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Odor maps in the brain: Spatial aspects of odor representation in sensory surface and olfactory bulb

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Abstract. The olfactory sense detects and distinguishes a multitude of different odors. Recent progress in molecular as well as physiological approaches has elucidated basic principles of neuronal encoding of odorants, common to insects and vertebrates. The construction of neuronal representations for odors begins with the task of mapping the multidimensional odor space onto the two-dimensional sensory surface, and subsequently onto the olfactory bulb or antennal lobe. A distributed expression of odorant receptors, albeit restricted to subregions of the sensory surface (large, intermediate or small for zebrafish, mouse or drosophila, respectively), ensures a robust representation, insensitive to mechanical insult. Olfactory receptor neurons expressing the same odorant receptors converge to form a receptotopic map in the olfactory bulb or antennal lobe. The emerging coding principle is a chemotopic representation of odorants at the first brain level, realized either as combinatorial or as monospecific representation, depending on the odorant.

Key words. Olfaction; chemotopic; imaging; olfactory bulb; glomeruli; odor map; combinatorial; coding.

Introduction

Sensory perception amounts to the deconstruction of the external world and subsequent reconstruction of an internal representation. The number and sophistication of channels or sensory modalities available for that purpose varies with the phylogenetic position of the species. Detection of molecules is the task of the chemical sense, the origin of which dates back to procaryotes. The chemical sense has evolved into four distinct modalities in most vertebrates. The main olfactory system, the accessory olfactory system, the gustatory system and the so-called common chemical sense mostly carried by trigeminal sensory neurons all differ with respect to receptor molecules, receptor cells and wiring of the receptor cells.

The common chemical sense mostly detects irritants, i. e. it is involved with categorizing or classifying chemical stimuli as potentially harmful [1]. For example, it strongly responds to CO_2, as one can easily notice upon putting one's face too deep in the dry ice storage container. Notably, the same chemicals often are perceived by the sense of smell as well (CO_2 being an exception). The sense of taste also functions to categorize chemical stimuli into wanted (sweet, salty, umami and fat) and unwanted (bitter and sour) [2–4]. Many chemically very different molecules can elicit the same taste sensation [5]. In contrast, the two olfactory senses are concerned with the identification of particular odorants. Very subtle differences in the chemical structure of odorants may lead to a robustly different olfactory perception. Thus, the task of the olfactory senses proper is not classification but recognition of individual chemosensory stimuli. The main olfactory system detects only volatile odorants, whereas the accessory system also picks up less volatile or even water-soluble odorants. It is generally thought that the accessory system specializes in pheromone detection, whereas the main system detects common odorants [6], but see [7, 8]. Recognition of pheromones may seem a little easier because the number of pheromones is much smaller than that of general or common odors. However, exacting recognition of the proper species-specific pheromones and secure differentiation from related substances serving as pheromones for other species is essential for adequate pheromone-guided behavior. Within the main olfactory system a multitude of different odors can be recognized and distinguished by the average vertebrate. Trained perfumers can distinguish up to 5000 dif-

ferent odors, albeit as a species humans rank rather low with respect to olfactory abilities.

How is this astonishing acuity achieved? In other words, what is the principle of neuronal encoding of this vast multitude of odors? Recent advances in imaging neuronal activity as well as molecular targeting of odorant receptors (ORs) have emphasized the contribution of spatial maps towards representing odors in the brain. This review summarizes earlier work in the field, focuses on recent progress and discusses the relative importance of spatial maps compared to other forms of neuronal encoding of odorants.

Odors, odorants and odor space

To appreciate the theoretical problems inherent in the idea of mapping odors to the sensory surface it is helpful to consider the nature of odor space, an abstract space, in which each possible odor or odorant (any particular odorous compound) can be characterized by its unique coordinates. Historically, dimensions of this odor space have been derived either from some form of factor analysis of different physicochemical parameters of the odorants such as size, shape, rigidity and charge, or from an analysis of human perceptual categories (fruity, pungent, musk-like, floral etc.) [9]. However, conscious perception is a rather late step in neuronal processing of odors, and physicochemical properties of odorants are relevant for odor perception only insofar as they determine the affinity to ORs.

It is important to emphasize that an odor or odorant is perceived as such because it binds and activates at least one OR. Recently the first ligand-response spectra of recombinant ORs (tuning curves) have become available [10–13], and in all likelihood many more such data will forthcome in the near future. I suggest therefore each OR be considered as one dimension of odor space. Different odorants will interact to a lesser or greater degree with a single OR, equivalent to smaller or larger coordinate values for that particular dimension of odor space (fig. 1). Note that enantiomers often, but not always smell differently [14], indicating that, first, odorant shape is relevant for binding to the OR (as is to be expected for receptor/ligand interactions) and, second, not all structural features of an odorant participate in the receptor/ligand interaction, i.e. partial fits are allowed (cf. fig. 3A).

As the gene family of ORs is large, it follows that odor space is multidimensional. Estimates for the size of the family range from 100 for fish and *Drosophila* ORs [15–18] to several hundred for humans [19] and up to 1000 for rodents [20]. Homologies are not recognizable between insect and vertebrate ORs [17] and are rather minor between fish and mammalian receptors [15, 16].

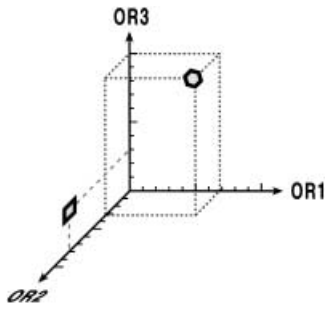

Figure 1. A hypothetical three-dimensional odor space spanned by OR1 to OR3. The many dimensions of the actual odor space cannot be depicted satisfactorily, thus a severely reduced subset is shown to explain the principle. One odorant (hexagon) reacts strongly with OR1, weakly with OR2 and maximally with OR3, coordinates (0.7, 0.3, 1.0). The other odorant (square) reacts not at all with OR1, strongly with OR2 and weakly with OR3, coordinates (0.0, 0.8, 0.3). Note that the set of coordinates is unique for each of the two odorants, despite low specificity of OR2 and OR3. The two odors are encoded by a combination of coordinate values, hence the term 'combinatorial encoding'.

Thus, there should exist large species differences in odor space, and consequently, in the perception of odorants, since the perceived quality of an odorant is determined by its coordinates in odor space (fig. 1). For example, humans smell fatty acids with low thresholds (and low pleasure), but the very same components are odorless for zebrafish [S. Fuss and S.I.K., unpublished observation]. Thus, extrapolation of results between species always has to be viewed with a certain caution, even though it often seems to work (see e.g. [21]). In fact, even within a species, allelic differences in the receptor repertoire may make one person's odor space different from that of another. A well-known example is androstenone, which is odorless for some people, smells like sandalwood to others and has a urinous smell for a third group [4].

Mapping odorants onto the sensory surface

All senses map their respective stimulus space to the sensory surface (sensory epithelium, fig. 2). For a low-dimensional stimulus space, this map is realized as an one- or two-dimensional array of continously changing stimulus properties, a solution not possible for the multidimensional odor space (fig. 2). The olfactory epithelium consists of thousands to millions of narrowly packed olfactory receptor neurons (ORNs), each expressing a single or a few OR genes (whether it is a single or a few genes seems to depend on the species and possibly the receptor [4, 13, 22–24]). Odors are mapped to the sensory surface in a distributed fashion, i.e. the direct neighbors of a particular ORN tend to be of another type. It is true that the expression of any OR is limited to a subregion of the sensory surface; however, different OR are intermingled

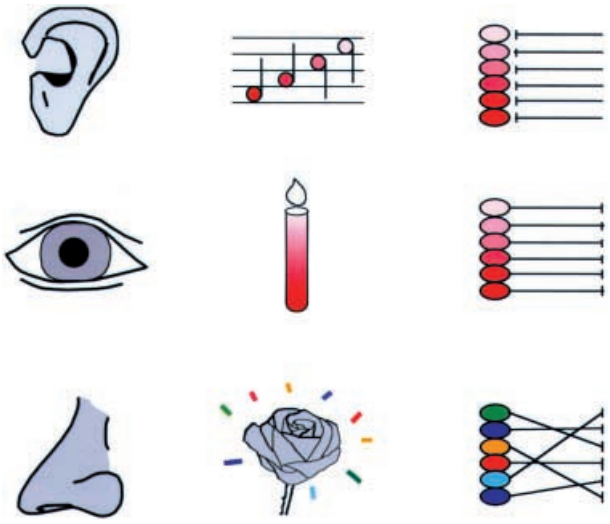

Figure 2. Mapping the stimulus to the sensory surface. (*Top Row*) Acoustic Sense: a one-dimensional stimulus (frequency) is mapped to a one-dimensional sensory surface (cochlea). The cochlea is topologically innervated. (*Middle Row*) Visual Sense: the projection of a three-dimensional world onto a two-dimensional sensory surface (retina). Topological projection from the retina. (*Bottom Row*) Olfactory Sense: a multidimensional stimulus is mapped onto the sensory surface (olfactory epithelium). Nontopological projection from the olfactory epithelium.

within these expression zones, domains or spots [15, 17, 25, 26]. Subregions are large for zebrafish, intermediate for rodents and small for *Drosophila.* Accordingly, electro-olfactograms (field potential recordings) of the sensory epithelium show only weak spatial preferences for particular odors [27]. Within the expression domains, positions of ORN expressing a particular OR appear to be random [F. Weth and S.I.K., unpublished observation]. Thus within the sensory surface, responses to odorants are not segregated with respect to OR type or to chemical similarity of odorants. That is, the representation of odorants is neither receptotopic nor chemotopic. This striking absence of order is usually explained by the superior stability of a distributed representation against mechanical insult. Protected only by a thin mucus layer, ORNs are maximally exposed to the environment. If some areas of the olfactory epithelium are damaged, the response to any particular odorant will be weaker, but will not be lost completely in the case of a distributed representation.

A non-topological projection of ORNs

Vertebrate and invertebrate ORNs send a single unbranched axon into a specialized brain region (olfactory bulb and antennal lobe, respectively) where ORNs form synapses with projection neurons (fig. 3). A hallmark of the olfactory system is the clustering of these synapses in so-called glomeruli, which gather input from hundreds to thousands of ORN axons. A glomerulus also contains many synapses to interneurons. ORNs synapsing onto a single glomerulus are widespread within the olfactory epithelium [28], whereas neighboring ORNs synapse onto different glomeruli. That is, neighborhood relationships of ORN somata are not retained in the target region (fig. 2 and 3). Neuroanatomical investigations have thus established the nontopological nature of the projection from the sensory surface to the brain. To the surprise of many investigators it was found that this criss-crossing of axons leads to an amazing degree of order in the functional arrangement of rodent ORN terminals in the olfactory bulb. Both direct in situ hybridization with OR probes and transgene expression under OR promoter control have shown that all terminals of same-type ORN (expressing the same OR gene) converge onto two (sometimes one or three) glomeruli that do not reveive input from other-type ORN [29, 30]. The coordinates of glomeruli within the bulbar surface are rather stereotyped [31]. One olfactory bulb contains two mirror image maps in rodents, but not in fish or insects. In the zebrafish and in many insects, stereotyped glomeruli can be recognized even by purely morphological criteria [9, 32, 33]. Although the number and arrangement of glomeruli is not completely invariant – distances between neighboring glomeruli may vary by one to two glomerular diameter [J. Strotmann, unpublished observation] – the olfactory bulb in effect contains a decent receptotopic map (fig. 3). A recent study has shown convergence of same-type ORN terminals into a single glomerulus with stereotyped coordinates for the antennal lobe of *Drosophila* as well [18]. Thus, receptotopic maps seem to be a general feature of vertebrate and insect olfactory systems alike.

Whether a receptotopic map translates into a chemotopic map is a further question. A map is called chemotopic if related odorants map to similar (though not identical) positions within the olfactory bulb, and other groups of odorants map to other positions. A recent study indicates that ORNs expressing closely related OR genes tend to project to closely neighboring glomeruli [34]. That is, a subtle difference in OR sequence translates into a subtle difference in position of the corresponding glomerulus. A pair of closely related ORs has distinguishably different, but very similar tuning curves [11]. Although certainly more results are needed before any firm conclusions can be drawn, these data are consistent with the hypothesis that chemically related odorants elicit spatially similar response patterns, i. e. consistent with the concept of a chemotopic map in the olfactory bulb.

How extended are these spatial patterns? In other words, how many different ORs are involved in the response to a single odorant? The number of ORs involved in representing an odorant directly pertains to the coding strategy. A higher number amounts to a less sparse vector in the odor space and consequently to a higher coding capacity.

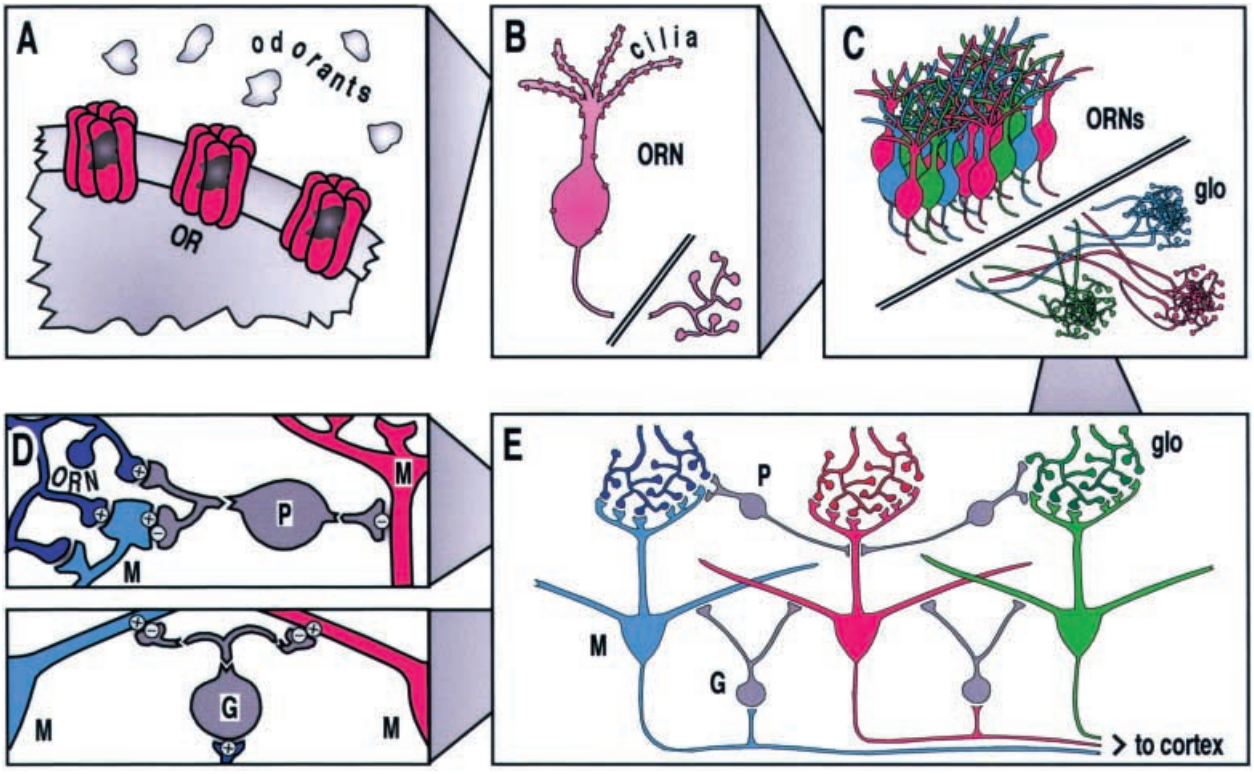

Figure 3. Levels of mapping and connectivity in the mammalian olfactory system. (*A*) Odorants to receptor: odorants react with odorant receptors (ORs). Odorants fit to a different degree into the binding pocket of the receptor. (*B*) OR to olfactory receptor neuron (ORN): an ORN contains only same-type OR. (*C*) ORN to glomeruli (glo): same-type ORN segregate en route to the glomeruli in the olfactory bulb. (*D*), Top Panel: Periglomerular neurons (P) are excited (⊕) by ORN and mitral cells and themselves inhibit (⊖) mitral cells. ⊕⊖, a bidirectional synapse. Bottom Panel: Granule cells (G) are excited by mitral cells and inhibit mitral cells. (*E*) Glomeruli to projection neurons: ORN synapse with mitral cells. Periglomerular cells (P) and granule cells (G) provide lateral connections between mitral cells. Secondary dendrites of mitral cells may reach much farther than shown here.

It also has consequences for the error-correcting capabilities of the code. It is theoretically possible, but highly impractical, to solve this question by analysis of odor response spectra of recombinantly expressed OR, even though recently partial tuning curves for a handful of ORs have been published [10-13]. To study this question one has to turn to techniques allowing the imaging of odorant-induced activity in many glomeruli at once. Such methods have been applied to the analysis of the olfactory system since more than 2 decades. New and improved methods continue to be developed which now allow repeated, high-resolution imaging [35–38].

Methods for imaging odorant-induced activity

Several such techniques are available which differ in the spatiotemporal resolution achieved (1 µm to 10 mm, 30 Hz to 3000 s), the directness of the approach (measured are neuronal activity or metabolic consequences of neuronal activity), the level of neuronal processing analysed (ORN terminals, mitral cells, interneurons, all of the above) and the ability to perform repeated measurements with the same animal (table 1).

Three methods are noninvasive: magnetoencephalography (MEG), also called magnetic source imaging (MSI), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). Unfortunately, all have insufficient spatial resolution to investigate encoding at the glomerular level (table 1). MEG measures the strength of the tiny magnetic fields generated by current flow in activated neurons. Excellent temporal resolution is balanced by the crude spatial resolution necessitated by the dimensions of the individual magnetic field detectors (superconducting quantum interference devices, SQUIDs) [39]. PET can measure regional cerebral blood flow via positron emission from an injected tracer substance ($H_2{}^{15}O$). PET has a low spatial resolution because of the size of the individual gamma ray detectors which detect the gamma photon pair created in the annihilation of a positron and also a low temporal resolution [40]. The most useful variant of fMRI (blood oxygenation level detection, BOLD) measures depletion of blood oxygen levels via the influence of (paramagnetic) deoxyhemoglo-

Table 1. Methods for imaging odor-induced activity.

Method	Parameter analysed	Resolution		Repeat possible?
		Spatial [μm]	Temporal [s]	
Magnetoencephalography (MEG)[a] [39]	field current	5000	0,001	yes
Positron Emission Tomography (PET)[b] [40]	regional cerebral blood flow	10000	60	yes
Functional Magnetic Resonance Imaging (fMRI)[c] [41–42]	blood oxygenation	200–1000	30	yes
2-Deoxyglucose Uptake [21, 43–46]	glucose uptake	10	3000	no
c-fos expression [47–48]	c-fos expression level	10	300	no
Intrinsic Signal Optical Imaging [41, 49–50]	blood volume and blood oxygenation	100	60	yes
Calcium Imaging [35, 51, 55]	cytoplasmic Calcium level	1–10	0,5	yes
Voltage-dependent Dye Imaging [36, 52]	membrane potential	10–100	0,5–0,03	yes

Spatial and temporal resolution limits are estimated from actual experiments in olfaction. Thus, limits given are generally higher than those physically attainable.

[a] (Also called magnetic source imaging, MSI).

[b] With another isotope, ^{18}F, 2-deoxyglucose uptake can also be measured.

[c] Several versions of fMRI exist. The one with the best spatiotemporal resolution uses blood oxygenation level detection (BOLD), as depicted here.

bin on proton magnetic resonance [41]. The spatial resolution is down to 0.2–1 mm, with a time resolution of half a minute [42]. Due to rather limited spatial resolution, these methods have mostly been restricted to identify the brain regions, nuclei and laminar layers involved in odor processing.

Two methods, 2-deoxyglucose uptake and c-fos labeling, are of the one-shot type, not allowing repeated imaging in the same animal (table 1). Both measure metabolic activity as an indirect indicator of neuronal activity. Spatial resolution can be trimmed down to the cellular level, but temporal resolution is very low. At least several minutes of an odor stimulus are necessary to elicit a measurable response. This is a cause of concern since odor detection and recognition occurs with a single sniff. [^{14}C]-2-deoxyglucose uptake induced by odor stimulation has been used for a long time, and several detailed mapping studies have been performed with a variety of odors using this method [21, 43–46]. c-fos is an immediate-early gene, the expression of which is transiently upregulated by neuronal activity in a calcium-mediated manner [47]. Odor-induced changes in c-fos expression levels have been demonstrated [48]. Imaging c-fos has the same limitations as imaging 2-deoxyglucose.

Three methods, all based on optical recording, allow repeated imaging in the same animal (table 1). Analysed properties range from intrinsic signals (reflecting metabolic activity) to cytoplasmic calcium levels (a measure of synaptic neuronal activity) to membrane potential (a direct and general indicator of neuronal activity). Intrinsic signals are measured as change in reflected light caused by changes in deoxyhemoglobin concentration, blood volume and blood flow. The spatial resolution is somewhat larger than single glomeruli, since the metabolic adaptive changes spread over an area larger than the initial depolarization [41, 49]. This is especially true for the changes in blood flow, which moreover lag behind the changes in blood oxygen levels by more than 1 s [50]. Temporal resolution is rather low compared with imaging with indicator dyes. Increases in cytoplasmic calcium levels are triggered by pre- and postsynaptic membrane depolarization. Signals are restricted to the synaptic areas and thus appear very crisp compared with those obtained wih voltage-dependent dyes (see below). Calcium levels are measured with one of several available fluorescent indicator dyes. Note that inhomogeneous staining may introduce artifacts not occurring with intrinsic signals. The temporal resolution is around 2 Hz; the spatial resolution can be as good as individual cilia [51] when a confocal microscope is used. Voltage-sensitive dyes measure membrane potential and allow video rate temporal resolution (30 Hz) [52]. However, in practice signal-to-noise ratios are rather small, so that usually extensive averaging is needed and temporal resolution mostly is similar to that of calcium dyes. The potential problem of inhomogeneous staining exists here as well. On the other hand, with dye-staining procedures it is possible to specifically stain selected neuronal populations, e. g. ORN, thus analysing exactly the contributions of these neuronal populations to odor encoding [35, 36].

Finally, electrical recordings of single cells and populations have been performed repeatedly, and sometimes attempts were made to map the injection sites, thus sampling the spatial aspects of odorant-induced activity [53, 54].

Despite their drastic differences, several of these methods have yielded rather consistent results, even across species and phyla. It will be seen below that the emerging principle of neuronal encoding of odors is a chemotopic representation of odorants, realized either as a combinatorial or monospecific representation, depending on the odorant.

Chemotopic representation of odorants

Responses to a particular odorant appear to be restricted to a small proportion of the total surface of the olfactory bulb [35–38, 42, 44]. Related odorants tend to elicit a response in roughly the same subregion. Thus at this coarse level of spatial patterning representation of odorants is chemotopic (fig. 4). These spatial patterns are interindividually invariant, presumably because they are a consequence of the genetically fixed receptotopic map in the olfactory bulb. The response areas comprise several to many activated glomeruli or glomerular modules. In rodents such subregions have been found for responses to fatty acids, and to aldehydes [21, 38, 46]; in zebrafish subregions occur for amino acids, bile acids, and nucleotides [35, 36]. Thus, the principle of chemotopic representation has been retained during evolution in the transition from water-breathing to air-breathing animals, even though the physicochemical nature of odor stimuli and therefore their cognate receptors have changed drastically. It is noteworthy that chemotopy is observed for both the incoming signals (ORN terminals) and the output compartment of the olfactory bulb (mitral cells). The zebrafish studies have been measuring calcium levels specifically in ORN terminals [35, 36] and a related approach – imaging isolated mouse ORN retrogradely labeled from bulbar subregions – has also shown some degree of chemospecificity in the responses [55]. Qualitatively the same picture emerges from extracellular recordings of mitral cells [53]. Accordingly, 2-deoxy-glucose uptake, which labels both input and output compartment, visualizes hot spots or regions on the bulbar surface

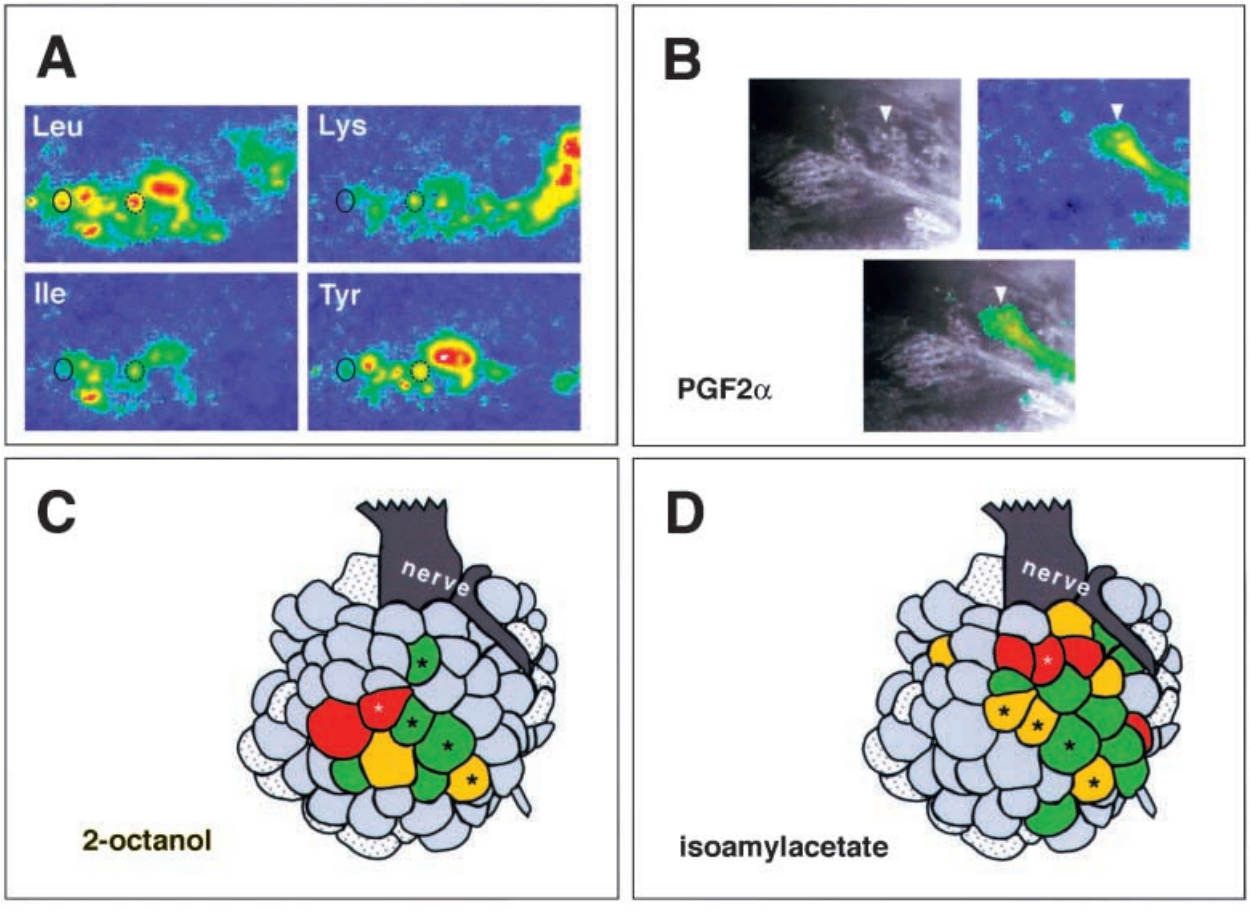

Figure 4. Combinatorial and monospecific coding in olfactory bulb and antennal lobe. (*A*) Four different amino acids (leucine, lysine, isoleucine and tyrosine) elicit partially overlapping response patterns in a lateral subregion of the zebrafish olfactory bulb. Patterns consist of many foci (glomerular modules) with differing specificities. Neuronal activity is indicated by rainbow colors from blue to red: background levels are blue, intense activity is red. Black circles: a broadly tuned module (stippled line) and a narrowly tuned one (solid line). (*B*) A pheromone, prostaglandin F2α, activates a single glomerulus in the medial olfactory bulb of zebrafish. First panel shows several glomeruli in this region, second panel shows response to PGF2α, third panel overlay of first and second panel. (*C*) 2-Octanol activates several glomeruli in the bee antennal lobe. Note the clustering of activated glomeruli. Colors green, yellow and red indicate half-maximal, three-quarter and maximal activity, respectively. Grey is background or lower activity; stippled, no measurement available. (*D*) Iso-amylacetate, a pheromone component, activates several glomeruli in the bee antennal lobe. Note the partial overlap to glomeruli activated with 2-octanol (asterisk). Figure contains data and figure elements from [35–37].

[43], which vertically extend in a columnar fashion throughout the bulbar layers [46], a result confirmed by c-fos visualization [48].
Despite the large evolutionary distance the same principle of chemotopic representation is seen even in insects. Of the ~160 glomeruli in the bee antennal lobe, a handful generally react to a particular odor [37] (fig. 4). This handful is not evenly distributed and often appears to be clustered.

Combinatorial representation of common odorants

Hot spots involved in response to a particular odorant often also participate in responses to other odorants [35, 36, 38, 44]. Overlapping responses are observed even at the level of individual glomeruli and glomerular modules (fig. 4). Thus, the tuning curves of the underlying ORs appear rather broad, with the exception of some pheromone receptors, which are narrowly tuned to individual pheromones [36, 56]. Tuning curves of dissociated single ORNs have been reported as even less specific [57, 58], but these responses may have been compromised by the loss of the enveloping mucus, which provides a particular extracellular ionic composition and contains odorant-binding proteins, possibly increasing the effective concentration of odorants. How can specific detection of an odorant be achieved using detection devices of rather low specificity? The answer lies in combinatorial representation. The combination of responses of several receptors, each with low, but different specificity, generates a unique fingerprint for each odorant or odor mixture [35, 37].
Combinatorial representation has a massive advantage as well as a serious problem. The advantage is the hugely increased coding capacity compared with more limited representation of odorants by fewer or single receptors. A well-known example from another modality is the perception of color: just three different photoreceptor pigments suffice to allow the perception of many thousands of different colors. The problem is the readout: somewhere in the brain different combinations of activated glomeruli ought to be mapped onto different neurons, which then may be said to encode the quality of an odor. Such a mapping might be realized as an array of neurons in the primary olfactory cortex, of which each individual neuron would receive synaptic input from a different array of mitral cells.

Monospecific representation of some odorants

Pheromones would seem to be good candidates for a more restricted representation by fewer or even single ORs. This class of substances is much smaller than that of common odorants without hard-wired behavioral or hormonal consequences. Thus, a limited coding capacity would not seem troublesome, and the advantage of easy readout may prevail. Insect pheromones, especially from moths, have been particularly well studied. Indeed, each pheromone component seems to be detected by a single type of highly specific and highly sensitive olfactory receptor neurons, which project to individual glomeruli within the macroglomerular complex [54]. Interestingly, bees, which lack a macroglomerular complex, represent pheromones by several glomeruli just like common odorants [37] (fig. 4). One might expect a monoglomerular representation especially for pheromone odors with some constraint on evolutionary diversification. Fish mating pheromones have retained their original function as mating hormones and thus should exhibit this constraint. Indeed, the two fish pheromones, for which imaging data are available, both show a monospecific representation by a single glomerulus [36] (fig. 4). Sensitivity for these pheromones is much higher than that for ordinary odorants [36]. Mammalian vomeronasal neurons detect pheromones with correspondingly high specificity and sensitivity [56]. Interestingly, a high specificity seems to go hand in hand with a high sensitivity, i. e. low threshold of detection, possibly because a snug fit to the binding pocket of the receptor allows for higher affinity of the binding interaction.
Thus, monospecific representation of odorants by highly specific ORs and their respective glomeruli emerges as a novel coding principle, complementing the more common combinatorial coding.

Representation or coding?

In the previous discussions I have used the terms ‘neuronal representation’ and ‘neuronal encoding’ of odors almost interchangeably. This is, strictly speaking, not correct. Neuronal representation refers to the factual patterns observed as odor-induced neuronal activity. Whether these factual patterns actually encode the odors which generate them is another question altogether. As a gedankenexperiment one may distort all connections within an olfactory bulb, massively displacing all elements, but not breaking any connections. Odor-induced spatial activity patterns would be altered beyond recognition, but the encoding might not be altered at all. This is in contrast to e. g. the detection of sound, where a change in cable length would disturb the coincidence detection via delay lines. Mapping odors to receptors and receptors to glomeruli necessarily generates a spatial pattern of odor responses. Developmental constraints on pathfinding of ORN terminals could well dictate a stereotyped glomerular map. Thus, the spatial response pattern might be an epiphenomenon of mapping an odor to the odor space

spanned by the odor response properties of all ORs. Related ORs may heed related pathfinding instructions, as this system probably has evolved alongside the odor detection system.

To examine which parts of the neuronal representation are relevant for encoding proper, one has to experimentally disturb the representation, e.g. by lesions, and study the consequences for odor perception. Conceivably, only some parts of the odor response pattern might suffice to elicit the proper odor percept, i.e. the neuronal representation might be redundant. In support of such a view experiments have been cited in which a previously learned odor preference for propionic acid was retained nearly unaltered despite lesions of a dorsomedial focal response area for the trained odor [59]. However, a single rodent olfactory bulb contains two odor maps, a lateral and a medial one, divided by a symmetry axis [29]. The symmetrical hot spot in the lateral map presumably had been spared in these lesion experiments, together with two other focal response areas [46]. These results argue for some redundancy in the olfactory code. More extended lesions removing more than 80% of the olfactory bulb do lead to some deficits in olfactory detection and discrimination. Interestingly, the severity of these deficits is correlated with the extent of the lesion [59]. Even in the absence of lesion effects on detection and discrimination of odorants there is no way to find out whether the rat's odor percept has been altered by the lesion. It may still be able to detect propionic acid and to discriminate it from acetic acid, but propionic acid might smell quite differently to the rat following the lesion.

Behavioral relevance of spatial maps

Odorant-induced spatial maps in general are complex, i.e. they involve responses of many components. Their information content – measured as pattern dissimilarity between different odorants – appears very high, even when background noise – pattern dissimilarity between repeat trials of the same stimulus – is taken into account. How much of this information content, visible to the experimenter, is actually relevant to the animal? For example, in zebrafish amino acid-induced response patterns are significantly different for all amino acids and even for different concentrations of a single amino acid [35]. Studies using goldfish and catfish have shown some degree of behavioral discrimination between amino acids [60, 61]; rats can distinguish between the structurally related propionic acid and acetic acid [59], and humans have partial success in distinguishing different functional groups as well as different chain lengths in homologous series of aliphatic compounds [62, 63]. However, clearly more work has to be done at the behavioral level to address this question in vertebrates. Detailed maps of odor-induced activity, with concentration-dependent responses, were also observed in the bee antennal lobe [37, 64]. One-trial odor learning in bees allows a detailed comparison of bee analytical capabilities at the antennal lobe and the behavioral level. It was found that odors giving rise to different patterns in the antennal lobe very often also could be discriminated behaviorally in pairwise comparisons [65]. Thus, a large proportion of the information content present in spatial maps actually may be transferred along the chain of neuronal odor processing, up to the final, behavioral level.

Spatial versus distributed coding

There has been some controversy over the extent to which representation of an odor or odorant is localized within the olfactory bulb [6, 9, 20, 43, 52, 66]. As discussed above, most imaging studies find rather localized odorant-induced responses, but studies using tiger salamander as an experimental animal have reported a rather distributed response to odors extending over much of the olfactory bulb [52]. However, in those studies activity of inhibitory and excitatory neurons was not distinguished, so that the degree of localization of the excitatory response may have been underestimated considerably. The salamander might also show species-specific peculiarities in odor representation, like the coarse morphological peculiarity of having layers within its olfactory bulb obliquely stacked, completely different from the usual concentric arrangement. Assuming the mammalian type of one OR-one glomerulus connectivity, a distributed representation of an odorant would involve the contribution of very many ORs of consequently very low specificity. The building of artificial noses with different dyes embedded in organic polymers as odor sensors has shown that it is in principle feasible to construct decently performing noses with sensors of rather low specificity and consequently with a very distributed representation of odorants [67]. However, nature seems to have opted for a higher, though still limited degree of specificity, and consequently for a more localized representation of odorants within the olfactory bulb. Actually, evolution may have found it rather difficult to generate a binding pocket within an OR that would be flexible enough to allow binding of many different odorants, i.e. possess very unspecific binding properties, but at the same time retain enough affinity to allow for efficient signal transduction.

Spatial versus temporal coding

There has been some controversy over the relative importance of spatial versus temporal patterns of odor-induced activity [6, 66, 68]. So far we have seen evidence

for a spatial map of the chemical nature of odorants. Interestingly, space in the olfactory bulb is not used to encode the spatial coordinates of odor sources in the environment. Rather, temporal patterns are analysed to achieve odor source localization. Temporal patterns also serve to encode temporal variations of the odor stimulus, which are relevant to odor detection in a number of species [69]. For the purpose of this review it is important to ask whether temporal patterns may also contribute towards encoding the chemical nature of the odor stimulus.

From the architecture of the olfactory bulb it is evident that activity distribution should change on a short time scale (fig. 3). The first ensemble of mitral cells activated by an odor stimulus will activate feedback loops, which will modify its activity. Indeed some mitral cell responses to odors change from excited to inhibited or vice versa [70]. In the bee antennal lobe spatial patterns tend to become less similar during stimulus pulse [71], possibly because inhibitory activity suppresses responses of some weakly activated receptors. This may serve to enhance contrast and thus improve odor discrimination. Such modulations could represent the 'running in' phase of the neuronal representation, and therefore would not serve to encode odorant features, but constitute a side effect of the temporal dynamics of the network.

A widespread type of temporal pattern is a population phenomenon, not detectable at the level of the individual neuron. Odor-evoked synchronization of subpopulations of neurons in the olfactory bulb, antennal lobe or procerebrum (snails) leads to oscillations in the field potential. It has been suggested that the synchronization of those mitral cells that respond to a particular stimulus results in binding of this mitral cell population and thus helps in encoding this odor [72, 73]. Indeed, mitral cells responding to the same odorant, but projecting to different glomeruli, i.e. receiving input from different ORNs, are found to be synchronized in odor-evoked oscillations [74]. In insects, oscillations in the antennal lobe are autonomous [75]; in vertebrates they might be influenced by the oscillating field potential of the sensory epithelium [76, 77]. The functional importance of oscillations towards encoding an odor has been concluded from experiments in which projection neurons were desynchronized by a γ-aminobutyric acid receptor (GABAA)-antagonist [75]. This treatment impaired the ability of bees to distinguish between aliphatic alcohols of different chain length, but left discrimination of more widely differing odorants unimpaired. However, blocking GABAergic transmission also broadens the tuning curves of individual mitral cells [78]. This should lead directly to deficits in discrimination of similar odorants, but should not affect dissimilar odorants, whose mitral cell representations are not similar to begin with. The ocurrence of such an effect has not been rigorously excluded in the bee experiments [75]. Thus a contribution of oscillation towards encoding odors remains an intriguing possibility, but has not been proven so far.

An important feature of a dynamically changing odor representation, i.e. a temporal pattern, is the time scale of the effect. In addition to the effects described above, changes in the neuronal representation of an odorant also have been observed during much longer time periods. Recording mitral cells in awake, behaving rats demonstrated a distinct variability in their odor responses [79]. Such changes seem to encode not the chemical nature, but the meaning of the odor stimulus, as they are observed whenever the contextual experience and expectation associated with that odor changes [80]. Similarly, a bee's representation of odors in the antennal lobe changes upon expectation of reward [81]. Taken together, temporal dynamics of neuronal representation of odors may have several functions, conceivably in the readout of mitral cell activity, and possibly in fine-tuning the basic machinery for odorant recognition and distinction.

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