimorphism (de Bruyne et al., 1999), in contrast to the dimorphism observed in PB-III numbers (Shanbhag et al., 1999). To search for possible
correlations between functional and structural subtypes of sensilla, a combined TEM and electrophysiological study will be required.

Recently, functional mapping was extended to antennal basiconic sensilla (de Bruyne et al., 2001), an investigation that is in many respects even more precise and complete than the palp study. For example, a total of 47 odors were tested and the set of "diagnostic" odorants was increased from seven to twelve. The data resemble in many respects those obtained in PB sensilla. Again, distinct response classes of ORNs and strict pairings of ORNs residing in the same sensillum were observed. Large antennal basiconic sensilla fall into three functional types (ab1, ab2, ab3). Ab1 sensilla reveal four different spike amplitudes, whereas in ab2 and ab3 only two responses are distinguishable. These data are in agreement with the four ORNs innervating LB-I/II4 and the two ORNs innervating LB-I/II2, respectively (Shanbhag et al., 1999). Each of the four neurons in ab1 and each of the two neurons in ab2 and ab3 shows its specific response spectrum, yielding a total of eight ORN classes. No evidence of additional types was found in a total of 145 recordings from large basiconic sensilla. The eight classes are distinct from the six palp classes mentioned before. As with palp recordings, the specificity of individual neurons ranges between two extremes, from ORNs responding to only one of the 47 odors to ORNs responding to nearly half of them. An example of the first type is ab1C, which responds strongly and exclusively to CO2. Another eight ORN classes arranged pairwise in four functional sensilla types (ab4–ab7) were identified in smaller antennal basiconic sensilla (corresponding to the TB and SB types of Shanbhag et al., 1999), and additional classes remain possible.

In contrast to the sensilla on the maxillary palp, the identified seven functional types of antennal basiconic sensilla (ab1–ab7) show a specific topographic pattern. Obviously, sensilla types ab1–ab3 are restricted to the LB region, while ab4–ab7 are localized more distally, overlapping the TB/SB region (see above and Fig. 3). Further distinctions are possible within these regions. For example, ab3 sensilla are restricted to the medial edge of the LB region and are absent from the LB stripe on the anterior surface of the funiculus. Yet, none of the LB subtypes corresponds to this pattern. Furthermore, ab4 and ab6 seem to occupy the TB-2 but not the SB region. Thus, ab1 sensilla correspond to LB-I/II4, ab2 and ab3 sensilla to the other LB types, while ab4/ab6 may be identical to TB-2. Additional correlations between morphological and functional subtypes are not revealed by comparing the two patterns.

No systematic functional mapping was performed yet for trichoid and coeloconic sensilla, although a preliminary characterization yielded evidence of at least seven ORN classes (Clyne et al., 1997). The most remarkable observation was that one subtype of trichoid sensilla responds to cis-vaccenyl acetate, a suspected pheromone in Drosophila (Bartelt et al., 1985; Feverveur et al., 1989), but not to any of 16 additional odors tested. A second subtype does not respond to cis-vaccenyl acetate, but to other odors. Spatial segregation suggests that subtypes 1 and 2 may correspond to T-2 and T-3 sensilla, respectively. At least two functional subtypes were observed in coeloconic sensilla (Clyne et al., 1997).

**Patterns of Odorant Receptor Gene Expression**

A breakthrough in olfactory research was the detection of a large multigene family encoding G-protein coupled seven-transmembrane ORs in mammals (Buck and Axel, 1991). In insects, a gene family fulfilling the criteria of OR genes was identified only recently, by searching the Drosophila genomic database for seven-transmembrane receptor genes uniquely expressed in olfactory tissues (Clyne et al., 1999b; Gao and Chess, 1999; Vosshall et al., 1999). The ORs encoded are neither related to mammalian ORs nor to ORs identified in the nematode C. elegans. Within their own family, the Drosophila ORs share common motifs but are otherwise extremely divergent. Evidence that at least some of these proteins indeed function as ORs comes from EAG recordings in flies in which one of these ORs was overexpressed in the funiculus (Störtkuhl and Ketler, 2001) or misexpressed in Xenopus oocytes (Wetzel et al., 2001). The acj6 gene (see above) appears to be involved in the regulation of subsets of OR genes (Clyne et al., 1999b). The following paragraph summarizes the published OR gene expression patterns on the funiculus and maxillary palp. The patterns of odorant-binding proteins—the putative carriers of odorants on their passage toward the ORs—are reviewed by Shanbhag et al. (pages 297–306, in this issue). For a summary of intracellular olfactory signalling processes initiated by ligand-OR binding, refer to Carlson (1996), Smith (1996), and Vosshall (2000).

Screening of the recently completed euchromatic genome sequence of Drosophila (Adams et al., 2000) with previously identified members of the fruitfly OR family indicated a total of 59 OR genes (Vosshall et al., 2000; Drosophila Odorant Receptor Nomenclature Committee, 2000). If this turns out to be close to the complete set, Drosophila would express at least an order of magnitude less ORs than mammals. Thirty-four of these genes show expression exclusively in the antenna and seven in the maxillary palps, yielding a tentative total of 41 OR genes with visible expression in olfactory tissues (Vosshall et al., 2000). However, for one of them, Or23a, other reports claim a combined antennal and palp expression (Gao and Chess, 1999; Gao et al., 2000). A puzzling extra gene, Or83b, is expressed in the entire set of antennal and palp ORNs, but nowhere else in the body (Vosshall et al., 1999, 2000). The expression patterns of the remaining seventeen OR genes are unknown. Apart from Or83b, individual ORNs may express either one or a small number of ORs, an issue that is under debate (Clyne et al., 1999a,b; Vosshall et al., 2000). Each OR is expressed by an invariant subset of OR genes (Fig. 5). They define a topographic map that is conserved between individuals. This suggests that a given OR may be associated with a specific structural and/or functional type of sensillum. The correlation between OR expression and morphological sensillum type has not yet been studied in detail. However, expression of certain ORs was found restricted to the LB region on the funiculus (Clyne et al., 1999b; Gao and Chess, 1999; Vosshall et al., 1999), and the palp-specific ORs are obviously expressed in PB neurons. Also, the expression of Or47b...
on the distal, lateral edge of the funiculus, which is rich in trichoid sensilla, together with its central target in a putative trichoid-specific glomerulus, make this OR a good candidate for trichoid-specificity. For the maxillary palp, the number of cells expressing a given OR gene is in rough accord with the number of cells in each functional response class (see Vosshall, 2000). The most straightforward though untested hypothesis is that each response class relates to the expression of a specific OR.

Lately, an additional family of 56 putative chemosensory genes was identified in *Drosophila*, although expression was observed for few of them only (Scott et al., 2001). Most of these were expressed in taste organs, except a few that were expressed in restricted sets of funicular sensilla. While the function of the encoded proteins is presently not know, the data suggest a highly interesting functional and evolutionary link between olfaction and taste.

### Three-Dimensional Reconstruction of the Antennal Lobe

As in vertebrates and in other insects, the primary olfactory center of *Drosophila* consists of structural units, called glomeruli (see Anton and Homberg, 1999). They harbor the sensory terminals as well as the dendritic arborizations of target interneurons. An earlier AL reconstruction in the fruitfly, based on afferent labeling, estimated a total of about 35 glomeruli and showed that many of them are identifiable by their size, shape, and location (Pinto et al., 1988; Stocker et al., 1983, 1990). Also, a monoclonal antibody that recognizes specific subsets of glomeruli was described (Störtkühl et al., 1994). However, the precise mapping of AL inputs and outputs, of glomerular-specific gene expression or functional imaging patterns requires a more detailed and readily available three-dimensional glomerular atlas. This was accomplished recently by confocal reconstructions of the AL labelled by a neuropil-specific antibody (Fig. 6) (Laissue et al., 1999), with permission of the publisher and the “Flybrain” image database: accession number AB00200, at http://www.flybrain.org). (Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.)
contrast to the Hawaiian species *D. heteroneura* and *D. silvestris*, in which two dorsal glomeruli exhibit a sexually dimorphic size and arrangement (Kondoh and Yamamoto, 1998).

**Projections of Antennal and Maxillary Palp Sensilla in the Antennal Lobe**

The 1,200–1,300 afferents from the funiculus (Table 1) and another approximately 600 from the auditory Johnston’s organ in the second antennal segment travel together in the antennal nerve. At their entrance into the brain, the former turn dorso-medially into the AL, while the latter extend straight into the antennal mechanosensory and motor center (Power, 1946). The AL is also the target of the roughly 120 basiconic afferents from the maxillary palps (Table 1), passing via labial nerve and suboesophageal ganglion (SOG) (Singh and Nayak 1985). In contrast, the mechanosensory palp afferents terminate in the SOG itself.

Afferent projections in the AL—studied by orthograd filling from small clusters of sensilla with neuronal tracers or by cell-specifically expressing P-element lines—appear to obey the following rules (Lienhard and Stocker, 1987; Shanbhag et al., 1995; Singh and Nayak 1985; Stocker et al., 1983, 1990; Tissot et al., 1997): (1) Sensory terminals from sensilla on the funiculus are either bilateral or uni- (ipsi-) lateral, at a proportion of 5:1. Bilateral fibers innervate the same glomeruli in the ipsi- and contralateral AL, the latter by collaterals passing via the antennal commissure. Afferents from aristal sensilla are purely ipsilateral, while maxillary afferents are always bilateral. (2) Glomeruli V, VL1, VP1, VP5, VP8 are exclusive ipsilateral targets, while most (perhaps all) others receive bilateral input. (3) The terminals of a given sensory fiber are restricted to a single glomerulus. (4) The projection patterns of LB sensilla located along the proximo-distal axis of the funiculus are similar. Moreover, multineuronal sensilla at a given topographic location appear to project to multiple target glomeruli, which may be located far apart from each other in the AL. These data argue against a topographic type of funicular projections. (5) All available data allocate VP2 and VP3 glomeruli as specific targets of aristal sensilla, even if aristae are duplicated by the *engrailed* mutant. (6) Afferents from antennal LB and maxillary PB sensilla project at least partially into different subsets of glomeruli. (7) Sacculus sensilla appear to project to a large variety of target glomeruli, suggesting sensillar heterogeneity. Based on these data, glomerular target maps according to sensillum type were created (Shanbhag et al., 1995; Singh and Nayak 1985; Stocker et al., 1983, 1990; Tissot et al., 1997).

2-Deoxyglucose mapping in *Drosophila* (Rodrigues, 1988) and calcium imaging in the honeybee have shown that different odorants activate specific subsets of glomeruli (Galizia and Menzel, 2000; Joerges et al., 1997). This suggests that in insects, analogous to mammals, a chemotopic map may be represented in the AL. Hence, mapping of OR expression in olfactory tissues immediately raised the question of central connectivity. How would the afferents of scattered ORNs expressing a given OR behave in the AL? Would they converge onto the same target glomerulus, as in the mammalian system? What would be the relationship with the neuroanatomical tracing data? Remember that the number of 41 ORs with reported expression in subsets of antennal or maxillary ORNs (Vosshall et al., 2000) approximates the number of glomeruli.

Sensory projections were studied in transgenic flies in which OR gene promoters direct the expression of reporter genes, visualizing either the ORN cell bodies in the periphery or their afferent terminals in the AL. Remarkably, a distinct convergence of afferents from ORNs expressing the same OR onto one or a few glomeruli was observed (Fig. 7) (Gao et al., 2000; Scott et al., 2001; Vosshall et al., 2000). However, it is not clear whether individual fibers branch in one or in more than one of these glomeruli. All target glomeruli were shown to be topographically invariant. Target glomeruli of *Or23a* and *Or47a* were tentatively identified as D/DC3 and DM3, respectively (Gao et al., 2000).

The OR projection data are in many respects compatible with the neuroanatomical tracing data (Singh...
glomerulus after genetic ablation of LBs in V, which is in agreement with dye tracings from this region. Finally, a member of the novel putative chemoreceptor gene family mentioned above (Scott et al., 2001), Gr21D1, is expressed mainly in the LB region of the funiculus. The corresponding afferents seem to converge exclusively onto glomerulus V, which is in agreement with dye tracings from this region (Stocker et al., 1983) and with the loss of this glomerulus after genetic ablation of LBs in lozenge mutants (Stocker and Gendre, 1988).

These data show surprising parallels with the mammalian olfactory system, regarding both OR expression and central wiring. Evidence from both phyla suggests that ORNs may express only one type of OR. Moreover, afferents from ORNs expressing a given OR converge upon the same target glomeruli in the olfactory centers, although their cell bodies are scattered in the olfactory tissues. This design is well suited to improve the signal-to-noise ratio. Since every OR is able to bind multiple odorants and every odorant can bind to multiple ORs, specific molecules seem to activate specific subsets of glomeruli, an assumption that has been largely confirmed by functional mapping studies in the AL and olfactory bulb (Cinelli et al., 1995; Galizia and Menzel, 2000; Joerges et al., 1997; Malnic et al., 1999; Rodrigues, 1988; Rubin and Katz, 1999). Thus, in both flies and mammals olfactory projections appear to establish a chemotopic rather than topographic map of the periphery. The major difference between the two phyla then refers to the numbers of ORs, ORNs, and glomeruli. The considerably higher figures in mammals may allow the distinction of larger numbers of compounds, or distinction at higher precision. Yet, combinatorial activation of even a small set of glomeruli—as observed in the fruitfly—could be sufficient to discriminate between a large array of odorants.

**Olfactory Target Interneurons**

Activation of glomeruli through afferent signalling represents only the very first step in odor processing. Afferent signals are relayed to two major types of target interneurons in the AL: local interneurons and projection neurons (PNs). The former interconnect glomeruli, while the latter are the major output of the AL, providing links between glomeruli and higher olfactory centers, i.e., the mushroom bodies and/or the lateral protocerebrum (Stocker et al., 1990; Stocker, 1994). In the moth *Manduca*, local interneurons have been reported to exert inhibitory control over PNs (Christensen et al., 1993). In locusts, this mechanism appears to mediate oscillatory synchronization across the ensemble of PNs (MacLeod and Laurent, 1996), a process that is considered to contribute to odor discrimination (Laurent, 1999). A peculiarity of the insect olfactory pathway is a convergence of afferents toward PNs and a divergence from PNs toward their target neurons in the mushroom bodies, the Kenyon cells. For example, in *Drosophila*, the 1,300–1,400 afferents (Table 1) converge onto an estimated 100–150 PNs that synapse with 3,000 Kenyon cells. Yet, this striking design still lacks a satisfactory explanation in functional terms.

In *Drosophila*, a cell-specifically expressing P-element line revealed that PNs with dendritic arborizations in single glomeruli belong to two distinct developmental categories: persisting larval PNs that innervate a small AL precursor in the larva, and adult-specific PNs that arise during metamorphosis (Stocker et al., 1997). Apart from these categories, uniglomerular PNs fall into two morphological classes, characterized by lateral vs. anterodorsal cell bodies. A genetic recombination technique demonstrated that most of the glomeruli are innervated by either lateral or anterodorsal PNs (Jefferies et al., 2001). It also showed a third type of PNs with ventral cell bodies and multi-glomerular dendritic arborizations. The dendritic arbors of uniglomerular PNs are established before the arrival of the ORN axons, implying an ORN-independent specification of PNs. The functional implications of glomerular-specific assignments of PNs and their relations with incoming odor signals are not yet clear. However, the molecular and cellular tools available in *Drosophila* should soon lead to a better understanding of the input and output relations of the AL.

**Larval Olfactory System**

Fly larvae possess three major larval chemosensory organs on their cephalic lobes, the “antennomaxillary complex,” consisting of dorsal and terminal organs, and the ventral organ (for more detailed reviews, see Cobb, 1999; Stocker, 1994). Of these, only the dorsal organ fulfills the structural criteria of an olfactory sense organ. In both *Musca* (Chu and Axtell, 1971) and *Drosophila* (Oppliger et al., 2000; Singh and Singh, 1984), it consists of a prominent central “dome” surrounded by six additional small sensilla. The dome is perforated by thousands of pore tubules and accommodates projections by dendritic arborizations of 21 receptor neurons, properties that suggest an olfactory function. The six sensilla around the dome as well as the entire terminal and ventral organs exhibit distal pores implying a gustatory function. The 35–40 neurons of the entire dorsal organ are collected in a common ganglion, which accordingly contains both olfactory and gustatory receptor neurons. The afferents from the dorsal organ travel to the brain via the larval precursor of the antennal nerve (Heimbeck et al., 1999; Tissot et al., 1997). Individual fibers that probably derive from the 21 ORNs seem to terminate in small subregions of the larval AL (Python et al., unpublished data). The relation of these structures to adult glomeruli remains unknown at present. Other afferents in the antennal nerve, presumably from gustatory sensilla, project to SOG regions.

Indications that the antennomaxillary complex may indeed be involved in olfaction were obtained in a mutant with a suspected effect on the cellular composition of this complex (Park et al., 1997). Recently, two different approaches allowed for the definite assignment of an olfactory function to the dorsal organ. By using a cell-specifically expressing P-element line, tetanus toxin was transgenically expressed in the neurons of...
the dorsal organ (Heimbeck et al., 1999). In a preference test such larvae, in which the synaptic transmission of these neurons was blocked, showed anosmic behavior to most odors. Direct functional evidence about the dorsal organ was obtained by electrophysiological recordings after stimulation with volatile compounds (Opplinger et al., 2000).

As illustrated by the complex array of smell and taste sensilla in the dorsal organ, the olfactory and gustatory portions of the larval chemosensory system are not as strictly separated as in the adult. This mixture may be related to the predominant short-range orientation of larvae, which usually live directly on their food supply. In such a situation a distinction between smell and taste stimuli may not be very crucial. Alternatively, the connection between the two senses may reflect a phylogenetically more primitive state in which the smell system has not yet become fully independent of the taste system.

Another issue worth considering is the cellular simplicity of the larval chemosensory system compared to its adult counterpart. This reduction, which is particularly striking for the olfactory portion, may be due again to the restricted requirements of long-range orientation of a crawling larva. It is probably safe to conclude that the 21 larval ORNs allow for less discriminative power than the 1,300 ORNs in the adult. Yet, the simplicity in terms of cellular organization may not necessarily indicate poor functional capabilities. Complexity is conceivable at other levels of organization than mere cell numbers. For example, each neuron could be unique, rather than belonging to a group of alike neurons. Also, individual neurons could possess higher integrative capacities than their adult counterparts, e.g., by functional compartmentation of different cellular regions. Larvae have, indeed, been shown to respond in a concentration-dependent way to a variety of volatile substances including alcohols, acetates, aldehydes, ketones, fatty acids, and esters, similar to adults (Ayyub et al. 1990; Cobb et al. 1992; Cobb and Dannet, 1994; Cobb and Domain, 2000; Heimbeck et al., 1999; Monte et al. 1989; Opplinger et al., 2000). The behavioral measures used—preference test of odorant vs. solvent—do, however, only allow conclusions about odorant detection. Conclusive evidence for odorant discrimination in larvae is still lacking. An interesting recent approach is to use cross-adaptation as an assay (Cobb and Domain, 2000).

Even if the olfactory capacities of larvae were reduced in comparison to the adult, their performance based on such a small number of ORNs remains a puzzle. This issue is particularly intriguing considering the recent OR expression data in the adult (see above), and raises questions about the cellular and molecular organization of the larval olfactory system (see Cobb, 1999, for a recent discussion). At the one extreme, the larval system may be organized according to the same rules as the adult system, with each ORN expressing multiple ORs, analogous to *C. elegans*. Consistent with this hypothesis would be the fact that larval ORNs are lost during metamorphosis and become replaced by a new set of adult-specific ORNs. Still, a radical change in design from the larval to the adult system is not very likely, considering that nervous system metamorphosis is largely governed by economical constraints (Tissot and Stocker, 2000). A distinction between these alternatives will have to await knowledge about OR expression patterns in the larval system. Yet, regarding the technological advantages offered by *Drosophila*, the prospects for answering this intriguing question are very good.

**CONCLUSIONS**

The primary goal of this paper was to present an up-to-date view of the neuronal basis of smell, based on a series of recent systematic data obtained in the *Drosophila* model system. Except the olfactory system of *C. elegans*, which seems to be designed in a very special way, no other olfactory system has been investigated as thoroughly as the one of the fruitfly. On the structural level, a painstaking electron microscopic study mapped almost 80% of the funicular sensilla. Large-scale electrophysiological recordings then allowed for classification of the odor response spectra of about half of all olfactory sensilla. An important breakthrough was the identification and mapping of putative ORs in the olfactory tissues. At the central level, a three-dimensional glomerular map of the AL helped trace the central projections of ORNs expressing a given OR. Perhaps the most remarkable outcome of these data is a striking parallel in the numbers of identified ORN classes (29), of ORs expressed in subsets of ORNs (41), and of glomeruli (43). Considering the glomerular convergence of individual ORs, one is tempted to speculate that ORNs expressing a given OR may be equivalent to a particular response class and project to a specific target glomerulus. Hence, as a next, though painstaking, step in this analysis, a systematic correlative approach should now be undertaken.

The second objective of this review was to emphasize the surprising parallels between the olfactory system of *Drosophila* and mammals as revealed by these data. In both cases, ORNs appear to express only one type of OR (though this is not yet completely settled in the fruitfly). Moreover, ORNs expressing a given OR are scattered in the olfactory tissues, but their afferents converge onto a few target glomeruli only. This suggests that in both systems the periphery is represented in the brain as a chemotopic map, an assumption that has been largely confirmed by imaging studies. Hence, the major difference between fruitfly and mammalian systems appears to refer to the numbers of ORs, ORNs, and glomeruli. Yet, even the reduced set of glomeruli of the former—if activated in a combinatorial fashion—could allow discrimination between a large array of odors.

Taken together, *Drosophila* has emerged as a powerful model system for studying odor processing. This is not only because its olfactory system looks like a simplified mammalian version, but also because of its experimental potential. Cloning of olfactory-specific genes and the expression of transgenes in selected neurons may eventually allow us to describe and function-
ally dissect the entire system, both at cellular and molecular levels. In this respect, techniques for imaging specific cell types may be particularly fruitful. Also, flies as holometabolous insects dispose of a second, larval olfactory system as an alternative model system, which is yet further reduced in cellular terms. Last but not least, the transformation of the simple larval to the complex adult system is attractive for approaching developmental issues of olfactory systems.

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REFERENCES


