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Group Report: Olfactory Microcircuits

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OVERVIEW

Most organisms rely on an olfactory system to detect and analyze chemical cues in the environment in the context of essential behaviors. The basic layout of the first processing centers in the olfactory nervous system is remarkably similar in diverse phylogenetic classes, including insects and vertebrates. Chemicals are detected by odorant receptor proteins expressed by olfactory sensory neurons (OSNs), which send an axon to the first processing center in the brain, the olfactory bulb in vertebrates and the antennal lobe in insects. OSNs terminate in anatomically distinct input modules, the olfactory glomeruli. In all vertebrate and invertebrate species investigated to date, each OSN expresses only one or a few odorant receptors, and each glomerulus receives convergent input from only one type of OSN. Glomeruli are, therefore, considered functional units integrating sensory input from idiotypic afferents. Even simple odors stimulate multiple odorant receptors and thus evoke odor-specific patterns of afferent activity across the array of glomeruli. Within glomeruli, OSNs make excitatory synapses onto the output neurons, the mitral cells in vertebrates, and projection neurons in insects, as well as with local inhibitory interneurons. As a result of synaptic interactions within this network, the output of a given projection neuron is not simply determined by the sensory input to the glomeruli it innervates, but also by the activity of inputs channeled through other glomeruli. In addition, synaptic interactions temporally pattern olfactory bulb/antennal lobe output activity on at least two timescales. It is currently debated how odor information is encoded in the olfactory bulb/antennal lobe, and how neuronal circuits process odor information conveyed by sensory afferents. Moreover, the development and plasticity of olfactory circuits are only beginning to be elucidated. These issues are of particular interest because OSNs and interneurons in the olfactory bulb undergo continuous turnover throughout life in vertebrates.

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FUNCTIONS AND CONSTRAINTS OF THE OLFACTORY SYSTEM

The function of any neuronal circuit can only be understood in the context of the operations it has to perform and by considering the constraints under which it operates. In other systems, it has proven fruitful to analyze their function under the assumption that sensory processing has evolved to detect statistical features of natural stimuli. For example, the receptive fields of visual or auditory neurons resemble basis functions optimized for the reconstruction of natural scenes or sounds, respectively (Olshausen and Field 1996; Lewicki 2002). The statistics of the olfactory stimulus space, however, have been analyzed only in a few specialized situations. Thus, correlations in the world of natural chemical stimuli are currently unknown. Some correlation in the response profiles of glomeruli is likely to result from the similarity of ligand binding by odorant receptors with overlapping tuning profiles. In a thought experiment, it is interesting to consider that the visual system recognizes an input pattern as a coherent object only when it has certain properties (e.g., contours delineating the shape of a house), but not when the input pixels are randomly distributed (e.g., "snow" on a TV screen). Similar considerations apply to the perception of sounds and noise by the auditory system. In olfaction, by contrast, it appears that any odorant or odorant mixture evokes a perception that is qualitatively similar to that evoked by a "meaningful" odor, similar to the perception of a mixture of colors as another color. The olfactory system may, therefore, not be specifically adapted to extract particular structure from a stimulus. Clearly, further insights into the statistics of odor stimuli and the interactions between odorant receptors and their ligands are required to understand the relationship between olfactory stimulus space and neural processing of odors.

Another consideration is that the operations performed by neuronal circuits should be reflected in the behavioral or psychophysical characteristics of the system. Humans cannot identify individual compounds in mixtures containing more than a few (3–4) components (Laing and Francis 1989). Rather, the perception of a mixture is either dominated by one intense component, or it acquires a novel character. Thus, the olfactory system appears to synthesize, rather than segment, information conveyed by different sensory channels. Sensory inputs through separate channels, such as glomeruli, therefore, likely interact during early processing in the brain.

CONSTITUENTS OF MICROCIRCUITS IN THE OLFACTORY BULB/ANTENNAL LOBE

The neuron types in the primary olfactory processing centers can be assigned to a relatively small number of classes in vertebrates and invertebrates (Table 14.1), although some differences occur across species and phyla (see Sachse and

Table 14.1 Brief overview of neuron types in the olfactory bulb/antennal lobe. In addition to sensory input from olfactory sensory neurons (OSNs), neurons in the olfactory bulb/antennal lobe also receive input from higher brain regions. These inputs are not reviewed here in any detail. For more comprehensive reviews of neurons and circuits in the olfactory bulb see Shipley and Ennis (1996), Shepherd and Greer (1998). Neurons in the invertebrate antennal lobe are reviewed in more detail by Sachse and Galizia (this volume). ACh: acetylcholine; GABA: gamma-aminobutyric acid; Glu: glutamate; M/T: mitral/tufted.

	Vertebrates			Insects		
	Known neuron classes	Transmitter phenotype	Properties	Known neuron classes	Transmitter phenotype	Properties
Sensory input	Olfactory sensory neurons	Excitatory (Glu, taurine)	Confined to glomerulus	Olfactory sensory neurons	Excitatory (ACh)	Confined to single glomerulus
Principal neurons	M/T cells	Excitatory (Glu)	Extensive extraglomerular dendrites; see text	Projection neurons	Excitatory	See text
Interneurons	Periglomerular cells ($\geq$ 5 subclasses)	Mostly inhibitory (GABA); some dopaminergic; some glutamatergic	Short or medium range	Local neurons ($\geq$ 5 classes)	Inhibitory (GABA, histamine)	Innervating all or subsets of glomeruli
	Granule cells ($\geq$ 2 subclasses)	GABAergic; small glutamatergic subpopulation	Small dendritic arbor; interacting with extensive M/T cell dendrites			
	Others: short axon cells, Van Gehuchten cells, unidentified cell	? Some glutamatergic				

Galizia, this volume). The principal neurons (mitral/tufted cells in vertebrates and projection neurons in invertebrates) receive sensory input and provide the output to higher brain regions. In many species (nonmammalian vertebrates and some invertebrates), a single principal neuron receives sensory input from a few glomeruli, whereas in mammals and other invertebrates (e.g., flies and bees), most adult principal neurons are uniglomerular. The vertebrate olfactory bulb further contains two classes of predominantly GABAergic interneurons, the periglomerular cells and the granule cells, each of which can be further subdivided. Morever, additional types of interneurons have been described in the olfactory bulb whose properties have not been examined extensively (Table 14.1). The antennal lobe of invertebrates contains GABAergic and, in some species, histaminergic interneurons that can be further subdivided into at least two classes based on their dendritic arborization in all or a subset of glomeruli.

MICROCIRCUITS IN THE OLFACTORY BULB/ANTENNAL LOBE

Microcircuits in the olfactory bulb/antennal lobe can be delineated at three levels:

1. Microcircuits on the synaptic scale are formed by reciprocal dendrodendritic synapses between principal neurons and inhibitory interneurons (Shepherd and Greer 1998). The principal neuron makes an excitatory synapse with an interneuron, which feeds back inhibition onto the principal neuron through an immediately adjacent synapse. In vertebrates, such microcircuits occur between mitral/tufted and periglomerular, as well as between mitral/tufted and granule cells. Another synaptic microcircuit consists of "synaptic triads" within glomeruli of vertebrates, where OSN input terminates on a periglomerular dendrite, which makes a synapse onto a mitral cell in the immediate vicinity. In insects, reciprocal dendrodendritic synapses and synaptic triads are formed by projection neurons and local neurons.
2. Glomeruli are viewed as microcircuits because they are among the most distinct anatomical modules in the brain and receive input from convergent, functionally uniform OSNs. Moreover, mitral cells associated with the same glomerulus are coupled by fast glutamate spillover and gap junctions at their apical dendritic tufts (Schoppa and Westbrook 2001; Urban and Sakmann 2002). In many species, glomeruli are encapsulated by a glial shell that may act as a diffusion barrier.
3. Microcircuits across glomeruli involve different interneurons. In insects, long-range interactions are mediated by inhibitory local neurons receiving synaptic input from OSNs and projection neurons and providing output to OSNs, local neurons, and projection neurons in some or all other glomeruli. In vertebrates, interactions beyond a single glomerulus are mediated by at least three different pathways. First, dendrites of periglomerular and short axon cells receive input from OSNs and mitral cells within a single glomerulus and provide dendritic output to the same, as well as axonal output to other glomeruli. Glutamatergic periglomerular and short axon cells appear to terminate on external tufted cells and presumably GABAergic periglomerular cells. These pathways extend over a short or medium spatial range and are presumed to mediate inhibition between sensory inputs to one glomerulus and mitral cells associated with the same and other glomeruli (Aungst et al. 2003). Second, mitral/tufted cells emit long-range axon collaterals that terminate on granule cells, which in turn contact distant mitral cells. Third, mitral cell synapses on extraglomerular dendrites stimulate granule cells, which in turn inhibit the same and other mitral cells. Because of the large extent of extraglomerular mitral/tufted dendrites, these interactions are long range.

The interglomerular circuits reviewed above all exert inhibitory effects on the principal neurons, which is different to other systems such as neocortex. Recent evidence from *Drosophila melanogaster*, however, suggests that lateral excitatory interactions between projection neurons also exist (Wilson et al. 2004), which would have important implications for circuit function. Currently, no candidate pathway mediating such interactions has been described in insects. In vertebrates, lateral excitation could be mediated by a small and transient glutamatergic subpopulation of granule cells (Didier et al. 2001) or by glutamate spillover between extraglomerular mitral cell dendrites (Isaacson 1999). Furthermore, the possible functions of the less intensively studied interneuron types (Table 14.1) remain to be elucidated.

PHYSIOLOGICAL FUNCTION OF MICROCIRCUITS

Reciprocal dendrodendritic microcircuits are assumed to mediate auto-inhibition of mitral cells, possibly without the need to elicit a spike in the interneuron (Chen et al. 2000; Lagier et al. 2004). Synaptic triads within glomeruli could effectively lead to a sign-inversion of OSN input onto mitral cells. Physiological evidence in moths indicates that two local neuron synapses can occur between OSNs and a projection neuron. Thus OSN input causes excitation of the projection neuron by disinhibition (Christensen et al. 1993).

The glomerular microcircuit is likely to perform multiple functions:

- The high convergence ratio of idiotypic OSNs onto principal neurons ($\sim$100:1 to 1000:1) is likely to increase the signal-to-noise ratio of the input channel and average out temporal noise.
- The coupling between apical dendrites is likely to distribute and amplify excitation across mitral cells, which may further increase the signal-to-noise ratio.
- Due to the glial barrier, the extracellular milieu within a glomerulus may be controlled independently of other glomeruli. During synaptic activity, the intraglomerular concentration of transmitters or potassium may change significantly (Jahr and Nicoll 1981). Furthermore, a change in the extracellular chloride concentration may alter the chloride reversal potential and change the effect of GABAergic synaptic transmission.
- GABA and dopamine released from periglomerular cells activate $GABA_B$ and D_2 receptors, respectively, on OSN nerve terminals in a paracrine fashion (Wachowiak and Cohen 1999; Aroniadou-Anderjaska et al. 2000; Ennis et al. 2001). This leads to a down-regulation of transmitter release and thus may mediate adaptation or gain control of individual input channels.
- Further physiological functions, for example, mediated by dendrodendritic interactions between periglomerular cells or local neurons and the principal neurons, may remain to be discovered (e.g., Hayar et al. 2004).

Multiple physiological functions have been associated with interglomerular circuits:

- Each principal neuron's spike output depends on the dendritic integration of sensory and interneuronal input. Interglomerular interactions are thus likely to shape the stimulus–response profile of output neurons in a complex fashion (see below).
- During an odor response, a fast and widespread oscillation is recorded in the local field potential that reflects the rhythmic synchronization of odor-specific subsets of neurons. This oscillatory activity is mediated by reciprocal interactions between principal neurons and inhibitory interneurons (MacLeod and Laurent 1996; Lagier et al. 2004). Inhibitory feedback onto principal neurons is provided by local neurons in insects and granule cells in vertebrates, is mediated by $GABA_A$ receptors, and does not appear to require sodium action potentials. Interglomerular interactions, therefore, underlie the synchronization of distributed, odor-specific sets of output neurons. In mammals, oscillatory synchronization appears to be facilitated by intrinsic resonant properties of mitral cells (Desmaisons et al. 1999).
- Distributed inhibitory feedback onto the output neurons may exert a function akin to gain control, both on the level of single output neurons' activity and on the level of the total output activity across the population (Friedrich and Laurent 2004).

Despite significant knowledge about microcircuits in the olfactory bulb/antennal lobe, their roles in the representation and processing of odor information are currently debated. The remainder of our report focuses on sensory representations and neural computations in the olfactory bulb/antennal lobe.

SPATIAL ORGANIZATION OF ODOR-EVOKED ACTIVITY

OSNs expressing the same odorant receptor converge onto one or a few glomeruli within the olfactory bulb/antennal lobe (Ressler et al. 1994; Vassar et al. 1994; Mombaerts et al. 1996) and appear to be functionally equivalent in their odor response properties (Wachowiak et al. 2004), thus establishing a spatial map of receptor expression. Multiple axon guidance mechanisms cooperate in this very precise targeting of OSN axons, including the odorant receptor itself (Mombaerts 2001). Recent results indicate that at least the final precision of glomerular targeting is controlled by homotypic interactions between odorant receptors expressed on OSN axon terminals (Mombaerts and Feinstein, this volume).

The number of glomeruli is correlated with the number of functional odorant receptor genes in different species. *Drosophila melanogaster* has at least 61

odorant receptor genes and 43 glomeruli, mice have ~1000 odorant receptor genes and ~2000 glomeruli, whereas rats have ~1500 functional odorant receptor genes and ~3000 glomeruli. In mammals, each odorant receptor is associated with, on average, ~2 glomeruli in each olfactory bulb. The roughly 1:1 correspondence between the number of odorant receptor genes and the number of functionally different glomeruli lead to the model that each glomerulus integrates the input to the olfactory bulb/antennal lobe conveyed by one receptor type. Glomeruli, therefore, represent separate input channels or dimensions that are, however, not orthogonal to each other.

In mammals, but not in lower vertebrates and invertebrates, the map of receptor expression is mirror symmetric about a roughly vertical plane; that is, most idiotypic OSNs project to glomeruli at similar coordinates in the medial and lateral hemisphere of each olfactory bulb. Moreover, external tufted cells receiving input from a given glomerulus project to locations in the granule cell layer in the vicinity of the homotypic glomerulus in the other olfactory bulb hemisphere. Currently, the functional importance, if any, of the mirror-symmetric organization of the mammalian bulb is unresolved.

The spatial coordinates of idiotypic glomeruli are preserved, but not with exquisite precision. Rather, the position of a given glomerulus can vary within 1–2% of the surface of the olfactory bulb across individuals and between hemispheres of the same olfactory bulb. As a consequence, immediate neighborhood relationships between glomeruli are variable (Strotmann et al. 2000).

Odor-evoked activity across the array of glomeruli has been visualized by a variety of techniques, including 2-deoxyglucose uptake, *c-fos* expression, fMRI, intrinsic signal imaging, and calcium imaging (Stewart et al. 1979; Guthrie et al. 1993; Friedrich and Korsching 1997; Johnson et al. 1999; Rubin and Katz 1999; Sachse et al. 1999; Meister and Bonhoeffer 2001; Wachowiak and Cohen 2001; Xu et al. 2003). Even single chemical compounds activate multiple glomeruli and single glomeruli respond to multiple odorants, presumably because each odorant receptor can be activated by multiple compounds (Araneda et al. 2000). Odor information is, therefore, contained in a combinatorial pattern of activity across the array of glomeruli. Patterns evoked by chemically related odorants are often similar. Thus, microcircuits in the olfactory bulb/antennal lobe must analyze spatially distributed activity patterns to extract stimulus information.

An important question is whether the spatial relationships between glomeruli in the map reflect similarities between the respective odorant receptors' response profiles. Such an organization could create a *chemotopic* map, in which features of the chemical stimulus space are spatially mapped onto the array of glomeruli. Glomeruli responding similarly to a subset of odors sharing obvious chemical features are sometimes clustered spatially. For example, in experiments using 2-deoxyglucose uptake, intrinsic signal imaging, and fMRI, aliphatic aldehydes were found to activate glomeruli in an anteromedial region of

the dorsal olfactory bulb. However, even within this region only a subset of glomeruli responded to aliphatic aldehydes, and these odors also stimulated glomeruli in other locations. Studies using imaging of calcium indicators or a transgenic fluorescent activity probe in OSN axon terminals (Wachowiak and Cohen 2001; Bozza et al. 2004) yielded only weak evidence for a chemotopy of aldehyde responses in the dorsal olfactory bulb. Moreover, individual glomeruli within a region loosely defined by its response to a class of odorants can also respond to other, dissimilar sets of stimuli. As a result, the spatial proximity of glomeruli appears to be only weakly correlated with the similarity of their overall response profile (Friedrich and Stopfer 2001). The structure of chemotopic maps is, therefore, not well understood and deserves further experimental attention. Nonetheless it is clear that a chemotopic organization, if it exists, is much more fractured than topographic maps in other sensory systems, possibly relating to the complexity and high dimensionality of the stimulus space (Friedrich and Stopfer 2001). It is also interesting to note that from the perspective of neuronal wiring, spatial distance between all glomeruli is equal in insects, because all interglomerular connections pass through the central area of the spherical antennal lobe (Sachse and Galizia, this volume).

It is now firmly believed that the identity of active units in the combinatorial pattern contains essential stimulus information. Currently unresolved, however, is the question whether the position per se of glomeruli in the map is important for the decoding of glomerular activity patterns. It is, for example, possible that the given arrangement of glomeruli simply minimizes the total wiring length of circuits in the olfactory bulb/antennal lobe or is a byproduct of the axon guidance mechanisms underlying glomerular targeting, that is, a developmental process. In a thought experiment, the shuffling of glomerular positions in the map does not affect the information conveyed by activity patterns. Moreover, the information could potentially be extracted in the same way after shuffling if all connections in the network were kept intact. However, the system may still require positional information for its function. For example, interactions through gap junctions or electrotonic mechanisms may require a particular spatial arrangement of functional units within the circuit. Furthermore, it is formally possible that the establishment of correct synaptic connections between target neurons and their inputs relies on axon guidance mechanisms that read positional cues and would be fooled when glomerular positions are scrambled. Currently, there is no conclusive evidence arguing either for or against a role for spatial position in olfactory system function. This is clearly one important open question. Ideally, the problem should be approached by (genetic) manipulation of glomerular positions without otherwise disturbing the system and subsequent tests of the olfactory system's performance. This is, however, beyond the current realms of experimental possibility.

In the deeper layers of the olfactory bulb, focal excitation of a few glomeruli produces a cone of activity that fans out with increasing depth (Guthrie et al.

1993). Hence, glomerular activation spreads laterally within the olfactory bulb and probably also in the antennal lobe (Wilson et al. 2004). It is still unresolved whether the olfactory bulb shares a columnar functional organization with other brain structures. A "reductionist" analysis of basic properties of olfactory microcircuits using focal stimuli may be fruitful to derive insights into the mechanisms by which microcircuits process more complex glomerular activity patterns evoked by realistic stimuli.

TEMPORAL PATTERNING OF OUTPUT FROM THE OLFACTORY BULB/ANTENNAL LOBE

Olfactory microcircuits are renowned for their temporal dynamics. Temporal patterning of the activity of output neurons on at least two timescales has been observed in all species studied, vertebrates and invertebrates alike: (a) slow, aperiodic modulations of firing rate on a timescale of one or a few hundred of milliseconds, and (b) fast oscillatory synchronization with a precision of a few milliseconds. Further temporal patterns are observed in some species.

Odor-evoked Slow Temporal Patterning

Output neurons respond to odor stimuli with modulations of their firing rate during the first hundreds of milliseconds after stimulus onset. These firing rate modulations can include successive excitatory and inhibitory epochs resulting from circuit interactions in the olfactory bulb/antennal lobe. In mammals, odor-specific modulations of firing probabilities occur during each breathing cycle. The mechanisms underlying slow temporal patterning of output neurons are still elusive. Candidate pathways mediating these effects include all of the interglomerular microcircuits mentioned above. In locusts, slow temporal patterns were not substantially affected by $GABA_A$ or $GABA_B$ antagonists (MacLeod and Laurent 1996).

The slow temporal modulation of firing probability evoked by one odor is different between output neurons, and different odors evoke distinct slow temporal firing patterns in the same output neuron. As a result, the pattern of activity (firing rate) across the population of output neurons evolves in an odor-specific manner after stimulus onset. After a rapid change during the initial phase of the odor response, activity patterns asymptotically approach a relatively stable state after a few hundred milliseconds.

In zebrafish, locusts, and possibly moths, it has been shown that the dynamic change of spiking activity patterns evoked by similar odors results in a decorrelation of activity patterns evoked by related odorants (Friedrich and Laurent 2001; Stopfer et al. 2003; Daly et al. 2004; Friedrich and Laurent 2004): immediately after response onset, activity patterns evoked by related odors are similar, possibly because output neurons are driven to a large extent by their sensory

inputs, which respond similarly to related stimuli. Subsequently, however, patterns of output activity change, following trajectories that are specific for each stimulus and diverge over time. As a result, activity patterns evoked by related stimuli become more distinct, and the discrimination of patterns becomes significantly more reliable during the first few hundred milliseconds of the response. Hence, olfactory microcircuits perform a computation (pattern decorrelation) that appears important for the discrimination of "odor images" across glomeruli.

Odor-evoked Fast Oscillatory Synchronization

Odor-evoked population activity in the olfactory bulb/antennal lobe has an oscillatory component with frequencies ranging between 15 and 40 Hz in insects and lower vertebrates, and in the beta (15–30 Hz) and gamma (30–100 Hz) range in mammals. This oscillatory synchronization is mediated by reciprocal interactions between principal neurons and inhibitory interneurons in interglomerular microcircuits (see above). The spatial pattern of this oscillatory activity is widespread and only weakly reflects the discrete pattern of glomerular input. Within each oscillation cycle, only an odor-specific subset of output neurons synchronizes, while others fire without any apparent temporal relation to the oscillation. Hence, odor-specific subsets of spikes transmitted to higher brain regions are synchronized.

Since the integration of synaptic inputs in neurons can be exquisitely sensitive to temporal proximity, synchronized spiking may transiently establish neuronal ensembles that carry particular information accessible by coincidence detection-based readout mechanisms. Indeed, Kenyon cells in the mushroom body receiving input from projection neurons in insects are efficient coincidence detectors (Laurent and Naraghi 1994; Perez-Orive et al. 2002). The short temporal integration window is established by two mechanisms. First, intrinsic mechanisms, probably involving voltage-gated Ca^{2+} and possibly Na^{+} channels, boost synaptic transients. Second, projection neurons also target a small pool of GABAergic neurons elsewhere in the brain, which in turn provides strong and nonspecific feedforward inhibition onto Kenyon cells. This inhibition arrives at the Kenyon cell dendrite with a delay relative to the excitatory projection neuron input during the same cycle, thereby defining a sharp integration time window. Each Kenyon cell receives input from a small fraction ($\sim$2.5 %) of the projection neuron population. Hence, Kenyon cells in the mushroom body analyze selectively synchronized spiking across an evolving subpopulation of neurons during each oscillation cycle (Laurent, this volume).

In vertebrates, little is known about the temporal integration properties of neurons downstream of the olfactory bulb. Moreover, while output from the antennal lobe is conveyed to only two target areas in insects, output from the olfactory bulb is transmitted to at least five different areas in vertebrates. Therefore, it is of prime importance to study the properties of neurons innervated by

mitral/tufted cells to understand which of the properties of the temporally structured pattern of activity across olfactory bulb outputs may be relevant for further processing.

The mechanisms of readout by Kenyon cells in the mushroom body suggest that these neurons selectively access information from synchronized spikes, while other spikes are discarded. This does not, however, imply that nonsynchronized spikes are irrelevant. They could, for example, play important roles in interglomerular microcircuits within the olfactory bulb/antennal lobe. Furthermore, it is possible that nonsynchronized spikes also convey information that may be retrieved by target neurons with longer integration time constants. Indeed, recent results support the hypothesis that patterns of nonsynchronized spikes convey important information accessible by using a longer integration window (Friedrich et al. 2004). These results suggest that due to the synchronization of subsets of output neurons, different messages may be multiplexed and conveyed simultaneously to higher brain regions by the across-neuron pattern of spiking in mitral/tufted cells.

The above considerations given to operations performed by olfactory microcircuits on afferent glomerular activity have important implications concerning the representation of stimulus information in the olfactory bulb/antennal lobe:

- In the inputs and the outputs of the olfactory bulb/antennal lobe, odor information conveyed by the response of single elements is limited because of their moderate odor selectivity. Rather, stimulus information has to be retrieved from the pattern of activity across many elements (glomeruli or output neurons). Microcircuits, therefore, appear to transform one combinatorial representation into another.
- Currently, it is uncertain whether the position of active units is necessary for the function of olfactory circuits. Theoretically, it is possible that the system relies on positional cues (e.g., during the development of connectivity), even though information is contained purely in the identity of active neurons. An experimental approach to this problem has thus far proven difficult.
- One computation appears to be a decorrelation of activity patterns by the dynamic distribution of activity across output neurons. The underlying synaptic mechanisms are, however, not known precisely.
- The transient synchronization of ensembles of output neurons is an important factor in determining the readout of antennal lobe activity by Kenyon cells in locusts. Synchronization may, therefore, play an important role in the transmission of information from the antennal lobe. Further results, however, are required to understand the role of oscillatory synchronization in other insect species and in vertebrates.
- Available evidence indicates that temporal activity patterns observed in output neurons reflect the dynamic reorganization of instantaneous

activity across the population. Theoretically, downstream neurons may also detect the temporal evolution of firing in single neurons or ensembles. However, there is currently no evidence for mechanisms supporting this hypothesis.

These considerations indicate that odor information resides in (a) the identity and instantaneous activity of elements in activity patterns and (b) their synchronization. These features would, therefore, be considered part of the "code." Other properties of odor-evoked activity in the olfactory bulb/antennal lobe, such as the position of glomeruli/neurons or the slow temporal patterning of activity, may not be analyzed directly by downstream targets; further results are needed to resolve this question. If so, they would constitute a "format" of odor-encoding activity patterns. Moreover, they are likely to play essential roles in important computations within the olfactory bulb/antennal lobe that affect the "code," such as the decorrelation of sensory inputs.

FUNCTION OF THE OLFACTORY BULB/ANTENNAL LOBE

Much contemporary research revolves around the general computations performed by microcircuits in the olfactory bulb/antennal lobe. It is, therefore, worth considering the function of the olfactory bulb/antennal lobe in more general terms. It is currently contended that in the periphery, odors are represented by distributed patterns of activity across OSNs or glomeruli. Due to overlapping response profiles of odorant receptors, and possibly due to correlations in the world of natural stimuli, these patterns are not evenly distributed within the neural space (in which each dimension represents the activity level of one OSN type/glomerulus). Patterns are instead clustered, complicating the discrimination of individual stimulus representations. This inherent structure in the world of peripheral odor representations leads to the assumption that one function of olfactory processing in the olfactory bulb/antennal lobe is to promote the separation of overlapping odor representations.

In the architecture of interglomerular microcircuits within the olfactory bulb, interactions resulting in inhibition of output neurons are prominent (see above). This fact gave rise to the hypothesis that lateral inhibition in the olfactory bulb/antennal lobe may contribute to odor discrimination. Drawing upon existing knowledge about other systems, the radial and horizontal processing of visual information in the retina has been suggested as a conceptual model. Horizontal cells modify the output of photoreceptors, whereas amacrine cells interact more directly with bipolar/ganglion cells (Shepherd and Greer 1998). In this analogy, the periglomerular cells are synonymous with horizontal cells and granule cells are equivalent to amacrine cells. This analogy leads to the hypothesis that the olfactory bulb/antennal lobe enhances contrast or detects edges in

odor-evoked patterns of sensory input by narrowing the response profiles of output neurons as compared to their inputs. Some experimental evidence supporting this hypothesis exists (Yokoi et al. 1995) but this evidence has recently been challenged (Laurent 1999). Moreover, recent analyses of the dynamics and reorganization of activity patterns are not consistent with a simple refinement of afferent "odor images." Despite some similarity in the general layout of circuits, the spatial retinal processing as a conceptual model for system function is, therefore, under debate. In another analogy to the retina, it has been proposed that odor processing in the olfactory bulb/antennal lobe may be more akin to the processing of colors by opponent channels. This proposal is intriguing and receives support from calcium imaging data (Sachse and Galizia, this volume). Due to the complexity of the olfactory stimulus space and the large number of channels (glomeruli), it is difficult to determine whether interglomerular microcircuits in the olfactory bulb establish "odor-opponency channels." Moreover, it does not account for the dynamic properties of olfactory bulb/antennal lobe output.

Another perspective has emerged recently, which views microcircuits in the olfactory bulb/antennal lobe as a (nonlinear) dynamical system (Laurent et al. 2001). The considered class of dynamical systems transforms stationary input patterns into time-varying output patterns, moving along input-specific trajectories in coding space (see Laurent, this volume). In this framework, a primary function of olfactory microcircuits would be to enable odor-specific dynamics that can decorrelate input patterns. Such a system would distribute clustered input patterns more evenly in coding space and, thus, optimize the use of the coding space for discrimination and other tasks. In this framework, the olfactory bulb/antennal lobe would reformat combinatorial representations so as to facilitate their readout. This view is generally consistent with the reorganization of odor-evoked olfactory bulb/antennal lobe output observed experimentally (Friedrich and Laurent 2001, 2004; Laurent 2002; Stopfer et al. 2003). Such a redistribution of activity in coding space would be considered successful (or "optimized") if single downstream neurons could immediately extract any relevant information from it. In other words, after evenly distributing representations in coding space, it should be possible to extract desired information by a simple classifier, such as a support vector machine (Fernandez Galan et al. 2004). Indeed, the extreme specificity of Kenyon cell odor responses in the locust indicates that very specific and high-level information can be extracted from the antennal lobe output in one synaptic step (Laurent, this volume).

An intriguing parallel is apparent between the dynamical systems view of the olfactory bulb/antennal lobe and liquid state machines, which have been proposed as a theoretical framework for the function of cortical circuits (Maass et al. 2002; Maas and Markram, this volume). While it is problematic to apply the liquid state machine model in its generalized form to the specific computations performed by the olfactory system, a more specialized form may lead to valuable theoretical insights into olfactory system function.

In summary, alternative general views of the function of olfactory microcircuits have emerged and are presently being debated vigorously. Common to these views is the notion that the olfactory bulb/antennal lobe does not extract highly specific information by creating outputs tuned very narrowly to particular stimuli or features. Rather, microcircuits appear to reformat odor representations for further use. Precisely how representations are reformatted, and what the use of the operations is for further processing, is controversial. According to one view, the output would be a refinement of afferent inputs without the need for dynamics, whereas under the other view, the output would be a fundamental reorganization of activity patterns requiring dynamics. Further research will certainly address these questions. Moreover, many views are motivated by the (perhaps subconscious) assumption that one primary goal of the olfactory system is to achieve fine odor discrimination, although olfactory circuits may, in addition, have evolved to achieve other tasks.

PLASTICITY OF OLFACTORY MICROCIRCUITS

Olfaction is often studied in the context of learning and memory. Interestingly, very few reports have appeared that describe synaptic plasticity associated with learning and memory in other systems, such as spike-timing-dependent synaptic modulation or structural dendritic plasticity in the olfactory bulb/antennal lobe. Nevertheless, experience-related plasticity is observed at multiple levels. For example, prenatal exposure of pregnant mothers to food odors causes enhanced sensory responses to these odors in pups after birth, and supervised and nonsupervised plasticity mechanisms can change odor-evoked spatial or temporal activity patterns in the olfactory bulb/antennal lobe (Freeman and Schneider 1982; Kendrick et al. 1992; Faber et al. 1999; Stopfer and Laurent 1999). The olfactory bulb/antennal lobe receives centrifugal inputs that express neuromodulators (acetylcholine, serotonin, and norepinephrine in vertebrates and octopamine, dopamine, and serotonin in insects). These neuromodulators act at different sites and may modulate the function of olfactory microcircuits in a concerted fashion (e.g., Castillo et al. 1999). Noradrenergic inputs have, in particular, been implicated in the local modulation of dendrodendritic synaptic microcircuits between mitral and granule cells in the context of olfactory memory formation (Kendrick et al. 1992). In insects, octopamine and dopamine are likely to be important neuromodulators in the antennal lobe and higher brain regions (Hammer and Menzel 1998; Schwaerzel et al. 2003).

A remarkable feature of the vertebrate olfactory system is the lifelong turnover of both OSNs and interneurons in the olfactory bulb (see Lledo, this volume). Neuronal turnover is not observed in the olfactory system of invertebrates, possibly because their lifespan is usually much shorter. The life span of a mature vertebrate OSN is about 90 days but can be prolonged to 12 months under certain conditions, indicating that it is regulated by environmental factors.

Blocking airflow through one naris reduces the formation of new neurons, raising the question as to which mechanisms control stem cell proliferation. One obvious role of ongoing turnover of OSNs is the replacement of OSNs that have been damaged by exposure to pathogens or otherwise. It is currently unknown whether the turnover of OSNs can also contribute to the adaptation of individuals to slow changes of the natural odor space.

Within the adult olfactory bulb, interneurons are continuously replaced by new neurons that originate from the subventricular zone and migrate to the olfactory bulb in the rostral migratory stream. In the embryo, bulbar interneurons are derived from neuronal precursors in a different proliferation zone, the lateral ganglionic eminences. Up to 80,000 new neurons arrive in the adult olfactory bulb every day, and ~1% of the granule cells are turning over at each moment. Conceivably, the turnover of neurons in the adult olfactory bulb could modify the function of olfactory microcircuits in important ways, on a timescale of weeks. Moreover, it is an interesting question how the function of olfactory microcircuits is maintained during the continuous integration of new neurons. New neurons in the olfactory bulb gradually mature over a period of ~4 weeks. However, under normal conditions, ~50% of the newborn neurons will undergo apoptosis within a few days following their integration in the network. The rate of apoptosis, but not the rate of turnover, depends on external factors (see below). Hence, the addition of new neurons to the olfactory bulb can be regulated by modulating neuron survival.

If newborn interneurons are necessary for bulbar function or plasticity, disruption of cell migration in the rostral migratory stream would be expected to affect olfactory processing or learning. Indeed, in PSA-NCAM-mutant mice, the number of newborn granule cells is reduced by ~40% and odor discrimination is impaired (Gheusi et al. 2000). One hypothesis is that the impairment is due to reduced GABAergic inhibition of mitral cells by granule cells, which is likely to play a role in the function of interglomerular microcircuits (see above). Furthermore, the rate of apoptosis is reduced in animals exposed to an enriched olfactory environment. This effect is associated with more robust and extended long-term memory measured in a simple task. In general, these results suggest a relationship between interneuron number and system performance.

The maturation of adult-generated neurons does not recapitulate the maturation of the same interneuron types during embryogenesis (Carleton et al. 2003). An important difference in the maturation of granule cells is that Na^+ channels conferring spiking activity are expressed early during maturation in the embryo but appear very late in the maturation of adult-generated granule cells. This may be a mechanism to prevent the interference of immature granule cells with the functional circuits already in place. An important step in the maturation of newborn neurons is the exit from the rostral migratory stream into the granule cell layer of the olfactory bulb. Because migration is predominantly radial after leaving the rostral migratory stream, this step determines the region where the new

neuron will be integrated. Exit from the rostral migratory stream is blocked by NMDA receptor antagonists, raising the possibility that the recruitment of newborn neurons is site-specific and regulated by activity in the olfactory bulb. Ongoing experiments, therefore, address the question of whether sensory experience or odor learning may recruit newborn neurons specifically to those microcircuits that participate in the relevant behavior.

CONCLUSIONS AND AVENUES FOR FUTURE RESEARCH

The function of the olfactory system has been studied at multiple levels, ranging from molecular, biophysical, and anatomical studies on individual neurons to systems function, theory, and behavior. Obviously, all of these levels are essential to arrive at an integrated understanding of the system with its various levels of microcircuit organization. In comparison to other neural systems, such as the cerebral cortex, some essential questions—especially at the systems level—appear easier to approach in the olfactory system. For example, the statistics of neural inputs to the system are directly measurable, and its output may be more directly interpretable in the context of behavior. It has, therefore, been proposed that the olfactory system provides an opportunity to obtain meaningful data at the systems level, which is often a bottleneck in our understanding of complex neural circuits. Such data would also provide a basis for detailed theoretical approaches.

Currently lacking is precise information on the connectivity matrices between individual neurons and neuron types, both within and beyond the olfactory bulb/antennal lobe. This is required to understand how system functions arise from the integration of neurons into circuits and should be addressed by anatomical and physiological studies.

Although the olfactory bulb/antennal lobe has been the main focus of this review, functional insights at other levels of the olfactory system are also of primary interest, both in their own right and for the interpretation of the function of the olfactory bulb/antennal lobe. To understand the goal of olfactory processing better, the statistics of the stimulus space and glomerular odor representations must be known. Addressing these issues entails the analysis of natural olfactory habitats and studying interactions between odorant receptors and their ligands. At the same time, knowledge about the mechanisms by which the output of the olfactory bulb/antennal lobe is read by higher brain structures is necessary to recognize relevant features of odor-encoding activity patterns. Especially in vertebrates, more experimental data are needed.

Although our report has emphasized the commonalities between olfactory circuit structure and function, obvious differences also occur between species. For example, in some species (most vertebrates and some insects), principal

neurons are multiglomerular, while in others, they are uniglomerular. By analyzing the correlation between structural and functional differences across species in a comparative approach, insights into the function of microcircuits or the contribution of their constituents may be derived.

The plasticity of microcircuits, particularly the ongoing replacement of interneurons throughout life in vertebrates, is a remarkable characteristic of the olfactory system. Further studies of this phenomenon are of interest both with respect to understanding neuronal plasticity and with respect to the function of stem cells and neurogenesis during adulthood.

Finally, many issues discussed above are currently under debate and need to be addressed further. For example, no general consensus has been reached with respect to the role of oscillatory synchronization, or about the fundamental computations performed in the olfactory bulb/antennal lobe. Furthermore, chemotopic maps and the possible role of position in olfactory system function deserve further attention. It is anticipated that multiple and extensive experimental and theoretical efforts will be needed to resolve these questions.

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