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# Function follows form: ecological constraints on odor codes and olfactory percepts

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Sensory system *function* has evolved to meet the biological needs of organisms, but it is less often regarded that sensory system *form* has by necessity evolved to contend with the stimulus. For an olfactory system extracting meaningful information from natural scents, the ecological milieu presents unique problems. Recent studies provide new insights into the perceptual and neural mechanisms underlying how odorant elements are assembled into odor wholes, how odor percepts are reconstructed from degraded inputs, and how learning and experience sculpt olfactory categorical perception. These data show that spatial ensemble activity patterns in piriform cortex are closely linked to the perceptual meaning and identity of odor objects, substantiating theoretical models that emphasize the importance of distributed templates for the perception, discrimination, and recall of olfactory quality.

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## Introduction

It is estimated that the chemical senses — smell and taste — emerged about one billion years ago (give or take a few hundred millions). For a bacterium tumbling through the Pre-Cambrian stew of chemicals, the sense of smell represented a keen, if rudimentary, biological adaptation, sufficing for the chemical detection of sugars, amino acids, and other small molecules. This limited olfactory response repertoire enabled unicellular organisms to meet their immediate needs for survival: locating food, finding home, identifying mates, evading predators, and dodging their own metabolic waste.

In more complex organisms with antennae, snouts, and noses, olfactory systems continue to meet the same biological needs, albeit with greater sophistication. It

goes without saying that insects, rodents, and canines possess an unusual delicacy of smell, but even the human sense of smell astonishes: humans can tell apart two odorants differing by only one carbon atom [1] and can detect certain odorants with an acuity better than that of rats [2]. According to Titchener, the Botocudos of Brazil and the indigenous people of the Malay Peninsula could hunt and track their game by scent [3], and recent behavioral data suggest this aptitude is extant in 18–26-year-old California residents [4]. And to the great Renaissance scholar Erasmus, the functional and anatomical capacity of the human nose could be truly far-reaching (pun intended) (Box 1).

If biological necessity defines the *function* of an olfactory system, then odor 'ecology' — that is, the natural state of odors encountered in the environment — defines its *form*. In other words, the ecological milieu of the olfactory landscape sets important constraints on what an olfactory system can or cannot do, and delimits its anatomical and functional organization. The general argument that the sensory stimulus itself shapes biological design has been elegantly set forth by David Dusenbery in his book, *Sensory Ecology* [5]. However, such ideas are sometimes marginalized from the neuroscientific discourse of olfaction, which tends to emphasize physiology over ethology, focusing on *how* the olfactory brain responds to odors, rather than *why* it responds to odors.

In the spirit of broadening this discourse, the current review considers recent neural and behavioral studies (from a variety of species) within a sensory ecological framework, illustrating how the olfactory system meets the challenges of extracting meaningful information from an odorous environment (Figure 1).

## Odorant parts, perceptual wholes

The great majority of natural scents are composed of dozens, or even hundreds, of different molecular constituents. Pressure-cooked pork liver contains 179 compounds [6], and chocolate contains over 600 compounds [7], yet the olfactory system seamlessly knits these disparate parts into unified perceptual wholes. How this is accomplished remains largely unknown.

There is a long research tradition of using binary odorant mixtures [8,9] to approximate the ecological experience of smelling real-world aromas. A flurry of recent studies demonstrates that both peripheral and central factors, including odorant–receptor interactions [10], odorant

**Box 1** Many functions have been attributed to the human sense of smell. The behavioral relevance of human olfaction did not escape the notice of Erasmus (1466/1469–1536), humanist and scholar who detailed a myriad of remarkable features concerning the nose. The following excerpt is from the essay, 'Of Benefice Hunters', in *The Colloquies of Desiderius Erasmus: Concerning Men, Manners and Things*, by Desiderius Erasmus Roterodamus, 1516, translated from the Latin by N Bailey, London, 1725. At the bottom are some of the original doodles that Erasmus included to decorate this passage.

*Characters: Pamphagus, having just returned home after decades abroad in the Antipodes; and his old companion Cocles, who in greeting Pamphagus hastens to remark upon his friend's telltale facial feature still recognizable even after all those years:*

COCLES (CO): . . . Well then, do you admire that I know you that have so remarkable a Nose.

PAMPHAGUS (PA): I am not at all sorry for this Nose.

CO: No, nor have you any Occasion to be sorry for having a Thing that is fit for so many Uses.

PA: For what Uses ?

CO: First of all, it will serve instead of an Extinguisher, to put out Candles.

PA: Go on.

CO: Again, if you want to draw any Thing out of a deep Pit, it will serve instead of an Elephant's Trunk.

PA: O wonderful.

CO: If your Hands be employ'd, it will serve instead of a Pin.

PA: Is it good for any Thing else ?

CO: If you have no Bellows, it will serve to blow the Fire.

PA: This is very pretty; have you any more of it ?

CO: If the Light offends you when you are writing, it will serve for an Umbrella.

PA: Ha, ha, ha ! Have you any Thing more to say ?

CO: In a Sea-fight it will serve for a Grappling-hook.

PA: What will it serve for in a Land-fight ?

CO: Instead of a Shield.

PA: And what else ?

CO: It will serve for a Wedge to cleave Wood withal.

PA: Well said.

CO: If you act the Part of a Herald, it will be for a Trumpet; if you sound an Alarm, a Horn; if you dig, a Spade; if you reap, a Sickle; if you go to Sea, an Anchor; in the Kitchen it will serve for a Flesh-hook; and in Fishing a Fish-hook.

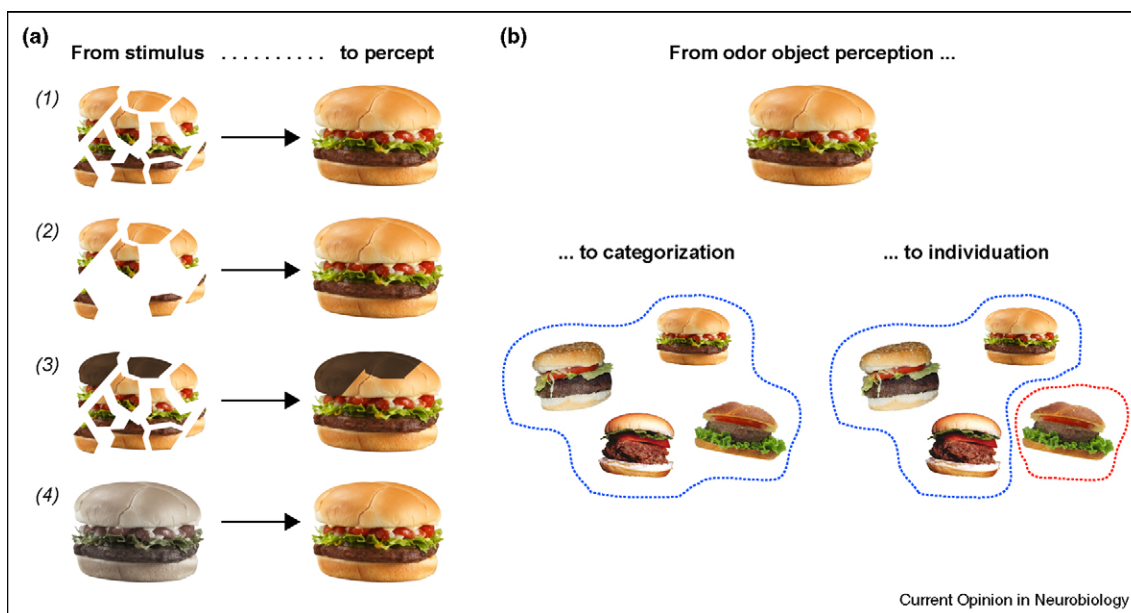
PA: I am a happy Fellow indeed, I did not know I carry'd about me a Piece of Household Stuff that would serve for so many Uses.



structural similarity [11], component concentration [12,13], sensory enrichment and experience [14,15], and task strategy [16], determine whether an odor mixture is perceived as the mere sum of its parts (elemental processing) or as different from its parts (configural processing). That experiential and cognitive factors can alter the perceptual relationship between odorant parts and odor wholes [14–16] implies that the brain has simultaneous access to elemental and configural representations, enhancing the range of adaptive behavior.

Intriguing work from the Kay lab [17,18] indicates that the degree of spatial correspondence between odorants in the rodent olfactory bulb (OB) (as assessed using 2-deoxyglucose [2-DG] mapping) does not predict whether a given odorant mixture will smell similar or different to its components. These data challenge the idea that bulbar activation maps provide a linear read-out of odor quality perception [19], suggesting instead that higher order areas may play a greater role in odor mixture processing. This latter possibility

Figure 1



Contending with a complex odor landscape. **(a)** Real-world smells emitted from odorous objects (e.g. a hamburger) are usually composed of many different volatile molecular constituents. The brain can integrate these elemental stimuli (a1, left) into a unitary percept (a1, right) and can reassemble the original percept even when some of the elements are missing (a2). However, the presence of novel stimulus constituents (a3) may generate a new percept (e.g. charred hamburger) easily distinguished from the original. The brain can also regenerate olfactory perceptual identity from weak or degraded (a4) sensory information. **(b)** Perceptual generalization and differentiation form two poles of odor object classification. In this example, a given odor object may be categorized with other smells if they all share the same perceptual meaning, but if this object has acquired unique meaning through learning, experience, or cognitive set, then it may be perceptually individuated from the other smells.

would accord with recent human imaging studies revealing that odor mixtures evoke selective responses in higher order regions such as orbitofrontal cortex (OFC) [20,21].

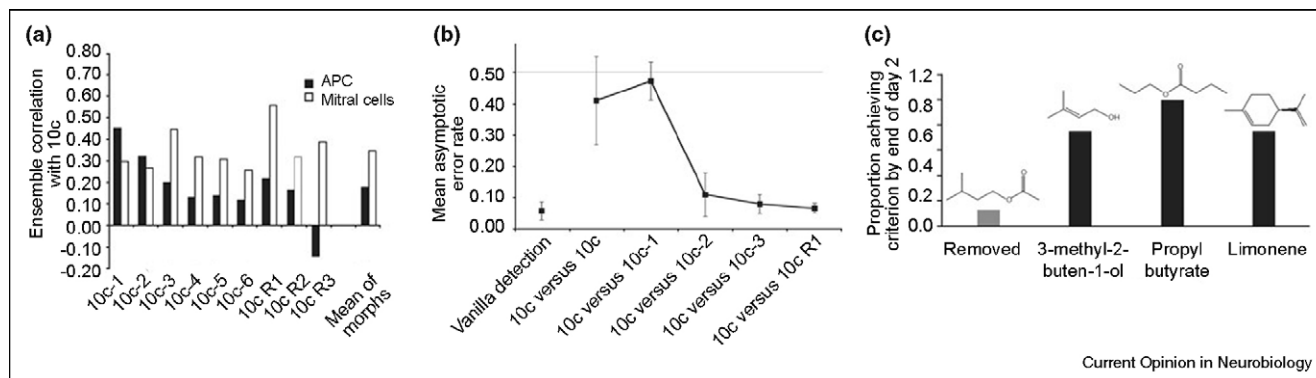
Innovative studies have begun examining the neural and perceptual processing of real-world odors directly. By coupling gas chromatography/mass spectrometry (GC/MS) technology with odor delivery and electrophysiology techniques, researchers can now measure neural activity in response to individual components of naturally occurring scents [22,23,24<sup>••</sup>]. This work suggests that the neural code for natural odors is characterized by distributed spatiotemporal responses in rodent OB (or the insect analog in the antennal lobe), and that responses to the behaviorally relevant components of the mixture essentially sum to form the integrated neural code [23,24<sup>••</sup>]. For example, GC/MS analysis of a floral bouquet innately attractive to *Manduca sexta* moths identified 9 (out of more than 60) volatile constituents eliciting robust multiunit ensemble activity in the moth antennal lobe, and a synthetic combination of these 9 constituents induced foraging behavior, faithfully mimicking the action of the natural bouquet [24<sup>••</sup>].

### Inconstant stimuli, invariant percepts

Naturally encountered odors are highly subject to environmental vagaries. Changes in the speed and direction of the wind may influence the strength (intensity) of an airborne scent, and temperature and humidity fluctuations in the weather may change the proportion of less-volatile odorants within a natural odor mixture. Dietary factors also play a role: odiferous furans, sesquiterpenes, and cyanates are more variable in the urine of wild African elephants who indulge in a more 'cosmopolitan' diet (which includes a wider diversity of grasses, tree leaves, and woody vegetation), compared to their captive brethren [25]. Each of these ecological factors can degrade the signal fidelity of an odor long before it reaches the olfactory epithelium, but remarkably the olfactory system is capable of reconstructing odor meaning from odorant fragments. How does the olfactory brain ensure perceptual constancy in the wake of an ecologically fickle stimulus?

A number of recent studies have considered the neural mechanisms underlying the stability of odor perception. In a clever experiment by Barnes *et al.* [26<sup>••</sup>], rodents were unable to discriminate a 10-component mixture (10c) from a related mixture lacking one of the original components (10c – 1), but could distinguish 10c from a

Figure 2



Pattern completion and separation in rodent anterior piriform cortex (APC). Virtual neuron ensembles of single-unit activity were compiled by incorporating all cells tested in either aPC or olfactory bulb. **(a)** In APC, ensemble responses evoked by a 10-component odor mixture (10c) progressively decorrelated from related mixtures as more components were removed (10c – 1, 10c – 2, etc.) or replaced (10cR1, 10cR2, etc.). No such effects were observed in mitral/tufted cells. **(b, c)** Mixture discrimination at the behavioral level paralleled neural discrimination changes in APC. Adapted from Barnes *et al.* [26\*\*] by permission from Macmillan Publishers Ltd: Nature Neuroscience, copyright 2008.

mixture in which one component was replaced with a novel molecule (10cR1). In a separate group of rats, single-unit recordings from anterior piriform neurons mirrored these behavioral effects: virtual ensemble activity of the 10c mixture (compiled across all cells and animals) was modestly correlated to 10c – 1, but poorly correlated to 10cR1 (Figure 2). Together these findings suggest that ensemble patterns in anterior piriform cortex (APC) fill in missing information about a complex odor mixture when one component is absent (pattern completion), ensuring perceptual stability of the original stimulus. At the same time, anterior piriform ensembles generate separable patterns about an odor mixture when one component is replaced (pattern separation), optimizing perceptual discrimination for compounds that may contain new meaningful information.

Other studies have focused on how the olfactory system maintains perceptual invariance across a range of odor concentrations. Both rodent [27] and fly [28] models converge on the idea that with increasing stimulus concentration, there is increasing inhibitory tone upon olfactory projection neurons, thereby damping down the spread of activation to nonrelevant regions that might otherwise distort neural representations of the stimulus. Computational simulations of rodent OB [27] show that global feed-forward inhibition by interglomerular networks effectively normalizes mitral cell activity patterns, suggesting a parsimonious mechanism by which an odor's quality is intensity independent.

### Odor categorization: lumping not splitting

Given the multitude of different volatile odorous molecules (call this  $n$ ), along with the vast combinatorial opportunities for blending these together (where  $C$  represents the number of components embedded within

an odor blend), the set of potential odors ( $O$ ) naturally encountered in the environment is immense:

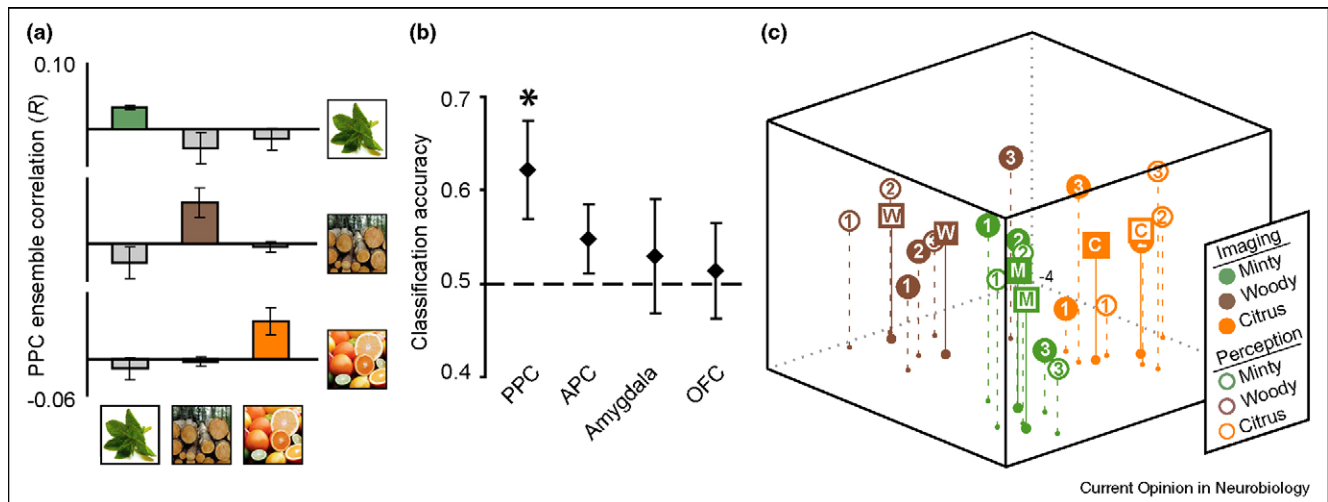
$$O = \sum_{c=1}^C \frac{n!}{C!(n-C)!}$$

It has been estimated that humans have the capacity to distinguish upwards of 400 000 smells [19], but the true number is probably much greater still — using the above equation, all possible blend combinations of just a 20-odorant set would yield over one million unique mixtures. (Note however that the actual number of odors that exist or the actual number of odors that can be detected is both unknown and controversial.) Without a way of carving this multidimensional odor landscape into perceptually relevant categories, organisms would be confronted with a computationally oppressive problem, approaching each new smell with complete naiveté and forced to learn its meaning afresh. Thus the ability to group together odors sharing similar meaning is a critical first step in using prior stored information to predict the functional relevance of novel odors.

Recent behavioral and neural data from different species are beginning to shed new light on odor categorical perception. Honeybees generalize their responses across perceptually distinct binary mixtures of floral odorants after learning that each leads to the same rewarding outcome [29]. Rodents trained to dig for a reward in response to an odor cue generalize toward structurally similar odorants depending on the saliency and strength of associative learning [30]. Both of these studies underscore the importance of behavioral contingency for category formation.

On the basis of single-unit recordings, Yoshida and Mori propose that individual neurons in rodent APC encode

Figure 3



Odor categorical perception in human posterior piriform cortex (PPC). Multivoxel patterns of fMRI ensemble activity were obtained from nine perceptually distinct odorants (three exemplars per each of minty, woody, and citrus categories). **(a)** Ensemble correlations were significantly higher for *within*-category odorants than for *across*-category odorants in PPC, but not in APC, amygdala, or OFC. **(b)** Classification accuracy (proportion of within > across category correlations for all pairwise comparisons) exceeded chance only in PPC. **(c)** Multidimensional scaling was used to project perceptual distances (similarity ratings) and fMRI distances (PPC ensemble correlations) for all pairwise odorant comparisons onto a common three-dimensional space. Odorants belonging to the same category clustered together *within* each map, and clustering of odor quality categories was closely aligned *between* the imaging and perceptual maps. Adapted from Howard *et al.* [34\*\*] by permission from Macmillan Publishers Ltd: Nature Neuroscience, copyright 2009.

categorical information about odorants commonly found in natural foods [31], and that many of these neurons respond to combinations of odorants belonging to different food categories (onion/garlic, potato/sweet pepper, leaf green/cucumber, mustard/radish, resin/citrus, floral, fruity/banana, and fishy/spoiled). However, because each food category was tested using a panel of structurally similar odorants (e.g. terpene hydrocarbons  $\alpha$ -pinene, d-limonene,  $\alpha$ -phellandrene, and myrcene comprised the resin/citrus category), it remains difficult to establish whether the anterior piriform profiles specifically reflect categorical coding of food percepts *per se*, or, in line with other recent data from this brain area [32,33], are more representative of odorant chemical identity.

Recent work by Howard *et al.* [34\*\*] combined high-resolution olfactory functional magnetic resonance imaging (fMRI), sensory psychophysical assays, and multivariate analyses to measure odor-evoked piriform spatial activity patterns and odor quality perception within the same set of human subjects, who smelled three stimulus exemplars per each of three odor categories (minty, woody, and citrus). Multivoxel ensemble patterns in posterior piriform cortex (PPC) coincided with perceptual ratings of odor quality, such that odorants with more (or less) similar fMRI patterns were perceived as more (or less) alike. These effects were not observed in APC, amygdala, or OFC, demonstrating that ensemble coding of odor categorical perception is regionally specific for

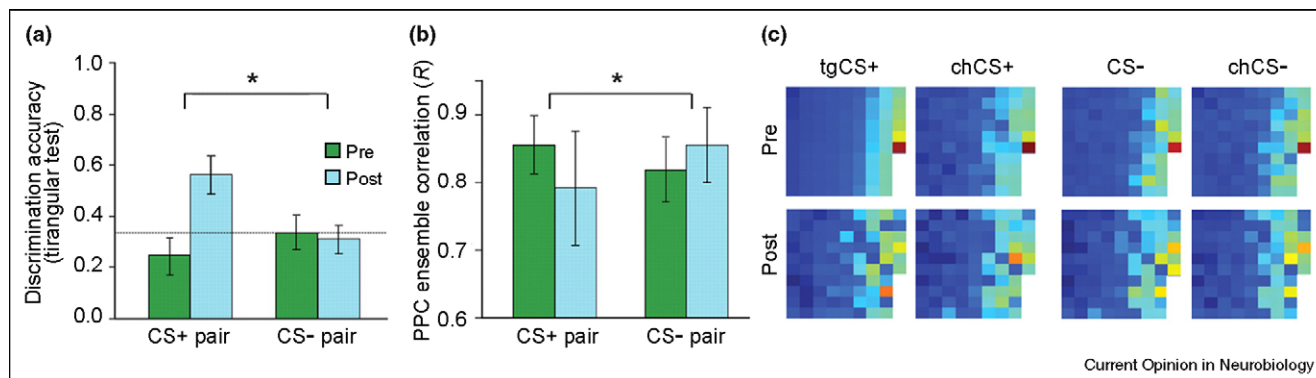
PPC (Figure 3). It is reasonable to speculate that the degree of correlation between odor-evoked PPC spatial patterns and pre-existing odor 'templates' [35] would provide a convenient metric by which the brain could infer similarities among odorants and classify odor objects into discrete, meaningful categories.

### Odor individuation: splitting not lumping

In an odiferous environment, perceptual generalization becomes counterproductive if it obscures perceptual discrimination. This potential conflict is minimized for olfactory systems 'hardwired' to detect certain odors with intrinsic behavioral value (typically pheromones), but poses a much greater issue for the perception of naturally encountered odors that only gain their value via learning and experience. For example, the smell of lion and the smell of housecat are arguably both members of the 'feline/dander' odor category, but the ability to discriminate between these two smells maximizes an organism's response sensitivity while minimizing reckless or impulsive behaviors.

Prolonged presentation of an odorant (~60 s), even in the absence of explicit training, induces stimulus-specific perceptual and neural habituation, a nonassociative learning mechanism that sharpens receptive fields in rodent APC, but not in mitral/tufted cells, for chemically similar odorants [36]. Recent investigations suggest that such a mechanism plays a key role in perceptual segmentation of

Figure 4



Learning to discriminate indistinguishable odors in human PPC. In an fMRI version of olfactory fear learning, subjects smelled pairs of odor enantiomers that were perceptually indistinguishable. One of these enantiomers, designated the target CS+ (tgCS+), was subsequently paired with mild footshock. Neither its chiral counterpart (chCS+), nor a control pair (CS– and chCS–), was paired with shock. From preconditioning to postconditioning, perceptual discrimination between tgCS+ and chCS+ selectively increased (a), in parallel with fMRI ensemble decorrelation (less pattern overlap) in PPC (b). Ensemble activation maps across PPC voxels in one subject (c) show increasing pattern divergence between tgCS+ and chCS+ following learning. Adapted from Li *et al.* [47\*] with permission from AAAS, copyright 2008.

a new odorant from a stable odor background [37,38]. Other studies have shown that adult rats can distinguish chemically similar odorants, as well as odorant components from mixtures, following a 20-day odor enrichment period, though surprisingly, these perceptual gains are not specific to the enriched odorants [15,39,40]. In contrast, a recent fMRI study of olfactory perceptual learning in adult humans arrived at a different conclusion [41]. Here, a single 3.5-min exposure to one odorant enhanced perceptual differentiation for up to 24 hours, but only among perceptually related odorants. For example, a subject exposed to minty L-carvone gained expertise in distinguishing minty odorants, but not floral odorants. These changes were accompanied by experience-dependent plasticity in PPC and OFC, whereby the same invariant odor input was capable of evoking a different fMRI response depending on prior experience. What factors ultimately dictate the generalization of learning to odor stimuli outside of the specific training set remain to be determined.

Paradigms of associative conditioning have long yielded important insights into the ontogeny and refinement of olfactory discrimination [42]. Building on animal models of olfactory fear learning [43–46], Li *et al.* implemented a similar fMRI paradigm in human subjects, testing the impact of aversive Pavlovian conditioning on the perceptual and neural discrimination of odor enantiomers (mirror-image molecules) that are initially indistinguishable [47\*]. As a result of pairing one of these chiral odorants (the conditioned stimulus, or CS+) with mild footshock (the unconditioned stimulus, or US), perceptual discrimination between the CS+ and its unshocked chiral counterpart was significantly enhanced. In parallel, spatial ensemble patterns of fMRI activity for these two odorants significantly

decorrelated in PPC, indicating greater pattern discriminability (Figure 4). These findings indicate that aversive learning induces piriform plasticity with corresponding gains in perceptual odor discrimination. That completely indiscriminable smells can be transformed into discriminable percepts accentuates the potency of learning and experience to enhance human olfactory perception.

Complementary research is providing new insights into the biochemical and physiological mechanisms supporting the type of learning-related piriform plasticity described above. In adult mice, mRNA expression of brain-derived neurotrophic factor (BDNF), a key molecule involved in learning and memory, is elevated in PPC and basolateral amygdala, but not in OB or APC, two hours following odor-shock conditioning [48]. Likewise, single-unit recording data from Schoenbaum and colleagues show that neurons in PPC are highly associative and more likely than APC neurons to reverse their responses when the odor cue–outcome contingency is switched [49], suggesting that posterior piriform areas encode odor meaning rather than odorant identity *per se*. In postnatal rat pups, odor aversion (but not odor preference) learning was consistently associated with activity in PPC, as assessed using 2-DG uptake, implying that the specific hedonic value or meaning of an odor is coded here [50]. Finally, evidence that descending mono-synaptic connections from OFC to APC are strengthened after odor discrimination learning directly highlights the role of top-down feedback in modulating the response properties of piriform cortical neurons [51\*].

## Conclusions

The main goal of this review article has been to illustrate some, but certainly not all, of the ways that the attendant

sensory ecology of odorous objects critically shapes olfactory perception and coding. That this review is divided into separate subsections serves a useful heuristic, but unavoidably errs on the side of ‘splitting’ over ‘lumping.’ In fact all of the ecological concepts discussed above share considerable overlap. For example, to ask whether a binary odor mixture (AB) is perceived as the sum of its parts (A + B) or as a unique object (C) reformulates the question of whether two related odors are treated as members of the same perceptual category, or as members of different categories. Similarly, the perceptual competition between pattern completion and pattern separation closely reflects the dynamics of odor mixture processing, that is, the circumstances determining whether a complex mixture and a variant mixture are treated the same or different.

A common theme emerging across these recent studies is the pivotal associative role of piriform cortex in bridging sensation and perception. This hypothesis nicely accords with computational studies, which have long proposed that a spatially distributed architecture in piriform cortex would serve as a robust neural template for odor coding, memory, and recall [52,53]. Up until recently the idea that ensemble activity patterns in olfactory cortical structures could resolve an ecologically degraded odor input was derived mainly from anatomical data and network simulations, in the absence of direct functional evidence. By directly linking brain states to perceptual states, new findings in both rodents and humans now show that pattern-based odor representations in piriform cortex are specifically involved in firstly, binding together odorant parts into perceptual wholes, secondly, reassembling olfactory meaning out of fragmented stimuli, and thirdly, defining perceptual boundaries of odor qualities and categories. Together these properties are essential for the perceptual reconstruction of odor objects destabilized by the ecological whims of a noisy environment. Future research that incorporates the lessons of odor ecology into more robustly natural models of olfactory coding and perception will undoubtedly bring new scientific depth to our understanding of smell.

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