

What Can an Orbitofrontal Cortex-Endowed Animal Do with Smells?

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ABSTRACT: It is widely presumed that odor quality is a direct outcome of odorant molecular structure, but increasing evidence suggests that learning, experience, and context play important roles in human olfactory perception. Such data suggest that a given set of olfactory receptors activated by an odorant does not map directly onto a given odor percept. Rather, odor perception may rely on more synthetic, or integrative, mechanisms subserved by higher-order brain regions. Results presented here explore the specific role of human orbitofrontal cortex (OFC) in the formation and modulation of odor quality coding. Combining olfactory psychophysical techniques and functional imaging approaches, we have found that sensory-specific information about an odorant is not static or fixed within human olfactory OFC, but is highly malleable and can be rapidly updated by perceptual experience. Critically, the magnitude of OFC activation predicts subsequent behavioral improvement in olfactory perception. Our findings highlight the pivotal role of OFC in linking olfactory sensation, perception, and experience. It is worth considering that many of the current proposed functions attributed to the (distinctively mammalian) OFC are an extension of mechanisms that originally evolved to mediate response flexibility between chemosensory signals and appropriate behavioral actions.

KEYWORDS: orbitofrontal cortex; limbic system; olfactory cortex; olfaction; smell; sensory processing; perceptual learning; aversive conditioning

INTRODUCTION

The original title of this chapter was “Smelling to Learn in Human Orbitofrontal Cortex,” and much of what follows will focus on the topics of smelling, learning, and experience. However, after organizing my oral presentation for the New York Academy Sciences conference on orbitofrontal cortex

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(OFC), I was inclined toward a different title that more faithfully captures the broad themes raised in the Keynote talks: “What Can an Orbitofrontal Cortex-Endowed Animal Do with Smells?” This somewhat non-traditional approach to the topic of chemosensory processing and the OFC is motivated by a simple fact (which was admittedly difficult for an olfactory neuroscientist, such as myself to accept). The fact is, the sense of smell does not require an OFC.

A casual glance at the animal kingdom makes this abundantly clear. There are thousands of vertebrate and invertebrate species using their sense of smell quite efficiently without the least remnant of prefrontal cortex (PFC) or OFC. Maternal bonding, kinship identification, mating choice, hunting and feeding, defining home and territory, evading predators—all of these behaviors are frequently under the spell of odor stimuli, but for many of the animals engaged in these activities, there is no OFC to which olfactory information can even be projected. So while it may be true that the smells are processed in the OFC, or that odor inputs gain access to OFC in as few as three synapses, these statements are not especially enlightening or informative, because the real question is to understand the *unique* features that an OFC contributes to odor processing.

A brief evolutionary interlude may shed some light on these issues. Phylogenetic analyses (FIG. 1) indicate that PFC first emerged in vertebrate evolution about 175 million years ago,¹ traced back to a mammalian ancestor that gave rise to one line of now-extinct mammals and to one line of modern mammals (including egg-laying monotremes, pouch-bearing marsupials, and placentals). Of the remaining living vertebrates, this leaves roughly 30,000 species of bony fish, 6,000 species of amphibians, 8,000 species of reptiles, and 10,000 species of birds, all surviving quite well without prefrontal neocortical brain structures. Thus it is clear that smelling, tasting, hunting, scavenging, eating, and copulating can all be accomplished in the absence of a PFC.

An interesting corollary follows from these considerations: what are the behavioral limitations of an animal *without* a PFC? The green lizard *Lacerta* provides a good example of PFC-less behavior. Wagner showed 75 years ago that *Lacerta* is compelled to approach the color green² (discussed in Schneirla³), an innate response that no doubt has social and nutritional importance for a green species living in a green environment. When Wagner allowed the lizard to choose between a tasty mealworm placed in front of a red panel, and a noxious (salt-saturated) mealworm placed in front of a green panel, it consistently selected the salty worm, and only learned to switch its response pattern after hundreds of trials, if at all.

The great difficulty of this reptile to use experience to modify its behavior adaptively illustrates the advantages of a PFC. The ability to suppress natural response tendencies, to form new predictions about old stimuli, and to update information about sensory inputs, particularly for “emotionally” (biologically) important events, are some of the unique features that PFC and OFC contribute

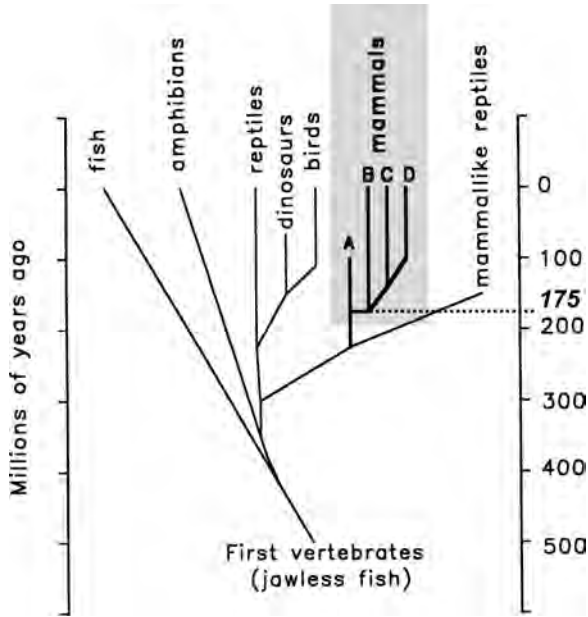


FIGURE 1. Evolutionary appearance of prefrontal cortex. This phylogenetic diagram of vertebrate evolution illustrates that prefrontal cortex arose approximately 175 million years ago in an ancestral species common to the line of modern-day mammals (grey box), including monotremes (**B**), marsupials (**C**), and placentals (**D**). The group of now-extinct mammals, such as trichonodons and multituberculates, is indicated at **A**. It is important to emphasize that thousands of non-mammalian vertebrate species, spanning fish, amphibians, reptiles, and birds, have an acute sense of smell despite the absence of a prefrontal cortex. [Figure modified from Fig. 1.3 of: H.J. Jerison, *Evolution of prefrontal cortex*. 1997. In N.A. Krasnegor, G.R. Lyon & P.S. Goldman-Rakic, Eds., *Development of the prefrontal cortex: evolution, neurobiology, and behavior*, Baltimore, MD: Paul H. Brookes Publishing Co., Inc. Copyright (1997), reprinted and adapted by permission of Brookes Publishing and the author.¹]

to olfactory processing. It is intriguing to speculate that further neocortical differentiation over the last 175 million years has enabled an appropriation of neural machinery originally tuned to handle the interface of odor, behavior, and experience. The OFC of modern-day mammals ensures that a wide variety of experiences, including non-olfactory sensations and interoceptive states, can guide behavior adaptively, with maximal flexibility.

Defining the OFC of modern-day mammals presents its own challenges. The rat is endowed with a tremendous sense of smell but with very little recognizable OFC, at least on cytoarchitectonic grounds, given the absence of granular cortex. Its frontal agranular neocortex has been loosely divided into a medial wall (including medial orbital [MO], infralimbic [IL], and prelimbic [PL] areas) and a ventral/lateral segment (including ventral and posterior

agranular insula [AIv and AIp], ventrolateral orbital [VLO], and lateral orbital [LO] areas).⁴ This latter group of structures (AIv, AIp, VLO, LO) receives direct projections from rodent piriform cortex and responds with short-latency action potentials to electrical stimulation of the olfactory bulb.⁵ From electrophysiological recordings in rodents, it is evident that these same structures are involved in olfactory discrimination learning,^{6,7} lending support to the idea that the OFC of “sub-primate” mammals was chiefly dedicated to the handling of behaviorally salient odor information.

The olfactory OFC in monkeys is broadly comparable to the rodent, though evidence for a definitive homology is still lacking.⁵ Physiological^{8,9} and anatomical^{5,10} studies suggest that primary olfactory cortex (including piriform cortex, olfactory tubercle, and cortical amygdaloid nuclei) projects most densely to posterior orbital cortex in areas Iam, Iapm, and 13a, corresponding to the rodent areas AIv, AIp, and VLO, respectively. Research by Tanabe and colleagues in the 1970's on monkeys suggested that an odor has access to neocortical structures by either of two routes: a direct path from piriform cortex to OFC or an indirect path from piriform cortex to OFC via an intermediary in mediodorsal thalamus.^{8,9} Thus an odorous sensation at the nasal periphery is no more than two synapses removed from olfactory neocortex.

By comparison, the putative human olfactory OFC appears to be strikingly more anterior than one would predict on the basis of the animal data. A recent meta-analysis of 13 human olfactory imaging studies¹¹ demonstrates that odor stimulation consistently activates a bilateral area close to the transverse orbital sulcus (the horizontal limb of the “H”-shaped sulcus), roughly corresponding to the posterior part of granular OFC area 111 in human OFC.¹² Methodological issues notwithstanding, it is interesting to speculate that these cross-species anatomical differences might reflect behavioral differences in the role that the sense of smell plays in these two species. For example, the amygdala provides strong input to agranular OFC, but very scant projections to central anterior OFC (such as area 111), implying that limbic (amygdala) influences on odor processing in OFC may be limited in the human brain.

This brief survey is meant to illustrate the considerable anatomical variation in the organization of olfactory OFC across mammalian species, suggesting important potential constraints upon extrapolating human OFC function from animal data (for detailed discussion see Gottfried and Zald¹¹). These differences are likely to be even more exaggerated in rostral areas of OFC, where increasing cellular granularity leads to further interspecies divergence. Now with these provisos impartially aired, the remainder of this chapter will focus on OFC and olfaction in the human brain. Specifically, as an epitome of the neuro-behavioral interface between sensation, learning, and experience, the following section describes two recent functional magnetic resonance imaging (fMRI) experiments from our laboratory demonstrating the role of human OFC in olfactory perceptual learning and associative (Pavlovian) conditioning. Together these studies reveal how experience-dependent modification of

odor representations in OFC underlies the capacity for sensory refinement of human olfactory perception.

METHODS AND RESULTS

Olfactory Perceptual Learning

The idea that sensory exposure and experience can induce long-term changes in behavior and brain function, even in the absence of direct behavioral reinforcement, is referred to as perceptual learning.^{13,14} This form of plasticity has been documented in numerous non-olfactory systems including visual,^{15,16} auditory,^{17,18} and somatosensory¹⁹ cortices.

In the olfactory domain, perceptual learning is well documented at the behavioral level. For example, repeated presentations of an odor reduce olfactory detection thresholds^{20,21} and can boost olfactory sensitivity in anosmic subjects.^{22,23} Exposure to wine²⁴ or beer²⁵ is sufficient to improve sensitivity toward stimuli whose chief sensory property is olfactory. Experience and familiarity significantly enhance odor quality discrimination,^{26,27} while exposure to odor mixtures alters the perceived quality of the individual components.²⁸ Notably, despite growing behavioral evidence for olfactory perceptual learning, how this form of learning updates odor quality codes in the human brain is unknown.

In the present study,²⁹ Dr. Wen Li and I combined fMRI techniques with an olfactory habituation paradigm^{30–32} to test whether prolonged olfactory exposure (as a simple form of perceptual learning) leads to sensory plasticity within the human brain. Our main hypothesis was that prolonged sensory experience would modulate neural representations of odor quality in areas previously implicated in coding of this perceptual feature, including piriform cortex^{33,34} and OFC.^{6,33,35–37} Moreover, in parallel to the neural effects, we hypothesized that odor experience would facilitate perceptual differentiation between odorants sharing critical qualitative or structural attributes. Note, as used throughout the rest of this chapter, the term “odor quality” is meant to refer to the specific character or identity of a smell emanating from an odorous object (such as its mintiness or floweriness), in contrast to other features, such as intensity, pleasantness, or pungency.

During event-related fMRI scanning, 16 human volunteers (mean age, 24 years) smelled a target odorant (TG) destined for habituation; a quality-related odorant (QR, either “floral” or “mint”); a functional group-related odorant (GR, either ketone or alcohol); and a control odorant (CT) unrelated to TG either in quality or group, both before and after 3.5-min continuous exposure to the TG stimulus (FIG. 2). As orthogonal factors in the study design, the GR odorants systematically differed in perceptual quality, and the QR odorants systematically differed in functional group. Thus, inclusion of the

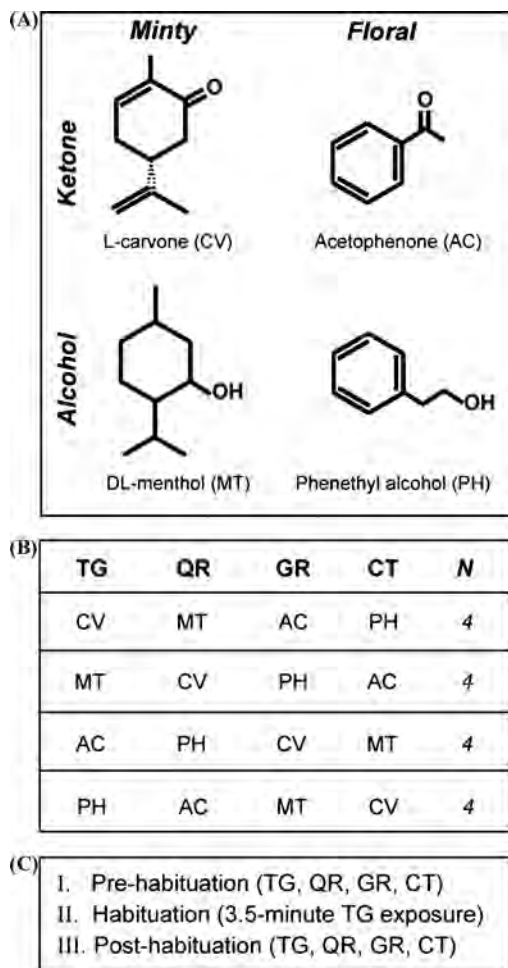


FIGURE 2. Experimental paradigm of olfactory perceptual learning. (A) Subjects smelled four different odorants that systematically differed in perceptual quality (minty or floral) and in molecular functional group (ketone or alcohol). (B) Odorants were assigned to four conditions: a target odorant (TG) destined for habituation, an odorant related in perceptual quality (QR) to TG, an odorant related in molecular functional group (GR) to TG, and a control odorant (CT) unrelated in either quality or functional group to TG. Across subjects, the assignment of a given odorant as the TG stimulus was evenly counterbalanced (N , number of subjects), thereby minimizing perceptual differences between TG, QR, GR, and CT conditions. (C) fMRI scanning was divided into three sequential sessions. During pre-habituation and post-habituation, there were 14 2-sec presentations of each of the four odorants. During habituation, the TG odorant was presented continuously for 3.5 min. [Reprinted and modified from Figs. 1 and 2 in: W. Li, E. Luxenberg, T. Parrish & J.A. Gottfried, Learning to smell the roses: experience-dependent neural plasticity in human piriform and orbitofrontal cortices, *Neuron*, Vol. 52, Pages 1097–1108, Copyright (2006), with permission from Elsevier.²⁹]

QR and GR conditions enabled us to probe the specificity of learning-induced changes across the dimensions of odor quality and odorant group independently, while the CT condition provided a base line to adjust for non-specific effects. Importantly, the selection of odorants (L-carvone, menthol, acetophenone, and phenethyl alcohol) made it possible to assign the stimuli to each of the four conditions (TG, QR, GR, CT), counterbalanced across subjects, to minimize odorant-specific confounds. Pairwise similarity ratings of odor quality,²⁸ collected 30 min before and 30 min. after prolonged TG exposure, provided a behavioral index of perceptual learning.

Using an integrated parallel acquisition technique known as GRAPPA, we obtained T2*-weighted echoplanar images on a Siemens Trio 3-T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with an 8-channel head array coil. In combination with a matrix size of 128 mm, a slice thickness of 2 mm, an echo time (TE) of 20 ms, and a tilted acquisition angle (30° to the intercommissural line), this imaging protocol exhibits excellent sensitivity for detecting BOLD (blood-oxygen-level dependent) contrast changes in olfactory regions of the brain that are highly susceptible to signal dropout and distortion.

Behaviorally, from pre-exposure to post-exposure, quality similarity ratings decreased (indicating more *dissimilarity*) for the TG:QR pair and the TG:GR pair, compared to control pairs (FIG. 3). The implication is that sensory experience with the TG odorant successfully enhanced the discriminative capacity (or expertise) for odorants similar in perceptual quality or chemical structure. For example, subjects exposed to L-carvone (the minty ketone) became mint “experts,” and they simultaneously became experts at distinguishing among ketone-bearing odorants. Importantly, the four odorants did not differ in intensity at the time of pre-testing or post-testing, making it unlikely that subjects relied on intensity factors to make their similarity judgments. Moreover, by the end of the post-habituation session, there were no significant behavioral differences in valence or pungency among the four odorant conditions, ruling out the likelihood that the impact of TG exposure on odor quality differentiation was due to mere perceptual variations in these other perceptual features. Finally, a complementary behavioral study on an independent group of 16 subjects revealed that these perceptual effects persisted for up to 24 hours after initial exposure and even generalized to novel odorants within the same odor category.²⁹

Analysis of the fMRI data set was performed using the software package SPM2 (www.fil.ion.ucl.ac.uk/spm/). Subject-specific comparisons (contrasts) between the different odor conditions, at pre-habituation versus, post-habituation, were entered into a series of one-sample *t*-tests or ANOVAs, each constituting a group-level (random-effects) analysis, permitting population-based inference testing. These results demonstrated experience-dependent response enhancement in both piriform and orbitofrontal cortices, in parallel to (and preceding) the behavioral effects. In posterior piriform cortex, neural activity elicited by the QR odorant increased from pre-habituation to

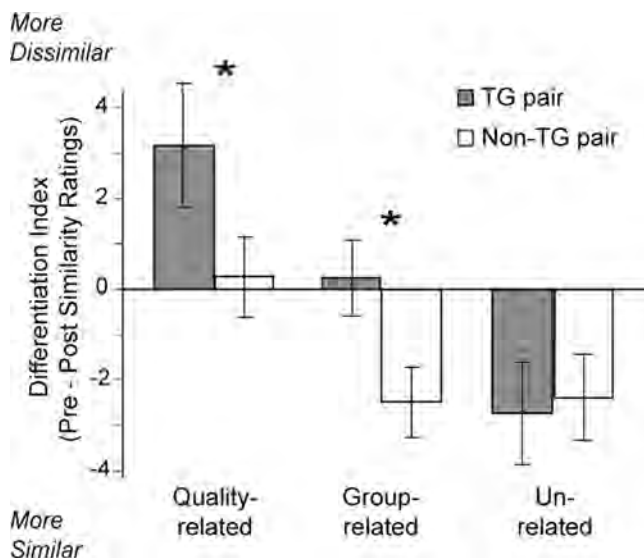


FIGURE 3. Odor exposure enhances perceptual expertise. Similarity ratings of odor quality between pairs of odorants indicate that from pre-exposure to post-exposure, subjects were better able to differentiate odorant pairs related in perceptual quality (TG:QR), in comparison to unrelated pairs (TG:CT) and in comparison to quality-related pairs (GR:CT) whose qualitative features differed from the TG category (for example, if TG and QR were both minty smells, then GR and CT were both floral smells). Discrimination was also improved between odorants sharing functional groups (TG:GR). These effects persisted for 24 hours (data not shown). *Significant compared with non-TG pairs; $P < 0.05$. [Reprinted and modified from Fig. 4 in: W. Li, E. Luxenberg, T. Parrish & J.A. Gottfried, Learning to smell the roses: experience-dependent neural plasticity in human piriform and orbitofrontal cortices, *Neuron*, Vol. 52, Pages 1097–1108, Copyright (2006), with permission from Elsevier.²⁹]

post-habituation; in olfactory OFC, increased activation was seen in response to both the QR and GR odorants.

The above findings provide solid evidence for behavioral and neural plasticity in response to sensory experience, but are unable to demonstrate whether there is a predictive relationship between the magnitude of response change in OFC (or piriform cortex) and the behavioral improvement in perceptual learning. To address this question, we conducted a correlation analysis by regressing subject-specific changes in neural activity (post-habituation minus pre-habituation) against changes in odor quality similarity (post minus pre). In olfactory OFC, there was a significant correlation ($R = 0.75$; $P < 0.05$ corrected for small volume) between neural and behavioral indices of learning (FIG. 4). No such effect was observed in piriform cortex. These additional results suggest that OFC is a critical locus for guiding experience-dependent behavioral improvements in perceptual expertise.

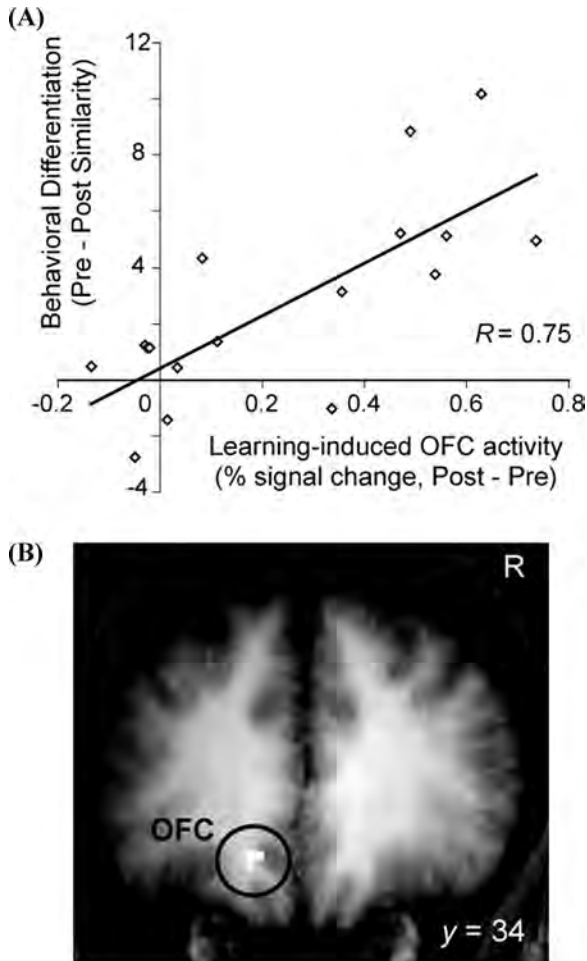


FIGURE 4. Neural activity in OFC predicts subsequent enhancement in perceptual differentiation. (A) Regression analysis demonstrates that the magnitude of learning-induced change in OFC (abscissa) directly correlates with the degree of perceptual enhancement (ordinate), on a subject-by-subject basis. Each *diamond* represents a different subject. (B) The mean effect of the behavioral correlation in OFC ($N = 16$ subjects) is shown superimposed on a coronal section of the group-averaged T1-weighted anatomical scan (threshold, $P < 0.005$ uncorrected). [Reprinted and modified from Fig. 5 in: W. Li, E. Luxenberg, T. Parrish & J.A. Gottfried, Learning to smell the roses: experience-dependent neural plasticity in human piriform and orbitofrontal cortices, *Neuron*, Vol. 52, Pages 1097–1108, Copyright (2006), with permission from Elsevier²⁹.]

Together these findings demonstrate that mere odor exposure is sufficient to enhance odor differentiation and elicit perceptual expertise for both odor perceptual quality and odorant functional group. These behavioral effects are paralleled (and preceded) by experience-induced neural plasticity in OFC and

piriform cortex. Our data suggest that experience specifically updates sensory-specific representations in olfactory OFC, guiding subsequent improvements in odor perception.

Olfactory Aversive Conditioning

As a model of associative learning, classical (Pavlovian) conditioning has been used to investigate how neutral sensory cues in the environment become endowed with behavioral salience. Non-olfactory studies of aversive conditioning in animals^{38–40} and humans^{41–44} indicate that this form of learning elicits robust neural changes in sensory-specific brain regions. For example, in an aversive conditioning task that used a tone as the conditioned stimulus, fMRI responses were robustly enhanced in auditory regions of the brain for a conditioned (but not for a non-conditioned) tone, reflecting experience-dependent plasticity in sensory-specific cortex.^{43,44} Findings such as these indicate that the pairing of a sensory stimulus (the conditioned stimulus, or CS+) with an emotionally charged event (the unconditioned stimulus, or UCS) is sufficient to modulate neural representations of the original sensory input. In turn these learning-dependent changes in sensory coding may underlie subsequent modifications in sensory perception. In preliminary studies we have devised an aversive conditioning fMRI paradigm between an odor (CS+) and an electric shock (UCS) to test the following questions: What is the effect of emotional learning on human odor perception? Does associative pairing between an odor and shock alter cortical representations of smell? Is the magnitude of experience-dependent neural change predictive of behavioral perceptual enhancement?

To address these questions, Dr. Wen Li and colleagues in my laboratory presented healthy human subjects with four odorants: two pairs of odor enantiomers (mirror-image “chiral” molecules) that were perceptually indistinguishable, based on Laska *et al.*⁴⁵ After a baseline (pre-conditioning) session, subjects underwent aversive conditioning between one of the four odorants and an electric shock. The level of electrical stimulation was titrated individually for each subject, to a point which was uncomfortable but still tolerable. The other three odorants (including the chiral twin of the conditioned odorant, and the other enantiomer pair) were never paired with shock. This conditioning session was followed by a final post-conditioning phase, identical to pre-conditioning, which permitted a direct examination of conditioning-specific neural plasticity by comparing post-conditioning and pre-conditioning sessions. To assess the impact of conditioning on behavioral discrimination, subjects also took part in a triangle test both at the start and at end of the scanning study, in which they were given sets of three bottles (two containing the same odorant, a third containing its chiral opposite) and asked to identify the “odd” bottle.

Our preliminary results⁴⁶ suggest that prior to conditioning, subjects were unable to discriminate between the enantiomer pairs, as expected. However, as a result of aversive conditioning, behavioral discrimination was selectively enhanced for the conditioned odorant and its chiral opposite, but discrimination remained at chance for the other pair of enantiomers that had not been involved in the conditioning procedure. In parallel to these behavioral effects, the amplitude of OFC activity evoked by the odor CS+ increased in response to conditioning. Interestingly, OFC response enhancement was also observed for the chiral-related odorant (which itself had never been associated with electric shock), suggesting that associative learning partially generalizes to odorants similar in perceptual quality. Finally, on a subject-by-subject basis, the magnitude of learning-induced OFC activity closely correlated with the level of behavioral odor discrimination. Although further work remains to be done, these initial findings suggest that olfactory aversive learning can enhance sensory discrimination, such that odorants initially smelling the same become perceptually distinct. These perceptual changes are accompanied by conditioning-specific neural plasticity in OFC, with generalization to odorants sharing qualitative attributes. Together our data suggest that OFC plays a critical role in the modulation of odor perception via emotional experience.

DISCUSSION

The data presented here indicate that sensory-specific neural representations of odor quality are not static or fixed in OFC, but are modifiable and can be updated by sensory, emotional, and associative experience. The idea that context, learning, and experience can modulate odor perception receives support from a variety of recent fMRI studies. For example, O'Doherty and colleagues⁴⁷ were among the first to show that appetite and motivational state could influence sensory-specific odor representations in human OFC. On alternating fMRI blocks, subjects were presented with banana or vanilla odor, both before and after a lunch of bananas until they became satiated for this item. As a result of this manipulation, the neural activity evoked by the banana odor (but not the vanilla odor) was selectively diminished in OFC, indicating that this brain region was sensitive to the current rewarding properties of an olfactory stimulus. Using a different paradigm, Gottfried and Dolan⁴⁸ showed that visual semantic context also modulates odor coding in OFC. Neural activation in this area was increased when an odor (e.g., smell of a rose) was presented in combination with a congruent image (e.g., picture of a flower), as opposed to an incongruent image (e.g., picture of a bus). Thus, the same sensory input evoked different responses depending on whether it was experienced in a semantically appropriate context. Similar effects of sensory context on odor processing in OFC have been demonstrated with combinations of odors and tastes⁴⁹ and odors and verbal labels.⁵⁰ That OFC activity is common to



FIGURE 5. Neural representations of odor quality^{29,33} in OFC (*white crosses*) overlap the putative human olfactory OFC¹¹ (*white circles*) and are adjacent to regions that code the reward value of food smells⁴⁷ and flavors^{51,52} and the predictive reward value of olfactory reinforcers⁵³ (*black crosses*). Area 111 in human OFC is roughly approximated by the dashed black lines, following Fig. 2 of Ongur and Price.¹² For presentation, activations are presented on a normalized axial T1-weighted image and collapsed across the z-axis (superior-inferior) in order to display all activations on a single slice. The right side of the image corresponds to the right side of space. See text for further details.

all of these studies highlights its pivotal role in linking olfactory sensation, perception, and experience.

Interestingly the region of OFC shown here to participate in the modulation of odor quality coding²⁹ overlaps fairly closely with the human orbitofrontal areas involved in sensory-specific satiation of food odors⁴⁷ and flavors^{51,52} and in reinforcer devaluation of pleasant food odor,⁵³ as well as with neural representations of odor quality itself.³³ In the majority of these fMRI studies, the activations fall within human anterior OFC area 111 (with reference to the human cytoarchitectonic map of Ongur *et al.*¹²), clustering near the putative human olfactory OFC.¹¹ This anatomical correspondence (FIG. 5) raises the intriguing idea that experimental manipulations designed to devalue odor reward might actually elicit qualitative changes in the odor itself. For example, the same odor experienced in a state of hunger may take on a different

perceptual quality when later experienced in a state of satiety, over and above changes in reward value. The possibility that satiety induces sensory-specific changes in odor quality has a certain ecological plausibility (if for instance one considers the sensory reaction to a grilled 40-oz dry-aged porterhouse steak before and after its consumption), and also raises general questions about the use of devaluation procedures to assess reward-related processing in the brain.

It is worth considering that experience-dependent fMRI plasticity in OFC (as well as in posterior piriform cortex) might actually reflect inputs from lower-level regions. For example, as a result of tight feedback loops between piriform cortex and olfactory bulb,⁵⁴⁻⁵⁶ any changes in response plasticity seen in piriform cortex may simply mirror equivalent changes in olfactory bulb. Indeed, centrifugal feedback from learning-modified regions in piriform cortex might be highly instrumental in sculpting sensory response profiles in olfactory bulb, streamlining bottom-up information processing for behaviorally salient odors. Alternatively, it is possible that the response plasticity in orbitofrontal and piriform cortices is related to a common input from the amygdala, which in rats^{54,57} and monkeys^{5,58} projects to both of these areas. However, it is not clear whether amygdala projections to piriform cortex arise from the same amygdala nuclei that project to OFC,^{54,59} and in any event we have not observed fMRI evidence for experience-dependent updating of odor quality information in the amygdala. Rather, our own prior studies are more compatible with the role of amygdala in the learning of novel associations between emotionally provocative odors and neutral cues^{60,61} and in the signaling of motivationally salient odors.^{53,62}

Notably, our studies have not identified learning-induced neural plasticity in *anterior* piriform cortex. We speculate that the absence of changes in this region would ensure stimulus constancy of the original sensory input, in keeping with the purported role of anterior piriform in encoding odorant structure.³³ It is plausible that the observed differences in neural plasticity between anterior and posterior piriform cortex⁶³ accentuate the underlying anatomical connectivity of these regions: anterior piriform is the principal target of olfactory bulb⁵⁵ and therefore contains a labeled line for odorant structure, whereas posterior piriform receives the bulk of its inputs from associational fiber systems and would be a better candidate for experience-dependent modulation.^{55,63}

The ability of experience to sculpt sensory processing at both the behavioral and neural levels has important implications for contemporary models of olfaction. In particular, the findings described here indicate that the perceptual quality of an odor does *not* necessarily follow from its underlying molecular chemical composition. Ever since the first multigene family of olfactory receptors was identified in rodents,⁶⁴ the dominant view of odor perception is that molecular chemical knowledge of an odorant is sufficient to predict its perceptual attributes. Behavioral studies in rodents demonstrate that odors evoking similar electrophysiological patterns in the olfactory bulb are perceived as being more similar,⁶⁵⁻⁶⁸ leading to the idea that odor-specific spatial

maps in the olfactory bulb may underpin odor perception and that neural representations of odor quality are reflected in ensemble olfactory bulb activity encoding complex configurations of molecular features.⁶⁹

On the other hand, these “bottom-up” models of odor perception conflict with a growing number of studies suggesting that even elementary aspects of olfactory processing are highly contingent on learning and experience. Odor detection thresholds, adaptation rates, and intensity judgments are all strongly modulated by visual, perceptual, and cognitive factors.^{70–73} Olfactory discrimination in general is highly plastic and can be modified by contextual cues.^{26,27,74–76} It is often noted that the perception of an odor is a synthetic process—the smell of chocolate may contain dozens, if not hundreds, of volatile organic compounds,⁷⁷ yet the olfactory system synthesizes this complex mixture seamlessly into one odor. Recent psychophysical studies have demonstrated the integrative nature of odor perception.^{28,78,79} In this manner, the smell of a rose is as much defined by a myriad of molecular determinants as by previously stored odor representations and ongoing sensory context.⁷⁹

In all likelihood there are multiple personifications of an odor map or code, with progressive transformations occurring at each level of the olfactory neuraxis. However, the critical issue is to understand the form these maps take that ultimately determines sensory perception and to understand how learning and experience refine these maps in the service of behavior. These questions are not unique to the olfactory system, but apply generally to all of the sensory channels—even for a widely studied sense like vision, it is by no means clear how a behaviorally relevant percept is assembled out of visual maps in the brain. Some of the data presented here suggest that olfactory OFC is a primary target of odor experience, but in comparison to the olfactory bulb and piriform cortex, virtually nothing is known about its finer details. As discussed in the chapter by Shepherd (this volume), a challenge of future work will be to delineate the intrinsic neuronal properties, synaptic organization, and connectivity of olfactory OFC.

Prior fMRI data from our laboratory indicate that neural representations of odor quality and odorant structure (molecular functional group) are encoded in separable olfactory areas of the human brain.³³ Importantly, the identification of odor quality codes across a network of olfactory regions, including posterior piriform cortex, OFC, and hippocampus,^{36,37} was independent of any simple molecular configuration.³³ Our recent data on perceptual learning and aversive conditioning extend these findings by implying that neural codes of odor quality rely on experience and learning for their formation, rather than simply existing as a product of structure-based ensembles. We suspect that neural representations of odor quality are a dynamic product of lower-level coding from olfactory bulb and higher-level cortical inputs, under the regulation of learning and experience,⁷⁹ attention,⁸⁰ sensory context,^{48,73} and language.^{50,75,81} The results presented here indicate that the OFC (as a distinctively mammalian brain region) is a critical neurobiological interface

that flexibly links affect and action, providing advantages for adaptation and survival that exceed the everyday reach of our OFC-impoverished vertebrate (piscine, amphibian, reptilian, avian) kin.

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