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The value of identity: olfactory notes on orbitofrontal cortex function

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Neuroscientific research has emphatically promoted the idea that the key function of the orbitofrontal cortex (OFC) is to encode value. Associative learning studies indicate that OFC representations of stimulus cues reflect the predictive value of expected outcomes. Neuroeconomic studies suggest that the OFC distills abstract representations of value from discrete commodities to optimize choice. Although value-based models provide good explanatory power for many different findings, these models are typically disconnected from the very stimuli and commodities giving rise to those value representations. Little provision is made, either theoretically or empirically, for the necessary cooperative role of object identity, without which value becomes orphaned from its source. As a step toward remediating the value of identity, this review provides a focused olfactory survey of OFC research, including new work from our lab, to highlight the elemental involvement of this region in stimulus-specific predictive coding of both perceptual outcomes and expected values.

Keywords: orbitofrontal cortex; predictive coding; olfactory perception; associative learning; reward value; object identity

Introduction

This paper serves as a minority opinion to the consensus theme of a recent conference held at the New York Academy of Sciences (NYAS) in New York City (March 30–April 1, 2011) that the critical contribution of the orbitofrontal cortex (OFC) is to encode, assign, update, integrate, monitor, compare, and/or compute reward value, predicted value, negative value, stimulus value, action value, and/or subjective value. To the extent that a choice between two or more items requires comparing their values in a common currency, recent work even proposes that the OFC is pivotal in rendering a measure of abstract value from each item in order to inform rational choice.[1,2] Of course, the prevailing message that the OFC manufactures value (Fig. 1) was partly based on a selection bias engineered by the NYAS organizing committee (including myself): among the many illustrious neuroscientists invited to speak at this conference, most explicitly study reinforcement learning and goal-directed decision making, of which value is a common and highly prized thread.

The aim of this paper is not to dispute the value-based framework of OFC function. There is little doubt regarding the key role of the OFC in regulating affect and emotion, as immortalized in nature's case of Phineas Gage, railroad worker, and in the insalubrious surgical cases of frontal lobotomies popular in the 1940s and 1950s. The last couple of decades has brought incredible scientific rigor to the question, with an ever-growing number of behavioral, lesional, imaging, and electrophysiological studies demonstrating that the OFC encodes representations of value. Further, the neuroeconomical question of whether all values, rewards, and pleasures are commensurate, that is, differing only in quantity but not quality, importantly extends an ancient dialog stretching at least as far back as the Greek philosopher, Democritus (c. 460 to c. 370 BCE), who noted that "men get pleasure from scratching themselves: they feel an enjoyment like that of lovemaking."[3]

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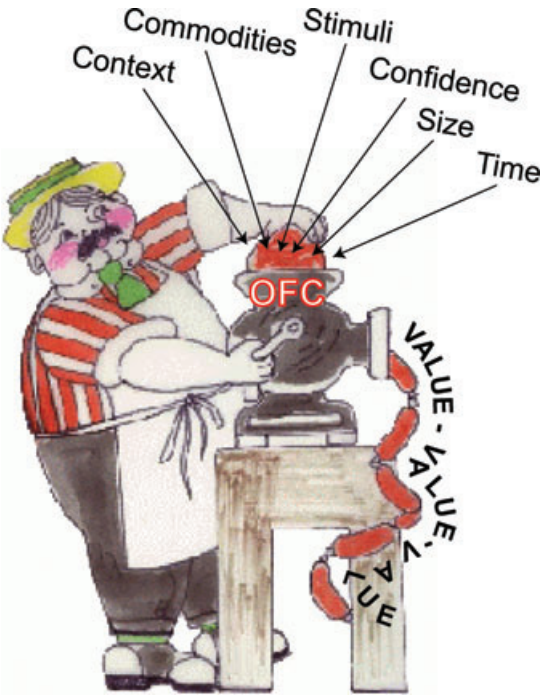

Figure 1. This cartoon depiction of a jovial butcher at the sausage grinder has been updated to show how a leading proposed function of the OFC is to manufacture value. Image source: http://www.foodmuseum.com/sausage.html; reproduced and modified with courtesy of The FOOD Museum Collection © 2011.

Instead, my aim in this paper is to illustrate that all that glitters in the OFC is not value. In spirit, the paper aligns with that by Schoenbaum *et al.* in this volume, but with a decidedly olfactory emphasis. The central tenet is that value is only as valuable as its referent. Abstracting a neural representation of value from a bag of M&M's will have limited sway over action selection unless that value retains its selective association with the chocolate-y melts-in-your-mouth-not-in-your-hands commodity that is M&M's. Note that owing to space limitations, this paper is unable to provide an overview of the nonolfactory research literature that naturally complements the following discussion.

Why odors?

As a prelude and backdrop to the subsequent discussion, this section highlights some of the potential advantages of using odor stimuli to investigate orbitofrontal function. Five of these advantages are listed below.

First, the afferent flow of odor information from the olfactory epithelium into the OFC is a short three-synapse arc (receptor neurons → olfactory bulb → piriform cortex/amygdala → OFC).[4–6] By comparison, sensory information in other modalities is progressively elaborated over numerous synapses in the brainstem, thalamus, and cortex prior to its arrival in the OFC. Thus, the anatomical simplicity of the olfactory system makes it highly tractable for studying the neurophysiology, connectivity, and function of the OFC.

Second, odors confer identity and stimulus specificity to the majority of food rewards used as incentives and outcomes to probe OFC function. For example, cranberry juice and blackcurrant juice are similar in sweet taste and oral texture; it is largely their (retronasal) olfactory components that perceptually distinguish these stimuli. Insofar as the goal-directed actions of animals are frequently oriented toward food search and consumption, the use of odor stimuli seems a natural choice for studies of learning and decision making.

Third, human olfactory perception and discrimination, especially for complex mixtures of odors, is relatively slow,[7,8] encouraging a natural prolongation of response times.[9] This means that the olfactory system is ideally suited for using functional imaging techniques to delineate neural processes in the human OFC (and elsewhere in the brain) that evolve over time, including perceptual decision making, evidence integration, and predictive coding.

Fourth, as explained below, many rodent studies have successfully used ethologically relevant cues—namely odors—to investigate the neurobiology of reinforcement learning and goal-directed decision making, providing a highly compatible foundation of work for cross-species comparisons between human and rodent models of OFC function.

Fifth, in many visual-based goal-directed neurobehavioral tasks, subjects declare their choice by making an action in space: for example, given cue choice X, press the left button, saccade to the left, or enter the left maze-arm. Indeed, spatially selective action plans are thought to be a key determinant of action value signals in the brain that underlie choice behavior.[1] However, visual stimulus cue X, itself, inherently contains information about its location or direction in space, the result being that neural representations of action values and stimulus

values, and even the actions themselves, may be intertwined and difficult to dissociate.[2] In the olfactory domain, more effective separation between these task components can be achieved due to the fact that odor stimuli are spatially impoverished and poorly rooted to their proximate source.[10,11]

Olfactory processing in the OFC: value, identity, or both?

Chances are that if one reads a research article on odor stimulation and the OFC, he or she will learn very little about olfactory processing. In the context of rodent and monkey studies, odors have been conveniently used as stimulus cues in discrimination learning tasks, delayed match-to-sample tasks, and reinforcer devaluation paradigms. Olfaction begins and ends with the cue, and any actual task effects on olfactory representations in the OFC are generally treated as collateral data of tangential interest. Rather, the take-home message from these studies is that the main business of the OFC is to encode predictive values and expected outcomes.

This selective viewpoint of OFC function (admittedly, a slightly polemical viewpoint) is discomfiting, because it is at odds with the actual findings. For example, in a classic experiment, rats took part in a go/no-go olfactory discrimination task in which they learned to respond to one odor cue in order to receive a water reward and to withhold responding to another odor cue in order to avoid a punitive time-out period.[12] Each trial consisted of several sequential trial events: trial initiation, nose poke into the odor port, odor sampling, response at the water port, delay period, and fluid delivery. Simultaneous single-unit recordings were made from the OFC (mostly lateral orbital [LO] and agranular insular [AI] areas), while the rats performed the discrimination task. What is remarkable is that individual neurons fired selectively during *each* of the trial events. Moreover, in some cells, responses during odor sampling were modulated by the associated reward value of that odor, but in other cells, responses were very much tied to odor identity.

In fact, coding of both odor identity and odor significance (acquired value; expected outcome) at the time of odor cue sampling is the rule rather than the exception in rodent OFC, and numerous other studies across different labs and paradigms have demonstrated that OFC encodes specific odor–outcome conjunctions.[12–23] This point is nicely illustrated in an odor-guided delayed nonmatch-to-sample paradigm in which delivery of water reward on a given trial was contingent on the rats recognizing that the sampled odor was different from (did not match) the odor on the preceding trial.[17] Among 43 odor-selective neurons in the OFC (representing 15.6% of all recorded neurons), 21 of these (48.8%) fired differentially on match and nonmatch trials, indicating that response properties in this region reflect an interaction of odor identity and its associated behavioral significance.

Although these findings naturally point to the idea that the OFC is involved in integrating cue identity and cue-predictive outcome, current conceptualizations of OFC function tend to turn a blind eye to the sensory relevance of the cue or of the outcome. This stance is captured most starkly in a recent review: "a defining trait of the representation of value found in the OFC and the vmPFC is that values are encoded independently of the sensorimotor contingencies of choice" (Padoa-Schioppa, p. 348).[2] Interestingly, even among research labs that strongly favor an integrative role for the OFC where odor and outcome information is combined, a subtle bias against olfactory sensory coding per se still exists, as in this passage summarizing OFC representations: "neurons in these areas in rats appear to encode the associative significance of cues, even odor cues, rather than their sensory features" (Roesch *et al.*, p. 643).[21]

Monkey studies of odor discrimination have also tended to emphasize value over identity coding in the OFC. In one influential experiment,[13] monkeys were trained on a go/no-go task to lick in response to eight different odors to receive sucrose taste and to withhold licking to two other odors to avoid saline taste. Single-unit recordings from the OFC, including the medial and lateral OFC, showed that among 1,580 recorded neurons, 48 of them (3%) responded to odor. Among these 48 cells, 34 (71%) exhibited differential responses to the different odors. Among these 34 cells, 65% preferentially responded to odor quality and 35% responded to the associated taste. In complementary studies, odor-evoked responses in seven of nine OFC neurons (78%) were decreased after feeding in a sensory-specific manner,[24] and odor-evoked responses in 19 of 28 OFC neurons (68%) were modified after a reversal of odor–taste reward contingencies.[25] These high relative proportions of reward-associative cells, together with

information-theoretic analyses of the data, prompted the conclusion that "many of these orbitofrontal olfactory neurons are concerned more with the representation of the reinforcement association of the odorants rather than the discrimination of odorants" (Rolls *et al.*, p. 1995).[26] That being said, these investigators did recognize the importance of reward-independent representations of odor identity in the OFC, not only to control the sensory specificity of feeding behavior, but also to ensure that selective satiety of a given food odor does not wholly eradicate the perceptual representation of that odor.

The olfactory OFC: clues from human work

Investigations of olfactory processing and the human OFC have taken several different directions. Early patient lesion studies implicated orbitofrontal areas, but not other prefrontal cortical areas, in odor identification and discrimination.[27–29] With the advent of olfactory functional imaging,[30] many studies have demonstrated odor-evoked orbitofrontal activation (too many to list; see Ref. 31 for a review), and recent fMRI work from our lab has strongly implicated the OFC in perceptual coding of odor identity.[32–35] Such studies have helped reinforce the idea that fine discrimination of olfactory quality takes place in this region, in accord with early physiological findings in monkeys.[36,37]

Another line of investigation has shown that pleasant and unpleasant odors induce differential patterns of fMRI (or PET) activity in human OFC.[38–43] Some of this work has suggested a dissociation of odor valence within the medial OFC (pleasant odor) and lateral (unpleasant odor) OFC, though the anatomical reliability of these distinctions has been called into question.[31] In a thematically related study, odor-evoked activity in the OFC was reduced following selective satiety to a food containing that odor,[44] and satiety effects in the OFC have also been observed in direct response to the sated foods themselves.[45,46]

Given that emotional valence is a prominent dimension of olfactory perception,[47,48] pleasant and unpleasant odors have been successfully used as appetitive and aversive reinforcers, respectively, in fMRI studies of associative learning. Pairing of visual conditioned stimuli (CS^+) with these olfactory unconditioned stimuli (UCS) yielded spatial and temporal dissociations of OFC activity that varied according to the learning mode (either appetitive or aversive), underscoring differences in the functional networks supporting these two learning schemes.[49] Complementary fMRI studies have more clearly established that CS^+-evoked representations in the OFC and ventromedial prefrontal cortex signal olfactory predictive value, either through sensory-specific satiety manipulations to devalue a pleasant food odor UCS[50] or through sensory-specific inflation techniques[51] to enhance the aversive value of an unpleasant odor UCS.[52]

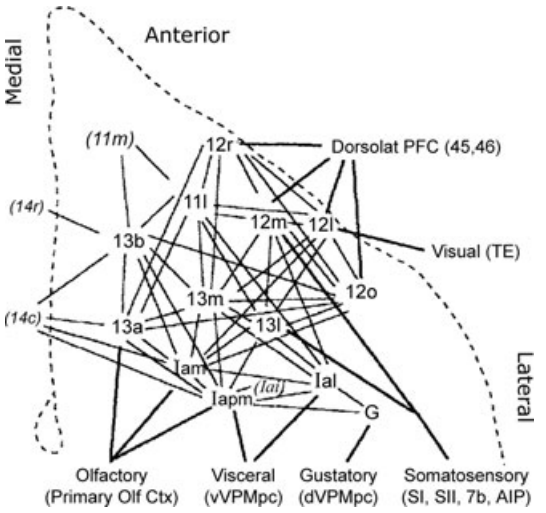

Figure 2. **The orbital prefrontal network. This schematic of the ventral surface of the macaque basal frontal lobe shows the rich network of sensory projections from different sensory modalities into the OFC. In general, unimodal sensory inputs terminate in posterior areas of the OFC (with the exception of visual inputs terminating in lateral area 12l) and then project to overlapping areas in more anterior and central areas of the OFC, providing a potential medium for cross-modal interactions and heteromodal processing. Modified from Ref. 54, with permission of John Wiley and Sons © 1996.**

One other research direction has followed from animal anatomical and physiological observations that the OFC is an area of dense convergence for multiple sensory modalities[53–55] (Fig. 2). Several human imaging studies have shown that the OFC responds to multisensory combinations of odors and tastes,[56–59] odors and pictures,[60] odors and colors,[61] odors and words,[62] and odors and intranasal trigeminal stimuli.[63] These investigations further show that the level of cross-modal semantic congruency (e.g., rose odor/rose picture vs. rose odor/pine tree picture) modulates the magnitude of fMRI activity, highlighting the importance of context and

experience in formation of multisensory representations in human OFC.

This brief overview indicates that human olfactory OFC encodes (or is involved in encoding) discrete representations of odor identity, odor valence, acquired olfactory value, and olfactory multimodal stimuli. Although fMRI clearly lacks the spatial resolution of single-unit recordings, in many instances there is considerable regional overlap among the different types of representations,[31] centered along the transverse orbital sulcus near areas 11l and 13m (following the nomenclature of Price[64]), suggesting a clustering of different functional properties within the same local territory of the OFC. That this wide range of neural computations can be assigned to human OFC is more than reminiscent of the functional panoply of response types, as discussed above, in rodent OFC.

Human OFC encodes expected olfactory outcomes

Recently published work from our lab[65] provides a theoretical framework to help reconcile the diverse reported findings in human olfactory OFC and to bring the human and rodent olfactory data on the OFC better in line (the relative lack of olfactory studies in monkeys makes it difficult to achieve a trispecies comparison). This section will present our recent work. The next and last section will provide a final synthesis and conclusions.

A key neuroscientific question with relevance for perception, attention, and behavior is whether the brain uses sensory "predictive codes" to anticipate forthcoming sensory events.[66,67] Access to predictive representations, typically acquired via prior knowledge and experience, confers distinct perceptual advantages upon organisms trying to negotiate complex and unpredictable sensory environments. While the topic of predictive coding has generated increasing interest, particularly among the visual neurosciences,[68–71] the underlying assumption that stimulus-specific (or feature-based) codes are unequivocally established prior to stimulus encounter has been difficult to confirm.

Combining an olfactory attentional search task with event-related fMRI and multivariate (pattern-based) analyses, Dr. Christina Zelano in our lab tested the hypothesis that the human olfactory brain establishes predictions of an upcoming smell before its actual arrival.[65] During scanning, healthy subjects were presented on separate trials with either odor A, odor B, or their mixture (AB), and in separate blocks of trials were instructed to search for either the A or B target odor (Fig. 3). This design enabled us to dissociate the identity of the attended target and the identity of the actual delivered odor in a feature-specific way, resulting in six conditions: target A with stimulus A, B, or AB (A|A, A|B, A|AB); and target B with stimulus A, B, or AB (B|A, B|B, B|AB). By comparing conditions with the *target* held constant to conditions with the *stimulus* held constant, we were able to look for target-related and stimulus-related activity patterns and observe how those patterns evolved from pre- to poststimulus. For example, we reasoned that if a given region of interest reflected the targeted note, then the *prestimulus pattern* in response to condition A|A would correlate more strongly to A|B (same target but different stimulus) than to B|A (different target but same stimulus).

Behaviorally, subjects were faster and more accurate in reporting the presence of an odor when it matched the prestimulus target cue (Fig. 3B,C). Analysis of the fMRI pattern data revealed that ensemble correlations between same-target conditions were significantly higher than correlations between different-target conditions in the anterior piriform cortex (APC), posterior piriform cortex (PPC), and OFC (Fig. 3D), in line with the idea that odor-specific prestimulus patterns are present throughout much of the olfactory system. In the OFC and APC, the target specificity of these predictive codes persisted into the poststimulus period, even when the delivered stimulus did not match what was expected (Fig. 3E). By comparison, in PPC, predictive coding prior to stimulus onset gave way to stimulus coding following odor onset. This transformation from predictive to perceptual code selectively in PPC may reflect its unique associative connectivity, with robust access to both bottom-up inputs and top-down cortical feedback that together could provide dynamic state-dependent modulation of odor representations.

The combined behavioral and imaging findings suggest that subjects can generate feature-specific information about an odor prior to its receipt, with a corresponding facilitation of perceptual performance. Interestingly, the magnitude of the prestimulus effect in PPC (but not in APC or PPC) was significantly correlated with task accuracy, indicating

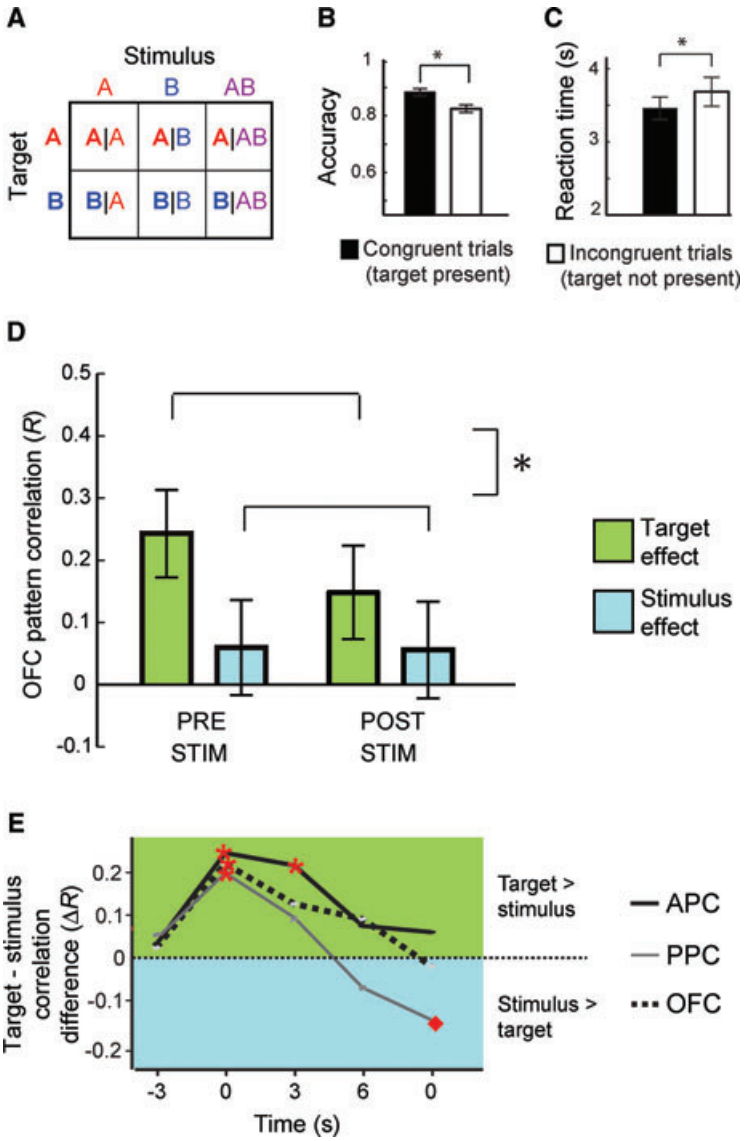

Figure 3. Olfactory predictive coding in human OFC. (A) The experimental design of the fMRI odor search paradigm conformed to a factorial design in which either odorant stimulus (A, B, or AB) or odor target (A or B) was varied. Subjects were informed whether the target was A or B at the start of each fMRI run. (B–C) Subjects performed more accurately (B) and more quickly (C) when the searched-for target was present in the delivered stimulus (congruent trials), compared to when the target was not present (incongruent trials). (D) Ensemble pattern analysis of the fMRI data in the OFC showed that same-target conditions (e.g., A|A compared to A|B) were more correlated than different-target conditions (e.g., A|A compared to B|A), both before and after stimulus arrival. $^*P < 0.05$; error bars, ± SEM. (E) Pattern correlation differences between same-target and different-target conditions were plotted over time, where each point represents the mean over two successive time points. Odor onset began at time 0 sec. Correlation differences in the positive direction signify target-specific effects (green area); those in the negative direction signify stimulus-specific effects (blue area). Target-specific patterns emerged early in the prestimulus period for both the OFC and APC; in PPC, prestimulus target patterns transformed to stimulus patterns after odor onset. Stars, significant target effect; diamonds, significant stimulus effect; $P < 0.05$. Modified from Ref. 65 © 2011, with permission from Elsevier.

that the availability of predictive codes for guiding olfactory perceptual decisions specifically resides in PPC. Another important implication of the study is that in the OFC and APC, ensemble patterns more closely resemble what is being sought out rather that what is being delivered to the nose. The idea that the olfactory system smells what it expects rather than what it sniffs extends early key work by Walter Freeman, which suggested that odor-evoked spatial patterns of EEG activity in the rabbit olfactory bulb reflect the expectations and experiential associations related to the odor, as opposed to representations of the odor per se.[72,73]

Olfactory processing in the OFC: a functional palette for predictive coding

This final section is an attempt to find common ground across the functional response diversity and species differences in the OFC, as refracted through an olfactory lens, or perhaps more fittingly, as decanted through an olfactory sieve.

Let me attempt to reconcile these data by closely comparing two studies discussed above: the Zelano *et al.* 2011 study on olfactory predictive coding in humans[65] and the Schoenbaum and Eichenbaum 1995 study on olfactory discrimination learning in rodents.[12] A passing comparison between the human and rodent studies might overlook much of a similarity, given that the focus of the former is on sensation and perception, whereas the focus of the latter is on learning and reward. However, both cases demonstrate that the OFC encodes expected outcomes in advance of their receipt.

In the Zelano study,[65] the OFC encodes the expected perceptual outcome of an upcoming odor. This representation emerges during presentation of a three-second preparatory cue ("3. . .2. . .1. . .sniff") prior to odor delivery, and continues into the start of the odor-sampling period. Importantly, the cued outcome prediction is highly sensory specific. Information about what outcome to expect (either odor A or B) is established through recent learning and experience, whereby the subjects are introduced to the target odors and their letter designations (A and B) at the start of the experiment and receive specific task instructions about which odor to expect at the start of each experimental block. Behavioral access to the predictive cue enhances the speed and accuracy of olfactory detection of the expected odor.

In the Schoenbaum and Eichenbaum study,[12] the OFC encodes the expected motivational outcome of an upcoming reward contingency. This representation emerges during the *odor-sampling period* (odor cue presentation) prior to reward delivery and continues into the start of the next trial period. Importantly, the cued outcome prediction is highly sensory specific. Information about what outcome to expect (either water or no water) is established through associative learning, whereby over time the rats progressively gain knowledge of the odor–reward contingencies. Behavioral access to the predictive cue enhances the speed and accuracy of olfactory discrimination and increases consumption of water reward.

Actually, the *odor poke period* in the Schoenbaum and Eichenbaum study[12] aligns the human and rodent studies even more closely. Here, it is clear that even when the rats poke their nose into the odor port—but before receiving an odor—there are neurons in the OFC whose firing rates are influenced by the identity of the odor presented in the preceding trial. More impressively, because the panel of eight odorants was delivered to the rats in a sequence containing predictive relationships between certain odor pairs (e.g., odors 5 and 6 were always followed by odor 7), it was possible to show that odor poke cells fired more strongly for predicted (vs. unpredicted) occurrences of upcoming odors (Fig. 4). Thus, by analogy to the Zelano *et al.* findings, the nose poke into the odor port effectively functions as a pre-odor cue that reliably predicts the upcoming odor.

Indeed, in many respects, the multiphasic predictive associations observed between odor poke and odor sampling, odor poke and water poke, odor sampling and water poke, and so on are like a multilayer stack of single-layer predictive codes manifest in the Zelano *et al.* olfactory study. To the extent that the olfactory system is considered one of the more primordial sensory systems and is paramount for behavioral control of feeding, reproduction, threat avoidance, and social interactions in many different species,[74,75] it is reasonable to speculate that orbitofrontal functions that initially evolved to predict odor-cued events have since been appropriated to handle a wider assortment of predictive cues with greater associative flexibility.

The suggestion that the overarching role of the OFC is to predict future events and

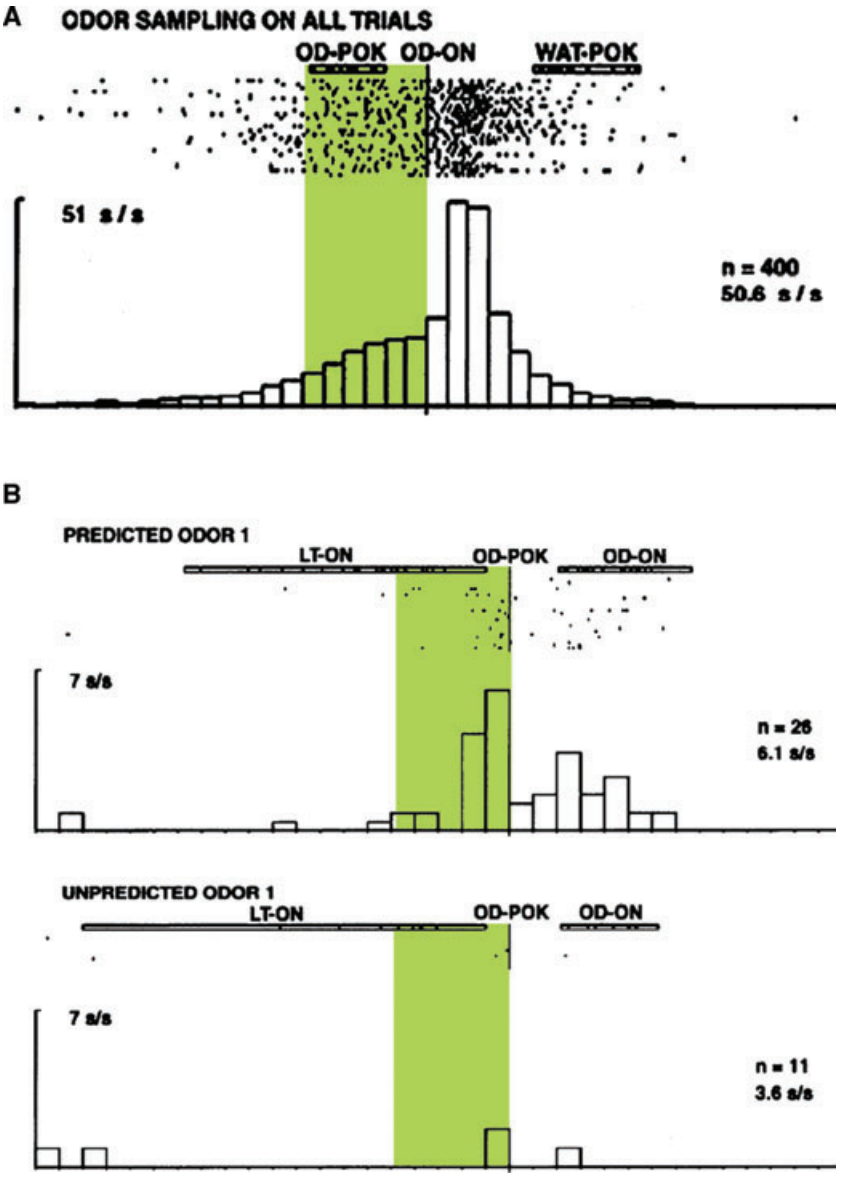

Figure 4. Signaling expected odors in rodent OFC during an olfactory discrimination task. (A) This raster plot (~25 representative trials) and histogram of mean activity (averaged over 400 trials) from an OFC neuron shows that when activity is aligned to the odor sampling period ("OD-ON"), responses already begin increasing during the odor poke period ("OD-POK"), before actual delivery of odor. (B) Neural activity in the OFC during the odor poke period (approximated by the green shading) shows differential firing on trials when the rat was able to predict the forthcoming onset of odor 1 (top), based on prior learned predictive associations within the odor sequence, compared to trials when the rat had no predictive information that odor 1 was to be delivered (bottom). Each time-bin is 100 ms. Modified from Ref. 12, with permission of the authors.

outcomes, as gleaned through this olfactory-based overview, is hardly a novel proposal. However, one appealing aspect of this proposition is that it meshes well with many of the other reported functions of the OFC. That is, the ready availability of different types of representations and mechanisms within the OFC provides a kind of functional palette with which relevant predictive associations can be efficiently assembled and updated:

- the encoding of sensory-specific representations in the OFC would be essential for maintaining the object identity of predictive cues and also of their expected outcomes, surely minimal criteria to ensure formation of reliable cue-outcome associations;
- the encoding of outcome values and rewards in the OFC, and its sensitivity to motivational and physiological states, would be important for regulating the impact of predictive cues on goal-directed behavior, in line with an animal's current needs;
- stimulus-specific predictive coding in the OFC, before stimulus onset, would present opportunities for assigning and comparing outcomes and events to their antecedent cues; and
- multisensory integration of cross-modal sensory inputs in the OFC would provide a useful mechanism for generating links between cues and outcomes, which are typically derived from different sensory modalities.

Together, these mechanisms ensure that the behavioral significance/value of the outcome retains its links to the predictive cue in an identity- or stimulus-specific manner. This broad conception of OFC function marks a subtle shift away from the overzealous emphasis on outcome value coding per se. It is perhaps quite likely that abstract values of different stimuli (commodities), generated under stimulus-free (model-free) conditions in a feature-irrelevant (goods-based) space, are encoded in the OFC. However, it cannot be ignored that in the absence of feature-based sensory-specific information about cues, commodities, and outcomes, such abstract value representations become neutered of an identity, with the risk of crediting value to their antecedents erroneously. Future neurobiological models will need to incorporate the elements of stimulus specificity and object identity into value-based models in order to provide a fully comprehensive account of OFC function.

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Conflicts of interest

The authors declare no conflict of interest.

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