Chem. Senses 26: 551–576, 2001

Parallel-distributed Processing in Olfactory Cortex: New Insights from Morphological and Physiological Analysis of Neuronal Circuitry

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Abstract

A working hypothesis is proposed for piriform cortex (PC) and other olfactory cortical areas that redefines the traditional functional roles as follows: the olfactory bulb serves as the primary olfactory cortex by virtue of encoding 'molecular features' (structural components common to many odorant molecules) as a patchy mosaic reminiscent of the representation of simple features in primary visual cortex. The anterior olfactory cortex (that has been inappropriately termed the anterior olfactory nucleus) detects and stores correlations between olfactory features, creating representations (gestalts) for particular odorants and odorant mixtures. This function places anterior olfactory cortex at the level of secondary visual cortex. PC carries out functions that have traditionally defined association cortex—it detects and learns correlations between olfactory gestalts formed in anterior olfactory cortex and a large repertoire of behavioral, cognitive and contextual information to which it has access through reciprocal connections with prefrontal, entorhinal, perirhinal and amygdaloid areas. Using principles derived from artificial networks with biologically plausible parallel-distributed architectures and Hebbian synaptic plasticity (i.e. adjustments in synaptic strength based on locally convergent activity), functional proposals are made for PC and related cortical areas. Architectural features incorporated include extensive recurrent connectivity in anterior PC, predominantly feedforward connectivity in posterior PC and backprojections that connect distal to proximal structures in the cascade of olfactory cortical areas. Capabilities of the 'reciprocal feedforward correlation' architecture that characterizes PC and adjoining higher-order areas are discussed in some detail. The working hypothesis is preceded by a review of relevant anatomy and physiology, and a non-quantitative account of parallel-distributed principles. To increase the accessibility of findings for PC and to advertise its substantial potential as a model for experimental and modeling analysis of associative processes, parallels are described between PC and the hippocampal formation, inferotemporal visual cortex and prefrontal cortex.

Introduction

Findings from morphological and physiological studies of the piriform cortex (PC) have been synthesized into functional hypotheses in a number of previous reviews and simulations. However, subsequent to these efforts a number of studies have provided evidence that, rather than subserving unimodal processing functions as previously assumed, PC is intimately involved in associative and behavior-level processes. Particularly convincing in this regard is a study of single unit activity in PC of rats performing an olfactory discrimination task (Schoenbaum and Eichenbaum, 1995). There is also much new data on the nature of coding by olfactory receptor neurons, the representation of olfactory information in the olfactory bulb, and the morphology and physiology of PC, all of which necessitates a substantial update of previous models. This paper provides an overview that includes these new findings as background information for the accompanying papers from the AChemS cortical symposium and for a new working hypothesis that is presented for the olfactory cortex. The hypothesis incorporates higher-order cortical areas with which PC has extensive connections, and smaller olfactory cortical areas that have been omitted from previous models. The hypothesis builds on principles developed in studies of biologically plausible artificial networks with parallel distributed architectural features similar to those observed in PC. Also included are brief non-quantitative summaries of the mechanisms of operation and capabilities of the artificial networks on which the hypothesis is based. Readers are referred to Rolls and Treves (Rolls and Treves, 1998) for additional biologist-friendly background on neural networks and to Hertz *et al.* (Hertz *et al.*, 1991) for a more technical introduction.

Figure 1A shows a lateral view of the olfactory pathways in the rat. This review focuses on PC, which is the largest of the olfactory cortical areas. Olfactory receptor neurons (ORNs) in the olfactory mucosa send their axons to the

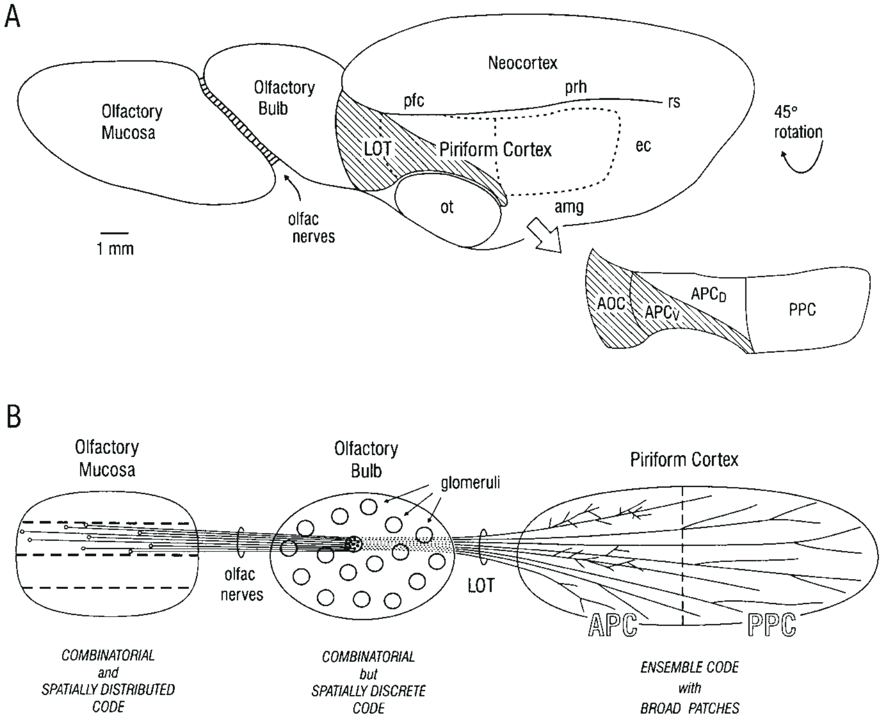


Figure 1 **(A)** Rat cerebral hemisphere and adjoining olfactory mucosa that contains olfactory receptor neurons, shown from a ventrolateral perspective. The olfactory bulb receives input from receptor neurons, the lateral olfactory tract (LOT) conveys output from the olfactory bulb, and the piriform cortex (PC) is the largest of the olfactory cortical areas. The inset at right shows the location of the anterior olfactory cortex (AOC) (that has been inappropriately termed the anterior olfactory nucleus) and subdivisions of PC (APC_V, ventral part of anterior; APC_D, dorsal part of anterior; PPC, posterior). Note that the LOT overlies AOC and APC_V, but not APC_D or PPC. **(B)** Block diagram of major connections. Axons from receptor neurons (small circles) that express the same molecular receptor pass through the olfactory nerves and converge onto specific glomeruli in the olfactory bulb. Axons from a glomerular group of mitral and tufted cells that receive input from a single glomerulus pass through the LOT and spread widely at the surface of PC. Synaptic terminations of these axons have patchy concentrations in APC, but are spatially dispersed in PPC. Amg, amygdala; ec, entorhinal cortex; ot, olfactory tubercle (ventral striatum); pfc, prefrontal cortex; prh, anterior perirhinal cortex; rs, rhinal sulcus.

olfactory bulb where they synapse in discrete glomeruli. ORN axons excite dendrites of the two populations of principal cells, mitral and tufted cells, whose axons pass through the lateral olfactory tract (LOT) to PC (Figure 1) and other olfactory cortical areas. PC has direct projections to a large number of cortical areas including widespread portions of prefrontal cortex, amygdaloid cortex, perirhinal cortex and the entorhinal cortex, through which it has disynaptic access to the hippocampal formation.

Olfactory coding: general features

A central issue for analysing olfactory cortical function is obviously the nature of odorant-related activity in the array of afferent axons from the olfactory bulb. Although uncertainties remain, there is an emerging consensus regarding many aspects of the encoding of olfactory information (Buck, 1999; Mori *et al.*, 1999). At the olfactory receptor level, this code is disturbingly complex: there are an estimated 4×10^7 olfactory receptor neurons (ORNs) in the mouse, each one of which expresses a molecular receptor selected from a repertoire of ~1000. The 4×10^4 copies, on average, of each variety of ORN are sprinkled over four large zones in the olfactory mucosa, introducing a highly distributed spatial component to the code (Figure 1B). However, a remarkable 'hard wired' convergence of axons reduces this spatial component by several orders of magnitude on the way to the olfactory bulb: all ORNs that express a particular receptor converge onto a small number of glomeruli—perhaps a single pair for most receptors. As a result of this specific convergence there is an elegant 'spot code' at the input level of the olfactory bulb where each receptor quality is represented by a small subset of glomeruli out of the total of ~1000 pairs in the mouse (Johnson *et al.*, 1999; Rubin and Katz, 1999; Uchida *et al.*, 2001).

One might think that the discrimination task faced by the olfactory cortex is a comparatively simple one by brain standards—that of recognizing which spots are activated by an unknown odorant. However, despite the great reduction in spatial dimension, the olfactory code at the glomerular level remains highly complex. A major source of the complexity is the combinatorial nature of this code (i.e. based on overlapping combinations) that stems from the nature of receptors and olfactory stimuli:

1. Single molecular species can activate multiple receptors as a result of a specificity for shared molecular features rather than for whole molecules (Malnic *et al.*, 1999).
2. Many biologically relevant odorants are ‘complex’ in nature, i.e. consist of large mixtures of molecules and/or receptor qualities. For example, the aroma of coffee contains >100 volatile molecular species, each one of which would be expected to activate one or more sets of ORNs. Even if the aroma that distinguishes your favorite brand were to be determined by a single one of these compounds, your olfactory system would have to recognize the pattern of neuronal activity evoked by this component in the presence of overlapping activity evoked by the other components.
3. Odorants are rarely experienced in isolation. When a rabbit encounters a fox in a field from which it barely escapes with its life, in order to avoid such encounters in the future the rabbit must be able to separate the fox-related odor from the odors associated with the flowers, grasses and rodents in the field.
4. High concentrations of odorant activate a greater number of receptor neurons and glomeruli than low concentrations; hence there is ambiguity in the encoding of ‘quality’ and ‘quantity’ (Harrison and Scott, 1986; Rubin and Katz, 1999).

Two recent discoveries suggest mechanisms that may substantially reduce the complexity of the olfactory code as it proceeds from glomeruli through the olfactory bulb to the olfactory cortex. The first is a lateral inhibition between glomerular groups that can enhance the specificity of responses within groups of similar compounds (Yokoi *et al.*, 1995). This process is analogous to certain operations performed by the visual cortex; for example, the enhancement of specificity for wavelength in the primary visual cortex. In view of the wealth of inhibitory circuitry in the olfactory bulb that extends over long distances as well as between neighboring mitral and tufted cells, one might suppose that the olfactory bulb also performs many other, as yet undetected, shaping operations.

The second discovery, which is described in detail in this volume (Wilson, 2001), is a rapid, odorant-specific habituation of responses to stimuli that are sustained for more than a few seconds (Wilson, 1998a,b, 2000a,b). This specific habituation may have a function of fundamental importance: the selectivity for change in stimulus pattern that it imposes should greatly assist in the learning and discrimination of odorants that are embedded in complex backgrounds. For example, the rabbit’s response to odorants from the field would likely have habituated before the fox appeared—hence the pattern of neuronal firing evoked by fox odorants would have occurred in relative isolation at the cortical level. Specific habituation clearly shapes motor aspects of olfactory discrimination: how we position our noses and regulate airflow when attempting to identify an odorant, and at least some aspects of a dog’s movements when following a scent trail (continuous changes in nose position actively modulate the strength of the desired scent relative to other scents and background odors).

Although the reduction in spatial dimension, shaping of specificities, and specific habituation reduce the demands on cortical-level processing, difficult correlations are clearly required to link the various spatial and perhaps temporal components of responses, both with each other and with defining temporally associated information and context. For example, fox odor presumably consists of a number of volatile compounds that activate many different sets of olfactory receptors. Learning to discriminate such an odorant first requires a linking of the set of glomerular groups in which activity is correlated in the presence of a fox. Second, the co-activated set of odor components must be linked with fox-defining information such as fear associated with being chased.

Since PC has long been designated as primary olfactory cortex, one might assume that its functional role is analogous to that of other primary sensory areas that extract highly specific stimulus features. However, a recent study in awake-behaving rats (Schoenbaum and Eichenbaum, 1995) has turned that mindset on its head by showing that cells in PC do not respond to olfactory input alone, but also fire vigorously in relationship to non-olfactory components of an odor discrimination task. Furthermore, this study showed that cellular responses to odor in PC can be altered by changes in reward value, and that neurons in APC can begin to fire before odor onset when the task allows its occurrence to be predicted.

Parallel distributed strategies for discrimination and association of complex patterns

Figures 2–5 depict approaches that could be used by the central olfactory pathways for discrimination, association and learning. Figure 2A shows a simple hardwired circuit that can analyse a combinatorial code. This network generates a cell-specific response to a hypothetical ‘old-book’ odorant consisting of three compounds that activate three populations of receptors in overlapping combinations. The circuits in Figures 2B–5 are parallel-distributed (neural) networks that have discriminative and associative abilities derived from adjustments in synaptic strength rather than specified connectivity. The multilayer feedforward network in Figure 2B is similar to that in 2A, but has complete connectivity between layers. Thresholds are set so that activation of two inputs with strong synapses (solid arrows) elicits output (filled circles). The illustrated circuit discriminates between two patterned inputs with 50% overlap (two of four input neurons are activated by both). Feed-forward networks with hidden layers as in Figure 2B provide

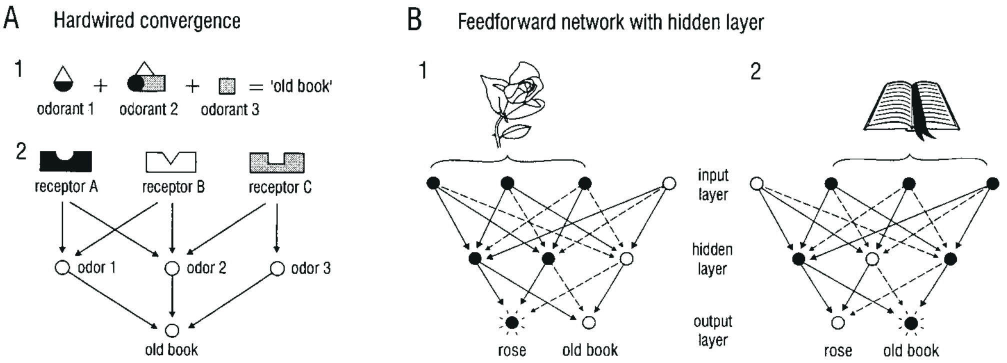


Figure 2 Analysis of combinatorial patterns by feedforward parallel-distributed neural networks. **(A)** Circuit with 'hardwired' convergence that generates a cell-specific response to a three-component odorant. **(A1)** The triangle, circle and square represent hypothetical molecular components that bind to different olfactory receptors. **(A2)** Specific cellular responses are first generated for the three compounds that constitute 'old book' odorant; a second level of convergence then creates a specific 'old book cell'. Arrows represent excitatory connections. **(B)** Parallel-distributed network with multi-layer feedforward architecture. Each 'neuron' connects with all neurons in the adjoining layer (i.e. complete connectivity), but the strengths of connections are adjusted so that activity spreads through the network following different pathways for different inputs. Thresholds are set so that output is generated (filled circles) when two strong connections (solid arrows) onto a given cell are activated (i.e. input from two solid circle–solid line combinations). Connectional strengths are set so that the three cells activated by the rose **(B1)** lead to an all-or-none activation of one of the two output cells, and the set activated by the book **(B2)** activate the other output cell (note that connection strengths are the same in B1 and B2). An important characteristic of parallel-distributed networks is that individual neurons and connections participate in the coding of multiple patterns: note that one of three cells in the hidden layer is activated by both inputs. Also note that discrimination occurs despite a 50% overlap in input patterns (two of four cells are activated by both inputs). Multi-layer feedforward networks with this architecture have powerful pattern recognition capabilities; however, no algorithm that uses biologically reasonable processes has yet been discovered that allows them to be programmed to generate discrete outputs as in this example. In contrast, the networks illustrated in subsequent figures can undergo unsupervised learning using algorithms that can be implemented biologically.

powerful pattern analysis capabilities and are in widespread use. Currently, such multilayer feedforward networks can only be programmed to perform operations such as that illustrated in Figure 2B where each member of a set of patterned inputs evokes a different predetermined output, through the use of highly iterative 'backpropagation' algorithms that are not biologically feasible. However, with certain constraints on their architectures, it has been shown that networks of this form can self-organize using purely local, activity-driven learning rules; that is, functionally join input patterns to arbitrary sets of output neurons (as opposed to predetermined sets).

Single layer feedforward networks with biologically reasonable architectures and properties (including slow nonlinear analog processes) can perform brain-like functions when they contain a sufficiently large number of elements and incorporate certain tricks such as competitive processes. Such circuits will be termed 'feedforward pattern correlation networks'. The incorporation of synapses whose strengths are increased in response to local conjugations of activity can impart unsupervised learning capabilities on feedforward networks. Biologically, this Hebbian synaptic plasticity can be implemented with NMDA receptors (Brown and Chattarji, 1994) and is commonly termed long-term potentiation (LTP). Long-term depression (LTD) is also incorporated into most practical pattern correlation networks, but will not be considered in this brief account. Feedforward pattern correlation networks, as illustrated in Figures 3 and 4, implement content addressable memory, where stored information is recalled through matches between input prompts and content. Content addressable memory contrasts with the location addressable memory that is used in current personal computers, where stored information can only be accessed through arbitrarily assigned addresses.

Figure 3A illustrates a feedforward pattern correlation network with two input pathways: a patterned input (left) consisting of three branching axons (Figure 3C) that synapse on all neurons, and a specialized strong input pathway with non-modifiable synapses, termed a driving input (right), that generates action potentials in a specific set of neurons (cells a and b). If axonal branches extend to all neurons as in Figure 3A (a biologically unrealistic assumption) connectivity is said to be complete. Before learning, the patterned input (axons 1–3) evokes a subthreshold response. Learning occurs when this patterned input is paired with firing in postsynaptic neurons evoked by the driving input so that the synapses indicated by plus signs are strengthened by a Hebbian process (Figure 3A1). When the original patterned input or a degraded version is subsequently presented as illustrated in Figure 3A2, recall is evoked that consists of firing in the same set of cells that, before learning, required the driving input. This simple example illustrates how such simple feedforward networks can not only carry out unsupervised learning that results in the formation of functional associations between sets of input and output patterns, but can also perform pattern completion, where appropriate outputs can be evoked by imperfect replicas of learned patterns. A key architectural feature required for such pattern completion is axonal branching, which provides the redundancy that enables different subsets of axons to evoke facsimiles of a learned pattern.

The feedforward pattern correlation network in Figure 3B has two patterned inputs, dilute rather than complete connectivity and a nonspecific enabling input rather than a driving input. Coactivation of the two patterned inputs while the enabling input is active results in a strengthening of the indicated synapses (Figure 3B1). During subsequent recall, either one of the patterned inputs, presented alone,

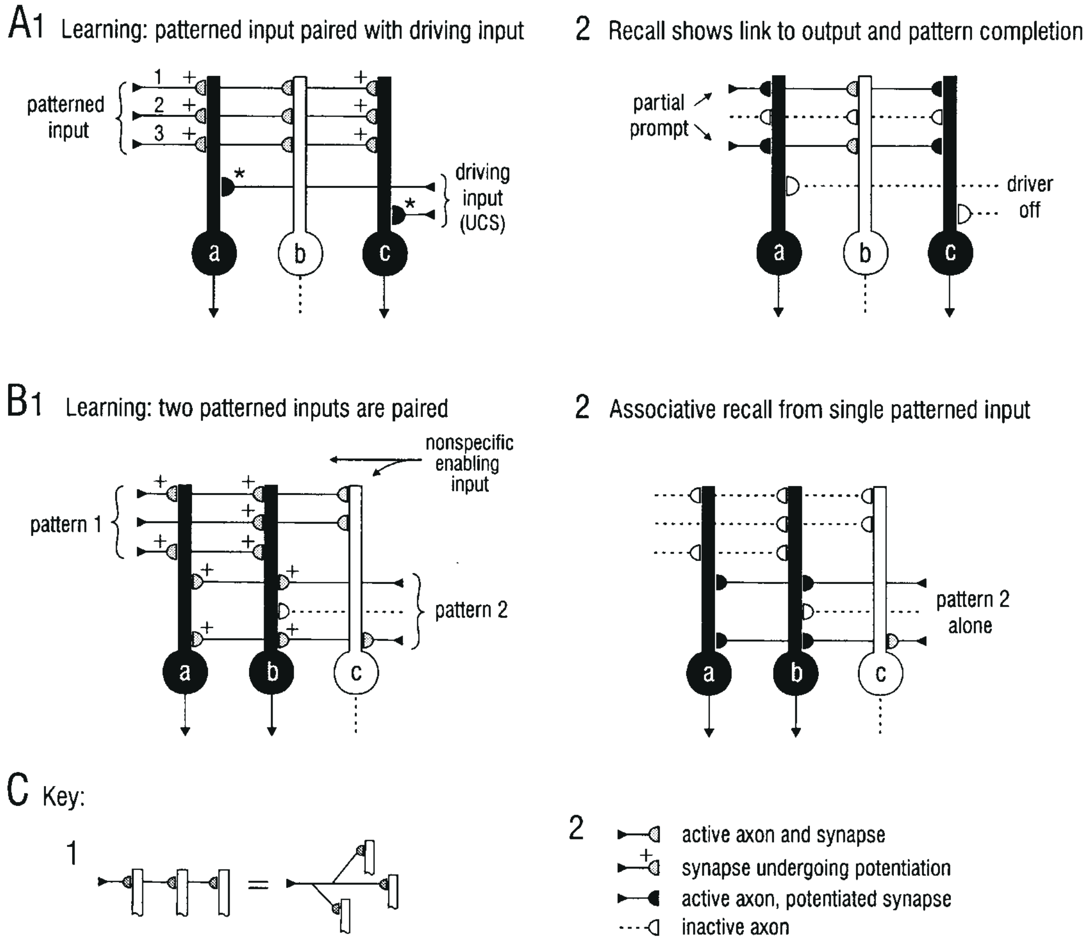


Figure 3 Simple feedforward pattern correlation networks that allow unsupervised learning using biologically plausible rules and processes. **(A)** Circuit in which a patterned input with learning-modifiable synapses is paired with postsynaptic activity (output) elicited by a driving input that generates a fixed (non-modifiable) firing pattern. Three neurons (a–c) receive excitatory synapses on their dendrites. The patterned input pathway (left) has complete connectivity (each axon branches and contacts all neurons with comparatively weak synapses: activation of all three synapses on a given neuron fails to evoke firing). The driving input (right) has two axons, each one of which has a strong synapse (asterisk) that elicits firing from its postsynaptic cell (black shading) when activated. **(A1)** Learning occurs when conjugations of activity in patterned-input synapses (glutamate release, biologically) and strong postsynaptic depolarization from the driving input (dendritic spikes or graded synaptic depolarization, biologically) induce Hebbian potentiation of synapses on neurons a and c (indicated by + signs). **(A2)** After learning, presentation of a degraded form of the original patterned input evokes output from the same cells that were activated by the driving input during learning (activity in axons 1 + 3 evokes output from cells a + c). In other words, this simple network generates functional linkages between input and output patterns and displays content addressability (i.e. performs pattern completion on recall). Thresholds are set so that activation of two potentiated synapses evokes output. **(B)** Feedforward pattern correlation network with two patterned input pathways, dilute connectivity (not all axons synapse on all neurons), and a nonspecific enabling input that facilitates Hebbian potentiation. Enabling inputs accompany learning-appropriate conditions (e.g. hunger or pain) and can act by a wide variety of mechanisms (Hasselmo, 1995; Kanter *et al.,* 1996; Patil *et al.,* 1998; Neville and Lytton, 1999). **(B1)** Learning occurs when both patterned input pathways are activated while the enabling input is active. **(B2)** Subsequently, either patterned input alone elicits the same output that required coactivation during learning (cells a + b fire in response to either pattern 1 or pattern 2). That is, heteroassociative linkages have been set up between arbitrarily different input and output patterns. Thresholds are set so that firing is evoked by activation of four non-potentiated (light gray) or two potentiated (black) synapses on a given neuron. **(C)** Key showing how branching axons **(C1)** and various combinations of activity in axons and synapses **(C2)** are represented in this and subsequent figures. Practical networks of feedforward correlator form incorporate processes that are not shown, including competitive interactions that decrease the extent to which different patterns engage the same synapses and neurons (implemented by a combination of lateral inhibition and local recurrent excitation) and long-term depression of synaptic strengths that prevents saturation.

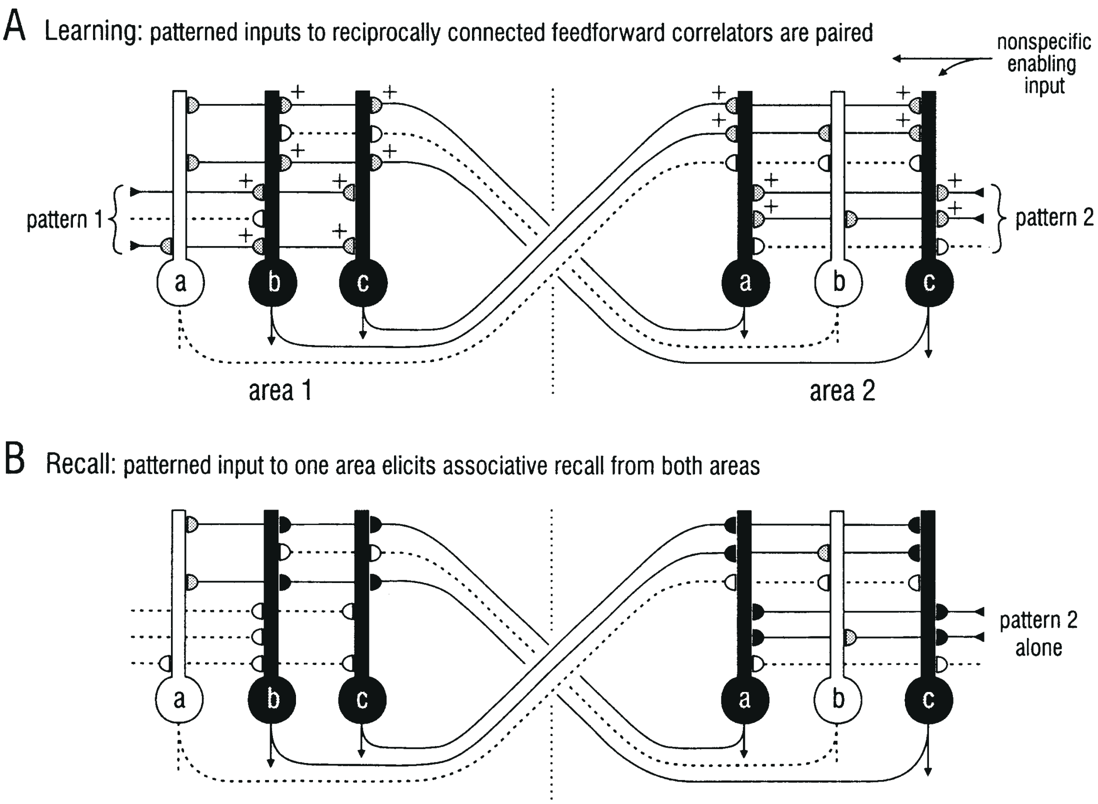


Figure 4 Associative network consisting of two bidirectionally coupled pattern correlation networks (reciprocal feedforward correlation architecture) as postulated for PPC and adjoining high-order cortical areas (Figure 11). Thresholds are the same as in Figure 3. **(A)** When pattern 1 (left) activates area 1 at the same time that pattern 2 activates area 2, the synapses with plus signs undergo Hebbian potentiation. **(B)** After several repetitions, either input pattern presented alone elicits the firing patterns in both areas that initially required coactive inputs (cells b + c in area 1 and cells a + c in area 2 are activated by either pattern 1 or pattern 2). Also note that the occurrence of a learned pattern of firing in one area can evoke a retrograde reconstruction of a previously associated pattern of firing in a second area. See text for discussion of how recurrent activation of reciprocal feedforward correlation networks increases their power and how associative gating associated with this architecture limits the level of irrelevant background activity.

can evoke output from the neurons that, before learning, fired only when both patterned inputs occurred together (Figure 3B2). This process whereby pairs of unrelated patterns are stored and retrieved is termed heteroassociation.

Figure 4 illustrates a system that consists of a pair of bidirectionally connected pattern correlation networks (referred to below as ‘reciprocal feedforward correlation architecture’). This system implements heteroassociative learning and recall; i.e. a pattern of neuronal activity in one brain area becomes functionally joined to an unrelated pattern in a second area (a process that will be referred to as linking) so that occurrence of one pattern reconstructs the other. Such associative linking is a key property of higher brain function. For example, the first time our rabbit smelled the fox, the distributed pattern of neuronal firing evoked in olfactory cortex was defined in large part through the associative linkages that developed with emotion from the ensuing chase, the visual image of the fox, etc. Subsequently, the odor of the fox could elicit fear and visual memory, and the sight of a fox could likewise elicit odor memory and other associations. Additional properties of this architecture are considered in some detail as part of the working hypothesis for olfactory cortex.

Figure 5 illustrates a fundamentally different form of circuit, termed a recurrent network, where the excitatory connections are in a feedback configuration (i.e. neurons are interconnected). Figure 5B illustrates the response to a novel patterned input that evokes an output pattern consisting of three discharging cells. The nine synapses on the recurrent collaterals that are opposed to the active cells undergo Hebbian potentiation (+ signs). Figure 5C depicts subsequent recall where an altered version of the original learned pattern (same book but different bookmark) evokes the original output. As seen in Figure 5C1, this pattern completion occurs because the synapses that were reinforced during learning exert a sufficiently strong drive to restore the original firing pattern when the initial pattern evoked during recall is cycled back as input (Figure 5C2). This process, whereby outputs are returned as inputs, is termed autoassociation. Circuits of this form are called attractor networks when autoassociation is allowed to continue until a

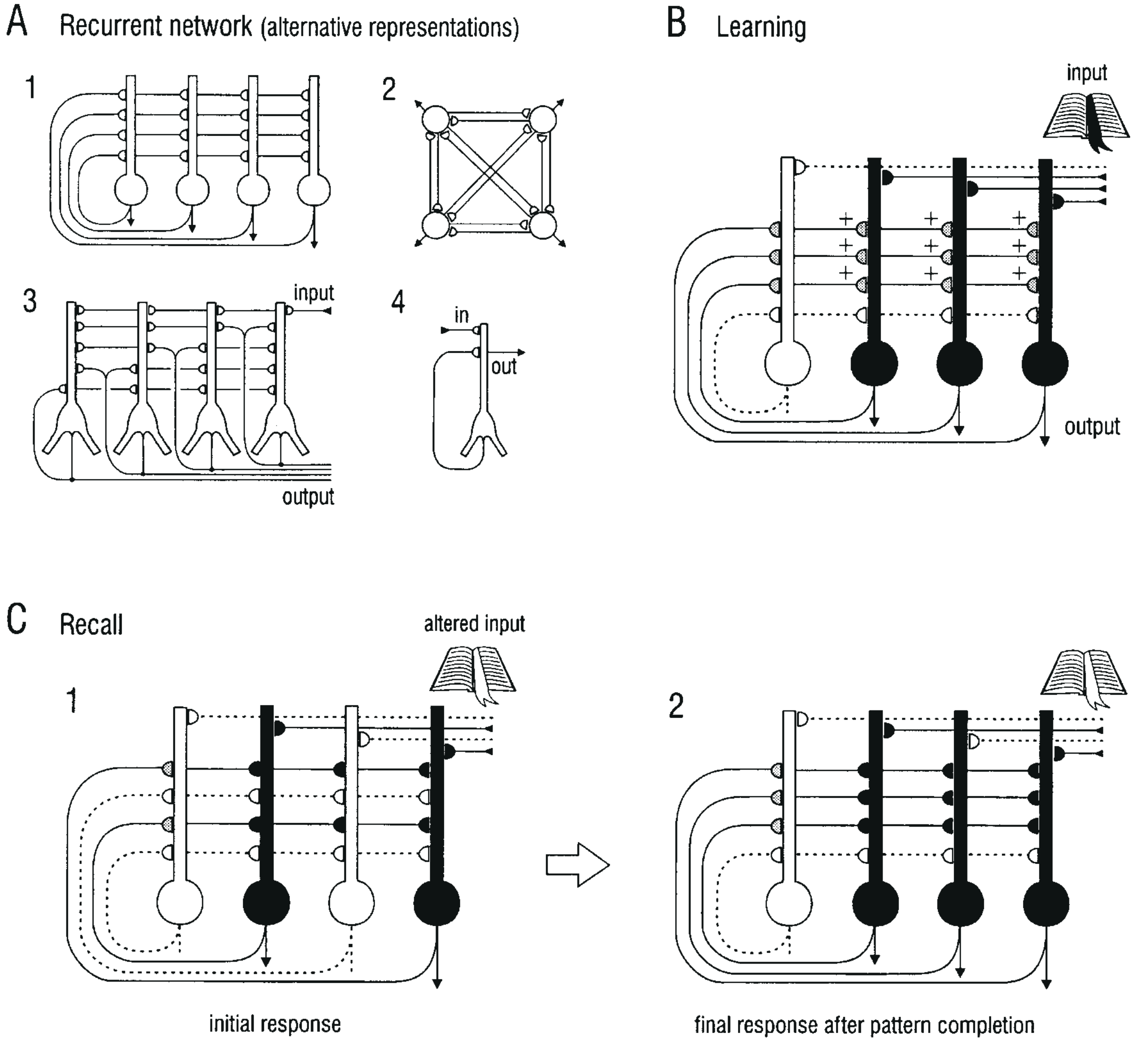


Figure 5 Recurrent network and autoassociative pattern completion. **(A)** Alternative depictions of the same basic recurrent network. **(A1)** Common form in artificial network literature. Each neuron gives rise to a recurrent (feedback) connection that contacts all neurons in the system (connectivity is complete and symmetrical). **(A2)** Representation of same network that emphasizes interconnectivity (autapses are omitted). **(A3)** More biologically realistic depiction that includes an input pathway. **(A4)** Compressed version of A3 (used in subsequent figures) where a single schematic neuron represents an entire population. **(B)** Recurrent networks are capable of unsupervised learning when synapses support Hebbian potentiation. In the illustrated example, the book evokes firing in three of four neurons (black shading), resulting in activity in the recurrent axons to which they give rise, and potentiation of the nine synapses on the three active neurons (plus signs). Note that the three synapses from active axons that contact the inactive neuron are activated but do not become potentiated. **(C)** Pattern completion through autoassociation where an altered or degraded version of a learned pattern leads to recall of the pattern of neuronal firing that was evoked by the original. C1 shows the pattern that is initially evoked by an altered prompt (same book used to train the network in B but with a different bookmark). C2 shows the final response after autoassociative activity has restored the original pattern (the potentiated synapses boost activity in the middle neuron to its original level). Note that the memory trace consists of a distributed set of potentiated synapses. As illustrated in Figure 6, despite the storage of multiple patterns on top of each other (i.e. same synapses and neurons participate in storage of many patterns), original stored patterns can be evoked by partial or degraded inputs. This implements a content addressable memory where recall is based on the degree of match between new and stored patterns, that also can be implemented with feedforward pattern correlation architecture (Figures 3, 4).

stable pattern is achieved (Hopfield, 1982). In early models of this form, connectivity between neurons was complete; however, recent work has shown that relatively sparse connections between neurons comparable to those in the cerebral cortex can actually enhance the capacity of recurrent networks to process patterns with overlapping (correlated) elements and increase the storage capacity for patterns of moderate complexity (Rolls and Treves, 1998). As in feedforward pattern correlation networks, specificity is determined by the constellation of synaptic strengths, and the same neurons and synapses participate in the memory traces for many different patterns. As illustrated in Figure 6, recurrent networks have powerful pattern completion and other content addressable memory capabilities, and can

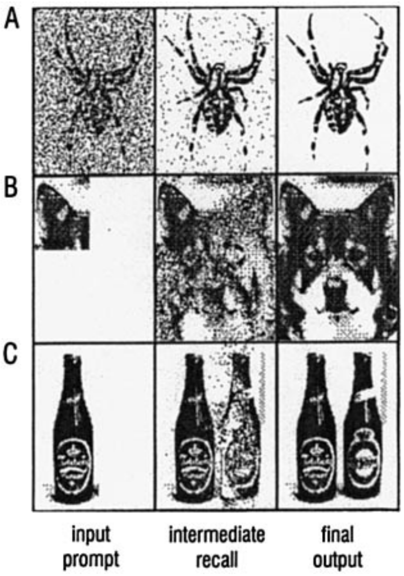


Figure 6 Demonstration of content addressable memory in a parallel-distributed network with recurrent architecture as in Figure 5. Seven patterns were stored across a large array of neurons with random and dilute (incomplete) connectivity; individual neurons and synapses contributed to the storage of all patterns (ensemble coding), but an individual pattern could be retrieved, as shown, with a corrupted input prompt. Left column shows prompts; middle column shows intermediate step in recall; right column is final retrieved pattern. **(A)** Reconstruction from noisy prompt. **(B)** Pattern completion starting with a small fragment. **(C)** 'Associative recall' where pattern completion generates the second of a pair of stored patterns when prompted by the first. Reproduced, with permission, from Hertz *et al.*, (Hertz *et al.*, 1990).

generate associative links that serve to define inputs (Figure 6C) as described above for the reciprocal feedforward correlation architecture.

General issues of significance for olfactory discrimination

Columnar/modular/patchy organizations

A striking organizational feature observed in the olfactory bulb and many other cortical areas is a spatial segregation of neurons with similar response properties and connections into discrete modules (termed 'patches' or 'columns' in the cerebral cortex and 'glomerular groups' in the olfactory bulb). Comparison of the architectural and physiological features of these modular organizations in sensory cortex, including the olfactory bulb, suggests that they serve to bring into spatial proximity groups of cells that interact to extract stimulus features. In the olfactory bulb there is increasing evidence that glomerular groups that encode structurally similar moieties are mapped in the same region (Mori *et al.*, 1992; Johnson *et al.*, 1999; Rubin and Katz, 1999; Uchida *et al.*, 2001) and that inhibitory interactions between adjoining glomerular groups can sharpen response specificities (Yokoi *et al.*, 1995).

Gestalt-based versus component-wise analysis

Everyday experience tells us that olfactory perception has a holistic quality whereby odorants that consist of many components (e.g. from an old book) evoke unique, unitary sensations rather than multiple-component percepts such as those evoked by complex visual patterns. Psychophysical and behavioral studies have confirmed that the olfactory system has little capacity to recognize components of odorant mixtures: the anecdotal ability of professional perfumers to identify large numbers of components in mixtures has not stood up to scrutiny (Livermore and Laing, 1996) and rats have minimal ability to recognize the reward value of odorants that are linked to reinforcement as members of mixtures with more than two components (Staubli *et al.*, 1987; Linster and Smith, 1999). Furthermore, Wilson's (Wilson, 2000a,b) studies of specific habituation in APC suggest that odor quality is represented as a gestalt rather than as a set of components: after the cellular response to a pair of odorants is habituated, there is no detectable change in the response to the components presented alone.

An intriguing question is whether the holistic character of olfactory discrimination and sensation somehow afforded a survival advantage, or if it represents an evolutionary shortcoming. An important consideration for addressing this question is that, as described earlier, the olfactory cortex uses specific habituation in conjunction with active exploration to perform figure–ground separation, thereby eliminating the necessity for a systematic analysis of stimulus components (e.g. identification of a fox in a field without 'structural' analysis of the fox plus field composite as required for visual identification). With this critical need satisfied, it appears that a component-based analysis of complex odorant mixtures either is of minimal utility, or would necessitate an unfavorable trade-off with a more critical ability. (In pattern vision, meaningful information is extracted through structural analysis of images; e.g. predicting a path through obstacles. Although important information could be obtained through a 'chemical analysis' of odorant mixtures, the interpretation of such information could pose a far more formidable problem than its extraction.) For olfaction, it is proposed that the critical feature that was optimized during evolution is the capacity to discriminate between complex mixtures that share large numbers of components. A visual system analogy illustrates this point: if several hundred small pieces of paper of arbitrary shape are displayed in random non-overlapping fashion, then the consistent detection of alterations in a few pieces would require prolonged study because, in contrast to olfaction, the visual system has minimal capacity for holistic discrimination of arbitrary patterns. (However, for identification of faces that consist of complex spatial patterns with many shared components, the visual system also employs gestalt-based processes.)

Pattern completion and generalization

An important aspect of sensory processing is the capacity to maintain discriminability despite alterations in stimulus patterns, variations in encoding, or changes in system anatomy. The process whereby a corrupted input pattern is restored to its original learned form is termed 'pattern completion' (see Figure 6). A related process, whereby a novel input elicits recall of a similar pattern from memory, is termed 'generalization'. Parallel-distributed networks, like the nervous system, excel at such operations by virtue of their content addressability (Figure 6).

In unimodal sensory areas, pattern completion is required to maintain perceptual invariance. For example, odor quality changes little up to the point that perception ceases when the nasal passages are partially blocked or large numbers of olfactory receptor neurons are killed by infection. This robust character is clearly due in part to the exceedingly high degree of convergence (numerical and spatial) in the projection from olfactory receptor neurons to glomeruli in the olfactory bulb (Figure 1B), which greatly increases the signal-to-noise ratio and introduces a spatial redundancy. Also, the maintenance of perceptual invariance is relatively simple for olfaction because it does not appear to carry out complex 'constancy' operations like those in other sensory systems (e.g. computation of color from wavelength, or shape when orientation changes). Nevertheless, despite the robust nature of sensory encoding and the relative simplicity of processing, some degree of pattern completion is presumably required, particularly to compensate for structural changes resulting from neuron loss and alterations in connectivity. Pattern completion may also be required for maintaining perceptual constancy with changes in odor concentration—see Figure 5 in Rubin and Katz (Rubin and Katz, 1999). The recall of associatively linked memories can also be thought of as a form of pattern completion; for example, recall of the visual image of a fox from its odor, or vice versa. Such associations could be stored as mixed memories within individual cortical areas (Figure 6C), or across multiple areas that are interconnected (Figure 4).

Whereas the goal of pattern completion is to restore original patterns of neuronal firing as faithfully as possible, generalization allows an input to retrieve information with which it was never previously associated by virtue of its similarity to a previous input. An example: a rabbit learns to associate fear with the smell of red fox, then flees when it smells a gray fox even though it has never been chased by one. An important constraint on generalization is that it not alter sensory perception (the rabbit maintains the ability to discriminate red and gray fox odors despite the crossover in associated information). Thus, if generalization were to occur at the level of perception, the capacity to make fine discriminations would be compromised. For example, compounds with similar structures that we can readily discriminate could smell the same if generalization were to occur too early in the olfactory cortical pathway.

Retrograde reconstruction

An idea that originated with abstract arguments but has now been supported by considerable data (Chen *et al.*, 1998; Crick and Koch, 1998; Zeki and Bartels, 1998; O'Craven and Kanwisher, 2000), is that when a complex multimodal memory is recalled, the accompanying activity occurs not just in high-order association cortex, but also extends to unimodal sensory areas. For example, when a subject is asked to form a mental image of a face, functional imaging reveals activity throughout the chain of secondary and unimodal association areas for vision, not just in multimodal association cortex. It has been widely postulated that backprojections from association areas mediate this unimodal recall. The process whereby recall of a mixed memory trace elicits the patterns of activity in the unimodal areas from which the trace was constructed will be referred to as 'retrograde reconstruction'.

Architecture and physiology of olfactory cortex

Anterior and medial olfactory cortex

Cortical areas at the junction between the olfactory bulb and cerebral hemisphere can be divided into two groups on the basis of their locations and connections with the olfactory bulb. Most of the anterior olfactory nucleus (AON) has heavy reciprocal connections with the olfactory bulb, whereas the medially placed dorsal peduncular cortex (DPC) and ventral tenia tecta (VTT) (Figure 8) have sparse connections with the olfactory bulb but strong connections with PC and other cortical areas (Haberly and Price, 1978a; Luskin and Price, 1983). As a result of the confusion resulting from the traditional terminology (particularly the inappropriate designation of AON as a nucleus when it is a pyramidal cell-based cortical system), new terms are introduced. AON is redefined as the 'anterior olfactory cortex' (AOC), and DPC and VTT are grouped as the 'medial olfactory cortex' (MOC). In this account, the term AOC will include lateral, dorsal and ventroposterior divisions of 'AON', but exclude external and medial divisions that have unique neuronal morphologies and connections (Haberly and Price, 1978b). AOC and MOC have functionally intriguing differences in their connections with PC. AOC has heavy reciprocal connections with APC, but virtually none with PPC. In contrast, MOC has reciprocal connections with the PPC as well as the entorhinal cortex, and a strong unidirectional projection to AOC (Haberly and Price, 1978a; Luskin and Price, 1983). As illustrated in Figures 7D and 8, MOC is a rather large expanse of well-differentiated three-layered cortex that provides a disynaptic backprojection pathway from caudal to rostral structures in the olfactory cascade (direct backprojections are sparse).

Architecture of neuronal circuitry in piriform cortex

Early studies with axon tracing techniques (Price, 1973) and current source–density analysis (Haberly and Shepherd, 1973) revealed a rather remarkable feature of PC: a combination of a precise order in the vertical (depth) dimension and a highly distributed overlapping order in the horizontal dimension (parallel to the surface) (Haberly, 1998). As summarized in Figure 9, the vertical segregation imposes a spatial order on synaptic inputs to pyramidal cells. Afferent input is confined to distal apical dendrites, whereas associational connections between pyramidal cells are on more proximal portions of apical dendrites, and on basal dendrites. Associational connections are themselves highly ordered, with local connections focused on basal dendrites (not shown), and longer connections stratified on apical dendrites at depths that depend on their region of origin. Inhibitory inputs from different populations of GABAergic neurons (not illustrated) are also spatially segregated on the cell bodies, axon initial segments and dendrites of pyramidal cells (Haberly, 1998). Studies with axon transport techniques have shown that the dense systems of associational axons that interconnect pyramidal cells in PC and

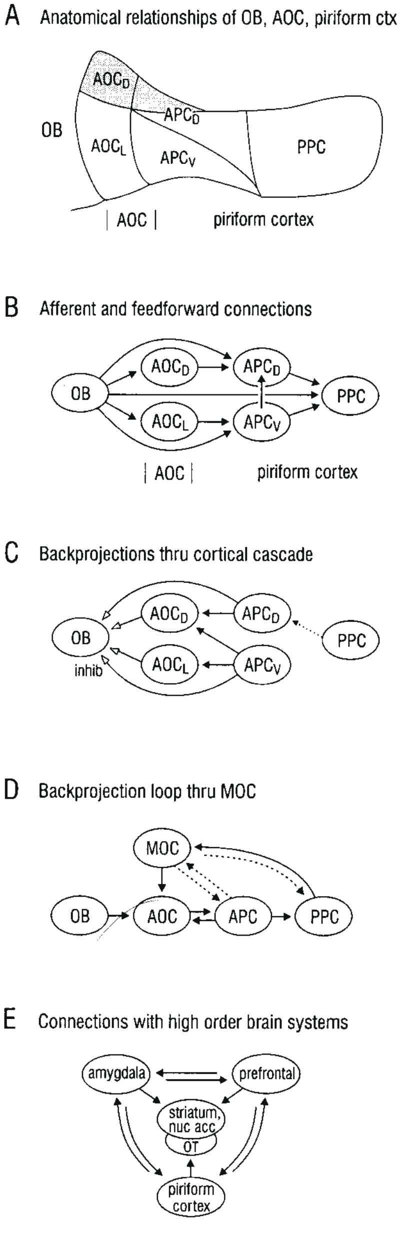


Figure 7 Block diagram of olfactory cortical connections. **(A)** Subdivisions of PC and AOC; see Figure 1A for orientation and abbreviations; shaded region is buried in the rhinal sulcus. **(B)** Forward connections. Note the parallel pathways through dorsal and ventral parts of AOC (AOC$_D$ and AOC$_L$, respectively) to APC$_D$ and APC$_V$. **(C)** Backprojections through lateral olfactory cortical structures. Note lack of backprojections from APC$_D$ to APC$_V$, and from PPC to APC$_V$, and the sparse backprojection from PPC to APC$_D$. All illustrated backprojections to the olfactory bulb end on granule cells and are thought to be inhibitory. **(D)** Disynaptic backprojection loop by way of the *medial olfactory cortex* (MOC) (dorsal peduncular cortex and ventral tenia tecta; Figure 8). **(E)** Connections of piriform cortex with brain areas that have rather direct roles in behavior. Note the unidirectional input to the olfactory tubercle (ventral striatum) and bidirectional connections with the amygdala and prefrontal cortex.

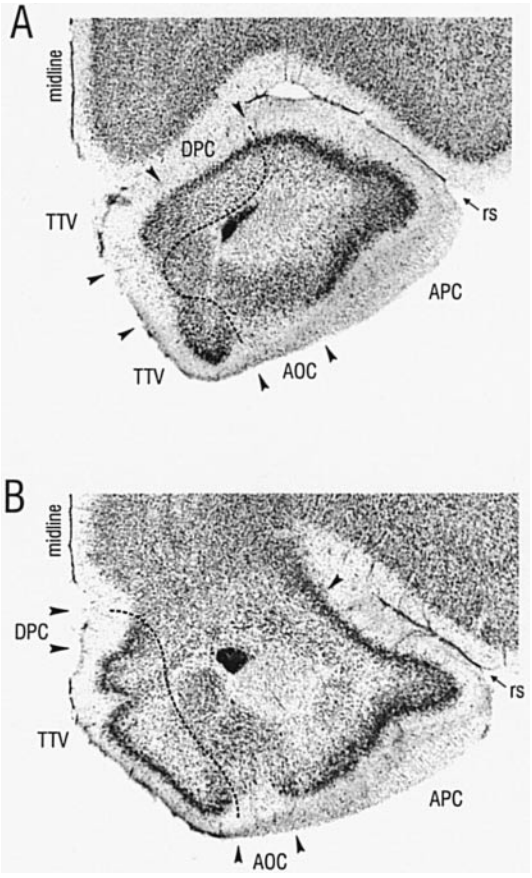


Figure 8 Nissl-stained coronal sections showing the ventral tenia tecta (TTV) and dorsal peduncular cortex (DPC) that together are defined as the medial olfactory cortex. These structures consist of well-differentiated three-layered cortex located between the olfactory bulb and piriform cortex. Together they provide a strong disynaptic backprojection pathway from caudal to rostral olfactory cortical areas (Figure 7D). TTV is divided into two parts at the level illustrated in A (Haberly and Price, 1978b).

extend to many adjacent cortical areas, are highly distributed spatially (Figure 10). However, these connections are not distributed at random; rather, there are broad, overlapping spatial patterns in both the origins and terminations of association axons (Haberly and Price, 1978a,b; Luskin and Price, 1983; Datiche *et al.*, 1996).

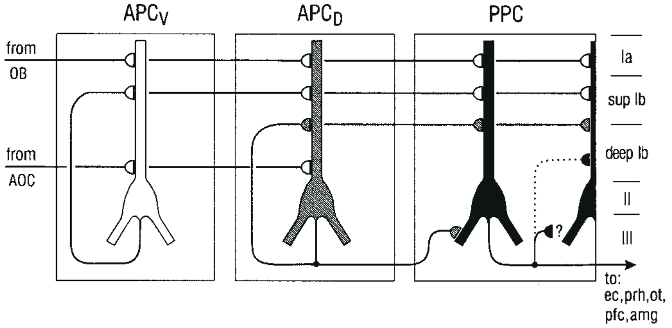


Figure 9 Summary of major excitatory connections in PC. Each schematic cell represents the entire population of pyramidal cells in a subdivision (see Figure 5A4); lines represent populations of highly branched axons. Local interconnections via basal dendrites and backprojections are not shown. The accumulative stacking of afferent, feedforward and recurrent connections on apical dendrites in layer I provides a progressively greater correlational capacity in progressively more caudal structures. Note that input from anterior olfactory cortex (AOC) is exclusively to APC and violates the otherwise distal-to-proximal progression in stacking order of inputs received from progressively more caudal structures. Also note the recurrent connectivity in APC (both APC$_V$ and APC$_D$) versus feedforward intrinsic connectivity in PPC that terminates largely in layer III, perhaps on basal dendrites. See Figure 1 for abbreviations.

Subdivisions of piriform cortex

PC is commonly separated into anterior and posterior parts (APC and PPC, respectively) as illustrated in Figure 1A. The most obvious difference between APC and PPC is that the LOT stops short of PPC. Physiological and modeling analysis has shown that afferent activation of APC is fast relative to the duration of postsynaptic potentials (Ketchum and Haberly, 1993a,b). In contrast, since PPC receives afferent input from thin axon collaterals from the LOT that stream tangentially across its surface, it is sequentially activated at a comparatively low rate. APC and PPC also differ in the organization of intrinsic associational systems. Although cellular-level analysis will be required for confirmation, population-level morphological studies indicate that long associational axons are both rostrally and caudally directed throughout APC, and largely caudally directed in PPC (Haberly and Price, 1978a; Luskin and Price, 1983; Datiche *et al.*, 1996) (D.M.G. Johnson, unpublished data). This is important, as detailed below, because the omnidirectional connections between pyramidal cells in APC provide a substrate for recurrent processes (Figure 5), whereas the strong caudal bias of associational connections in PPC suggests a dominance of feedforward processes. Finally, there is a marked difference in the extent of

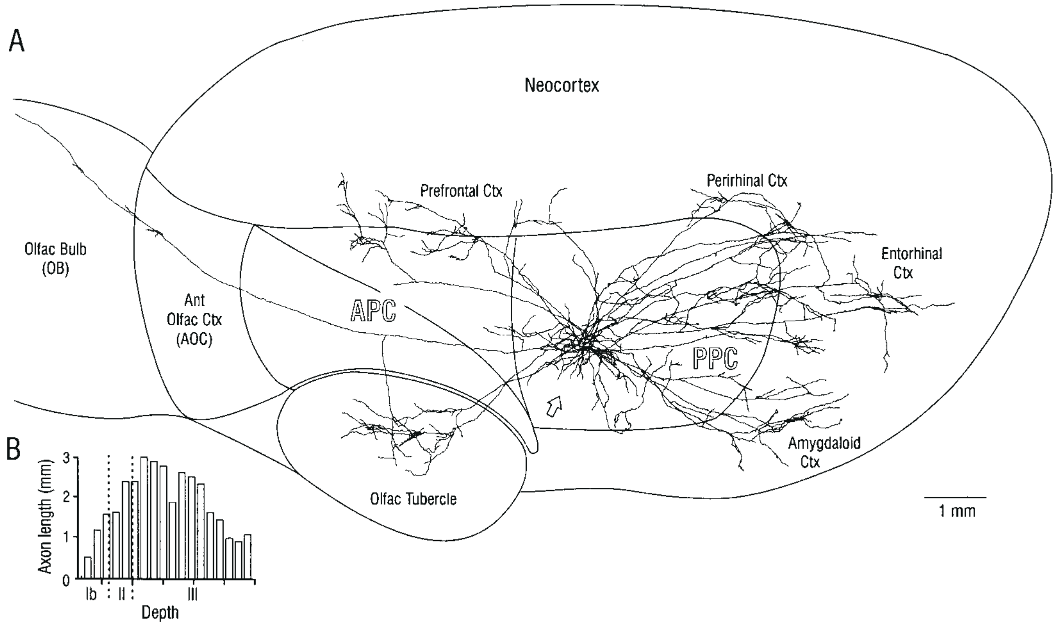


Figure 10 Reconstructed axonal arbors from two neighboring layer II pyramidal cells located in the rostral part of rat PPC, stained by intracellular injection *in vivo*. **(A)** Surface view; 45° upward rotation as in Figure 1A. Note that associational axons from the two cells extended over nearly the full rostral-to-caudal extent of the cerebral hemisphere and branched extensively in PC and in neighboring high-order cortical areas (prefrontal, perirhinal, entorhinal, amygdala) and the olfactory tubercle (ventral striatum). The open arrow indicates the location of the cell bodies (center of region with dense local collaterals). **(B)** Depth distribution of associational axons in PPC: total axon length is shown as a function of depth for five intracellularly injected layer II pyramidal cells; tick marks are 100 μm intervals. Note that associational arbors from PPC pyramidal cells are highly concentrated in layer III at the depth of pyramidal cell basal dendrites and inhibitory cells, rather than at the depth of apical dendrites as are association axons from APC.

Table 1 Intrinsic and extrinsic connections of piriform cortex

	Afferent and feedforward inputs	Recurrent[a]	High-order areas with reciprocal connections
APC_V	OB, AOC_L	heavy	orb
APC_D	OB, AOC_D, APC_V	heavy	ofc, ilc[b], amg[c], ec[c]
PPC	OB, APC_V, APC_D	light	ofc, ilc, amg, prh, ec
ec, amg, prh[d]	OB, APC_V, APC_D, PPC	–	–

Amg, amygdaloid cortex; AOC_D, dorsal division of anterior olfactory cortex; AOC_L, lateral division; APC_D, dorsal division of anterior piriform cortex; APC_V, ventral division; ec, entorhinal cortex; OB, olfactory bulb; ofc, orbitofrontal cortex (orbital and insular prefrontal); orb, orbital portion of orbitofrontal cortex; PPC, posterior piriform; prh, perirhinal cortex.

[a] Extent of spatially distributed pyramidal-cell interconnectivity within individual subdivisions of piriform cortex.

[b] Infralimbic prefrontal cortex (ilc) gives rise to a strong input to APC_D and APC_V, but receives only weak input from APC_D and virtually none from APC_V.

[c] More limited than to PPC.

[d] Anterior perirhinal cortex (prh) [posterior agranular insula in terminology of Krettek and Price (Krettek and Price, 1977)] receives direct olfactory bulb input (Shipley and Geinisman, 1984). More anterior cortical areas in the perirhinal region, including ventral agranular insular and orbital subdivisions of prefrontal cortex, receive little or no direct input from the olfactory bulb in the rat (L.B. Haberly, unpublished).

backprojections to the olfactory bulb from APC and PPC. These are heavy from all parts of APC, and lighter from PPC (Figure 7C) (de Olmos *et al.*, 1978; Haberly and Price, 1978a; Shipley and Adamek, 1984). The exceedingly large number of backprojecting pyramidal cell axons from APC (much larger than in the LOT) suggests that, despite its inhibitory action on mitral/tufted cells, this system is intimately involved in information processing (i.e. more than nonspecific feedback regulation of activity). Furthermore, granule cells in the olfactory bulb, on which this projection terminates, express CAMKII (Zou and Firestein, 2000), suggesting that its synapses support NMDA-dependent LTP. In a computer simulation model for olfactory cortex it has been proposed that this system underlies a ‘hierarchical clustering’ analysis whereby olfactory stimuli are categorized in an increasingly specific fashion over successive sniff cycles (Ambros-Ingerson *et al.*, 1990).

The APC can itself be divided into dorsal and ventral parts, with the LOT overlying the ventral division (APC_V) but not the dorsal (APC_D) (inset in Figure 1A). An intriguing feature is that APC_V and APC_D receive input from different regions of AOC (AOC_L and AOC_D, respectively), forming parallel feedforward pathways in the olfactory cascade (Figure 7B; note that both APC_V and APC_D receive direct afferent input from the olfactory bulb and relayed afferent input through AOC) (Haberly and Price, 1978a; Luskin and Price, 1983). The AOC_L–APC_V pathway is located deep to the LOT, and the AOC_D–APC_D pathway is lateral to the LOT. As described below, there are substantial differences in the connections of these fast ‘sub-LOT’ and slower ‘para-LOT’ pathways with higher-order cortical areas. In addition to receiving feedforward projections, APC_V and APC_D both have heavy backprojections to AOC. As indicated in Figure 7C, these have less regional specificity than the forward projections.

Extrinsic connections of piriform cortex

A striking feature of PC is that all parts have direct cortico-cortical connections with high-order association areas of the cerebral cortex (areas concerned with multimodal learning, emotion and behavior-related functions) (Johnson *et al.*, 2000), as well as rather direct pathways to subcortical structures concerned with autonomic and endocrine functions (Shipley *et al.*, 1995). However, the extent and patterns of these connections are strongly subdivision-dependent. Particularly intriguing from a functional standpoint is a progression in the extent of backprojections to successive structures in the olfactory pathway: these are sparse to APC_V, intermediate to APC_D and extensive to PPC. Although APC_V gives rise to the heaviest associational projections to other structures, it receives minimal backprojections from most of these targets, including APC_D and PPC (Table 1; Figure 7C). The only higher-order cortical region with strong reciprocal connections with APC_V is orbital cortex (specifically, VLO and LO) (Price *et al.*, 1991; Reep *et al.*, 1996; Ekstrand *et al.*, 2001a). APC_V also receives a unidirectional projection from infralimbic cortex (prefrontal area with strong links to autonomic functions) (Hurley *et al.*, 1991). In contrast, PPC has remarkably extensive reciprocal connections with insular and infralimbic regions of prefrontal cortex, much of the amygdala, and perirhinal and entorhinal cortices (Haberly and Price, 1978a; Luskin and Price, 1983; McIntyre *et al.*, 1996; Burwell and Amaral, 1998; Johnson *et al.*, 2000). APC_D is intermediate by virtue of reciprocal connections with insular cortex, and less extensive return projections from the amygdala, entorhinal cortex, and perirhinal cortex than PPC (Luskin and Price, 1983; Burwell and Amaral, 1998). APC_D also receives a light back-projection from PPC (Luskin and Price, 1983; Datiche *et al.*, 1996).

The extrinsic connections of the rostral part of APC_V

(APC_{VR}) differ somewhat from the remainder of APC_V and appear to provide a specialized pathway from the olfactory bulb to orbital prefrontal cortex (Ekstrand *et al.*, 2001a). APC_{VR} receives afferent input from tufted cells in the olfactory bulb in addition to mitral cells that supply the remainder of PC, and projects heavily to the ventrolateral orbital cortex (VLO) where chemosensory, visual, auditory, autonomic and perhaps spatial information converges (Price *et al.*, 1996; Rolls, 1997). Furthermore, immunocytochemical analysis has revealed unique features of inhibitory circuitry in APC_{VR} (Ekstrand *et al.*, 2001a), suggesting that it processes the information it conveys to VLO in a specialized fashion.

Cellular-level connectivity

Although population-level axon tracing studies with extracellularly injected tracers have examined intrinsic and extrinsic connections of PC in considerable detail, there are a number of key issues that will require cellular-level analysis for resolution. These include: (i) the degree to which the distributed order revealed by population-level studies reflects branching axons from individual cells as opposed to divergent projections from neighboring cells; (ii) the number of cells contacted by axons from individual pyramidal cells; (iii) the number of synapses that each of these axons makes on individual targeted cells; and (iv) the degree and nature of cellular-level topographical mapping. A recent study of intracellularly injected pyramidal cells has provided some insight into these questions for PPC (Johnson *et al.*, 2000). A surprise from this analysis is that individual layer II pyramidal cells in PPC have extensively branching axons that are distributed to most of the highest-order behavior-related areas in the cerebral cortex (Figure 10). Areas that are targeted by individual layer II pyramidal cells include the orbital and insular regions of prefrontal cortex, the amygdala (cortex and deep nuclei), the olfactory tubercle (ventral striatum), and both perirhinal and entorhinal cortex (providing access to the hippocampal formation). Combined analysis of the distribution of boutons and dendritic morphology suggested that individual pyramidal cells make a small number of synaptic contacts on each one of a very large number of other cells located over a wide area of PC and other target structures. Another intriguing feature is a heavy caudal bias in the direction of associational projections from PPC pyramidal cells (in Figure 10, note the broad, caudally directed sweep of associational axons within PPC before they exit into other cortical target area).

Laminar ordering of inputs to apical dendrites

As illustrated in Figure 9, another remarkable feature of PC is the orderly stacking of inputs to pyramidal cell apical dendrites in layer I (Haberly, 1998). Since all of the contributing fiber systems are predominantly caudally directed, the number of systems in the stack increases from proximal to distal along the olfactory cascade. At the caudal boundary of PPC the stack consists of afferent fibers in layer Ia, followed at successively greater depth in layer Ib by associational inputs from each subdivision of PC arranged according to the order in which they receive afferent input. Associational fibers from APC_V synapse in superficial Ib immediately adjacent to the afferent fiber layer, fibers from APC_D follow in mid-Ib, and fibers from PPC synapse next to cell bodies. A striking exception to the stacking by activation order is the feedforward afferent pathway from AOC that terminates at the depth of proximal-most apical dendrites in APC.

Temporal ordering of neuronal interactions in olfactory cortex

Studies of oscillatory field potentials (Freeman, 1975; Bressler, 1988; Ketchum and Haberly, 1991; Kay and Freeman, 1998) suggest that there is a high degree of temporal order in the operation of the olfactory system, despite the slow time-course of olfactory stimuli. From results obtained by current source–density analysis (Ketchum and Haberly, 1988), it has been postulated that the fast (~50 Hz) gamma oscillation that is elicited by odors, breaks each inspiratory cycle into a series of brief snapshots of ~20 ms duration, during which afferent input from the olfactory bulb, intrinsically generated associational activity and inhibition are paired in a stereotyped spatial and temporal order (Haberly, 1998). Such synchronous operation could have a substantial impact on the integration of synaptic inputs and NMDA-dependent adjustments in synaptic strengths (i.e. shunting of distal inputs by proximal, and optimization of temporal relationships for LTP) and has been speculated to be involved in analysis of temporal information in the olfactory code (Ketchum and Haberly, 1991). The extent to which associational activity could be sustained in the recurrent connections in APC depends on the depth (extent) to which the gamma oscillation modulates excitatory activity. A deep modulation of pyramidal cell firing by this rhythm would temporally restrict recurrent excitation to brief periods (<20 ms). This would be sufficient time for one or perhaps two cycles of distributed positive feedback within APC, but would limit the operation of this area as an attractor form of autoassociative network (Hopfield, 1982). However, odor-induced gamma oscillations in PC of the awake-behaving rat are highly irregular in amplitude (Kevin Neville, personal communication), suggesting that the extent to which intrinsic associational activity is sustained varies over a wide range. Both local and central neuromodulatory mechanisms could allow the depth of oscillation to be controlled on the basis of a wide variety of conditions or needs.

The sniff cycle, like the theta rhythm in hippocampus to which it can be temporally linked (Macrides *et al.*, 1982), generates a 4–8 Hz oscillation that imposes temporal order on relatively slow integrative and plastic processes. Gamma and sniff oscillations form a nested rhythm in the olfactory system like that in the hippocampus (Penttonen *et al.*, 1998; White *et al.*, 2000) where gamma cycles occur on the inspiratory part of sniff cycles as opposed to theta cycles. Particularly intriguing is that in PC (Haberly *et al.*, 1994) as in hippocampus (Larson *et al.*, 1986), stimulation of afferent or association fibers with a simulated theta–gamma rhythm is highly effective for inducing NMDA-dependent long-term potentiation of synaptic strength.

Encoding of olfactory information in piriform cortex

There have been two studies in APC of the unanesthetized rat in which single unit responses to odor have been examined. In one of these (Schoenbaum and Eichenbaum, 1995), activity was recorded during performance of a previously learned olfactory discrimination task, whereas in the other (McCollum *et al.*, 1991), activity was recorded while trained rats were learning to discriminate novel odors. Conclusions regarding the specificity of coding were virtually opposite. In the study in performing rats it was concluded that cellular responses in APC are 'coarsely tuned' to odor, since most responded to several odorants out of the eight tested despite the consistently correct performance. In the study of novel discrimination learning it was concluded that coding is 'exceedingly sparse', since very few of the odor-responsive cells (4/62) continued to fire when trials were repeated, and all but one of these cells responded to just one of the test odorants. Although the differences in task or recording sites certainly could have contributed to the observed difference, the differing stimulus repetition rates would appear to be a major factor. In the acquisition study, the intertrial interval was sufficiently brief so that responses would have habituated over trials, whereas in the performance study the interval was substantially longer. This interpretation is supported by the similarity in the proportion of cells in the two studies that responded to odor before habituation would have developed, although a follow-up study is clearly needed to resolve this question.

In the study of specific habituation described earlier, it was discovered that neurons can discriminate between alkanes that differ in chain length (Wilson, 2000a,b), similar to mitral/tufted cells in the olfactory bulb (Mori and Yoshihara, 1999). A key question regarding coding strategy is whether the same neurons in APC that make such fine discriminations also respond to structurally dissimilar molecules. Ongoing study in a similar preparation (Illig and Haberly, 1999; unpublished) has revealed that cells in APC do exhibit such combinatorial responses. It therefore appears that it is inappropriate to characterize olfactory coding in APC as either coarse or specific; rather, it has elements of both. Coding is coarse in the sense that cells typically respond to many dissimilar odorants; however, these same cells can have highly discriminative responses within groups of structurally similar odorants.

Early studies with the 2-deoxyglucose uptake method failed to reveal odor-evoked spatial patterns in PC. However, in cellular-level studies using *c-fos* induction as an activity marker, spatial patterning is apparent in APC (Illig and Haberly, 2000). These spatial patterns consist of patches of Fos-positive cells; however, the patches are large, overlap extensively for different odors, are related to odor concentration as well as quality, and only a small subset of the cells in a patch are strongly activated by a given odorant. This is in marked contrast to the olfactory bulb and primary visual cortex, where patches of stimulus-specific cells are small and discrete (i.e. well segregated from neighboring patches). The Venn-diagram-like overlap in APC suggests that, rather than serving to enhance the degree of specificity via competitive interactions as in other primary areas, the patchiness represents loose groupings of cells that affect the extent to which correlations are detected and learned. It can be speculated that different forms of non-olfactory information also have patchy representations that overlap to various extents with those for odorants. Such patchy concentrations could reflect associative linkages that are determined genetically or during early learning when axonal projection patterns are highly plastic. It is also important to recognize that, despite the patchy concentrations of cellular activity, olfactory encoding in APC is ensemble in character. This conclusion follows from the broad overlap, the low proportion of active cells within patches and the substantial number of Fos-positive cells in APC outside of patches. A question of obvious importance is the nature of the mechanisms that shape the patchy concentrations of odor-evoked activity in APC. Both axon tracing techniques (Ojima *et al.*, 1984; Buonviso *et al.*, 1991) and optical imaging (Puche *et al.*, 1998) have provided evidence that afferent input to APC is patchy in distribution; however, it is not known to what degree this feature (as opposed to intrinsic connections and interactions) shapes the patchiness in cellular responses.

Odor-evoked *c-fos* activation in PPC is strikingly different from that in APC. Fos-positive cells in PPC are diffusely distributed with no apparent spatial order, rather than concentrated in patches. Different odorants evoke indistinguishable patterns of cellular activation in PPC, suggesting that information is represented as a spatially featureless ensemble code (Illig and Haberly, 2000).

Is there a feature detector hierarchy in piriform cortex?

A basic question is why PC contains subdivisions that differ substantially in circuitry, connections and response properties. The presence of these subdivisions, together with the marked non-uniformity of their interconnections, indicates that PC does not operate in unitary fashion; for example, as a large autoassociative network. One possible functional correlate of this organization is that, as in the visual system, different subdivisions of PC extract different forms of information from olfactory stimuli. However, a number of arguments suggest that the olfactory system is fundamentally different from the visual system in this regard—that beyond the olfactory bulb the analysis of olfactory information is dominated by ensemble-coded, parallel-distributed processes with minimal dissection of complex patterns into components. Support for this conception includes the presence of highly distributed connectivity, the much lower degree of spatial ordering of olfactory information in PC than in the olfactory bulb, the combinatorial nature of cellular responses to odor and the holistic character of olfactory discrimination.

Working hypothesis for olfactory cortex

General parallels between the morphology and physiology of PC and artificial networks have been previously considered (Haberly, 1985; Haberly and Bower, 1989); however, these parallels will be re-examined since new findings place additional constraints on potential mechanisms.

Olfactory pathways from a parallel distributed network perspective

A striking feature of PC is its subdivisions that are connected in series and parallel along the afferent pathway from the olfactory bulb. The anterior olfactory cortex is also integrated into this cascade, as are several of the cortical areas to which PC projects (Figures 7 and 9; Table 1). From a parallel-distributed perspective, the flow of information in this system can be summarized as follows. Each structure in the cascade receives direct input from the olfactory bulb, feedforward input from preceding stages and a varying amount of recurrent input (self-excitatory feedback) and backprojections from downstream areas. This arrangement provides a substrate for extensive correlational analysis of afferent information from the olfactory bulb and the information it elicits from the cortical cascade. Each cortical area carries out afferent-associational correlations and passes the result to subsequent structures in the cascade, as well as to upstream cortical areas and the olfactory bulb, in varying degree. The feedback and recurrent inputs to each structure consist of highly branched axons that give rise to overlapping two-dimensional arrays of excitatory synapses. Each structure contains a stack of these synaptic arrays, each one of which contacts the dendrites from a common population of pyramidal cells. When conjugations of activity in the superimposed synaptic arrays excite pyramidal cells, their branched axons provide output to multiple target areas as well as recurrent activation. Based on physiological findings for PC, the working assumption can be made that such conjugations of synaptic activity also mediate learning-related adjustments in synaptic strengths under appropriate conditions (Haberly *et al.*, 1994).

Assumptions and limitations

As a starting point for developing a mechanism-level understanding of PC that takes its newly reported global involvement in brain function into account, a working hypothesis is outlined. This hypothesis is thought to meet the constraints imposed by the latest findings regarding architecture, connections and physiology of PC, and to be compatible with principles developed in studies of biologically plausible artificial networks with similar architectures. However, it is recognized that there are other models that also meet these constraints, and that changes will be required as new findings impose additional constraints and new concepts are developed. In addition to considering the relationship of PC to higher-level cortex, the hypothesis incorporates the cortical areas at the junction between the olfactory bulb and PC that have been omitted from previous models. Following the presentation of the working hypothesis that assumes multimodal encoding in PC, an alternative is outlined whereby olfactory association can be accomplished despite a unimodal representation of olfactory information in PC.

The functional hypotheses focus on the large matrix of pyramidal cells in layers II and III that is the primary source and target of intrinsic and extrinsic associational connections. Non-pyramidal excitatory cells (semilunar and deep multipolar cells) and inhibitory cells are not explicitly included in the hypothesis. Although inhibitory processes are exceedingly diverse in PC as in all parts of the cerebral cortex (Haberly, 1998), and play many essential roles in cortical function as anyone who has attempted to develop a biology-based network simulation is well aware, the assumption is made that general principles of operation can be understood without a detailed knowledge of inhibitory circuitry. Findings from morphological and physiological studies of inhibitory neuronal circuitry in PC (Haberly, 1998; Ekstrand *et al.*, 2001b) suggest that the available repertoire of processes is sufficient to mediate all inhibitory mechanisms that are implicitly incorporated in the functional hypothesis (competitive interactions between cells, regulation of synaptic plasticity, control of positive feedback, and the generation and synchronization of oscillations). Finally, it is assumed that ‘plasticity-enabling’ inputs to olfactory cortex (Figures 3B1 and 4A) from the basal forebrain, amygdala, or brainstem aminergic cell groups are activated in learning-appropriate situations (novelty, strong emotion, aversive taste, etc.) (Hasselmo, 1995; Haberly, 1998), but these are also not explicitly included.

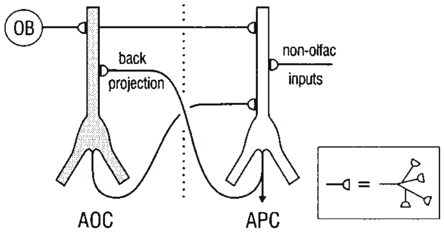
Hypothesis for anterior olfactory cortex (AOC)

A number of arguments suggest that AOC plays a central role in olfactory discrimination. (i) In cortical pathways for non-chemical senses, unimodal coding is maintained through levels where simple features are assembled into representations of complex stimuli (e.g. for vision, through inferotemporal cortex where faces and complex objects are represented). In the olfactory system, it had been assumed until recently that PC is the equivalent of high-level unimodal areas in other sensory systems—that it assembles molecular features extracted in the olfactory bulb into representations of complex multiple-component odors.

However, if PC represents multimodal activity as suggested by the experiments of Schoenbaum and Eichenbaum (Schoenbaum and Eichenbaum, 1995), AOC would be the only candidate for a unimodal feature correlator. (ii) Morphological study (L.B. Haberly, unpublished data) has shown that AOC receives a highly distributed projection from the olfactory bulb, that provides the substrate needed for correlating activity in spatially disparate glomerular groups in the olfactory bulb. Furthermore, there appears to be no significant input to AOC from high-order cortex that could directly convey patterned non-olfactory information. (iii) A highly speculative argument in support of AOC as the olfactory ‘gestalt-maker’ can also be made on the basis of conscious perception. Increasing evidence, particularly from functional imaging, suggests that sensation is linked to neuronal firing in cortical areas that represent information from single modalities. This criterion is not met by PC if firing is ambiguous with regard to odor quality: if the same neuron that fires during odor sampling can also fire in relationship to behavioral tasks, and firing during odor sampling is related to both the identity and reward valence of odorants (Schoenbaum and Eichenbaum, 1995). Even if the olfactory bulb meets the unimodal criterion, the gestalt-nature of olfactory perception is not consistent with the disconnected representation of molecular features in glomerular groups. (Just as we perceive color that is represented in secondary visual areas rather than wavelength that is represented in primary cortex, we perceive gestalts that are represented in olfactory cortex rather than individual components of odor mixtures that are discretely represented in the olfactory bulb.) That leaves AOC, which not only has the requisite circuitry to correlate molecular features, but also appears to receive patterned input almost exclusively from the olfactory bulb and olfactory cortex.

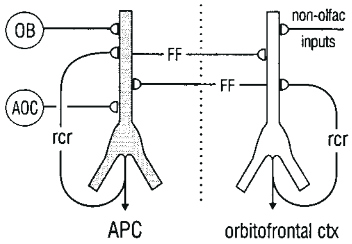
Two predictions can be made regarding the neuronal circuitry in AOC from the postulate that it assembles olfactory gestalts. First, if pattern completion is required for consistent olfactory discrimination as argued earlier, it follows that synapses of olfactory bulb afferents on the apical dendrites of pyramidal cells in AOC must support NMDA-mediated plasticity as they do in PC. Second, it is

A Anterior olfactory cortex



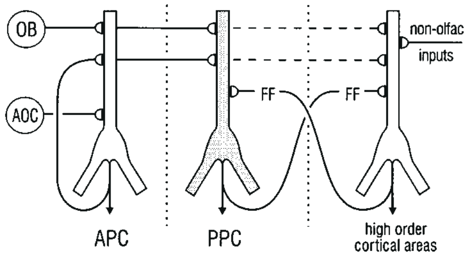
generates and ‘retrogradely reconstructs’ olfactory gestalts

B Anterior piriform cortex



learns, recalls, and generalizes olfactory-significance associations

C Posterior piriform cortex



learns and recalls diverse associations

Figure 11 Schematics showing key connections in the functional models for AOC **(A)**, APC **(B)** and PPC **(C)**. Each schematic cell in A–C represents a large population of pyramidal cells; each line represents a highly branched axon (inset at right in A); FF, feedforward; rcr, recurrent connections. **(A)** It is proposed that AOC detects and learns correlations in firing of principal cells in spatially disparate regions of the olfactory bulb; i.e. is the olfactory ‘gestalt-maker’. This is accomplished through a feedforward pattern correlation mechanism (Figure 3) implemented with highly branched afferents from the olfactory bulb and synapses that support Hebbian plasticity (NMDA-dependent LTP). It is further proposed that a common population of pyramidal cells in AOC receives Hebbian synapses both from olfactory bulb afferents and from backprojecting APC axons. This would provide a substrate for heteroassociative learning and recall (Figure 3B), thereby enabling ‘retrograde reconstruction’ of learned odor-evoked firing patterns in AOC in response to non-olfactory prompts funneled through APC. **(B)** It is proposed that APC is a hybrid network that performs feedforward correlation on input patterns (Figure 3B) and has extensive recurrent connections that both enhance the power of the feedforward pattern correlator (see text) and support autoassociative learning and recall (Figure 5B, C). Since APC receives a combination of olfactory and non-olfactory information (in particular, information regarding odor significance), it can support associative recall (olfactory input can elicit previously associated non-olfactory information with which it was temporally associated and vice versa). Autoassociation in APC enables robust pattern completion and generalization; for example, a rabbit’s first whiff of gray fox odor could elicit the fear that accompanied a previous traumatic encounter with a red fox. **(C)** PPC has extensive two-way feedforward connections with adjoining high-order cortical areas (prefrontal, amygdaloid, perirhinal, entorhinal). It is proposed that these connections form a set of reciprocal feedforward correlation networks between PPC and each one of these higher-order areas (as in Figure 4). Dashed lines indicate direct inputs that extend from the olfactory bulb to high-order cortical targets of PC with the exception of prefrontal cortex. According to this hypothesis: (i) memory traces develop in PPC that encode linkages between olfactory and many other forms of information; (ii) re-entrant activity in the reciprocal connections between PPC other areas enhances associative recall; and (iii) PPC participates in separating the components of mixed-modality activity recalled from APC (see text).

predicted that AOC lacks widespread intrinsic recurrent connections as observed in APC. The propensity for recurrent circuitry to generalize during recall would be incompatible with a discriminative perceptual process as discussed earlier.

Hypothesis for anterior piriform cortex (APC)

A striking feature of APC is its extensive intrinsic associational circuitry that is both rostrally and caudally directed over long distances. It is proposed that, as a result of this spatially distributed recurrent connectivity, both APC_V and APC_D support autoassociative processes (Figures 5 and 6). A key question then becomes whether the powerful capabilities of such circuitry (particularly pattern completion and generalization) are used for unimodal olfactory discrimination, associative links between olfactory and other information, or both. It is postulated that APC mediates learning and recall of olfactory associations rather than representing purely olfactory information. This postulate is based on the strong reciprocal connections between APC and adjoining orbitofrontal cortex, the presence of prominent behavior-related cellular activity in APC and the dependence of odor responses in APC on their expected reward value (Schoenbaum and Eichenbaum, 1995; Schoenbaum *et al.*, 2000; Yonemori *et al.*, 2000). A particularly important functional role of APC could be a fast generalization of the threat significance of odorants (a function for which a high degree of generalization would be particularly advantageous). The recurrent circuitry and connections of APC appear to be ideally suited for this process.

Studies of artificial neural networks with biologically plausible architectures have demonstrated a critical need for the incorporation of features that decrease the extent to which different stimuli are encoded by common synapses and neurons. Based on analyses by Wilson and Bower (Wilson and Bower, 1988) and Rolls and Treves (Rolls and Treves, 1998), it is proposed that olfactory information in APC is stored as composites that include temporally correlated significance and context received from prefrontal cortex. In simulations with a PC-like network (J. Chover, unpublished data) this can enhance the capacity to link similar complex patterns (e.g. aromas of Starbuck's versus Victor Allen's Italian roast coffees) to different outputs.

A further postulate, also based on the qualitatively indistinguishable cellular activity in APC and adjoining prefrontal cortex in the behaving rat, is that interconnectivity is sufficient to allow APC and orbitofrontal cortex to operate as a loosely coupled autoassociative network with regional variations in inputs and outputs (Figure 11B). Particularly compelling support for such blending of content addressable capabilities in APC and orbitofrontal cortex again stems from the study of Schoenbaum and Eichenbaum (Schoenbaum and Eichenbaum, 1995), where an apparent associative recall of odor information in response to non-olfactory prompts was observed in the form of an initiation of 'odor-onset' activity in APC and orbitofrontal cortex before odorant was delivered (the task allowed the rat to make predictions regarding odor presentations and a sufficient delay to allow recall before initiation of delivery). This finding suggests that, based on the context and initial steps in the discrimination task (information that would be represented in prefrontal cortex), the patterns of odor-evoked activity that occurred in APC during training were reconstructed. Readers are referred to Kleinfeld (Kleinfeld, 1986) for a mechanism that allows recurrent networks to incorporate the temporal dimension, thereby enabling such predictive recall.

A feature of the olfactory pathway that has been largely overlooked in previous accounts is that the relayed afferent input to APC from AOC, not the direct input from the olfactory bulb, is optimally positioned to dominate excitatory action. The feedforward relay from AOC to APC is thought to terminate on proximal-most apical zones of the same principal cell dendrites that receive olfactory bulb afferents on their distal zones (Figures 9 and 11). This feature is consistent with the proposal that AOC is a 'unimodal correlator' that links activity in the distributed array of glomerular groups that constitutes the code for most real-world odorants.

The same pyramidal cells in APC that participate in autoassociative activity also receive feedforward inputs from the olfactory bulb, AOC and prefrontal cortex (Table 1). Furthermore, synapses from at least some of these inputs support associative, NMDA-dependent LTP (Kanter and Haberly, 1993; Patil *et al.*, 1998). In other words, APC_V and APC_D are hybrid recurrent/feedforward pattern correlation networks that integrate and learn correlations between raw afferent input, secondarily processed input from AOC, and recurrent input. The properties and capabilities of such hybrid networks do not appear to have been systematically explored in the artificial neural network literature and it appears that all biology-based network simulations for PC have assumed that Hebbian synaptic plasticity occurs in either afferent (Ambros-Ingerson *et al.*, 1990) or recurrent synapses (Barkai *et al.*, 1994), but not both. One functional role for the hybrid architecture is that a feedforward correlational processing of inputs allows adjustment of the relative potencies of different inputs as prompts for associative recall. In other words, those input patterns that are recognized provide a stronger postsynaptic response and ensuing autoassociative activity. From the point of view of the feedforward correlational component of such hybrid networks, recurrent connectivity greatly increases the number of neurons and synapses that become involved in encoding and recall, thereby increasing their power and capacity (J. Chover, unpublished simulations).

The spatially distributed backprojection from APC to AOC provides a pathway that could allow recalled patterns of neuronal firing in APC with mixed olfactory–non-olfactory content, to reconstruct retrogradely the olfactory component in AOC (i.e. a facsimile of the odor-evoked firing pattern that occurred during learning). This could be performed through a simple heteroassociative process (Figures 3B and 11A). If input from the olfactory bulb were to dominate firing during learning, then unambiguous odor-related coding could be preserved in AOC during retrograde reconstruction, despite the presence of firing in APC that is related to both olfactory and non-olfactory components of the event that prompts recall.

If olfactory discrimination and perception are based on gestalts generated in AOC, then it must be asked why there is direct input from the olfactory bulb to PC that conveys raw olfactory-component information. One possibility is that there is a substantial repertoire of monomolecular odorants (for which specific receptors might have evolved) that have particular significance for survival and are processed in parallel at two levels: (i) in AOC as consciously perceived gestalts that include all odorous components of the mixtures in which they are contained and (ii) in PC and higher-order cortex for associative processing of the specific component. A direct triggering of associations or behavior by such survival-relevant odorants in PC, as well as in the ventral striatum, amygdala, entorhinal cortex and perirhinal cortex, which also receive direct olfactory bulb input, could elicit faster and more robust avoidance reactions. The predator-associated odorant, TMT, which elicits unconditioned autonomic and endocrine effects with minimal awareness (Morrow *et al.*, 2000) and rotting-meat odor that triggers an unconditioned avoidance response in our own species are potential examples of such odors. Since different glomerular groups in the olfactory bulb may preferentially terminate in patches at different locations in APC (Buonviso *et al.*, 1991; Puche *et al.*, 1998) and the cells of origin for associational projections to different cortical areas are also concentrated at different locations in APC (Haberly and Price, 1978a) (D.M.G. Johnson, unpublished data), it can be speculated that these two sets of patches overlap in meaningful ways with regard to the generation of unconditioned responses.

Hypothesis for posterior piriform cortex (PPC)

In marked contrast to APC, the associational projections of pyramidal cells in PPC have a strong rostral-to-caudal bias in direction; consequently, the capacity for system-wide autoassociation appears to be much less than in APC. It is proposed that the matrix of pyramidal cells in PPC serves largely as a feedforward pattern correlation network, with reciprocal connections to feedforward pattern correlators in adjacent high-order cortical areas (Figure 11C). This configuration would be ideal for the learning and recall of associations between odorants and the many forms of information that are represented by these adjoining areas with which PPC is bidirectionally connected (Figures 10 and 13B).

An important feature of the reciprocal feedforward correlation configuration (Figure 4) is that it controls the extent to which activity in input projections from other areas drives neuronal firing. Such control is needed because the number of areas that are interconnected with PPC is such that if ensemble coded information were shared to the same extent as between APC and adjoining orbitofrontal cortex, the background activity unrelated to tasks at hand could be overwhelming. The reduction in irrelevant postsynaptic activation, that will be termed ‘associative gating’, is a consequence of the exchange of inputs during learning in reciprocal pattern correlation networks. As seen by inspection of Figure 4, the strength of excitatory drive exerted in PPC by inputs from perirhinal cortex, for example, depends on two factors: the extent to which these inputs have been reinforced by previous coincidence with postsynaptic activity in PPC, and the level of activity in the cells of origin in perirhinal cortex, which depends in part on the history of reinforcement of synapses it receives from PPC; hence the term, associative gating. As a result, only activity of mutual interest in a particular context generates strong postsynaptic activation.

Since the streams of caudally directed associational axons (Figure 10) give rise to large numbers of synapses along their paths within PPC before they exit into target areas (Johnson *et al.*, 2000), it is reasonable to speculate that there is an extensive feedforward network within PPC that enhances its ability to represent and link complex correlations. If this were the case, increasingly caudal pyramidal cells would receive input from the progressively greater numbers of more rostrally placed cells, creating, in essence, a feedforward network with overlapping ‘layers’. It is proposed that if NMDA-dependent synaptic plasticity is present, this architecture could support a self-organized emergence of high-order correlations, analogous to the self-organizing processes that have been studied in discrete-layered feedforward architectures (Linsker, 1986; Willis and Rolls, 1997). It must be noted, however, that the feedforward system within PPC terminates predominantly in layer III (Figure 10B), rather than at the depth of apical dendrites in layer I like other associational projections in PC. Since apical dendrites in layer III are limited to proximal segments from deep pyramidal cells, and the neuropil is dominated by basal dendrites and a variety of non-pyramidal cells including inhibitory neurons, the possibility must be considered that the intrinsic portion of the feedforward projection does not support NMDA-dependent LTP, which has only been convincingly demonstrated in apical dendrites of glutamatergic neurons.

The backprojections to PPC from its high-order cortical targets (prefrontal, amygdaloid, entorhinal and perirhinal) are concentrated in layer I; hence it is postulated that these backprojections synapse on apical dendrites of the principal cell population(s) from which they receive input, and participate in associative, NMDA-dependent LTP together with olfactory inputs. If PPC is a reciprocal feedforward correlation network of this form (Figure 4) it could drive the reconstruction of both olfactory and non-olfactory components of the memory traces in which it participates. Since PPC has minimal projections to either AOC or APC, it is proposed that retrograde reconstruction of the olfactory component occurs by way of its backprojection to MOC (Figures 7D and 8), a structure that receives little olfactory bulb input but has a heavy unidirectional projection to AOC (Haberly and Price, 1978b; Luskin and Price, 1983). It can be speculated that MOC contains specialized circuitry that serves as an interface for this retrograde reconstruction. This pathway through MOC may also be a route by which the olfactory components of episodic memories retrieved from the hippocampal formation are reconstructed, since connections between the entorhinal cortex and MOC are strikingly similar to those between PPC and MOC (Haberly and Price, 1978a; Luskin and Price, 1983).

The postulated capacity of PPC to drive the reconstruction of unimodal components of mixed memory traces in connected areas would be assisted by the fact that, despite the broadly distributed nature of its inputs and outputs, there are substantial regional variations in the extents of its connections with these target areas (Haberly and Price, 1978a). The spatial and temporal dispersion of activity in afferent and associational fiber systems that occurs in PPC (Ketchum and Haberly, 1993a,b) would also increase the extent to which information that originates at different locations and times can converge on common neurons. Such temporal and spatial 'buffering' would appear to be necessary for effective bidirectional communication between multiple cortical areas and for establishing the temporal relationships required for Hebbian synaptic plasticity.

To illustrate the mechanisms that have been proposed for PPC and the reciprocal feedforward correlation architecture, the following narrative describes the neuronal events that might be expected to accompany a rabbit's traumatic first encounter with a fox, and the subsequent recall of the memory of that encounter. It is assumed that a visual likeness of the fox is encoded by perirhinal cortex with which PPC is reciprocally connected and that novelty, emotion, or other aspects of the encounter activate nonspecific plasticity-enabling inputs that facilitate NMDA-mediated synaptic potentiation. The hypothetical scenario is as follows. Odor from the fox activates a spatially distributed constellation of synapses in PPC. Similarly, a visual representation of the fox is generated in perirhinal cortex through the chain of visual areas and inferotemporal cortex. Synaptic activity in PPC evokes firing in principal cells that project to perirhinal cortex and vice versa. At the same time, PPC is also receiving much additional information regarding the encounter from other areas, including amygdaloid and prefrontal cortex, all of which is incorporated into a composite memory trace through Hebbian adjustments in synaptic strength. This learning process would occur throughout the encounter during 100–200 ms windows within each sniff/theta cycle before slow GABAergic inhibition interrupts ongoing activity (neuronal firing) and 'resets' NMDA receptors (White *et al.*, 2000). The activation of plasticity-enabling inputs in learning-appropriate situations would facilitate potentiation of synapses, including those on neurons that fire too weakly to otherwise enable NMDA currents. A number of mechanisms could provide the temporal buffering (adjustments in time-course) that is needed to allow converging information from many sources to satisfy the temporal requirements for NMDA-mediated potentiation. These include persistence of NMDA activation, temporal dispersion of activity in fiber pathways, and working-memory buffers in prefrontal and hippocampal systems from which PPC receives heavy projections.

Recall occurs when sufficiently large numbers of the synapses that were reinforced during the fox encounter are activated, leading to a reconstruction of the original firing pattern. An adequate prompt for pattern completion might be strong fox-odor, a partially obscured view of a fox in the original environmental context, and so on. The highly branched axons that project from PPC to perirhinal cortex (Figure 10) are a key component of the mechanism for pattern completion as described earlier; a comparable set of branching axons is predicted for the projection from perirhinal to PPC. The faithful reconstruction of learned activity patterns is enhanced by the exchange of information between PPC, perirhinal and other bidirectionally connected higher-order areas following the initial response. Thus, the initial products of pattern completion in individual feedforward correlation networks (PPC, perirhinal cortex, etc.) are transmitted to other pattern correlators where, in conjunction with external prompts, the accuracy of recall is reinforced. A number of such exchanges could occur during the excitatory portions of sniff/theta cycles before ongoing activity is interrupted, thereby progressively improving the quality of reconstructed patterns in interconnected areas. An important point is that the time constant for integrative processes would be shorter during recall than learning because of the weaker NMDA activation and more active dendritic inhibition. This would increase the capacity for autoassociative 'attractor' activity (the number of reactivation cycles) that could occur within each sniff/theta period. Such between-area autoassociation is considered to be a key feature that increases the power of reciprocal feedforward correlation networks over isolated pattern correlators that are, in essence, single layer 'perceptrons' whose limitations have been well-documented (Hertz *et al.*, 1991). The recalled firing patterns in both PPC and perirhinal cortex are inextricably mixed modality-wise as during the encounter. However, as described earlier, backprojections can reconstruct original patterns of activity in unimodal cortex by way of content addressable processes thereby eliciting sensory recall, triggering autonomic states and escape behavior, etc.

Could encoding be unimodal in piriform cortex?

A number of aspects of the above working hypothesis depend on the conclusion that APC encodes both olfactory information and associated reward/behavioral/contextual information (Schoenbaum and Eichenbaum, 1995). However, it may be premature to discount the possibility that APC and perhaps all of PC is a unimodal olfactory processor, or that parallel unimodal and multimodal channels are maintained at a cellular level within PC. One possible scenario is that prefrontal-like neuronal activity in the behaving rat is mediated indirectly through 'attentional' processes as observed in unimodal visual cortex, i.e. cognition-based changes in spontaneous firing or response amplitude (Luck *et al.*, 1997; Ress *et al.*, 2000), or through changes in inspiratory pattern rather than directly by way of connections with higher-order cortex. Since an ostensibly odor-free environment can be odorous to macrosmotic animals, behavior-related changes in inspiration can elicit true odor-evoked neuronal activity. Support for this possibility can be found in a recent study in the behaving rat where a field potential monitor allowed changes in inspiratory behavior to be detected (Kay and Laurent, 1999). This revealed that rapid sniffing accompanied an increase in cellular activity that was observed in the olfactory bulb at the start of a learned behavioral sequence in the absence of introduced odorant, and that a shift to slow respiration accompanied a decrease in activity observed during consumption of a water reward. Consequently, it cannot be determined to what extent the observed behavior-related modulations in firing were directly mediated through centrifugal pathways to the olfactory bulb, as opposed to indirectly mediated by way of alterations in airflow over the olfactory mucosa. Although the behavior- and reward-associated changes in firing observed by Schoenbaum and Eichenbaum in APC and orbitofrontal cortex were more robust and greater in scope than have been observed in the olfactory bulb—and support for their postulate of a direct mechanism is provided by the similarities in olfactory-cued prefrontal activity to that cued by sensory modalities over which the subject has little or no control by way of motor processes (Goldman-Rakic *et al.*, 1993)—nevertheless, additional study will be required to determine the extent of indirect factors.

Alternative working hypothesis that assumes unimodal encoding in piriform cortex

If subsequent experiments confirm that neuronal firing in PC represents purely olfactory information throughout, it is important to recognize that this would not rule out an intimate involvement in behavioral-level associative processes. Changes in the 'multimodal working hypothesis' that accommodate unimodal encoding without eliminating associative capabilities are as follows. (i) Rather than serving as the sole gestalt-maker, AOC would be the first processor in a series extending through APC$_V$, APC$_D$ and PPC, where each structure would contribute to the representation of olfactory information. Each successive area would utilize the full set of afferent and feedforward inputs from preceding stages to learn and recall olfactory gestalts of increasing complexity (as opposed to a progressive addition of non-olfactory associations as proposed in the multimodal hypothesis). Intrinsic circuitry, particularly the extensive feedforward system in PPC (Figure 10), would also contribute to gestalt-building. If this unimodal conception proves to be correct, it would mean that difficult olfactory discriminations cannot be accomplished by a single feedforward pattern correlator (i.e. AOC) and that the set of olfactory cortical areas, as a group, implement the most demanding capabilities. This would be analogous to higher-order visual areas (including V4 and inferotemporal cortex) where responses to complex patterned stimuli are progressively assembled from simpler features. It is expected that the most difficult olfactory discriminations would be between odorants consisting of a large number of components where many are shared (e.g. odors of identical twins that dogs purportedly can discriminate). (ii) APC and PPC would be directly involved in encoding and retrieving olfactory–non-olfactory associations as in the original hypothesis, but non-olfactory information would be represented (i.e. drive neuronal firing) exclusively in the higher-order cortical areas with which PC has reciprocal feedforward relationships. In this model, PC would engage in heteroassociative learning and recall whereby the information contained in prompts from high-order areas could bear no relationship to the information that is retrieved. This means that the history of temporal associations between odorants and significant events would be encoded by synapses in PC, but that only the olfactory component would be expressed as neuronal firing on recall as during learning (analogous to the heteroassociative process described earlier for retrograde reconstruction in AOC where, during learning, input from the olfactory bulb is the major determinant of neuronal firing). In other words, associative gating in PC would be stronger than in the multimodal model. (iii) If APC is involved in strictly unimodal discrimination, then its extensive recurrent intrinsic connections would presumably not be involved in an autoassociative generalization process; rather this system would serve to increase the power of the feedforward pattern correlation circuitry in some fashion as discussed earlier. (iv) The disynaptic pathway from PPC and entorhinal cortex through MOC to AOC would be engaged in a function other than retrograde reconstruction of olfactory memories as proposed in the multimodal model.

Two additional scenarios that should be kept in mind as more data become available are as follows: (i) that back-projections to PC from higher-order areas provide a simple negative feedback regulation of a unidirectional outflow of olfactory information (i.e. that PC does not participate in non-olfactory association); and (ii) that higher-order cortical areas from which PC receives input participate in unimodal olfactory processing. A precedent for the latter is provided by evidence that inferotemporal cortex is involved in the recognition of faces, but that facial expressions are analysed in the amygdala and insular region of prefrontal cortex (Phillips *et al.*, 1998). In other words, inferotemporal visual cortex may receive unimodal visual information from higher-order cortex rather than emotion/reward/behavior-related information. This interpretation is supported by the presence of 'face cells' in inferotemporal cortex that display a two-phase response: an initial phase that conveys information regarding face identity and a subsequent phase that conveys information regarding facial expressions at a latency consistent with origination in the amygdala and insular cortex (Sugase *et al.*, 1999). This interpretation also accounts for the evidence that responses to visual stimuli in inferotemporal cortex are not altered by changes in reward contingencies as in the prefrontal cortex and amygdala, despite heavy input from both regions (Rolls *et al.*, 1977).

Parallels between piriform cortex and other cortical systems

There are a number of intriguing parallels between PC and other brain systems; in particular, the neuronal circuit architecture in PC strongly resembles that in the hippocampal formation, extrinsic connections of PC match those of inferotemporal visual cortex and cellular response properties are like those in orbitofrontal (prefrontal) cortex. These parallels are discussed in order to make PC accessible to a wider audience and to underscore questions where findings from other systems may assist in understanding olfactory mechanisms, or vice versa.

Parallels with the hippocampal formation

The olfactory system, like the entorhinal–hippocampal system, can be envisioned as a parallel-distributed network that consists of a number of component areas performing an integrated set of operations. Both systems have a dominant tangential pattern of connectivity (parallel to the surface) with a broad overlapping spatial organization similar to that in layer I of the neocortex (Cauller *et al.*, 1998) rather than the well-known vertical/columnar pattern in deeper layers of neocortex. Furthermore, both systems have a dominant 'forward' flow of information from an input structure, as well as backprojection loops that link distal to proximal structures in the information streams (Figure 12A1, B1). Finally, both systems consist of several divisions (with further subdivisions) that are arranged in a series-parallel cascade along the pathway of information flow (Figure 12A2, B2). In addition to these system-wide parallels, there are also several rather remarkable similarities in details of individual component structures and connections as summarized in Figure 12A2, B2 (Amaral, 1993). Some of the more striking parallels are the following. (i) The afferent structures (entorhinal cortex and olfactory bulb) project in parallel to all components of the respective cascades and synapse on the distal apical dendrites of pyramidal cells in the principal cortical structures (CA3/CA1 and APC/PPC). (ii) The initial components in each cascade (dentate gyrus and AOC) project exclusively to the first of two principal cortical areas (CA3 and APC) where they synapse on proximal-most apical dendrites (adjoining

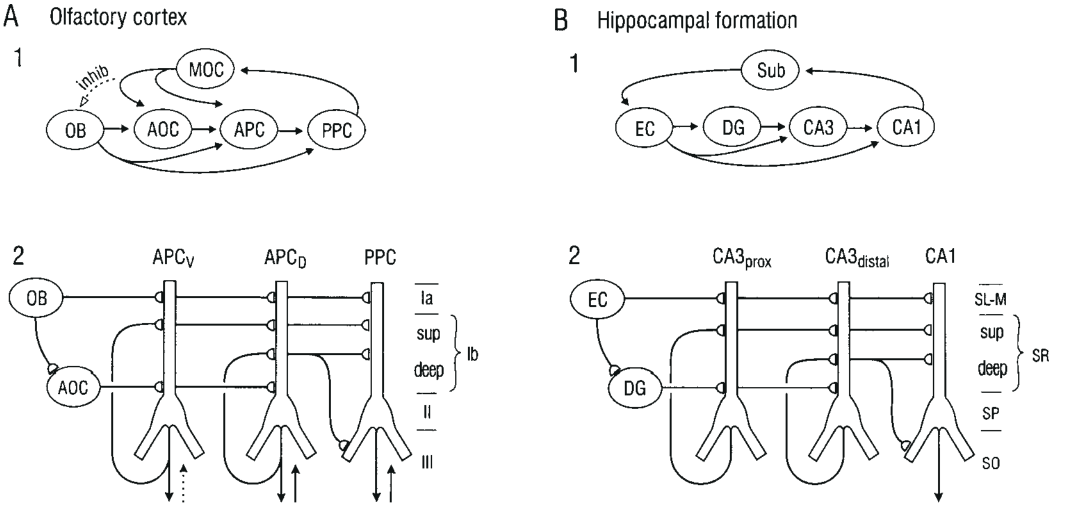


Figure 12 Parallels in intrinsic and extrinsic excitatory connections in the olfactory and hippocampal pathways. **(A1, B1)** Block diagrams showing the forward cascades in olfactory **(A1)** and entorhinal–hippocampal **(B1)** systems, and backprojection loops through the medial olfactory cortex (MOC) for the olfactory pathway and subiculum (Sub) for the hippocampal. **(A2, B2)** Striking similarities in laminar patterns of connectivity with the apical and basal dendrites of pyramidal cells in olfactory and hippocampal cascades. Vertical arrows at bottom show input and output connections with cortical structures outside the cascades; note that these are much more extensive for the olfactory than hippocampal pathway.

cell bodies). (iv) The pyramidal cell populations in CA3 and APC have perhaps the two most extensive recurrent excitatory projections in the vertebrate brain, both of which synapse on middle apical segments of the pyramidal cell populations from which they originate. (v) Output from the recurrent networks (CA3 and APC) is directed to CA1 and PPC where associational fiber systems have predominantly feedforward rather than recurrent architectures. The projections from recurrent to feedforward processors are largely unidirectional in both systems (backprojections from the feedforward to recurrent networks are sparse). (vi) Both recurrent cortical structures (CA3 and APC) are subdivided into proximal and distal regions (with respect to the information stream), each of which has similar intricately crafted laminar patterns of termination on apical and basal dendrites of pyramidal cells in their respective feedforward structures (CA1 and PPC; Figure 12A2, B2). (vii) Both systems have disynaptic backprojection loops by way of cortical areas that receive sparse afferent input (MOC in the olfactory system and the subiculum in the entorhinal–hippocampal system).

An obvious question is to what extent the similarities in architecture and connections reflect similarities in mechanism and function. A feature of both systems that is of particular interest in this regard is the separation of the principal cortical structures, PC and cornu ammonis (CA), into two parts with successive recurrent and feedforward architectures. The working hypothesis for APC–PPC has certain parallels with a longstanding hypothesis for CA3–CA1, most forms of which include the following (Rolls and Treves, 1998): (i) recurrent circuitry in CA3 constitutes an autoassociation network (Figure 5A) in which complex episodic memories are stored in a highly compressed form; (ii) pattern completion in this autoassociation network (Figure 5C) allows an input to CA3 that consists of a fragment of a learned pattern to activate the full multimodal memory trace; (iii) through feedforward pattern correlation circuitry in CA1 and a chain of areas extending through the subiculum and entorhinal cortex to unimodal cortex, the individual components of a recalled mixed-content memory trace in CA3 can be retrogradely reconstructed in the areas from which they originated when the encoded episode took place.

The current hypothesis for PC is that APC stores and retrieves mixed-content memory traces using an autoassociative process as in CA3; however, there are important differences in the proposed mechanism from the ‘standard model’ for hippocampus. Memory traces in APC are considered to be simpler—consisting of olfactory information and its associated significance and context derived from orbitofrontal cortex, as opposed to episodic memories in hippocampus that may include information from several sensory modalities. Furthermore, recall from CA3 in the standard model requires pattern correlation circuitry in CA1 and a chain of connected areas in order to separate and reconstruct the mixed-content memory traces, whereas it is proposed that output of recalled information from APC occurs directly by way of its connections with prefrontal cortex (for which CA3 has no parallel), as well as through PPC. This prediction follows from the proposal that ensemble activity and corresponding memory traces span APC and adjoining orbitofrontal cortex, and consist of qualitatively similar mixed-content in both areas. This allows associative recall to be triggered by olfactory information that enters through APC (e.g. recall of the reward value of an odor in a given context) and olfactory components of memory traces to be elicited when, for example, information regarding a sequence of events is funneled through the orbitofrontal cortex. In contrast to the hippocampus where the large number of components in its complex memory traces must be sorted out on recall, it is proposed that APC is primarily concerned with reconstructing the olfactory component of ensemble activity retrieved from mixed memory traces (through its backprojection to AOC), and the more complex behavior-related components are processed largely through the orbitofrontal cortex.

PPC resembles CA1 by virtue of largely feedforward associational connectivity to other cortical areas. However, despite this rather basic parallel, there are also departures in function and structure between PPC and CA1 that clearly dictate differences in mechanism. According to the current proposal, PPC operates with a greater degree of independence from the olfactory cascade than does CA1 with respect to the hippocampal cascade. Although the strongest input to PPC is from APC, mimicking the relationship between CA1 and CA3, PPC also has strong bidirectional connections with a number of cortical areas, in contrast to CA1 whose outputs to cortex are funneled through the subiculum. According to the standard model, CA1 plays a key role in separating and reconstructing individual components of the mixed-modality recall that occurs in CA3. It is proposed that while PPC serves a similar function for certain components of memory traces in APC, such as the limited information APC receives from the amygdala and entorhinal cortex, PPC also generates its own memory traces through direct connections with other cortical areas for which CA1 has no parallel. PPC correlates the many distributed patterns of activity it receives, including mixed (olfactory plus significance) information from APC that has undergone pattern completion or generalization, direct input from the olfactory bulb, and inputs from amygdaloid, prefrontal, perirhinal and entorhinal cortices. The correlations that are registered in PPC are linked into memory traces through Hebbian synaptic plasticity and serve as prompts for content-addressable recall. Memory traces in PPC are bidirectionally linked with those in adjoining higher-order areas, allowing olfactory information to be incorporated into the full gamut of cognitive and behavioral activities. On recall, the mixed-content information that PPC receives from APC becomes a part of the ensemble that includes

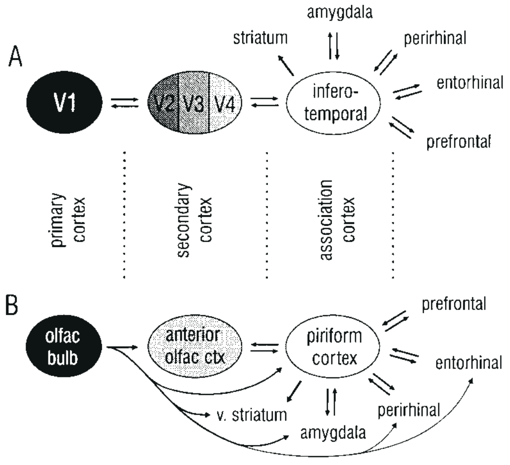


Figure 13 Comparison of olfactory and visual cortical pathways. The patterns of intrinsic and extrinsic connectivity and limited data for cellular response properties suggest: (i) the olfactory bulb is functionally equivalent to the primary visual cortex (area V1) and therefore warrants the designation, primary olfactory cortex; (ii) anterior olfactory cortex is equivalent to secondary cortical areas for vision (areas V2–V4); and (iii) piriform cortex is equivalent in connectivity to sensory association cortex (inferotemporal cortex for vision).

recalled information from other areas. Through its bidirectional connections with MOC and high-order cortex, PPC retrogradely reconstructs the olfactory and non-olfactory information it receives from APC and other areas.

Parallels with prefrontal cortex

Through physiological recording from APC and adjoining prefrontal cortex in rats performing an olfactory discrimination with a forced delay (delayed non-match to sample), Schoenbaum and Eichenbaum (Schoenbaum and Eichenbaum, 1995) have shown that single unit activity is qualitatively indistinguishable (and quantitatively very similar) in these areas as discussed earlier. An important question is the extent to which associative gating (as defined earlier) occurs in the feedforward pattern correlation inputs to the two recurrent networks. This question could be readily investigated by examining the extent to which task-related non-olfactory activity occurs in APC, and olfactory-driven activity in orbitofrontal cortex, during the performance of tasks that have no olfactory component. Additional study will also be required to determine the extent to which task-related and reward-modulated neuronal activity in PC is directly mediated through its interconnections with the prefrontal cortex, amygdala and other cortical areas, as opposed to indirectly through directed attention and motor control of airflow over the olfactory mucosa.

Parallels with inferotemporal cortex

As previously discussed (Johnson *et al.*, 2000), the extrinsic connections of PPC are equivalent to those of sensory association cortex rather than the primary (receiving) areas in neocortex with which it has been traditionally classed. Parallels between PPC and inferotemporal cortex, a unimodal visual association area, are summarized in Figure 13. Both areas have extensive bidirectional connections with high-order association cortex (amydaloid, perirhinal, entorhinal and prefrontal) and heavy unidirectional projections to the striatum (Figures 7E and 13). From a functional standpoint, a particularly intriguing parallel is provided by the evidence that representations of faces (Rolls *et al.*, 1989) and complex objects (Ishai *et al.*, 1999) have spatially distributed ensemble components in inferotemporal cortex as proposed for odorant representations in PPC, and that the perception of faces, as with multiple-component odors, has a strong gestalt quality. However, additional studies in awake-behaving animals will be required to determine the extent to which the functional role of PC resembles that of inferotemporal cortex as opposed to a behavioral-level role as with prefrontal cortex.

Epilogue

Sufficient data regarding central olfactory processes are available to tantalize, as reflected in this article, but are not sufficient to resolve any of the key issues regarding mechanism. Although this attempt at a global synthesis underscores the extent of the gaps in our knowledge, it is hoped that the many testable predictions that it suggests will facilitate an elaboration of the rudimentary blueprint that is presented for olfaction, as well as stimulating utilization of the olfactory cortex as a model to address questions of general significance for cerebral cortex.

Acknowledgements

Special thanks to Joshua Chover for extensive discussions of artificial neural networks and critical feedback on ideas, and to Kurt Illig for use of his preliminary Fos and single-unit recording data that played a key role in development of the working hypothesis. Thanks to Sherry Feig, Daniel Haberly, Kurt Illig, Bill Lytton, Kevin Neville and Bob Pearce for inspirational discussions regarding the relationship of recent findings for piriform cortex to artificial neural networks and for feedback on the manuscript. Supported by NIH grant DC 03271 from NIDCD.

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