

8/13/01

For: Handbook of Olfaction and Gustation (Second Edition)
Richard Doty, Editor, Marcel Dekker, Inc, New York, 2001

SENSORY PHYSIOLOGY OF CENTRAL OLFACTORY PATHWAYS

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Introduction

Central sensory pathways construct representations of the external world based on a combination of spatiotemporal patterns of receptor neuron input and a running average of internal activity patterns. In most sensory systems, the relationship between stimulus energy in the external world and the spatiotemporal pattern of receptor neuron activity appears relatively straight-forward. For example, spatial relationships of visual stimuli are maintained by spatial patterns of visual receptor cell activity in the retina and subsequent precise retinotopic projections to visual cortical centers. Similarly, auditory stimulus frequency information is extracted by a spatial gradient of frequency sensitivity along the basilar membrane of the cochlea and subsequent precise tonotopic projections to auditory cortical centers. Lateral inhibition along both the visual and auditory sensory pathways help more precisely define the specific visual spatial pattern or auditory frequency of the initiating stimulus.

However, how the olfactory system constructs a representation of the external odor world is not so obvious. Simple analytical chemistry does not appear to be sufficient to account for olfactory perception. Molecules that are structurally very similar may be perceptually very different, and visa versa. Furthermore, it is not clear at present which features of olfactory stimuli the olfactory system uses for odorant discrimination (e.g., carbon chain length, presence and location of functional groups, molecular resonant frequency). While further analysis of ligand-receptor interactions at the olfactory receptor sheet should help clarify this issue (Singer & Shepherd, 1994), it does appear that, similar to other sensory systems, odorant stimuli are broken down into component features, each recognized by a particular receptor, and the problem for the remainder of the olfactory pathway is to reconstruct those features into a perceptual whole.

In addition to discriminating pure, isolated stimuli, a problem for all sensory systems is that they must function in the real world. Thus, the visual system is able to recognize a stimulus partially obscured by other objects and the auditory system can interpret speech against a background of other noises. Similarly, the olfactory system is able to recognize garlic in the spaghetti sauce even when the odors from the freshly cut

lawn are blowing in the window. On the other hand that garlic odor is a mixture of many individual molecular components yet is perceived as a single stimulus.

This review will focus on what is currently known about the sensory physiology of central olfactory structures that allows odorant discrimination and odorant mixture analysis and synthesis to occur. This review will focus on terrestrial vertebrates although striking similarities with invertebrates will be noted (Christensen & White, 2000). While excellent work has been done on synaptic physiology of this system, much of which utilized in vitro preparations (see Haberly, 1998; Shepherd & Greer, 1998; Shipley & Ennis, 1996 for reviews), this review will focus on in vivo sensory physiology in vertebrates and response to odorants.

The central olfactory system of vertebrates (Fig. 1) includes the main olfactory bulb and the primary olfactory cortex (piriform cortex). In mammals, a higher order olfactory cortex exists, the orbitofrontal/insular cortex. The thalamic relay to the olfactory orbitofrontal cortex is the dorsomedial nucleus of the thalamus, although a direct projection from the piriform cortex to the orbitofrontal cortex also exists. While odorant responses have been examined in a number of other central brain regions, such as the amygdala (Cain & Bindra, 1972; Schoenbaum et al., 1999; Tanabe et al., 1975a) and hypothalamus (Karadi et al., 1989; Kogure & Onoda, 1983; Pfaff & Gregory, 1971; Scott & Pfaffmann, 1972), the sensory physiology of the main olfactory bulb, piriform cortex and orbitofrontal cortex will be emphasized here.

Main Olfactory Bulb

Glomerular layer

Olfactory receptor axons synapse onto second order olfactory neurons within the main olfactory bulb (Fig. 2). As described elsewhere in this volume, single receptor neurons appear to express a single receptor protein. Receptor neurons expressing the same receptor protein, while randomly scattered within one of four zones of the olfactory receptor sheet, converge on two individual glomeruli within the olfactory bulb, one located dorsomedially in the bulb and one more ventrolaterally (Buck, 1996; Mombaerts, 1999). Thus, the approximately 2000 glomeruli of the rodent olfactory bulb are believed to each receive relatively homogenous input from neurons expressing

one of the 1000 different receptor proteins. Furthermore, receptor neurons expressing similar or homologous receptor genes (Tsuboi et al., 1999), and with similar odorant receptive fields (Bozza & Kauer, 1998) tend to terminate in neighboring glomeruli, enhancing the possibility of lateral inhibitory interactions between similar molecular features. The high convergence ratio of olfactory receptor neurons to mitral cells within a glomerulus (1000 to 1) significantly amplifies sensitivity of the system by reducing odorant response threshold in mitral cells compared to olfactory receptor neurons (Duchamp-Viret et al., 1989).

Vertebrate olfactory receptor neurons have relatively broad odorant receptive fields (Duchamp-Viret et al., 1999; Kaluza & Breer, 2000; Malnic et al., 1999; Sato et al., 1994; Sicard & Holley, 1984). Similarly, individual main olfactory bulb glomeruli respond to multiple odorants, although each odorant produces a unique spatial pattern of glomerular activation as determined by 2-deoxyglucose autoradiography (Johnson & Leon, 2000; Johnson et al., 1998; Johnson et al., 1999; Jourdan et al., 1980; Stewart et al., 1979), c-fos immunohistochemistry (Guthrie et al., 1993; Sallaz & Jourdan, 1993), and optical imaging (Joerges et al., 1997; Rubin & Katz, 1999; Uchida et al., 2000). A recent optical imaging study of intrinsic signals in the rat revealed that the specific functional group present in an odorant determined the glomerular zone of activation (e.g., anteromedial or dorsolateral), while more subtle features of the odorant molecule (e.g., carbon chain length or branching pattern) determined which glomeruli within that zone would be activated (Uchida et al., 2000). This spatial pattern of glomerular activation is believed to encode the molecular features present in the sampled odorant. However, while individual odorant features may be encoded by individual glomeruli, odorants in a mixture can interact at the receptor level and/or within the glomerular layer to produce odorant mixture specific glomerular activation in both vertebrates (Bell et al., 1987) and invertebrates (Cromarty & Derby, 1998; Derby et al., 1991; Joerges et al., 1997). Thus, some aspects of odor synthesis may occur even before the first central synapse of the olfactory pathway.

Within glomeruli, olfactory receptor axons synapse onto the primary output neurons of the olfactory bulb, mitral cells, as well as onto a second class of output neurons, tufted cells (Fig. 2). Juxtglomerular cells, a class of olfactory bulb interneurons that mediate interglomerular inhibition also receive direct olfactory nerve

input. Olfactory receptor axons release the excitatory amino acid glutamate from their axon terminals and activate both NMDA and non-NMDA receptors on second order neuron dendrites (Berkowicz et al., 1994; Ennis et al., 1996).

Many juxtglomerular cells express both the inhibitory amino acid neurotransmitter GABA and dopamine (Gall et al., 1987; Kosaka et al., 1985). Juxtglomerular cells respond to odorants with simple depolarizations and bursts of spikes and may directly mirror olfactory nerve input (Wellis & Scott, 1990; Onoda & Mori, 1980). One role of juxtglomerular cell GABA release may be to pre-synaptically inhibit glutamate release from olfactory nerve axons (Aroniadou-Anderjaska et al., 2000; Nickell et al., 1994). Mitral/tufted cells also express GABA receptors (Bowery et al., 1987) and thus, juxtglomerular cell activation could mediate either lateral or feedforward inhibition of these output neurons. In the frog, activation of either GABA_B receptors or dopamine D₂ receptors in the glomerular/external plexiform layers results in a decrease in mitral cell spontaneous activity with a sparing of odorant-evoked activity (Duchamp-Viret et al., 1997; Duchamp-Viret et al., 2000). These results suggest that one role of inhibition in the glomerular layer may be to increase the signal-to-noise ratio of bulb output, and thus odor saliency. In the rat, dopamine D₂ receptors are located on pre-synaptic olfactory receptor cell axons (Coronas et al., 1997; Koster et al., 1999; Nickell et al., 1991). Stimulation of dopamine receptors reduces olfactory nerve evoked potentials in olfactory bulb (Gurski & Hamilton, 1996; Hsia et al., 1999; Nowycky et al., 1983), and more specifically activation of D₂ receptors in rat reduces glomerular layer odorant-evoked spatial patterns of 2-deoxyglucose uptake (Sallaz & Jourdan, 1992). In contrast, D₂ receptor blockade or reduction in olfactory bulb dopamine content enhances and blurs odorant-specific glomerular activation (Guthrie et al., 1990) and increases mitral/tufted cell responsiveness to odorants (Wilson & Sullivan, 1995). In accordance with these physiological results, the D₂ receptor agonist quipirole reduces odor detection performance in a dose dependent manner (Doty & Risser, 1989). Interestingly, systemic injection of the D₁ receptor agonist SKF38393 enhances odor detection performance (Doty et al., 1998).

Juxtglomerular cell dopamine expression is highly odorant experience dependent. Olfactory bulb dopamine levels increase following brief odorant exposure (Coopersmith et al., 1991), while odorant deprivation significantly reduces bulb

dopamine content (Brunjes et al., 1985; Wilson & Wood, 1992) via an experience-dependent decrease in tyrosine hydroxylase expression (Baker, 1990; Baker et al., 1993; Kosaka et al., 1987; Puche & Shipley, 1999). Given the described effects of dopamine on odorant responses, glomerular layer dopamine may function as a form of experience-dependent volume control – during periods of intense odorant stimulation, dopamine may suppress olfactory nerve input, perhaps to maintain bulb activity within an optimal dynamic range. During periods of weak odorant stimulation, dopamine levels fall to enhance sensitivity of the system. This enhanced sensitivity, however, comes at the price of a decrease in glomerular and mitral/tufted cell odorant discrimination (Guthrie et al., 1990; Wilson & Sullivan, 1995). A strikingly similar dopaminergic mechanism of gain control exists in the vertebrate retina. Dark adaptation leads to changes in dopamine release and a reduction in lateral inhibition in the retina which increases sensitivity but reduces spatial resolution (Daw et al., 1989).

The olfactory bulb glomerular layer thus creates an odorant specific spatial feature map through precise projection patterns of olfactory receptor axons, while inhibition in the glomerular layer acts as both an experience-dependent gain control and allows sharpening of the odorant-specific spatial patterns.

Olfactory bulb output neurons

In the rat, mitral cells extend an apical dendrite into a single glomerulus, with each glomerulus innervated by approximately 25 mitral cells (Fig. 2; Shepherd & Greer, 1998). Mitral cells respond to olfactory nerve input with both a fast AMPA receptor mediated depolarization and a slower, NMDA receptor mediated depolarization (Berkowicz et al., 1994; Ennis et al., 1996). Mitral cell responses to odorants are generally more complex than the simple responses described for juxtglomerular neurons above, reflecting the additional circuit processes affecting these cells. Intracellular recordings of mitral/tufted cell responses to odorants reveal prominent short- and long-latency hyperpolarizations, in addition to the depolarization and evoked spikes presumably mediated by direct glutamatergic excitation from the olfactory nerve (Hamilton & Kauer, 1985; Hamilton & Kauer, 1989; Wellis et al., 1989). Similar multiphasic membrane potential responses to odorant have been observed with

intracellular recordings from invertebrate antennal lobe neurons (Christensen et al., 1998).

Low intensity odorant stimulation within the mitral cell odorant receptive field evokes a low amplitude depolarization that may be suprathreshold for spike initiation (Hamilton & Kauer, 1989; Wellis et al., 1989). In salamander, this depolarization is frequently preceded by a brief hyperpolarization (Hamilton & Kauer, 1989). As stimulus intensity increases, the amplitude of the odorant-evoked depolarization increases and latency decreases, resulting in a high frequency burst of spikes. This burst is then followed by a second period of hyperpolarization that can last several 100's of msec under artificial respiration conditions. As stimulus intensity increases further, the second period of hyperpolarization begins to truncate the evoked spike burst, in some cases leading to a single, short latency evoked spike followed by hyperpolarization in response to high-intensity odorant. These membrane potential results correspond well with extracellular spike train recordings in a variety of terrestrial species (Chaput & Holley, 1985; Duchamp-Viret & Duchamp, 1997; Harrison & Scott, 1986; Imamura et al., 1992; Kauer, 1974; Mair et al., 1982; Mathews, 1972; Meredith, 1986; Scott, 1977).

Thus, in response to a single odorant pulse, a tri-phasic membrane potential response can be observed in mitral/tufted cells. Odorant intensity appears to be encoded by a rate code and/or a latency code, with responses to high intensity odorants often consisting of a single spike followed by inhibition. Given the short latency of the initial hyperpolarization, it is assumed to be mediated by juxtglomerular neurons in a feedforward manner. The initial depolarization is mediated by AMPA and NMDA receptor activation on apical dendritic tufts of mitral cells. There is also recent anatomical (Allen & Hamilton, 2000) and physiological (Aroniadou-Anderjaska et al., 1999; Friedman & Strowbridge, 2000; Isaacson, 1999) evidence for glutamatergic mitral-mitral cell excitation and/or autoexcitation. These mitral-mitral cell connections could contribute to the synchrony observed in odorant responses of neighboring mitral cells (Buonviso et al., 1992; Kashiwadani et al., 1999; Stopfer et al., 1997) which could also contribute to an intensity code, as well as play an important role in odorant quality coding as discussed below.

The late onset, slow hyperpolarization is mediated by GABAergic granule cell interneurons. Mitral and tufted cells connect with granule cells via dendrodendritic

reciprocal synapses along mitral/tufted cell lateral dendrites (Shepherd & Greer, 1998). Glutamate released by mitral/tufted cell dendrites excites AMPA and NMDA receptors on granule cells (Chen et al., 2000; Isaacson & Strowbridge, 1998; Jacobson et al., 1986; Schoppa et al., 1998; Trombley & Westbrook, 1990; Wilson et al., 1996) which in turn release GABA back onto mitral/tufted cell dendrites. Mitral cell lateral dendrites can extend for up to 1 mm around the olfactory bulb, and thus may contact many granule cells. The granule cells are believed to perform lateral inhibitory functions, with GABAergic synapses on distal lateral dendrites perhaps primarily functioning to reduce backpropagation of spikes along these extended dendrites, rather than directly influencing spike initiation at the initial segment. Direct evidence for such lateral inhibitory actions comes from in vitro studies showing that IPSC's can be evoked in both mitral cells and tufted cells by electrical stimulation of distant glomeruli (Christie et al., 2001). Tufted cells are influenced by a more narrow region of glomerular input (glomerular distances up to 400 μ) than mitral cells (glomerular distances up to 800 μ) which have much longer lateral dendrites (Christie et al., 2001). This, along with other structural differences (Ezeh et al., 1993; Macrides et al., 1985; Orona et al., 1983; Orona et al., 1984; Scott, 1981), suggests a potential important functional difference between the two principal bulb output neurons, although no detailed comparisons of odorant evoked activity have been made between these two cell types.

In addition to the phasic nature of the response within a single odorant pulse, single-unit studies in freely breathing animals demonstrate a strong respiratory cycle modulation of mitral/tufted cell activity (Chalansonnet & Chaput, 1998; Macrides & Chorover, 1972; Ogawa, 1998; Onoda & Mori, 1980; Pager, 1985). Mitral/tufted cell spontaneous activity generally oscillates with the respiratory cycle, with different cells maximally active at different phases of the cycle (inspiration or expiration). Odorant stimulation can either enhance the spontaneous patterning of a single cell, or shift cell activity to a different phase of the respiratory cycle (Chalansonnet & Chaput, 1998). The respiratory entrainment of activity during odorant stimulation is stable over a wide range of odorant concentrations, despite potential changes in lateral inhibition discussed above (Chalansonnet & Chaput, 1998). The effects of active sniffing (i.e., an increase in inhalation rate to 5-10 Hz during exploration and arousal) on odorant response patterns has not been thoroughly examined in vertebrates although it is assumed to modify

odorant access to the receptor sheet (Dethier, 1987; Youngentob et al., 1987) and appears to modify granule cell mediated inhibition in the bulb (Young & Wilson, 1999). More attention has been paid to effects of odorant stimulation frequency in invertebrates (Christensen & Hildebrand, 1988; Gomez et al., 1999; Loudon & Koehl, 2000; Schneider et al., 1998). In sphinx moths stimulated with puffs of odorant at different rates, antennal lobe neuron response patterns varied significantly, with some cells able to make discrete responses to odorant pulses at stimulation frequencies as high as 10 Hz (Christensen & Hildebrand, 1988). Given the ubiquity of active sniffing during exploration across animal species (Dethier, 1987), additional research into the consequences of variations in stimulus frequency on peripheral and central odorant coding seems warranted. For example, olfactory cortical targets of mitral cells must be able to discriminate between a mitral cell weakly excited by an odorant inhaled at normal respiration rates (perhaps evoking a short spike train at 10 Hz), from a mitral cell activated by an intense odorant while sniffing (perhaps evoking a single spike on each inhalation with inhalations occurring at 10 Hz).

Of course, in addition to detecting odorants and encoding odorant intensity, mitral/tufted cells encode odorant quality/identity. Odorant quality appears to be encoded by variations in odorant/molecular receptive fields of individual mitral/tufted cells and spatial clustering of cells with similar receptive fields within the olfactory bulb. As with olfactory receptor neurons (Bozza & Kauer, 1998; Malnic et al., 1999; Sato et al., 1994), odorant receptive fields of mitral/tufted cells are based on responsiveness to molecular features, rather than to an odorant as a whole. Odorants within the receptive field of an individual mitral/tufted cell evoke excitatory/suppressive changes in firing rate, generally in phase with the respiratory cycle, as described above. Because of the spatial clustering of cells with similar receptive fields and the lateral inhibitory networks described above, however, mitral/tufted cell receptive fields may be more focused or precise than receptor neurons.

Individual mitral/tufted cells respond to many odorants (Duchamp-Viret & Duchamp, 1997; Harrison & Scott, 1986; Imamura et al., 1992; Katoh et al., 1993; Kauer, 1974; Mair et al., 1982; Mathews, 1972; Meredith, 1986; Mori et al., 1992). The receptive field appears to include odorants that share a similar molecular feature (carbon chain length or functional group), although blend or mixture specific neurons have been

identified in the invertebrate antennal lobe (Vickers et al., 1998). Using a homologous alkane odorant series, cross-habituation studies demonstrate that habituation of mitral/tufted cell responses to one odorant within its receptive field significantly suppresses responses to other receptive field odorants (Wilson, 2000b), strongly suggesting that mitral/tufted cell responses to multiple odorants are mediated by a single input.

Odorant receptive fields of mitral/tufted cells appear to be organized in a roughly center-surround fashion (Meredith, 1986; Wilson & Leon, 1987). Using a stimulus set of homologous odorants varying in carbon chain length, individual mitral/tufted cells are excited by a range of chain lengths (Imamura et al., 1992; Katoh et al., 1993; Mori et al., 1992) and inhibited by neighboring longer or shorter chain lengths (Yokoi et al., 1995). This inhibitory surround is largely due to granule cell mediated lateral inhibition and can be reduced by GABA receptor antagonists (Yokoi et al., 1995).

The excitatory region of the receptive field is believed to be largely dependent on the glomerulus from which that cell receives its afferent input. Thus, just as there are odorant-specific spatial patterns of glomerular activation noted above, there are spatial patterns (or differential spatial responsiveness) of mitral/tufted cell odorant evoked unit activity (Imamura et al., 1992; Katoh et al., 1993; Kauer & Moulton, 1974; Mori & Yoshihara, 1995; Wilson & Leon, 1988) and local field potential activity (Adrian, 1953; Freeman & Skarda, 1985; Viana DiPrisco & Freeman, 1985). For example, mitral/tufted cells connected to glomeruli in the dorsomedial region of the olfactory bulb have receptive fields that include aliphatic acids and exclude alkanes, while cells in the ventrolateral olfactory bulb have receptive fields that include alkanes and exclude aliphatic acids (Imamura et al., 1993; Katoh et al., 1993; Mori & Yoshihara, 1995).

In addition to global variation in odorant receptive field characteristics, local circuit interactions produce more regional variations in odorant receptive fields. Mammalian glomeruli are approximately 100-150 μ in diameter and include apical dendrites of around 25 mitral cells (Royet et al., 1989; Shepherd & Greer, 1998). Mitral/tufted cells physically near each other, and thus likely to receive input from the same glomerulus (Buonviso et al., 1991a), are more likely to respond similarly to odorants, while cells more distant (> 150 μ) are more likely to respond differently (Buonviso & Chaput 1990; Meredith, 1986; Wilson & Leon, 1987). For example,

simultaneous recordings from pairs of mitral/tufted cells reveals that if a mitral/tufted cell is excited by amyl acetate, most cells within 100μ of that cell will also be excited, while cells greater than 150μ will most likely be inhibited or non-responsive (Buonviso & Chaput 1990).

Furthermore, cells stimulated simultaneously with odorant in their receptive fields tend to synchronize their firing (Buonviso et al., 1992; Kashiwadani et al., 1999). Given that individual odors are composed of many features, each of which activate glomeruli at some distance from each other, this synchronization of co-active neurons could be critical for binding of the features into perceptual wholes by higher order neurons (see below). Granule cell mediated feedback/lateral inhibition is again implicated in this synchronization (Buonviso et al., 1996; Kashiwadani et al., 1999; Rall et al., 1966; Bressler & Freeman, 1980). Similar observations have been made in the invertebrate olfactory system (Wehr & Laurent, 1996; Laurent, 1999). Desynchronizing antennal lobe output neurons with local infusion of GABA antagonists impairs behavioral odorant discrimination by honey bees (Stopfer et al., 1997).

In summary, mitral and tufted cells express odorant receptive fields for molecular features, similar to that described for olfactory receptor neurons. Receptive field characteristics are largely driven by the specific glomerulus from which the cell derives its afferent input, and thus, the specific receptive field expressed by a mitral/tufted cell is largely dependent on that cell's location in the olfactory bulb. The receptive field appears to include odorants sharing a common molecular feature. Cells near to each other have similar receptive fields and are under lateral inhibitory influences from neighboring glomeruli-output neuron groups. Odorant responses consist of excitatory-inhibitory sequences which are significantly shaped by both odorant intensity and quality. Respiration parses the response into 100-500ms long components depending on respiration rate. Within these respiratory cycles, activity is further organized by synchronization of simultaneously firing mitral/tufted cells.

Modulation and non-olfactory responses

Although mitral/tufted cells in the main olfactory bulb are second-order neurons in the olfactory system, they are already heavily influenced by both current behavioral state and past odorant experience. The olfactory bulb receives massive centrifugal

inputs from a variety of olfactory and non-olfactory structures (Shepherd & Greer, 1998). Centrifugal inputs include acetylcholine (ACh) from the horizontal limb of the diagonal band, norepinephrine from the locus coeruleus, and serotonin from the raphe nucleus, as well as strong feedback from olfactory cortical areas (feedback from olfactory cortical areas constitutes 80% of centrifugal inputs to the bulb; Haberly, 1998).

One of the initial paradigms demonstrating behavioral state modulation of olfactory bulb odorant responsiveness described food deprivation effects on responses to food odor (Pager et al., 1972). Multi-unit and single-unit recordings of mitral/tufted cells in awake rats revealed that responses to food odor or odors associated with food were greater in food deprived rats than in satiated rats (Pager et al., 1972; Pager, 1974; Pager, 1983). Deprivation state had no effect on responses to novel odorants (Pager, 1972; Pager, 1983). The enhanced responsiveness to food odor in deprived rats appears to be related to a state dependent reduction in habituation to the food odor mediated by centrifugal inputs to the bulb (Gervais & Pager, 1983). Lesions of centrifugal input to the bulb (olfactory peduncle cut) eliminates the deprivation-induced modulation of responses to food odor (Pager, 1978).

Similar behavioral state or non-olfactory modulation of mitral/tufted cell unit activity (Garcia-Diaz et al., 1985; Jiang et al., 1996; Kay & Laurent, 1999; Nickell & Shipley, 1988; Potter & Chorover, 1976; Scott, 1977; Wilson & Sullivan, 1990) or olfactory local field potentials (Chabaud et al., 2000; Viana DiPrisco & Freeman, 1985) has been demonstrated in other paradigms. Activation of centrifugal inputs to the main olfactory bulb can hyperpolarize mitral cells (e.g., anterior commissure; Nakashima et al., 1978), enhance mitral/tufted cell spontaneous activity (e.g., norepinephrine; Wilson & Sullivan, 1991); suppress spontaneous activity (e.g., acetylcholine; Nickell & Shipley, 1988) or enhance mitral/tufted cell responsiveness to weak afferent input (e.g., norepinephrine; Jiang et al., 1996). Olfactory bulb output and responsiveness to odorants, therefore, is under constant dynamic regulation by centrifugal inputs responsive to behavioral state and non-olfactory events. Thus, as in other sensory systems, olfactory bulb responses to odorants in behaving animals is a reflection not only of odorant quality and quantity, but also the context and state of the receiving animal.

Finally, not only do current conditions modulate mitral/tufted cell odorant response patterns, but also past odorant experience and olfactory learning. As mentioned above, periods of reduced odorant stimulation cause a decrease in glomerular layer dopamine which, upon subsequent return of odorant input enhances glomerular and mitral/tufted cell responses to odorant at the expense of odorant discrimination (Guthrie et al., 1990; Wilson & Sullivan, 1995). Olfactory associative conditioning also modifies subsequent glomerular (Coopersmith & Leon, 1984; Johnson et al., 1995; Sullivan and Leon, 1986), mitral/tufted cell (Wilson et al., 1987), granule cell (Woo et al., 1996) and local field potential responses (Viana DiPrisco & Freeman, 1985) to the learned odorant. Associative learning during early development enhances odorant-specific focal glomerular 2-deoxyglucose uptake to that odorant (Coopersmith & Leon, 1984; Sullivan & Leon, 1986). Furthermore, mitral/tufted single-units near these modified glomeruli display enhanced inhibitory responses selectively to the learned odorant, while cells distant to those glomeruli do not (Wilson et al., 1987; Wilson & Leon, 1988). These changes in olfactory bulb physiology require co-activation of centrifugal noradrenergic input from the locus coeruleus during odorant exposure for induction (Sullivan et al., 1989). The mitral/tufted cell response modification has been hypothesized to be due to learning-induced changes in granule cell mediated dendrodendritic inhibition (Wilson & Sullivan, 1994). Similar norepinephrine-dependent, learning induced changes have been observed in odorant-evoked spatiotemporal olfactory bulb local field potentials in adult animals (Viana DiPrisco & Freeman, 1985) and in the accessory olfactory bulb (Brennan & Keverne, 1997)

In summary, despite being the first central relay for olfactory information, a variety of non-olfactory signals converge on olfactory bulb neurons to allow dynamic modulation of odorant processing, as well as more permanent odorant memories. In fact, even the first synapse of the olfactory pathway between olfactory receptors and second order neurons is capable of experience dependent plasticity (e.g., LTP; Ennis et al., 1998) and neuromodulation that can shape spatial and temporal odorant response patterns.

Piriform cortex

A detailed description of the anatomy and synaptic physiology of the piriform is outside the scope of this review, however, several excellent reviews exist (Haberly, 1998; Bower, 1991; Lynch, 1986). What follows is a brief introduction of the functional organization of the piriform cortex, followed by a description of what is known about the sensory physiology of the piriform cortex.

Mitral/tufted cell axons project via the lateral olfactory tract to the olfactory cortex, which is composed of several structures including the anterior olfactory nucleus, a major source of commissural connections in the olfactory system, and the piriform cortex (Fig. 2). While the anterior and posterior regions of the piriform cortex appear to be both structurally (Haberly, 1998; Johnson et al., 2000) and functionally (Chabaud et al., 2000; Haberly, 1998; Illig & Haberly, 2000; Litaudon & Cattarelli, 1995; Litaudon et al., 1997a; Mouly et al., 1998; Wilson & Bower, 1992) quite distinct, there are several basic characteristics of piriform cortical functional organization that apply to the entire structure. The piriform cortex is a relatively simple, 3 layered cortical structure with pyramidal cell bodies arranged in a tight Layer II and more dispersed in Layer III. Dendrites of both groups of pyramidal cells extend into Layer I, where mitral/tufted cell axons terminate on approximately the most distal one half. The proximal half of the dendritic tree receives association and commissural input from other regions of the olfactory cortex. Both the afferent input via the lateral olfactory tract and the commissural/association fibers are glutamatergic, and cortical pyramidal cells express both NMDA and non-NMDA receptor types. GABAergic inhibitory interneurons are located in both Layers I and III.

Similar to mitral/tufted cells, piriform cortex neurons display both excitatory and inhibitory responses to odorants (Haberly, 1969; McCollum et al., 1991; Nemitz & Goldberg, 1983; Tanabe, et al., 1975; Wilson, 1998a). Intracellular recordings reveal somewhat more simple odorant evoked post-synaptic potentials in piriform pyramidal neurons than in mitral cells, although relatively few studies have been reported to date (Nemitz & Goldberg, 1983; Wilson, 1998a; Wilson, 1998b). In freely breathing rats, odorant stimulation evokes a short latency large depolarization, in phase with the respiratory cycle (Fig. 3; Wilson, 1998a). This odorant-evoked depolarization can be suprathreshold for evoking spikes, which can reach instantaneous frequencies of over

100 Hz, but generally are within the range of 50-100 Hz which corresponds to the odorant-evoked gamma frequency waves recorded in piriform. The respiratory entrained depolarization is often bounded by periods of hyperpolarization which accentuate the responses to each inhalation.

Despite the remarkable precision and topography of the olfactory nerve input to the olfactory bulb glomerular layer, the mitral/tufted cell projection to the piriform cortex is broadly non-topographic. Projections to the anterior piriform may have some spatial patterning, with individual axons terminating in small clusters rather than uniformly dispersed (Ojima et al., 1984; Buonviso et al., 1991b), however, in general any one region of the olfactory bulb can project to every region of the piriform cortex and any one region of the cortex can receive input from every region of the bulb (Haberly & Price, 1977; Scott et al., 1980). This broadly scattered input from a highly spatially ordered olfactory bulb has led to models of piriform cortex as a combinatorial array, ideally suited to combine odorant molecular features into perceptually whole odors. Thus, co-activation of spatially dispersed mitral/tufted cells encoding individual molecular features could in turn activate coincidence detecting pyramidal cells of the piriform cortex, each maximally responsive to a particular combination of features. Broadly dispersive intracortical association fibers further contribute to this associational network (Haberly & Price, 1978; Haberly, 1998; Johnson et al., 2000)

If the combinatorial array model of piriform function is correct, then odorant receptive fields of cortical pyramidal cells might, at least superficially, appear very similar to odorant receptive fields of mitral/tufted cells, although with the two cell classes responding to odorants for different reasons. That is, as discussed above, a particular odorant may be composed of several features. A mitral cell may respond to that odorant, and similar odorants, because of the presence of a single feature which dominates the receptor input to that mitral cell. A cortical pyramidal neuron, on the other hand, may respond to that odorant, and similar odorants, because of the unique combination of odorant features present (i.e., it responds to the odor(s) as a whole).

Odorant responses of piriform cortical single-units have been described in several species (frog, Duchamp-Viret et al., 1996; rat, Haberly, 1969; monkey, Tanabe et al., 1975a) and in both awake (McCollum et al., 1991; Schoenbaum & Eichenbaum, 1995a) and anesthetized preparation (Haberly, 1969; Giachetti & MacLeod, 1975; Nemitz &

Goldberg, 1983; Tanabe et al., 1975a; Wilson, 2000). In general, similar to mitral/tufted cells, piriform cortical pyramidal cells have broad odorant receptive fields (Fig. 3; Tanabe et al., 1975a; Wilson, 1998a; Wilson, 2000), although in frog cortex there is also a subpopulation of narrowly tuned cells (Duchamp-Viret et al., 1996). In one of the few direct comparisons of receptive fields between olfactory areas, Tanabe et al. (1975) suggest that piriform cortex single-units are somewhat more highly tuned (narrow receptive fields) than mitral cells, with cells in orbitofrontal cortex the most highly tuned – forming a hierarchy of odorant discrimination ability along the primary olfactory pathway (see below).

In a more direct test of the combinatorial array hypothesis outlined above, a comparison of odorant cross-habituation between mitral/tufted cells and anterior piriform cortex layer II/III single-units was made using a homologous series of alkane odorants. It was hypothesized that if mitral/tufted cells respond to multiple odorants because each of the effective odorants shares a common feature, then habituation to that feature should reduce responsiveness to all odorants by that cell. Piriform cortex cells however, should show less cross-habituation between similar odorants if cortical cells respond to collections of features, because each odorant would contain a unique feature ensemble. These precise results were obtained in urethane anesthetized, freely breathing rats (Fig. 3C; Wilson, 2000). In addition, anterior piriform single-units showed minimal cross-habituation between binary odorant mixtures and their components (Wilson, 1998a), further supporting the hypothesis that the piriform cortex synthesizes feature ensembles into perceptual odor wholes.

As described above, lateral inhibition forms a critical component of odorant response patterns in mitral/tufted cells of the olfactory bulb, shaping both the temporal nature of the response as well as emphasizing the spatial nature of the response inherent in olfactory bulb organization. While both feedforward and feedback inhibitory circuits exist in the piriform cortex (Haberly, 1998; Kanter et al., 1996; Kapur et al., 1997; Satou et al., 1982; Scholfield, 1978), and membrane hyperpolarization is expressed in cortical neuron response to odorant (Wilson, 1998a), no investigation of the role of inhibition in cortical odorant responses has yet been made. Lateral inhibition functions in most sensory systems to enhance existing spatial response patterns, allowing one cell (or group of cells) to inhibit neighboring cells with similar receptive

fields. This can enhance contrast and/or signal-to-noise characteristics of the system. If the piriform cortex truly lacks any spatial organization, then the role of lateral inhibition may be different in this system. Several studies have attempted to detect spatial patterns of evoked activity in the piriform cortex with limited success (Cattarelli, & Cohen, 1989; Cattarelli et al., 1988; Sharp et al., 1977), although some of the difficulty may have been due to the rapid odorant habituation that occurs in the piriform (Wilson, 1998a). Optical imaging of *in vivo* piriform responses to olfactory bulb electrical stimulation has shown some spatial specificity, with different regions of the bulb activating slightly different regions of anterior piriform, but with diffuse activation of more posterior regions (Litaudon et al., 1997a). Similarly, a more recent study using well spaced odorant stimuli and *c-fos* labeling has detected odorant-specific spatial patterns of activated neurons in the anterior piriform, but not in the posterior piriform (Illig & Haberly, 2000).

The noted functional difference between the anterior and posterior regions of the piriform cortex has been demonstrated with a variety of techniques including local field potential recordings (Chabaud et al., 1999; Chabaud et al., 2000; Mouly et al., 1998) and optical imaging (Litaudon & Cattarelli, 1995; Litaudon et al., 1997a). The anterior piriform may be further functionally divided into dorsal and ventral regions (Haberly, 1998). These functional distinctions presumably arise from the significant variation in such anatomical features as dominance of lateral olfactory tract input over association fiber input (greatest in the ventral region of the anterior piriform and least in the posterior piriform) and some differences in cell populations (Haberly, 1998) and modulatory inputs (e.g., ACh; Lysakowski et al., 1987). No studies to date have examined differences in odorant receptive fields between anterior and posterior piriform neurons, although there is some evidence that posterior piriform responses to odorants may be more plastic than anterior responses (Chabaud et al., 2000; Litaudon et al., 1997b; Mouly et al., 1998). Synaptic plasticity can be evoked in both afferent and association fiber synapses (Jung et al., 1990; Kanter & Haberly, 1990; Roman et al., 1987; Stripling & Patneau, 1999; Wilson, 1998b), although some evidence suggests that association fiber synapses may be under more modulatory control than LOT afferent synapses (Hasselmo et al., 1997; Hasselmo & Bower, 1992; Stripling & Patneau, 1999; Tang & Hasselmo, 1994). Together with the dominance of LOT input and

potential spatial patterns of odorant evoked activity in the anterior piriform, these results suggest that the anterior regions of piriform may be more involved in odorant discrimination and the posterior piriform more involved in odorant memory and odorant associations (Hasselmo & Barkai, 1995; Litaudon et al., 1997b).

Finally, single-units in the anterior piriform cortex of the rat appear to express spatial receptive fields, in addition to odorant receptive fields. Single-units in the anterior piriform cortex can be driven by odorants unilaterally presented to either the ipsilateral or contralateral naris. Different cells express preferred stimulation sites, with some cells responsive only to ipsilateral stimulation, some only to contralateral stimulation, some equally responsive to both, and some requiring bilateral stimulation (Wilson, 1997). The convergence of ipsilateral and contralateral inputs in piriform cortex may be involved in maintaining bilateral access to odorant memories (Kucharski & Hall, 1987), response amplification (Bennett, 1968; Klimek et al., 1998) or even stimulus localization (Wilson & Sullivan, 1999). Imaging work in humans suggests that the two nares may have somewhat different odorant tuning characteristics (Sobel et al., 1999), and that cortical odorant processing is lateralized (Zatorre et al., 1992). Thus, commissural pathways in both humans and rats may play a critical role in central odorant processing, the precise nature of which is yet to be described.

Modulation and non-olfactory responses

Odorant responses of anterior piriform cortex neurons are extremely dynamic, capable of showing marked habituation within a few inhalations of an odorant in anesthetized rats (Wilson, 1998a). As described above, this habituation is highly odorant specific, thus the cortex can filter out background or currently non-significant stimuli, while maintaining responsiveness to novel odorants. In awake rats in an odorant conditioning task, piriform cortex single-units also show a decrease in responsiveness to repeated odorants (McCollum et al., 1991). This rapid, experience-dependent, odorant-specific change in cortical receptive fields is similar to that reported in other sensory systems (Edeline, 1999), and may contribute to odorant identification and memory. Similar experience-dependent, odorant-specific decreases in odorant responses of single-units in the orbitofrontal cortex of primates have also been observed, as described below.

In the auditory system, both experience-dependent, stimulus-specific decreases and increases can be observed within receptive fields of cortical neurons, following habituation (Condon & Weinberger, 1991) and associative learning (Weinberger, 1998), respectively. While no direct studies of learning-induced changes in piriform cortex single-unit odorant-receptive fields have been reported, work in two other paradigms suggest that such associative changes can occur. Rats can learn to discriminate between “artificial” odorants induced by focal electrical stimulation of different regions of the olfactory bulb (Mouly et al., 1985). Evoked responses in the piriform cortex to these artificial odorants are enhanced as the animal learns this discrimination (Roman et al., 1987; Litaudon et al. 1997). Learning to discriminate real odorants in a similar discrimination paradigm enhances 2-deoxyglucose uptake in the anterior olfactory nucleus in response to the learned odorant (Hamrick et al., 1993). While no learning associated 2-deoxyglucose uptake changes were detected in the piriform cortex in this study, any changes may have been masked by the rapid cortical habituation described above.

As in the olfactory bulb, piriform cortex odorant responses can be influenced by behavioral state. The hunger modulation of food odor responses observed in the main olfactory bulb also occurs in local field potential responses to food odor in the piriform cortex, although largely in the posterior piriform and not in the anterior piriform (Chabaud et al., 2000). Similar to the olfactory bulb multi-unit responses, these hunger-induced changes in cortical responsiveness are specific to food odor (Chabaud et al., 2000).

Activity in the piriform cortex is also modulated by a variety of non-olfactory events, as determined by both single-unit (Schoenbaum & Eichenbaum, 1995a) and local field potential recordings (Kay & Freeman, 1998). Analysis of oscillatory local field potentials suggest that during odorant sampling 12-35 Hz β -frequency oscillations travel from rostral (olfactory bulb) to caudal regions (entorhinal cortex; Kay & Freeman, 1998; Chapman et al., 1998). However, in an odorant conditioning task prior to odorant sampling these oscillations travel in the reverse direction (Kay & Freeman, 1998). Single-unit recordings in freely moving rats performing an odorant discrimination task similarly show changes in cortical activity during many stages of the odorant discrimination task in addition to the odorant sampling period itself, including during preparation for odorant

sampling and during receipt of a water reward (Schoenbaum & Eichenbaum, 1995a). Furthermore, piriform odorant responses can be affected by the current learned hedonic valence of that odorant (Schoenbaum & Eichenbaum, 1995a). This is in contrast to the learned changes in olfactory bulb mitral/tufted cell single-unit responses described above. Learned changes in olfactory bulb responses are specific to learned odorants, but do not encode learned hedonic valence, i.e., learned aversive odorants and learned appetitive odorants are encoded similarly by the olfactory bulb (Sullivan & Wilson, 1991).

Much of this experience- or state-dependent modulation of cortical odorant responses is dependent on centrifugal inputs to the piriform cortex from neuromodulatory centers such as the horizontal limb of the diagonal band (ACh) and locus coeruleus (norepinephrine). Cholinergic modulation of piriform cortex function has received the most attention at both the experimental physiological and neural computation levels. ACh input to the olfactory system plays an important role in behavioral odorant memory. Blockade of ACh muscarinic receptors impairs both associative and non-associative odorant memory (DeRosa & Hasselmo, 2000; Hunter & Murray, 1989; Ravel et al., 1994).

ACh also has a variety of specific effects on piriform physiology (Barkai & Hasselmo, 1994; Hasselmo & Bower, 1992; Linster et al., 1999; Zimmer et al., 1999). In vitro physiology has demonstrated that muscarinic receptor agonists reduce piriform cortex pyramidal cell firing adaptation (i.e., increase duration of bursts evoked by depolarization; Barkai & Hasselmo, 1994; Tseng & Haberly, 1989), selectively suppress association fiber synaptic activation of pyramidal cells (with minimal effect on LOT afferent synapses, Hasselmo & Bower, 1992) and enhance associative synaptic plasticity in the piriform cortex (Hasselmo & Barkai, 1995). The muscarinic receptor mediated suppression of association fibers has been replicated in vivo by stimulation of the horizontal limb of the diagonal band to evoke ACh release in piriform (Linster et al., 1999; Rosin et al., 1999). Further in vivo work has demonstrated that electrical stimulation of the horizontal limb of the diagonal band increases excitability of piriform cortex single-units via a cholinergic muscarinic mechanism (Zimmer et al., 1999).

These physiological effects of ACh on piriform function have led to the hypothesis that ACh reduces interference between similar patterns of odorant input,

thus enhancing odorant discrimination and recognition of previously learned odorants (Hasselmo, 1995; norepinephrine may have similar effects in the piriform cortex: Bouret et al., 2000; Hasselmo & Bower, 1992). In support of this model, recent work has demonstrated that the ACh muscarinic receptor antagonist scopolamine applied to the piriform cortical surface or systemically injected reduces odorant discrimination by piriform single-units as demonstrated by enhanced cross-habituation (Wilson, 2001). Given that stimulation of the olfactory bulb and piriform cortex activates neurons in the horizontal limb of the diagonal band (Linster & Hasselmo, 2000), odorant stimulation itself can regulate ACh feedback to the cortex, and thus modify subsequent coding and plasticity.

In summary, the anterior piriform cortex may serve to synthesize odorant feature input from the olfactory bulb into perceptual odor wholes. Odorant discrimination within the piriform cortex is enhanced compared to mitral/tufted cells of the olfactory bulb and olfactory receptors. Extensive association connections within the cortex contribute to and reinforce odorant synthesis, as well as allow associative memory to tie odorants and odorant-related experiences together. Experience can produce highly specific changes in cortical odorant receptive fields, with association fibers and the posterior piriform cortex playing a prominent role in these memory functions. Behavioral state and past experience can shape both piriform odorant responsiveness and general cortical activity through extensive centrifugal inputs to the cortex. Finally, the piriform cortex is a major source of centrifugal input to the olfactory bulb, thus, as in thalamocortical sensory systems, the cortex can directly influence its own input via descending control of activity in more peripheral structures.

Orbitofrontal cortex

The major neocortical area processing olfactory information is the orbitofrontal region of the prefrontal cortex, which in rats includes the insular cortex. Neuroanatomical studies have demonstrated that the piriform cortex projects directly to the orbitofrontal cortex (Johnson et al., 2000; Krettek & Price, 1977; Price et al., 1991), as well as to the dorsomedial nucleus of the thalamus, which in turn projects to the orbitofrontal cortex (Krettek & Price, 1977; Price & Slotnick, 1983). Electrophysiological (Cinelli et al., 1987) and anatomical (Shiple & Geinesman, 1984)

evidence suggests there may also be a direct projection from the olfactory bulb to the orbitofrontal/insular cortex in rats. Orbitofrontal cortex efferents form feedback loops with primary olfactory structures including the piriform cortex and dorsomedial nucleus of the thalamus (Price et al., 1991). In both rats and primates, lesions of either the orbitofrontal cortex or the dorsomedial nucleus of the thalamus impair odorant discrimination learning (Eichenbaum et al., 1980; McBride & Slotnick, 1997; Staubli et al., 1987; Tanabe et al., 1975b; Zatorre & Jones-Gotman, 1991).

Single-units in the orbitofrontal cortex respond to, and can discriminate between, odorants in both rodents (Onoda et al., 1984; Schoenbaum & Eichenbaum, 1995a) and primates (Rolls & Baylis, 1994; Tanabe et al., 1975a). Odorant discrimination by single-units in the orbitofrontal cortex (as measured by receptive field size) is improved over that observed in the olfactory bulb and piriform cortex (Onoda et al., 1984; Tanabe et al., 1975a; Yarita et al., 1980), and odorant discrimination by ensembles of orbitofrontal neurons is improved over single-units (Rolls et al., 1996b; Schoenbaum & Eichenbaum, 1995b).

The orbitofrontal cortex also receives inputs from several sensory systems in addition to the olfactory system, including the gustatory, visual and somatosensory systems (Carmichael & Price, 1995; Cavada et al., 2000) as well as spatial location information (Lipton et al., 1999). In fact, these diverse inputs can converge on single neurons, leading to single cells that respond to olfactory, gustatory, visual or somatosensory stimuli alone or in combination (Rolls & Baylis, 1994; Rolls et al., 1999). Similar to that described for the piriform cortex, orbitofrontal neurons respond to many phases of odorant discrimination behavior, including during pre-odorant sampling behavior, odorant sampling and post-odorant reward consummation (Schoenbaum & Eichenbaum, 1995a).

While behavioral state and previous olfactory experience shape odorant responses in both the olfactory bulb and piriform cortex as discussed above, this state-dependent, associative nature of odorant processing appears highly refined in the orbitofrontal cortex. Thus, for example, the responses of most odorant-sensitive orbitofrontal cortex neurons to odorants is dependent on taste reward associations of that odorant (Critchley & Rolls, 1996a; Rolls et al., 1996b). That is, if the odorant is associated with a pleasant sweet taste, the response to that odorant may be greater

than if the odorant is associated with an unpleasant salt taste, or visa versa. These differential responses require repeated experience to emerge, and thus represent a learned, cross-modal association (Rolls et al., 1996a). Other learned cross-modal associations that influence primate orbitofrontal single-unit responses to odorants include vision (Rolls & Baylis, 1994) and somatosensation (Rolls et al., 1999). Cross—modal associations with odorants have been described in both the rat and primate orbitofrontal cortex (Lipton et al., 1999; Rolls et al., 1996a).

As in both the main olfactory bulb and piriform cortex, behavioral state also influences orbitofrontal cortical responses to odorants. Orbitofrontal cortex single-unit responses to food odors (or associated food gustatory, visual or somatosensory stimuli) are modulated by hunger (Critchley & Rolls, 1996b). Feeding to satiety selectively reduces orbitofrontal responsiveness to the odor of that food (Critchley & Rolls, 1996b). In humans, eating a single food to satiety selectively reduces pleasant ratings of that food odor, although simple exposure to a food odor for a comparable duration has a similar effect (Rolls & Rolls, 1997). Similarly to the single-unit work in monkeys, odorant pleasantness influences activity in the human orbitofrontal cortex as determined by PET studies (Royet et al., 2000), and feeding to satiety reduces orbitofrontal cortex activation in response to that food odor in humans as determined by fMRI (O'Doherty et al., 2000).

These results suggest that odorant coding in the orbitofrontal cortex is similar to that for other sensory stimuli processed by prefrontal cortex, namely that responses to stimuli reflect not only the sensory qualities of that stimulus, but also the current and past context of the stimulus, including sensory and hedonic associations and biological significance (Goldman-Rakic, 1987; Kolb, 1984; Rolls, 2001; Schoenbaum & Eichenbaum 1995a). Orbitofrontal cortex neurons in turn provide descending feedback to the piriform cortex and olfactory bulb (Cinelli et al., 1987; Haberly, 1998), which can modulate subsequent peripheral processing as described above for piriform cortex.

General principles

We can now return to the original problem stated in the introduction that all sensory systems must function in the real world (Fig. 2). Specifically, the olfactory system must be able to recognize garlic in the spaghetti sauce in the presence of odor

from a freshly cut lawn, and to recognize that odor as the perceptual entity of “garlic”, despite it being a mixture of many individual molecular components. Our current understanding of olfactory system sensory physiology outlined above, as well as extensive theoretical and computer modeling work (Freeman, 1981; Haberly, 1985; Hasselmo et al., 1990; Lynch, 1986; Mori & Yoshihara, 1995 ; Rolls, 2000; Wilson & Shepherd, 1995), leads to the following description of hypothetical events that may allow this remarkable feat.

Odorant molecules are broken into informational features by binding with specific receptors in the nose. Interactions between molecules and/or between features may occur at the receptor level, resulting in unique receptor output for some feature combinations (Cromarty & Derby, 1998; Derby et al., 1991). The contrast between features is then sharpened through precise projections to the main olfactory bulb glomerular layer and glomerular layer inhibition. Again, some feature mixing may occur at the glomerular layer (Joerges et al., 1997; Vickers et al., 1998). Thus, the spatial pattern of activity within the olfactory bulb glomerular layer represents the collection of molecular features, including an initial processing of some feature combinations present in the odorants sampled. Mitral/tufted cells then project this alphabet of features into the piriform cortex. Based on the current behavioral state (hunger?) and past experiences (memory of past food odors), the representation of some features by mitral/tufted cells will be selectively enhanced over others through olfactory bulb centrifugal modulation.

The piriform cortex takes the mitral/tufted cell input and furthers the process of combining the features into perceptually whole odors initiated in the periphery. This is performed by the combinatorial anatomy of the piriform and past experience with specific combinations of features. That is, features that have been associated together in the past will, due to experience dependent synaptic plasticity within the piriform cortex, be more effective at driving coincidence detecting piriform cortical neurons. Thus, rather than random association of odorant features within the piriform cortex, past experience will allow some combinations of features to be more easily combined and salient. This role of the piriform cortex in odorant feature synthesis is suggested by behavioral data showing that animals with piriform cortex lesions have difficulty learning odorant discriminations of complex odorant mixtures, but not of more simple odorants

(Staubli et al., 1987). Furthermore, piriform cortex neurons can discriminate between odorant mixtures and their components, suggesting a synthesis of odorant features (Wilson, 1998a). The re-assembly of molecular features based on past associative experience within the piriform cortex allows extraction and synthesis of perceptual odor wholes from the collection of molecular features (i.e., the stimuli garlic and grass odor are present), in a conceptually similar way to the synthesis of simple visual features into complex visual objects in higher order visual cortices (Logothetis & Sheinberg, 1996). In addition, the dynamic receptive fields and enhanced odorant discrimination of the piriform cortex allows selective filtering of background, or currently less relevant odorants. Again, specific activity patterns will be enhanced depending on the behavioral state of the animal. It is hypothesized that within the piriform cortex, identification of the sensory stimulus (what odor is it?) is largely complete. It should be noted, however, that piriform cortex lesions produce little effect on well learned odorant discrimination behavior, although they may impair learning to discriminate novel odorants (Slotnick & Schoonover, 1992; Staubli et al., 1987; Zhang et al., 1998)

In addition to association of odorant molecular features (sensory processing – this is garlic), the piriform cortex and orbitofrontal cortex combine to allow association of odorants with sensory context, memory and hedonic reactions (perceptual processing – I see food previously associated with garlic, I have eaten and enjoy garlic, I am hungry for garlic). Through descending connections this perception can influence subsequent peripheral sensory processing by the bulb and anterior piriform cortex. Efferent connections of the piriform and orbitofrontal cortices can then shape behavior appropriate for the given stimulus and current internal state. Something smells good, let's eat.

8/13/01

Acknowledgements

The authors wish to acknowledge the support of grants from NIDCD (DAW), NSF (DAW) and NICHD (RMS).

References

- Allen, D.M. and Hamilton, K.A. (2000) Ultrastructural identification of synapses between mitral/tufted cell dendrites. *Brain Res.*, 860:170-173.
- Aroniadou-Anderjaska, V., Ennis, M. and Shipley, M.T. (1999) Dendrodendritic recurrent excitation in mitral cells of the rat olfactory bulb. *J. Neurophysiol.*, 82:489-494.
- Aroniadou-Anderjaska, V., Zhou, F.M., Priest, C.A., Ennis, M. and Shipley, M.T. (2000) Tonic and synaptically evoked presynaptic inhibition of sensory input to the rat olfactory bulb via GABA_B heteroreceptors. *J. Neurophysiol.*, 84:1194-1203.
- Baker, H. (1990) Unilateral, neonatal olfactory deprivation alters tyrosine hydroxylase expression but not aromatic amino acid decarboxylase or GABA immunoreactivity. *Neurosci.*, 36:761-771.
- Baker, H., Morel, K., Stone, D.M. and Maruniak, J.A. (1993) Adult naris closure profoundly reduces tyrosine hydroxylase expression in mouse olfactory bulb. *Brain Res.*, 614:109-116.
- Barkai, E and Hasselmo, M.E. (1994) Modulation of the input/output function of rat piriform cortex pyramidal cells. *J. Neurophysiol.*, 72:644-658.
- Bell, G.A., Laing, D.G. and Panhuber, H. (1987) Odour mixture suppression: evidence for a peripheral mechanism in human and rat. *Brain Res.*, 426:8-18.
- Bennett, M.H. (1968) The role of the anterior limb of the anterior commissure in olfaction. *Physiol. Behav.*, 3:507-515.
- Berkowicz, D.A., Trombley, P.Q. and Shepherd, G.M. (1994) Evidence for glutamate as the olfactory receptor cell neurotransmitter. *J. Neurophysiol.*, 71:2557-2561.
- Bouret, S., Briois, L., Lestienne, R. and Sara, S.J. (2000) Locus coeruleus stimulation modulates responses to olfactory stimuli in piriform cortex. *Soc. Neurosci. Abstr.* 26: 657.35
- Bower, J.M. (1991) Piriform cortex and olfactory object recognition. In J.L. Davis and H. Eichenbaum (Eds.) *Olfaction: A model system for computational neuroscience.* MIT Press, Cambridge, MA, pp. 265-285.
- Bowery, N.G., Hudson, A.L. and Price, G.W. (1987) GABA_A and GABA_B receptor site distribution in the rat central nervous system. *Neurosci.*, 20:365-383.

- Bozza, T.C. and Kauer, J.S. (1998) Odorant response properties of convergent olfactory receptor neurons. *J. Neurosci.*, 18:4560-4569.
- Brennan, P.A. and Keverne, E.B. (1997) Neural mechanisms of mammalian olfactory learning. *Prog. Neurobiol.*, 51:457-481.
- Bressler, S.L. and Freeman, W.J. (1980) Frequency analysis of olfactory system EEG in cat, rabbit, and rat. *EEG Clin Neurophysiol.*, 50:19-24.
- Brunjes, P.C., Smith-Crafts, L.K. and McCarty, R. (1985) Unilateral odor deprivation: effects on the development of olfactory bulb catecholamines and behavior. *Dev. Brain Res.*, 22:1-6.
- Buck, L.B. (1996) Information coding in the vertebrate olfactory system. *Ann. Rev. Neurosci.*, 19:517-544.
- Buonviso, N., Berthommier, F. and Chaput, M.A. (1992) Temporal pattern analyses in pairs of neighboring mitral cells. *J. Neurophysiol.*, 68:417-424.
- Buonviso, N. and Chaput, M.A. (1990) Response similarity to odors in olfactory bulb output cells presumed to be connected to the same glomerulus: Electrophysiological study using simultaneous single-unit recordings. *J. Neurophysiol.*, 63: 447-454.
- Buonviso, N., Chaput, M.A. and Berthommier, F. (1996) Similarity of granular-induced inhibitory periods in pairs of neighboring mitral/tufted cells. *J. Neurophysiol.*, 76:2393-2401.
- Buonviso, N., Chaput, M.A. and Scott, J.W. (1991a) Mitral cell-to-glomerulus connectivity: An HRP study of the orientation of mitral cell apical dendrites. *J. Comp. Neurol.*, 307:57-64.
- Buonviso, N., Revial, M.F. and Jourdan, F. (1991b) The projections of mitral cells from small local regions of the olfactory bulb: An anterograde tracing study using PHA-L (Phaseolus vulgaris Leucoagglutinin). *Eur. J. Neurosci.*, 3:493-500.
- Cain, D.P. and Bindra, D. (1972) Responses of amygdala single units to odors in the rat. *Exp. Neurol.*, 35:98-110.
- Carmichael, S.T. and Price, J.L. (1995) Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. *J. Comp. Neurol.*, 363:642-664.

- Cattarelli, M. and Cohen, L.B. (1989) Optical recording of the in vivo piriform cortex responses to electrical stimulation of the lateral olfactory tract in the rat. *Chem. Senses*, 14:577-586.
- Cattarelli, M., Astic, L. and Kauer, J.S. (1988) Metabolic mapping of 2DG uptake in the rat piriform cortex using computerized image processing. *Brain Res.*, 442:180-184.
- Cavada, C., Company, T., Tejedor, J., Cruz-Rizzolo, R.J. and Reinoso-Suarez, F. (2000) The anatomical connections of the macaque monkey orbitofrontal cortex. A review. *Cerebral Cortex*, 10:220-242.
- Chabaud, P., Ravel, N., Wilson, D.A., Mouly, A.M., Vigouroux, M., Farget, V. and Gervais, R. (2000) Exposure to behaviourally relevant odour reveals differential characteristics in rat central olfactory pathways as studied through oscillatory activities. *Chem. Senses*, 25:561-573.
- Chalansonnet, M. and Chaput, M.A. (1998) Olfactory bulb output cell temporal response patterns to increasing odor concentrations in freely breathing rats. *Chem. Senses*, 23:1-9.
- Chapman, C.A., Xu, Y., Haykin, S. and Racine, R.J. (1998) Beta-frequency (15-35Hz) electroencephalogram activities elicited by toluene and electrical stimulation in the behaving rat. *Neurosci.*, 86:1307-1319.
- Chaput, M.A. and Holley, A. (1985) Responses of olfactory bulb neurons to repeated odor stimulations in awake freely-breathing rabbits. *Physiol. Behav.*, 34:249-258.
- Chen, W.R., Xiong, W. and Shepherd, G.M. (2000) Analysis of relationships between NMDA receptors and GABA release at olfactory bulb reciprocal synapses. *Neuron*, 25:625-633.
- Christensen, T.A. and Hildebrand, J.G. (1988) Frequency coding by central olfactory neurons in the sphinx moth *Manduca sexta*. *Chem. Senses*, 13:123-130.
- Christensen, T.A., Waldrop, B.R. and Hildebrand, J.G. (1998) Multitasking in the olfactory system: Context-dependent responses to odors reveal dual GABA-regulated coding mechanisms in single olfactory projection neurons. *J. Neurosci.*, 18:5999-6008.

- Christensen, T.A. and White, J. (2000) Representation of olfactory information in the brain. In: T.E. Finger, W.L. Silver and D. Restrepo (Ed.s) *The Neurobiology of Taste and Smell*, second ed., Wiley-Liss, Inc, New York. pp. 201-232.
- Christie, J.M., Schoppa, N.E. and Westbrook, G.L. (2001) Tufted cell dendrodendritic inhibition in the olfactory bulb is dependent on NMDA receptor activity. *J. Neurophysiol.*, 85:169-173.
- Cinelli, A.R., Ferreyra-Moyano, H. and Barragan, E. (1987) Reciprocal functional connections of the olfactory bulbs and other olfactory related areas with the prefrontal cortex. *Brain Res. Bull.*, 19:651-661.
- Condon, C.D. and Weinberger, N.W. (1991) Habituation produces frequency-specific plasticity of receptive fields in the auditory cortex. *Behav. Neurosci.*, 105:416-430.
- Coronas, V., Srivastava, L.K., Liang, J.J., Jourdan, F. and Moyse, E. (1997) Identification and localization of dopamine receptor subtypes in rat olfactory mucosa and bulb: A combined in situ hybridization and ligand bind radioautographic approach. *J. Chem Neuroanat.*, 12: 243-257.
- Critchley, H.D. and Rolls, E.T (1996a) Olfactory neuronal responses in the primate orbitofrontal cortex: Analysis in an olfactory discrimination task. *J. Neurophysiol.*, 75:1659-1672.
- Critchley, H.D. and Rolls, E.T (1996b) Hunger and satiety modify the responses of olfactory and visual neurons in the primate orbitofrontal cortex. *J. Neurophysiol.*, 75:1673-1686.
- Cromarty, S.I. and Derby, C.D. (1998) Inhibitory receptor binding events among the components of complex mixtures contribute to mixture suppression in responses of olfactory receptor neurons of spiny lobsters. *J. Comp. Physiol. A*, 183:699-707.
- Daw, N.W., Brunken, W.J. and Parkinson, D. (1989) The function of synaptic transmitters in the retina. *Ann. Rev. Neurosci.*, 12:205-225.
- Derby, C.D., Girardot, M.N. and Daniel, P.C. (1991) Responses of olfactory receptor cells of spiny lobsters to binary mixtures. II. Pattern mixture interactions. *J. Neurophysiol.*, 66:131-139.

- DeRosa, E. and Hasselmo, M.E. (2000) Muscarinic cholinergic neuromodulation reduces proactive interference between stored odor memories during associative learning in rats. *Behav. Neurosci.*, 114:32-41.
- Dethier, V.G. (1987) Sniff, flick and pulse: an appreciation of interruption. *Proc. Am. Phil. Soc.*, 131:159-176.
- Doty, R.L., Li, C., Bagla, R., Huang, W., Pfeiffer, C., Brosvic, G.M. and Risser, J.M. (1998) SKF 38393 enhances odor detection performance. *Psychopharm.*, 136:75-82.
- Doty, R.L. and Risser, J.M. (1989) Influence of the D2 dopamine receptor agonist quinpirole on the odor detection performance of rats before and after spiperone administration. *Psychopharm.*, 98:310-315.
- Duchamp-Viret, P., Chaput, M.A. and Duchamp, A. (1999) Odor response properties of rat olfactory receptor neurons. *Science*, 284:2171-2174.
- Duchamp-Viret, P., Coronas, V., Delaleu, J.-C., Moyses, E. and Duchamp, A. (1997) Dopaminergic modulation of mitral cell activity in the frog olfactory bulb: A combined radioligand binding-electrophysiological study. *Neurosci.*, 79:203-216.
- Duchamp-Viret, P., Delaleu, J.-C. and Duchamp, A. (2000) GABA_B-mediated action in the frog olfactory bulb makes odor responses more salient. *Neurosci.*, 97:771-777.
- Duchamp-Viret, P. and Duchamp, A. (1997) Odor processing in the frog olfactory system. *Prog. Neurobiol.*, 53:561-602.
- Duchamp-Viret, P., Duchamp, A. and Vigouroux, M. (1989) Amplifying role of convergence in olfactory system: A comparative study of receptor cell and second-order neuron sensitivities. *J. Neurophysiol.*, 61:1085-1094.
- Duchamp-Viret, P., Palouzier-Paulignan, B. and Duchamp, A. (1996) Odor coding properties of frog olfactory cortical neurons. *Neuroscience*, 74:855-895.
- Edeline, J.M. (1999) Learning-induced physiological plasticity in the thalamo-cortical sensory systems: A critical evaluation of receptive field plasticity, map changes and their potential mechanisms. *Prog. Neurobiol.*, 57:165-224.
- Eichenbaum, H., Shedlack, K.J. and Eckmann, K.W. (1980) Thalamocortical mechanisms in odor-guided behavior. I. Effects of lesions of the mediodorsal thalamic nucleus and frontal cortex on olfactory discrimination in the rat. *Brain. Behav. Evol.*, 17:255-275.

- Ennis, M., Linster, C., Aroniadou-Anderjaska, V., Ciombor, K. and Shipley, M.T. (1998) Glutamate and synaptic plasticity at mammalian primary olfactory synapses. *Annals. N.Y. Acad. Sci.*, 855:457-466.
- Ennis, M., Zimmer, L.A. and Shipley, M.T. (1996) Olfactory nerve stimulation activates rat mitral cells via NMDA and non-NMDA receptors in vitro. *NeuroReport*, 7:989-992.
- Ezeh, P.I., Wellis, D.P. and Scott, J.W. (1993) organization of inhibition in the rat olfactory bulb external plexiform layer. *J. Neurophysiol.*, 70:263-274.
- Freeman, W.J. (1981) A physiological hypothesis of perception. *Perspect. Biol. Med.*, 24:561-592.
- Freeman, W.J. and Skarda, C.A. (1985) Spatial EEG patterns, non-linear dynamics and perception: the neo-Sherringtonian view. *Brain Res. Rev.*, 10:147-175.
- Friedman, D. and Strowbridge, B.W. (2000) Functional role of NMDA autoreceptors in olfactory mitral cells. *J. Neurophysiol.*, 84:39-50.
- Gall, C.M., Hendry, S.H.C., Seroogy, K.B., Jones, E.G. and Haycock, J.W. (1987) Evidence for coexistence of GABA and dopamine in neurons of the rat olfactory bulb. *J. Comp. Neurol.*, 266:307-318.
- Garcia-Diaz, D.E., Aguilar-Baturoni, H.U., Guevara-Aguilar, R. and Wayner, M. (1985) Olfactory bulb neurons respond to gastric distension. *Brain Res. Bull.*, 15:661-664.
- Gervais, R. and Pager, J. (1983) Olfactory bulb excitability selectively modified in behaving rats after local 6-hydroxydopamine treatment. *Behav. Brain Res.*, 9:165-179.
- Giachetti, I. and MacLeod, P. (1975) Cortical neuron responses to odours in the rat. In D.A. Denton and J.P. Coghlan (Ed.s) *Olfaction and Taste V*, Academic Press, New York. pp. 303-307.
- Gomez, G., Voigt, R. and Atema, J. (1999) Temporal resolution in olfaction III.: Flicker fusion and concentration-dependent synchronization with stimulus pulse trains of antennular chemoreceptor cells in the American lobster. *J. Comp. Physiol. A*, 185:427-436.
- Goldman-Rakic, P.S. (1987) Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: *Handbook of Physiology. The Nervous*

- System. Higher Functions of the Brain. Am. Physiol. Soc, Bethesda, MD. Pp. 373-417.
- Gurski, M.R. and Hamilton, K.A. (1996) Effects of dopamine and fluphenazine on field potential amplitude in the salamander olfactory bulb. *Exp. Brain Res.*, 108:236-246.
- Guthrie, K.M., Anderson, A.J., Leon, M. and Gall, C. (1993) Odor-induced increase in c-fos mRNA expression reveal an anatomical 'unit' for odor processing in olfactory bulb. *Proc. Natl. Acad. Sci.*, 90:3329-3333.
- Guthrie, K.M., Wilson, D.A. and Leon, M. (1990) Unilateral olfactory deprivation modifies olfactory bulb function. *J. Neurosci.*, 10: 3402-3412.
- Haberly, L.B. (1969) Single-unit responses to odors in the prepyriform cortex of the rat. *Brain Res.*, 12:481-484.
- Haberly, L.B. (1985) Neuronal circuitry in olfactory cortex: Anatomy and functional implications. *Chem. Senses*, 10:219-238.
- Haberly, L.B. (1998) Olfactory cortex. In: G.M. Shepherd (Ed.) *The Synaptic Organization of the Brain*, Oxford Univ. Press, New York. pp. 377-416.
- Haberly, L.B. and Price, J.L. (1977) The axonal projection patterns of the mitral and tufted cells of the olfactory bulb in the rat. *Brain Res.*, 129:152-157.
- Haberly, L.B. and Price, J.L. (1978) Associational and commissural fiber systems of the olfactory cortex of the rat. I. Systems originating in the piriform cortex and adjacent areas. *J. Comp. Neurol.*, 178:711-740.
- Hamilton, K.A. and Kauer, J.S. (1985) Intracellular potentials of salamander mitral/tufted neurons in response to odor stimulation. *Brain Res.*, 338:181-185.
- Hamilton, K.A. and Kauer, J.S. (1989) Patterns of intracellular potentials in salamander mitral/tufted cells in response to odor stimulation. *J. Neurophysiol.*, 62:609-625.
- Hamrick, W.D., Wilson, D.A. and Sullivan, R.M. (1993) Neural correlates of memory for odor detection conditioning in adult rats. *Neurosci. Letts.*, 163:36-40.
- Harrison, T.A. and Scott, J.W. (1986) Olfactory bulb responses to odor stimulation: Analysis of response pattern and intensity relationships. *J. Neurophysiol.*, 56:1571-1589.

- Hasselmo, M.E. (1995) Neuromodulation and cortical function: Modeling the physiological basis of behavior. *Behav. Brain Res.*, 67:1-27.
- Hasselmo, M.E. and Barkai, E. (1995) Cholinergic modulation of activity-dependent synaptic plasticity in the piriform cortex and associative memory function in a network biophysical simulation. *J. Neurosci.*, 15:6592-6604.
- Hasselmo, M.E. and Bower, J.M. (1992) Cholinergic suppression specific to intrinsic not afferent fiber synapse in rat piriform (olfactory) cortex. *J. Neurophysiol.*, 67:1222-1229.
- Hasselmo, M.E., Linster, C., Patil, M., Ma, D. and Cekic, M. (1997) Noradrenergic suppression of synaptic transmission may influence cortical signal-to-noise ratio. *J. Neurophysiol.*, 77:3326-3339.
- Hasselmo, M.E., Wilson, M.A., Anderson, B.P. and Bower, J.M. (1990) Associative memory function in piriform (olfactory) cortex: Computational modeling and neuropharmacology. *Cold Spring Harbor Symp. Quant. Biol.*, 55:599-610.
- Hsia, A.Y., Vincent, J.D. and Lledo, P.M. (1999) Dopamine depresses synaptic inputs into the olfactory bulb. *J. Neurophysiol.*, 82:1082-1085.
- Hunter, A.J. and Murray, T.K. (1989) Cholinergic mechanisms is a simple test of olfactory learning in the rat. *Psychopharmacol.*, 99:270-275.
- Illig, K.R. and Haberly, L.B. (2000) Odor-specific regional activation of piriform cortex. *Chem. Senses*, 25:605.
- Imamura, K., Mataga, N. and Mori, K. (1992) Coding of odor molecules by mitral/tufted cells in rabbit olfactory bulb. I. Aliphatic compounds. *J. Neurophysiol.*, 68:1986-2002.
- Isaacson, J.S. (1999) Glutamate spillover mediates excitatory transmission in the rat olfactory bulb, *Neuron*, 23:377-384.
- Isaacson, J.S. and Strowbridge, B.W. (1998) Olfactory reciprocal synapses: Dendritic signaling in the CNS. *Neuron*, 20:749-761.
- Jacobson, I., Butcher, S. and Hamberger, A. (1986) An analysis of the effects of excitatory amino acid receptor antagonists on evoked field potentials in the olfactory bulb. *Neurosci.*, 19:267-273.

- Jiang, M., Griff, E.R., Ennis, M., Zimmer, L.A. and Shipley, M.T. (1996) Activation of locus coeruleus enhances the responses of olfactory bulb mitral cells to weak olfactory nerve input. *J. Neurosci.*, 16:6319-6329.
- Joerges, J., Kuttner, A., Galizia, C.G. and Menzel, R. (1997) Representation of odours and odour mixtures visualized in the honeybee brain. *Nature*, 387:285-288.
- Johnson, B.A. & Leon, M. (2000) Modular representations of odorants in the glomerular layer of the rat olfactory bulb and the effects of stimulus concentration. *J. Comp. Neurol.*, 422: 496-509.
- Johnson, B.A., Woo, C.C., Duong, H., Nguyen, V. and Leon, M. (1995) A learned odor evokes an enhanced Fos-like glomerular response in the olfactory bulb of young rats. *Brain Res.*, 699:192-200.
- Johnson, B.A., Woo, C.C. and Leon, M. (1998) Spatial coding of odorant features in the glomerular layer of the rat olfactory bulb. *J. Comp. Neurol.*, 393:457-471.
- Johnson B.A., Woo, C.W., Hingco, E.E., Pham, K.L. and Leon, M. (1999) Multidimensional chemotopic responses to n-aliphatic acid odorants in the rat olfactory bulb. *J. Comp. Neurol.*, 409:529-548.
- Johnson, D.M.G., Illig, K.R., Behan, M. and Haberly, L.B. (2000) New features of connectivity in piriform cortex visualized by intracellular injection of pyramidal cells suggest that "primary" olfactory cortex functions like "association" cortex in other sensory systems. *J. Neurosci.*, 20:6974-6982.
- Jourdan, F., Duveau, A., Astic, L. and Holley, A. (1980) Spatial distribution of [14C]-2-deoxyglucose uptake in the olfactory bulbs of rats stimulated with two different odours. *Brain Res.*, 188:139-154.
- Jung, M.W., Larson, J. and Lynch, G. (1990) Long-term potentiation of monosynaptic EPSPs in rat piriform cortex in vitro. *Synapse*, 6:279-283.
- Katoh, K., Koshimoto, H., Tani, A. and Mori, K. (1993) Coding of odor molecules by mitral/tufted cells in rabbit olfactory bulb. II. Aromatic compounds. *J. Neurophysiol.*, 70:2161-2175.
- Kaluza, J.F. and Breer, H. (2000) Responsiveness of olfactory neurons to distinct aliphatic aldehydes. *J. Exp. Biol.*, 203: 927-933.

- Kanter, E.D. and Haberly, L.B. (1990) NMDA-dependent induction of long-term potentiation in afferent and association fiber systems of piriform cortex in vitro. *Brain Res.*, 525:175-179.
- Kanter, E.D., Kapur, A. and Haberly, L.B. (1996) A dendritic GABAA-mediated IPSP regulates facilitation of NMDA-mediated responses to burst stimulation of afferent fibers in piriform cortex. *J. Neurosci.*, 16:307-312.
- Kapur, A., Pearce, R.A., Lytton, W.W. and Haberly, L.B. (1997) GABAA-mediated IPSCs in piriform cortex have fast and slow components with different properties and locations on pyramidal cells. *J. Neurophysiol.*, 78:2531-2545.
- Karadi, Z., Oomura, Y., Nishino, H. and Aou, S. (1989) Olfactory coding in the monkey lateral hypothalamus: Behavioral and neurochemical properties of odor-responding neurons. *Physiol. Behav.*, 45:1249-1257.
- Kashiwadani, H., Sasaki, Y.F., Uchida, N. and Mori, K. (1999) Synchronized oscillatory discharges of mitral/tufted cells with different molecular receptive ranges in the rabbit olfactory bulb. *J. Neurophysiol.*, 82:1786-1792.
- Kauer, J.S. (1974) Response patterns of amphibian olfactory bulb neurones to odour stimulation. *J. Physiol.*, 243:695-715.
- Kauer, J.S. and Moulton, D.G. (1974) Responses of olfactory bulb neurones to odour stimulation of small nasal areas in the salamander. *J. Physiol.*, 243:717-737.
- Kay, L.M. and Freeman, W.J. (1998) Bidirectional processing in the olfactory-limbic axis during olfactory behavior. *Behav. Neurosci.*, 112:541-553.
- Kay, L.M. and Laurent, G. (1999) Odor- and context-dependent modulation of mitral cell activity in behaving rats. *Nature Neurosci.*, 2:1003-1009.
- Klimek, L., Hummel, T., Moll, B., Kobal, G. and Mann, W.J. (1998) Lateralized and bilateral olfactory function in patients with chronic sinusitis compared with healthy control subjects. *Laryngoscope*, 108:111-114.
- Kogure, S. and Onoda, N. (1983) Response characteristics of lateral hypothalamic neurons to odors in unanesthetized rabbits. *J. Neurophysiol.*, 50:609-617.
- Kolb, B. (1984) Functions of the frontal cortex of the rat: A comparative review. *Brain Res. Rev.*, 8:65-98.
- Kosaka, T., Hatagichi, Y., Hama, K., Nagtsu, I. and Wu, J. (1985) Coexistence of immunoreactivities for glutamate decarboxylase and tyrosine hydroxylase in some

- neurons in the periglomerular region of the rat main olfactory bulb: possible coexistence of gamma-aminobutyric acid (GABA) and dopamine. *Brain Res.*, 343:166-171.
- Kosaka, T., Kosaka, K., Hama, K., Wu, J.Y. and Nagatsu, I. (1987) Differential effect of functional olfactory deprivation on the GABAergic and catecholaminergic traits in the rat main olfactory bulb. *Brain. Res.*, 413:197-203.
- Koster, N.L., Norman, A.B., Richtand, N.M., Nickell, W.T., Puche, A.C., Pixley, S.K. and Shipley, M.T. (1999) Olfactory receptor neurons express D2 dopamine receptors. *J. Comp. Neurol.*, 411:666-673.
- Krettek, J.E. and Price, J.L. (1977) Projections from the amygdaloid complex to the cerebral cortex and thalamus in the rat and cat. *J. Comp. Neurol.*, 172:687-722.
- Kucharski, D. and Hall, W.G. (1987) New routes to early memories. *Science*, 238:786-788.
- Laurent, G. (1999) A systems perspective on early olfactory coding. *Science*, 286:723-728.
- Linster, C. and Hasselmo, M.E. (2000) Neural activity in the horizontal limb of the diagonal band of Broca can be modulated by electrical stimulation of the olfactory bulb and cortex in rats. *Neurosci. Letts.*, 282:157-160.
- Linster, C., Wyble, B.P. and Hasselmo, M.E. (1999) Electrical stimulation of the horizontal limb of the diagonal band of Broca modulates population EPSPs in piriform cortex. *J. Neurophysiol.*, 81:2737-2742.
- Lipton, P.A., Alvarez, P. and Eichenbaum, H. (1999) Crossmodal associative memory representations in rodent orbitofrontal cortex. *Neuron*, 22:349-359.
- Litaudon, P. and Cattarelli, M. (1995) Piriform cortex late activity revealed functional spatial heterogeneity. *NeuroReport*, 6:1377-1380
- Litaudon, P., Datiche, F. and Cattarelli, M. (1997a) Optical recording of the rat piriform cortex activity. *Prog. Neurobiol.*, 52:485-510.
- Litaudon, P., Mouly, A.M., Sullivan, R.M., Gervais, R. and Cattarelli, M. (1997b) Learning-induced changes in rat piriform cortex activity mapped using multisite recording with voltage sensitive dye. *Eur. J. Neurosci.*, 9:1593-1602.
- Logothetis, N.K. and Sheinberg, D.L. (1996) Visual object recognition. *Ann. Rev. Neurosci.*, 19:577-621.

- Loudon, C. and Koehl, M.A.R. (2000) Sniffing by a silkworm moth: Wing fanning enhances air penetration through and pheromone interception by antennae. *J. Exp. Biol.*, 203:2977-2990.
- Lynch, G. (1986) *Synapses, circuits and the beginnings of memory*. MIT Press, Cambridge, MA.
- Lysakowski, A., Wayner, B.H., Bruce, G. and Hersh, L.B. (1989) An atlas of the regional and laminar distribution of choline acetyltransferase immunoreactivity in rat cerebral cortex. *Neurosci.*, 28:291-336.
- Macrides, F. and Chorover, S.L. (1972) Olfactory bulb units: Activity correlated with inhalation cycles and odor quality. *Science*, 175:84-87.
- Macrides, F., Schoenfeld, T.A., Marchand, J.E. and Clancy, A.N. (1985) Evidence for morphologically, neurochemically and functionally heterogeneous classes of mitral and tufted cells in the olfactory bulb. *Chem. Senses*, 10:175-202.
- Malnic, B., Hirono, J., Sato, T. and Buck, L.B. (1999) Combinatorial receptor codes for odors. *Cell*, 96: 713-723.
- Mathews, D.F. (1972) Response patterns of single units in the olfactory bulb of the rat to odor. *Brain Res.*, 47:389-400.
- McBride, S.A. and Slotnick, B. (1997) The olfactory thalamocortical system and odor reversal learning examined using an asymmetrical lesion paradigm in rats. *Behav. Neurosci.*, 111:1273-1284.
- McCollum, J., Larson, J., Otto, T., Schottler, F., Granger, R. and Lynch, G. (1991) Short-latency single-unit processing in olfactory cortex. *J. Cog. Neurosci.*, 3:293-299.
- Mair, R.G. (1982) Response properties of rat olfactory bulb neurones. *J. Physiol.*, 326:341-359.
- Meredith, M. (1986) Patterned response to odor in mammalian olfactory bulb: the influence of intensity. *J. Neurophysiol.*, 56:572-597.
- Mombaerts, P. (1999) Molecular biology of odorant receptors in vertebrates. *Ann. Rev. Neurosci.*, 22:487-509.
- Mori, K., Mataga, N. and Imamura, K. (1992) Differential specificities of single mitral cells in rabbit olfactory bulb for a homologous series of fatty acid odor molecules. *J. Neurophysiol.*, 67:786-789.

- Mori, K. and Yoshihara, Y. (1995) Molecular recognition and olfactory processing in the mammalian olfactory system. *Prog. Neurobiol.*, 45:585-619.
- Mouly, A.M., Litaudon, P., Chabaud, P., Ravel, N. and Gervais, R. (1998) Spatiotemporal distribution of a late synchronized activity on olfactory pathways following stimulation of the olfactory bulb in rats. *Eur. J. Neurosci.*, 10:1128-1135.
- Mouly, A.M., Vigouroux, M. and Holley, A. (1985) On the ability of rats to discriminate between microstimulations of the olfactory bulb in different areas. *Behav. Brain Res.*, 17:45-58.
- Nakashima, M., Mori, K. and Takagi, S.F. (1978) Centrifugal influence on olfactory bulb activity in the rabbit. *Brain Res.*, 154:301-316.
- Nemitz, J.W. and Goldberg, S.J. (1983) Neuronal responses of rat pyriform cortex to odor stimulation: An extracellular and intracellular study. *J. Neurophysiol.*, 49:188-203.
- Nickell, W.T., Behbehani, M.M., and Shipley, M.T. (1994) Evidence for GABA_B-mediated inhibition of transmission from the olfactory nerve to mitral cells in the rat olfactory bulb. *Brain Res. Bull.*, 35:119-123.
- Nickell, W.T., Norman, A.B., Wyatt, L.M. and Shipley, M.T. (1991) Olfactory bulb DA receptors may be located on terminals of the olfactory nerve. *NeuroReport*, 2:9-12.
- Nickell, W.T. and Shipley, M.T. (1988) Neurophysiology of magnocellular forebrain inputs to the olfactory bulb in the rat: Frequency potentiation of field potentials and inhibition of output neurons. *J. Neurosci.*, 8:4492-4502.
- Nowycky, M.C., Halasz, N. and Shepherd, G.M. (1983) Evoked field potential analysis of dopaminergic mechanisms in the isolated turtle olfactory bulb. *Neurosci.*, 8:717-722.
- O'Doherty, J., Rolls, E.T., Francis, S., Bowtell, R., McGlone, F., Kobal, G., Renner, B. and Ahne, G. (2000) Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. *NeuroReport*, 11:399-403.
- Ogawa, Y. (1998) Firing properties of olfactory bulb neurons during sniffing in rats. *Physiol. Behav.*, 64:755-764.

- Ojima, H., Mori, K. and Kishi, K. (1984) The trajectory of mitral cell axons in the rabbit olfactory cortex revealed by intracellular HRP injection. *J. Comp. Neurol.*, 230:77-87.
- Onoda, N., Imamura, K., Obata, E. and Iino, M. (1984) Response selectivity of neocortical neurons to specific odors in the rabbit. *J. Neurophysiol.*, 52:6380-650.
- Onoda, N. and Mori, K. (1980) Depth distribution of temporal firing patterns in olfactory bulb related to air-intake cycles. *J. Neurophysiol.*, 44:29-39.
- Orona, E., Rainer, E.C. and Scott, J.W. (1984) Dendritic and axonal organization of mitral and tufted cells in the rat olfactory bulb. *J. Comp. Neurol.*, 226:346-356.
- Orona, E., Scott, J.W. and Rainer, E.C. (1983) Different granule cell populations innervate superficial and deep regions of the external plexiform layer in rat olfactory bulb. *J. Comp. Neurol.*, 217:227-237.
- Pager, J. (1974) Selective modulation of the olfactory bulb electrical activity in relation to the learning of palatability in hungry and satiated rats. *Physiol. Behav.*, 12:189-195.
- Pager, J. (1978) Ascending olfactory information and centrifugal influxes contributing to a nutritional modulation of the rat mitral cell responses. *Brain Res.*, 140:251-269.
- Pager, J. (1983) Unit responses changing with behavioral outcome in the olfactory bulb of unrestrained rats. *Brain Res.*, 289:87-98.
- Pager, J. (1985) Respiration and olfactory bulb unit activity in the unrestrained rat: Statements and reappraisals. *Behav. Brain Res.*, 16:81-94.
- Pager, J., Giachetti, I., Holley, A. and LeMagen, J. (1972) A selective control of olfactory bulb electrical activity in relation to food deprivation and satiety in rats. *Physiol. Behav.*, 9:573-579.
- Pfaff, D.W. and Gregory, E. (1971) Olfactory coding in olfactory bulb and medial forebrain bundle of normal and castrated male rats. *J. Neurophysiol.*, 34:208-216.
- Potter, H. and Chorover, S.L. (1976) Response plasticity in hamster olfactory bulb: Peripheral and central processes. *Brain Res.*, 116:417-429.

- Puche, A.C. and Shipley, M.T. (1999) Odor-induced, activity-dependent transneuronal gene induction in vitro: mediation by NMDA receptors. *J. Neurosci.*, 19:1359-1370.
- Price, J.L., Carmichael, S.T., Carnes, K.M., Clugnet, M.C., Kuroda, M. and Ray, J.P. (1991) Olfactory input to the prefrontal cortex. In J.L. Davis and H. Eichenbaum (Ed.s) *Olfaction: A Model System for Computational Neuroscience*. MIT Press, Cambridge, MA, pp. 101-120.
- Price, J.L. and Slotnick, B.M. (1983) Dual olfactory representation in the rat thalamus: An anatomical and electrophysiological study. *J. Comp. Neurol.*, 215:63-77.
- Rall, W., Shepherd, G.M., Reese, T.S. and Brightman, M.W. (1966) Dendrodendritic synaptic pathway for inhibition in the olfactory bulb. *Exp. Neurol.*, 14:44-56.
- Ravel, N., Elaagouby, A. and Gervais, R. (1994) Scopolamine injection into the olfactory bulb impairs short-term olfactory memory in rats. *Behav. Neurosci.*, 108:317-324.
- Rolls, E.T. (2000) The orbitofrontal cortex and reward. *Cerebral Cortex*, 10:284-294.
- Rolls, E.T. (2001) The rules of formation of the olfactory representations found in the orbitofrontal cortex olfactory areas in primates. *Chem. Senses*, (in press).
- Rolls, E.T. and Baylis, L.L. (1994) Gustatory, olfactory and visual convergence within the primate orbitofrontal cortex. *J. Neurosci.*, 14:5437-5452.
- Rolls, E.T., Critchley, H.D., Browning, A.S., Hernadi, A. and Lenard, L. (1999) Responses to the sensory properties of fat of neurons in the primate orbitofrontal cortex. *J. Neurosci.*, 19:1532-1540.
- Rolls, E.T., Critchley, H.D., Mason, R. and Wakeman, E.A. (1996a) Orbitofrontal cortex neurons: Role in olfactory and visual association learning. *J. Neurophysiol.*, 75:1970-1981.
- Rolls, E.T., Critchley, H.D. and Treves, A. (1996b) Representation of olfactory information in the primate orbitofrontal cortex. *J. Neurophysiol.*, 75:1982-1996.
- Rolls, E.T. and Rolls, J.H. (1997) Olfactory sensory-specific satiety in humans. *Physiol. Behav.*, 61:461-473.
- Roman, F., Staubli, U. and Lynch, G. (1987) Evidence for synaptic potentiation in a cortical network during learning. *Brain Res.*, 418:221-226.

- Rosin, J.F., Datiche, F. and Cattarelli, M. (1999) Modulation of the piriform cortex activity by the basal forebrain: an optical recording study in the rat. *Brain Res.* 820:105-111.
- Royet, J.P., Jourdan, F., Ploye, H. and Soucheier, C. (1989) Morphometric modifications associated with early sensory experience in the rat olfactory bulb. II. Stereological study of the population of olfactory glomeruli. *J. Comp. Neurol.*, 289:594-609.
- Royet, J.P., Zald, D., Versace, R., Costes, N., Lavenne, F., Koenig, O. and Gervais, R. (2000) Emotional responses to pleasant and unpleasant olfactory, visual, and auditory stimuli: A positron emission tomography study. *J. Neurosci.*, 20:7752-7759.
- Rubin, B.D. and Katz, L.C. (1999) Optical imaging of odorant representations in the mammalian olfactory bulb. *Neuron*, 23: 499-511.
- Sallaz, M. and Jourdan, F. (1992) Apomorphine disrupts odour-induced patterns of glomerular activation in the olfactory bulb. *NeuroReport*, 3:833-836.
- Sallaz, M. and Jourdan, F. (1993) C-fos expression and 2-deoxyglucose uptake in the olfactory bulb of odour-stimulated awake rats. *NeuroReport*, 4:55-58.
- Sato, T., Hirono, J., Tonoike, M. and Takebayashi, M. (1994) Tuning specificities to aliphatic odorants in mouse olfactory receptor neurons and their local distribution. *J. Neurophysiol.*, 72: 2980-2989.
- Satou, M., Mori, K., Tazawa, Y. and Takagi, S.F. (1982) Two types of postsynaptic inhibition in pyriform cortex of the rabbit: Fast and slow inhibitory postsynaptic potentials. *J. Neurophysiol.*, 48:1142-1156.
- Scholfield, C.N. (1978) A barbiturate induced intensification of the inhibitory potential in slices of guinea-pig olfactory cortex. *J. Physiol.*, 275:559-566.
- Schneider, R.W.S., Price, B.A. and Moore, P.A. (1998) Antennal morphology as a physical filter of olfaction: Temporal tuning of the antennae of the honey bee, *Apis mellifera*. *J. Insect Physiol.*, 44:677-684.
- Schoenbaum, G., Chiba, A.A. and Gallagher, M. (1999) Neural encoding in orbitofrontal cortex and basolateral amygdala during olfactory discrimination learning. *J. Neurosci.*, 19:1876-1884.

- Schoenbaum, G. and Eichenbaum, H. (1995a) Information coding in the rodent prefrontal cortex. I. Single-neuron activity in orbitofrontal cortex compared with that in pyriform cortex. *J. Neurophysiol.*, 74:733-750.
- Schoenbaum, G. and Eichenbaum, H. (1995b) Information coding in the rodent prefrontal cortex. II. Ensemble activity in orbitofrontal cortex. *J. Neurophysiol.*, 74:751-762.
- Schoppa, N.E., Kinzie, J.M., Sahara, Y., Segerson, T.P. and Westbrook, G.L. (1998) Dendrodendritic inhibition in the olfactory bulb is driven by NMDA receptors. *J. Neurosci.*, 18:6790-6802.
- Scott, J.W. (1981) Electrophysiological identification of mitral and tufted cells and distributions of their axons in olfactory system of the rat. *J. Neurophysiol.*, 46:918-931.
- Scott, J.W. (1977) A measure of extracellular unit responses to repeated stimulation applied to observations of the time course of olfactory responses. *Brain Res.*, 132:247-258.
- Scott, J.W., McBride, R.L. and Schneider, S.P. (1980) The organization of projections from the olfactory bulb to the piriform cortex and olfactory tubercle in the rat. *J. Comp. Neurol.*, 194:519-534.
- Scott, J.W. and Pfaffmann, C. (1972) Characteristics of responses of lateral hypothalamic neurons to stimulation of the olfactory system. *Brain Res.*, 48: 251-264.
- Sharp, F.R., Kauer, J.S. and Shepherd, G.M. (1977) Laminar analysis of 2-deoxyglucose uptake in olfactory bulb and olfactory cortex of rabbit and rat. *J. Neurophysiol.*, 40:800-813.
- Shepherd, G.M. and Greer, C.A. (1998) Olfactory bulb. In G.M. Shepherd (Ed.) *The Synaptic Organization of the Brain*. Oxford University Press, New York, pp. 159-203.
- Shiple, M.T. and Ennis, M. (1996) Functional organization of olfactory system. *J. Neurobiol.*, 30:123-176.
- Sicard, G. and Holley, A. (1984) Receptor cell responses to odorants: similarities and differences among odorants. *Brain Res.*, 232: 283-296.
- Singer, M.S. and Shepherd, G.M. (1994) Molecular modeling of ligand-receptor interactions in the OR5 olfactory receptor. *NeuroReport*, 5:1297-1300.

- Slotnick, B.M. and Schoonover, F.W. (1992) Olfactory pathways and the sense of smell. *Neurosci. Biobehav. Rev.*, 16:453-472.
- Sobel, N. Khan, R.M., Saltman, A., Sullivan, E.V. and Gabrieli, J.D.E. (1999) The world smells different to each nostril. *Nature*, 402:35.
- Staubli, U., Schottler, F. and Nejat-Bina, D. (1987) Role of dorsomedial thalamic nucleus and piriform cortex in processing olfactory information. *Behav. Brain Res.*, 25:117-129.
- Stewart, W.B., Kauer, J.S. and Shepherd, G.M. (1979) Functional organization of rat olfactory bulb analyzed by the 2-deoxyglucose method. *J. Comp. Neurol.*, 185:715-734.
- Stopfer, M., Bhagavan, S., Smith, B.H. and Laurent, G. (1997) Impaired odour discrimination on desynchronization of odour-encoding neural assemblies. *Nature*, 390:70-74.
- Stripling, J.S. and Patneau, D.K. (1999) Potentiation of late components in olfactory bulb and piriform cortex requires activation of cortical association fibers. *Brain Res.*, 841:27-42.
- Sullivan, R.M. and Leon, M (1986) Early olfactory learning induces an enhanced olfactory bulb response in young rats. *Dev. Brain Res.*, 27:278-282.
- Sullivan, R.M. and Wilson, D.A. (1991) Neural correlates of conditioned odor avoidance in infant rats. *Behav. Neurosci.*, 105:307-312.
- Sullivan, R.M., Wilson, D.A. and Leon, M. (1989) Norepinephrine and learning-induced plasticity in infant rat olfactory system. *J. Neurosci.*, 9:3998-4006.
- Tanabe, T., Iino, M. and Takagi, S.F. (1975a) Discrimination of odors in olfactory bulb, pyriform-amygdaloid areas, and orbitofrontal cortex of the monkey. *J. Neurophysiol.*, 38:1284-1296.
- Tanabe, T., Yarita, H., Iino, M., Ooshima, Y. and Takagi, S.F. (1975) An olfactory projection area in orbitofrontal cortex of the monkey. *J. Neurophysiol.*, 38:1269-1283.
- Tang, A.C. and Hasselmo, M.E. (1994) Selective suppression of intrinsic but not afferent fiber synaptic transmission by baclofen in the piriform (olfactory) cortex. *Brain Res.*, 659:75-81.

- Trombley, P.Q. and Westbrook, G.L. (1990) Excitatory synaptic transmission in cultures of rat olfactory bulb. *J. Neurophysiol.*, 64: 598-606.
- Tseng, G.F. and Haberly, L.B. (1989) Deep neurons in piriform cortex II. Membrane properties that underlie unusual synaptic responses. *J. Neurophysiol.*, 62:386-400.
- Tsuboi, A., Yoshihara, S., Yamazaki, N., Kasai, H., Asai-Tsuboi, H., Komatsu, M., Serizawa, S., Ishii, T., Matsuda, Y., Nagawa, F. and Sakano, H. (1999) Olfactory neurons expressing closely linked and homologous odorant receptor genes tend to project their axons to neighboring glomeruli on the olfactory bulb. *J. Neurosci.*, 19:8409-8418.
- Uchida, N., Takahashi, Y.K., Tanifuji, M. and Mori, K. (2000) Odor maps in the mammalian olfactory bulb: Domain organization and odorant structural features. *Nature Neurosci.*, 3:1035-1043.
- Viana DiPrisco, G. and Freeman, W.J. (1985) Odor-related bulbar EEG spatial pattern analysis during appetitive conditioning in rabbits. *Behav. Neurosci.*, 99:964-978.
- Vickers, N.J., Christensen, T.A. and Hildebrand, J.G. (1998) Combinatorial odor discrimination in the brain: Attractive and antagonist odor blends are represented in distinct combinations of uniquely identifiable glomeruli. *J. Comp. Neurol.*, 400:35-56.
- Wehr, M. and Laurent, G. (1996) Odour encoding by temporal sequences of firing in oscillating neural assemblies. *Nature*, 384:162-166.
- Weinberger, N.M. (1998) Physiological memory in primary auditory cortex: Characteristics and mechanisms. *Neurobiol. Learn. Mem.*, 70:226-251.
- Wellis, D.P. and Scott, J.W. (1990) Intracellular response of identified rat olfactory bulb interneurons to electrical and odor stimulation. *J. Neurophysiol.*, 64:932-947.
- Wellis, D.P., Scott, J.W. and Harrison, T.A. (1989) Discrimination among odorants by single neurons of the rat olfactory bulb. *J. Neurophysiol.*, 61: 1161-1177.
- Wilson, D.A. (1997) Binaral interactions in the rat piriform cortex. *J. Neurophysiol.*, 78:160-169.
- Wilson, D.A. (1998a) Habituation of odor responses in the rat anterior piriform cortex. *J. Neurophysiol.*, 79:1425-1440.

- Wilson, D.A. (1998b) Synaptic correlates of odor habituation in the rat anterior piriform cortex. *J. Neurophysiol.*, 80:998-1001.
- Wilson, D.A. (2000) Comparison of odor receptive field plasticity in the rat olfactory bulb and anterior piriform cortex. *J. Neurophysiol.*, 84:3036-3042.
- Wilson, D.A. (2001) The role of acetylcholine in odor discrimination and cross-habituation by anterior piriform cortex neurons. Association for Chemoreception Sciences Annual meeting abstracts, (in press).
- Wilson, D.A. and Leon, M. (1987) Evidence of lateral synaptic interactions in olfactory bulb output cell responses to odors. *Brain Res.*, 417:175-180.
- Wilson, D.A. and Leon, M. (1988) Spatial patterns of olfactory bulb single-unit responses to learned olfactory cues in young rats. *J. Neurophysiol.*, 59:1770-1782.
- Wilson, D.A. and Sullivan, R.M. (1990) Olfactory associative conditioning in infant rats with brain stimulation as reward. I. Neurobehavioral consequences. *Devel. Brain Res.* 53:215-221.
- Wilson, D.A. and Sullivan, R.M. (1994) Neurobiology of associative learning in the neonate: Early olfactory learning. *Behav. Neural Biol.*, 61:1-18.
- Wilson, D.A. and Sullivan, R.M. (1995) The D2 antagonist spiperone mimics the effects of olfactory deprivation on mitral/tufted cell odor response patterns. *J. Neurosci.*, 15:5574-5581.
- Wilson, D.A. and Sullivan, R.M. (1999) Respiratory airflow pattern at the rat's snout and an hypothesis regarding its role in olfaction. *Physiol. Behav.*, 66:41-44.
- Wilson, D.A., Sullivan, R.M., Gall, C.M. and Guthrie, K.M. (1996) NMDA-receptor modulation of lateral inhibition and c-fos expression in olfactory bulb. *Brain Res.*, 719:62-71.
- Wilson, D.A. and Wood, J.J. (1992) Functional consequences of unilateral olfactory deprivation: time-course and age sensitivity. *Neurosci.*, 49:183-192.
- Wilson, M.A. and Bower, J.M. (1992) Cortical oscillations and temporal interactions in a computer simulation of piriform cortex. *J. Neurophysiol.*, 67:981-995.
- Wilson, M. and Shepherd, G.M. (1995) Olfactory cortex. In M.A. Arbib (Ed.) *The Handbook of Brain Theory and Neural Networks*. MIT Press, Cambridge, MA. pp.669-673.

- Woo, C.C., Oshita, M.H. and Leon, M. (1996) A learned odor decreases the number of Fos-immunopositive granule cells in the olfactory bulb of young rats. *Brain Res.*, 716:149-156.
- Yokoi, M., Mori, K. and Nakanishi, S. (1995) Refinement of odor molecular tuning by dendrodendritic synaptic inhibition in the olfactory bulb. *Proc. Nat. Acad. Sci.*, 92:3371-3375.
- Young, T.A. and Wilson, D.A. (1999) Frequency dependent modulation of inhibition in the rat olfactory bulb. *Neurosci. Letts.*, 276:65-67.
- Youngentob, S.L., Mozell, M.M., Sheehe, P.R. and Hornung, D.E. (1987) A quantitative analysis of sniffing strategies in rats performing odor detection tasks. *Physiol. Behav.*, 41:59-69.
- Zatorre, R.J. and Jones-Gotman, M. (1991) Human olfactory discrimination after unilateral frontal or temporal lobectomy. *Brain*, 114:71-84.
- Zatorre, R.J., Jones-Gotman, M., Evans, A.C. and Meyer, E. (1992) Functional localization and lateralization of human olfactory cortex. *Nature*, 360:339-340.
- Zhang, Y., Burk, J.A., Glode, B.M. and Mair, R.G. (1998) Effects of thalamic and olfactory cortical lesions on continuous olfactory delayed nonmatching-to-sample and olfactory discrimination in rats (*Rattus norvegicus*). *Behav. Neurosci.*, 112:39-53.
- Zimmer, L.A., Ennis, M. and Shipley, M.T. (1999) Diagonal band stimulation increases piriform cortex neuronal excitability in vivo. *NeuroReport*, 10:2101-2105.

Figure Captions

Figure 1. Basic schematized organization of the vertebrate olfactory system. Circled structures receive direct input from the main olfactory bulb. Note that most areas receiving direct input from the main olfactory bulb project back to the bulb. Modulatory inputs project broadly to all primary olfactory structures, although there is substantial heterogeneity in laminar density of terminations within each area. Abbreviations: OB, main olfactory bulb; AON, anterior olfactory nucleus; Amy, amygdala; PC, piriform cortex; Ent, entorhinal cortex; PFC, prefrontal cortex; Hyp, hypothalamus; DMN, dorsomedial nucleus of the thalamus; LC, locus coeruleus, NE, norepinephrine; HLDB, horizontal limb of the diagonal band of Broca; ACh, acetylcholine; Raphe, raphe nucleus; 5-HT, 5-hydroxytryptamine (serotonin).

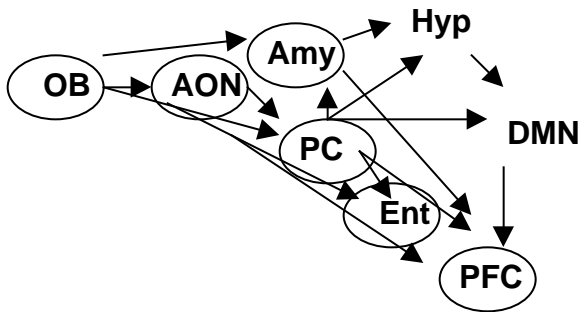
Figure 2. Basic schematized neural connectivity of the main olfactory bulb and piriform cortex. Individual receptors within the olfactory epithelium express one of 1000 different receptor proteins and are randomly scattered within one of 4 zones, yet receptors expressing the same receptor protein converge on to a small number of exclusive glomeruli (three receptor types are labeled A, B and C in this example). The receptors are hypothesized to be responsive to individual odorant features, rather than odorant molecules as a whole. Mitral cells receive receptor input from a single glomerulus (and thus convergent receptor input; e.g., A or B), and project to the piriform cortex. Within the olfactory bulb, inter-glomerular and inter-output neuron lateral inhibition is mediated by juxtglomerular and granule cells, respectively, heightening contrast between similar odorant features. Neurons in the piriform cortex appear to form a combinatorial array, allowing convergence of multiple odorant features (e.g., AB or ABC) and/or behavioral state/non-olfactory inputs to occur on single neurons. Both the olfactory bulb and piriform cortex receive extensive input from neuromodulatory and non-olfactory inputs.

Figure 3. Examples of odorant receptive fields (**A**) and an intracellularly recorded odorant response (**B**) in anterior piriform cortical neurons. The odorant receptive fields of piriform cortical neurons are similar to those described for both olfactory receptor neurons and mitral cells, with for example, responses varying with odorant carbon chain

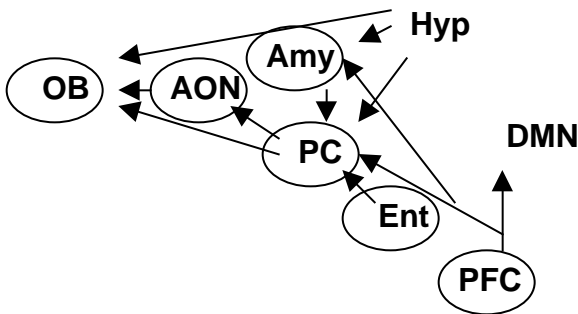
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length (**A**). Receptive fields in piriform cortex are highly dynamic, with rapidly habituating odorant responses (**B**). (**C**) In contrast to mitral/tufted cells in the main olfactory bulb, however, this habituation is highly odorant-specific. Responses to odorants differing by only 2 to 4 carbons in length are unaffected in piriform cortex, while mitral/tufted cells demonstrate more generalized habituation.

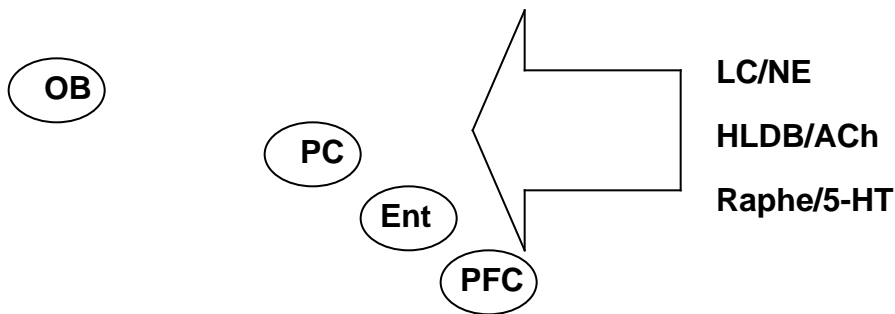
Ascending information flow

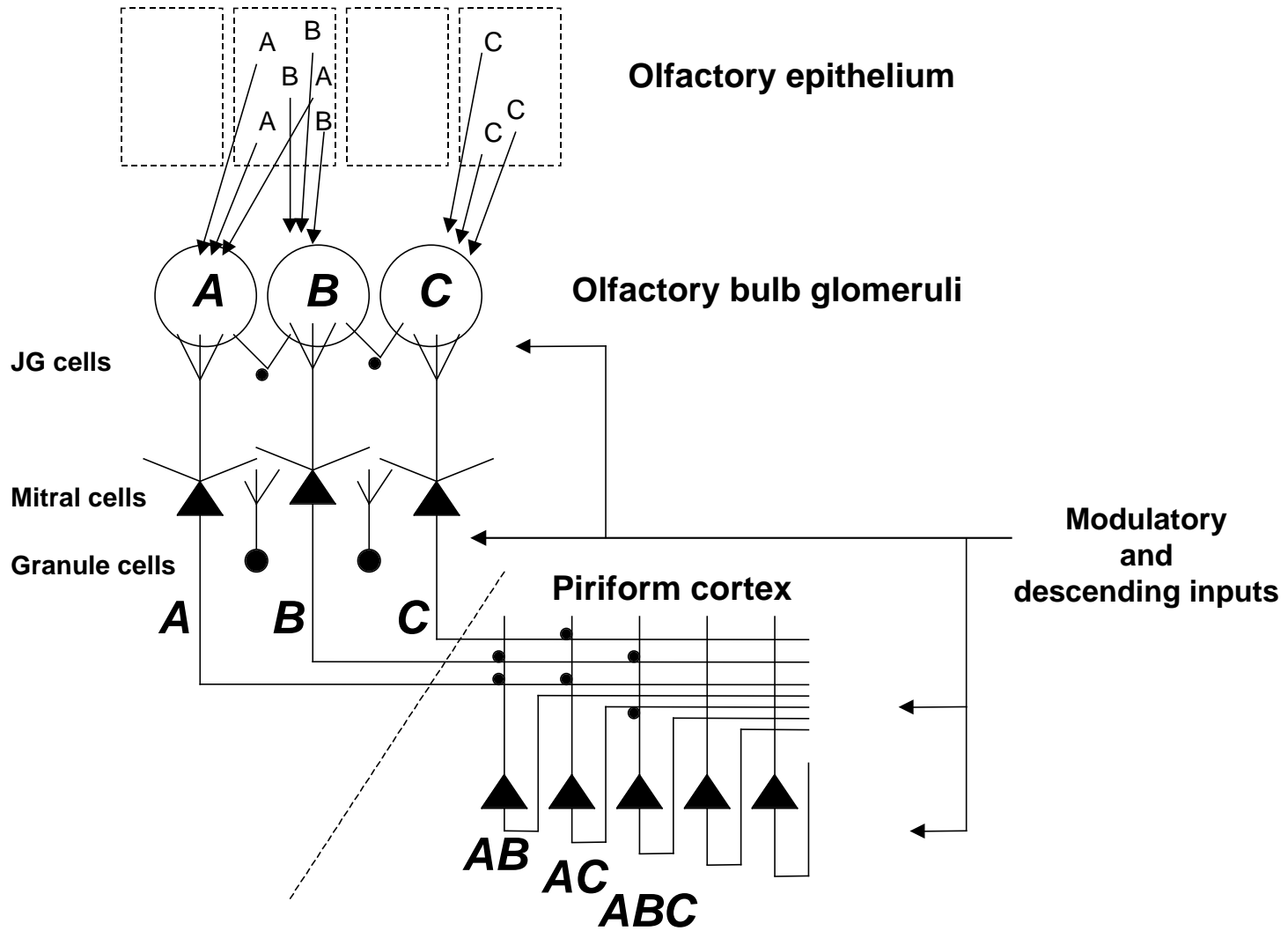


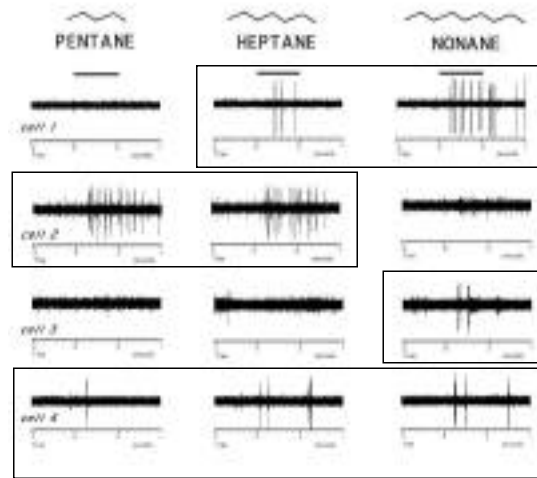
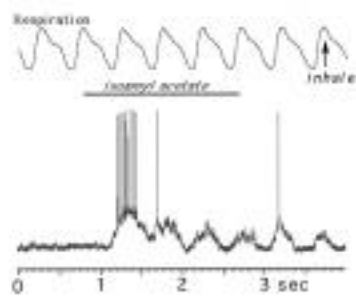
Descending/association information flow



Modulatory inputs





A**B****C**