The fundamental role of memory in olfactory perception

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Current emphasis on odorant physiochemical features as the basis for perception largely ignores the synthetic and experience-dependent nature of olfaction. Olfaction is synthetic, as mammals have only limited ability to identify elements within even simple odor mixtures. Furthermore, olfaction is experience-bound, as exposure alone can significantly affect the extent to which stimuli can be discriminated. We propose that early analytical processing of odors is inaccessible at the behavioral level and that all odors are initially encoded as 'objects' in the piriform cortex. Moreover, we suggest that odor perception is wholly dependent on the integrity of this memory system and that its loss severely impairs normal perception.

Olfactory discrimination of apples from oranges is a remarkable feat easily performed by most vertebrates and invertebrates. Understanding how such a feat is accomplished is the major focus of olfactory neuroscience. Traditionally, the first step in addressing this question has been to identify differing component features of the two stimuli and then to characterize neurons within the olfactory system that recognize and discriminate those features. For example, this approach has been highly successful for dissection of visual processing (e.g. Ref. [1]). Along this line, current work suggests that specific features of odorant molecules are recognized by members of a large family of receptor proteins [2]. A spatial representation of odorant features is created through precise receptor projections to olfactory bulb glomeruli [3–7]. This spatial representation is enhanced by convergence and lateral synaptic interactions within the olfactory bulb [8,9], resulting in olfactory bulb output neurons (mitral cells) with feature-detecting receptive fields [10]. Thus, odorants and odor mixtures appear to be processed analytically by the olfactory system.

However, this perspective is at odds with a growing body of evidence, from both psychology and neurobiology, which places primary emphasis on synthetic processing and experiential factors, rather than on the structural features of the stimulus, as crucial for odor discrimination. By synthetic processing, we refer to the fact that mammals have generally very limited ability to identify components within odor mixtures (or sub-molecular features of monomolecular odorants) and, rather, treat mixtures as single perceptual wholes. Thus, we propose that analytical feature discrimination is only an initial necessary step in what is ultimately a largely synthetic process in mammals. Furthermore, we suggest that, in contrast to other synthetic perceptual processes such as visual facial recognition, olfactory feature extraction and analytical processing are largely inaccessible at a behavioral or conscious level. Finally, we claim that memory and neural plasticity (perceptual learning [11,12]) play a fundamental role in odor synthesis and, thus, in odor discrimination and perception.

Synthetic olfactory perception

Synthetic odor processing is suggested by two types of finding. The first derives from experiments in which human participants are asked to identify the component parts of odor mixtures. Having first learned the labels for each of the odorants to be mixed, participants are presented with mixtures consisting of two or more constituents. Using a variety of different methods, participants can rarely identify an individual odor as being present when the mixture consists of three or more components [13]. Moreover, this identification ceiling is impervious to variations in the task [e.g. using 'poor-blending'- or 'well-blending' odors; using odor objects (e.g. cheese) or pure chemicals (e.g. skatole); or using different identification tasks) and is, crucially, the same in odor experts (perfumists and flavorists) as it is non-experts [13] (Fig. 1a). These findings are supported by related studies of odor complexity, in which various measures of complexity, both qualitative and behavioral, also reach a ceiling with three or more components [14]. In summary, these findings, along with similar results from animal studies [15], suggest that olfactory processing is mainly synthetic at the behavioral level.

Memory and olfactory perception

Several lines of evidence show that olfactory perception is also heavily dependent on learning and memory. First, participants are initially poor at discriminating unfamiliar odors from each other, but they improve rapidly with exposure [16,17]. Second, the qualities that are described by participants when smelling an odor can be acquired. In a series of studies we have shown that unfamiliar odors paired with sweet tastes are thought to smell sweeter, and those paired with sour tastes, sourer [18]. A similar effect occurs if a familiar and an unfamiliar odor are mixed

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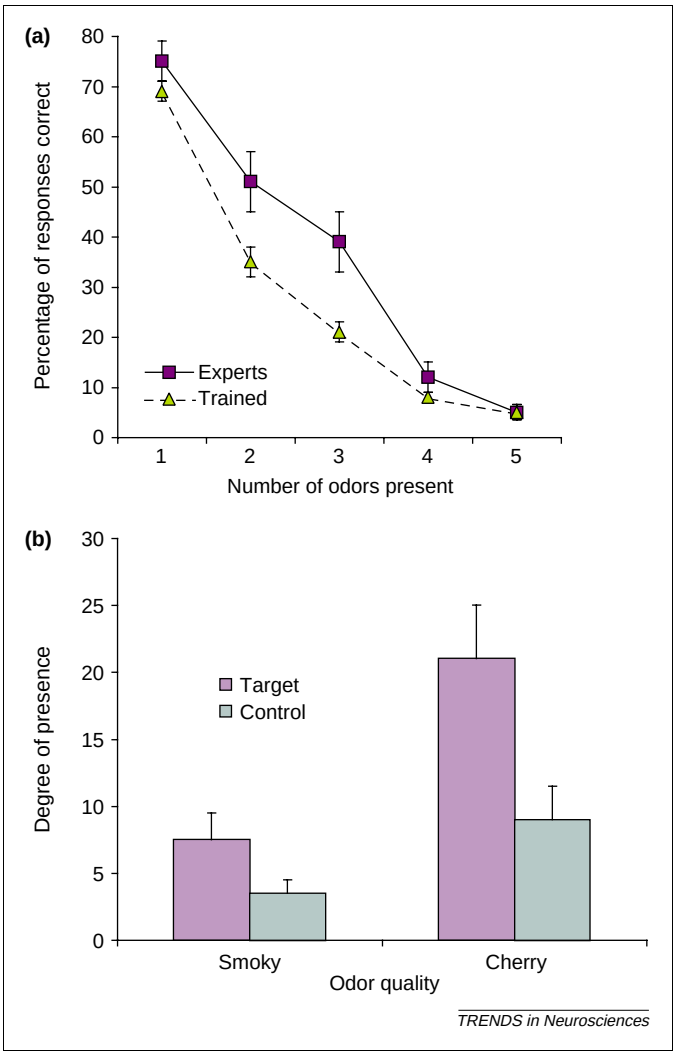

Fig. 1. Human olfactory processing is largely synthetic and highly dependent on past experience. (a) Expert flavorists and perfumists, and 'trained' novice participants (who learned the names of the odors), exhibited the same identification ceiling for odor discrimination, suggesting an absolute limit on identifying the components of odor mixtures. Note that the expert participants are, however, significantly better at identifying the components of two- and three-component odor mixtures. Adapted from Ref. [13]. (b) Odors can acquire characteristics from other odors. Here, a target odor experienced in a mixture with smoky-smelling guaicol smells smokier than a control odor. Likewise, a target odor experienced in a mixture with cherry smells more cherry-like than a control odor. Data from Ref. [20].

together. In such cases, the odors appear to acquire the characteristics of each other: thus, a smoky smelling odor mixed with a cherry odor can later result in the smoky odor smelling more cherry-like and the cherry odor smelling more smoky [19,20] (Fig. 1b). Third, such qualitative changes directly translate into differences in 'discriminability' [21]. Thus, when two odors have been mixed together, the two components become harder to tell apart. Fourth, a considerable body of evidence suggests that olfactory perceptual experts, particularly wine tasters, are better at discriminating between wines even in the absence of the linguistic skills associated with formal wine training [22,23] (Fig. 1a). Thus, in summary, mere exposure to odors can in certain cases enhance and in others cases reduce discriminability and, as a result, alter the characteristics that are reported when describing a smell. All these effects can occur rapidly and are long lasting [24].

The findings that odor percepts are synthetic and that odor quality and discriminability can be markedly affected by experience suggest a rather different type of information processing system from one in which the physiochemical properties of the stimulus dictate wholly the perceptual quality and discriminability. This point is made most strongly by human neuropsychological findings that suggest a primary reliance on intact odor memory for successful odor discrimination and perception of odor quality. The most telling example is that of the amnesiac H.M., who received bilateral resection of his medial temporal lobes, including the piriform cortex, as a treatment for intractable epilepsy. H.M. is readily able to distinguish the same odor presented at different concentrations and two qualitatively different odors presented at different concentrations [25]. However, H.M. is totally unable to discriminate qualitatively different odors when intensity cues are removed. In other words, to H.M., all odors smell alike. Similar findings have emerged from the study of other conditions that are known to affect memory, for example Korsakoff's syndrome [26]. In this syndrome, and in similar conditions, poor qualitative discrimination of odors can be observed independent of any changes in the ability of participants to detect the presence and intensity of odorants [27,28]. Taken together, these findings point to a synthetic perceptual system based primarily on learning and memory [24].

Olfactory sensory physiology

The relative behavioral inaccessibility of odorant features or odor-mixture component information, compared with the analytical abilities of other sensory systems, might reflect the unique shortened receptor-to-cortex pathway of the olfactory system (there is no thalamic relay between second-order neurons and the primary sensory cortex). In addition, or alternatively, it might reflect coding strategies required for processing of complex, dynamic olfactory stimuli that do not contain within themselves spatial information that could assist in perceptual grouping. Some aspects of synthetic coding could begin at the receptor itself, through ligand–ligand interactions with the receptor protein [29]. It is still unclear what constitutes an odorant feature [30,31], although one can assume that features correspond with ideal physiochemical ligands for receptor proteins. Thus, features could vary in their complexity from specific carbon chain lengths and functional groups to, perhaps, specific combinations of these more simple components. Whatever constitutes an odorant feature, however, glomeruli and second-order-neuron mitral cells appear to function as feature detectors, refining the feature information through lateral and feedback inhibition [8,9] and excitation [32]. A second opportunity for feature synthesis appears in the activity of mitral cells, where temporal binding of simultaneously active cells (via synaptic interactions on the expansive lateral dendrites of inhibitory granule cells) can lead to precise temporal synchrony of co-active cells that are potentially activated by different features or mixture components [33,34] (see Refs [35,36] for a discussion of similar processes in invertebrates).

This sort of dynamic synchrony of co-active cells is not, however, sufficient to account for both aspects of olfactory

behavior; that is, the highly synthetic processing of odorants and complex mixtures, and the limited ability to discriminate odorants from background odor or to analyze simple mixtures (Fig. 2). If synthetic coding were due entirely to ligand–ligand interactions at the receptor and temporal synchrony of co-active mitral cells, it is unclear whether the simple discrimination of odorants from background odors or the analysis of simple, binary mixtures could occur – yet they do [13] (Fig. 1a). Long-term experience-dependent plasticity can occur in mitral-cell receptive fields [37,38] but we propose that these changes reflect primarily the fine-tuning of feature processing.

Cortical mechanisms of olfactory perceptual learning

Based on new data that extend the theoretical work of previous investigators [39–42], we propose that the olfactory bulb circuitry creates odor-specific spatial–temporal patterns that are synthesized and stored in the piriform cortex through Hebbian synaptic plasticity (Fig. 3). The anatomical basis for such synthesis exists both in the projection of mitral cells conveying receptor-specific input that converges in overlapping terminal patches on the anterior piriform cortex [43] and, perhaps more importantly, through the extensive intracortical association-fiber system [44]. Experience with an odor (or odor mixture) in a variety of conditions allows that odor-specific activity pattern to be synthesized as a unique perceptual whole through cortical synaptic plasticity and, furthermore, allows that pattern to be subsequently recognized against other background patterns of activity or during partial input degradation [39,45]. This latter phenomenon could, in some cases, result in acquired perceptual properties for components of mixtures [18,20]. Without initial learning, or in the presence of complex additional inputs (e.g. as a component in a complex mixture), the learned pattern cannot be extracted and identified. Learned changes within the piriform cortex might not only modify the responses of the cortical neurons directly but also, via the extensive cortical feedback to the olfactory bulb [46], help to shape subsequent mitral and tufted cell response patterns – similar to the role of cortico–thalamic projections in other sensory systems [47,48]. Thus, in this model, as in the behavioral findings described above, learning and memory have a crucial role in basic odor discrimination.

This model has led to several testable predictions [49]. First, single neurons within the anterior piriform cortex should express enhanced ability to discriminate between familiar odors within their receptive fields compared with feature-detecting mitral cells. That is, each familiar odor should be treated as a unique odor object by the piriform cortex. Second, the enhanced odor discrimination in the piriform cortex should require some previous experience with the odorants. Third, the enhanced odor discrimination in the piriform cortex should be disrupted by manipulations that disrupt normal synaptic plasticity. Finally, the same manipulations that impair synthesis within the piriform cortex should impair experience-dependent enhancement in behavioral odor acuity (perceptual learning). In a recent series of experiments using a cross-habituation paradigm to determine odor discrimination at the single-unit and behavioral levels in rats, each of these predictions have been borne out. Thus, single-units of the piriform cortex discriminate (show little cross-habituation) between familiar odorants within their receptive fields, whereas mitral and tufted cells do not [50]. In fact, mitral and tufted cells appear to respond to both binary mixtures and their components based on the presence of a single overlapping feature, whereas piriform

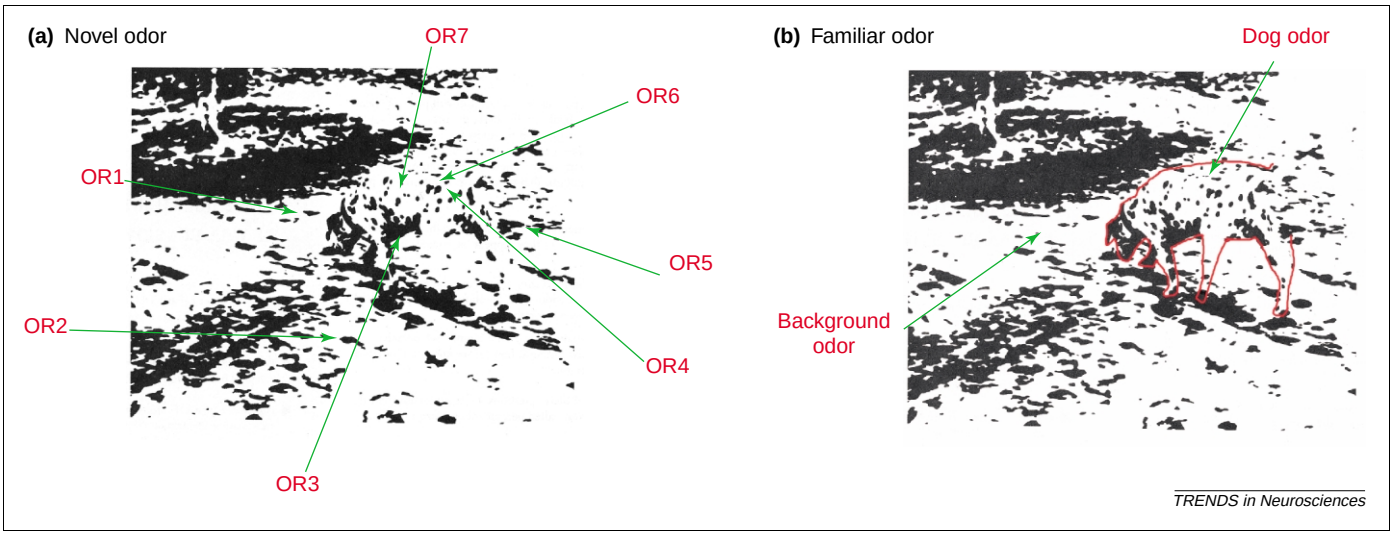

Fig. 2. Olfaction faces a similar problem to that involved in visual perceptual grouping – that is, from a large set of co-occurring stimulus features, some features must be grouped into perceptual objects distinct from other objects or the background. In vision, this perceptual grouping is facilitated by experience: once the observer has experience of grouping the features in the image, in this figure into a dog against a background (b), it is much easier to recognize those features as a dog (single perceptual object) in (a). It is also possible to group other features in this image into a tree and perhaps some other objects in the background. Olfactory perception is also highly synthetic (i.e. very effective at merging multiple stimulus components into a unique odor percept); however, in contrast to vision, olfactory perception is largely ineffective at stimulus analysis (i.e. at recognizing multiple individual perceptual objects in a complex mixture). This combination of perceptual characteristics might be due in part to the shortened olfactory pathway and/or the lack of a spatial dimension in olfactory stimuli that could facilitate grouping. Thus, this figure represents odorant features identified by individual olfactory receptors (OR) during an inhalation. We propose that prior experience with dog-odor allows synthetic processing within the piriform cortex of multiple features into a single dog-odor percept, distinct from the background.

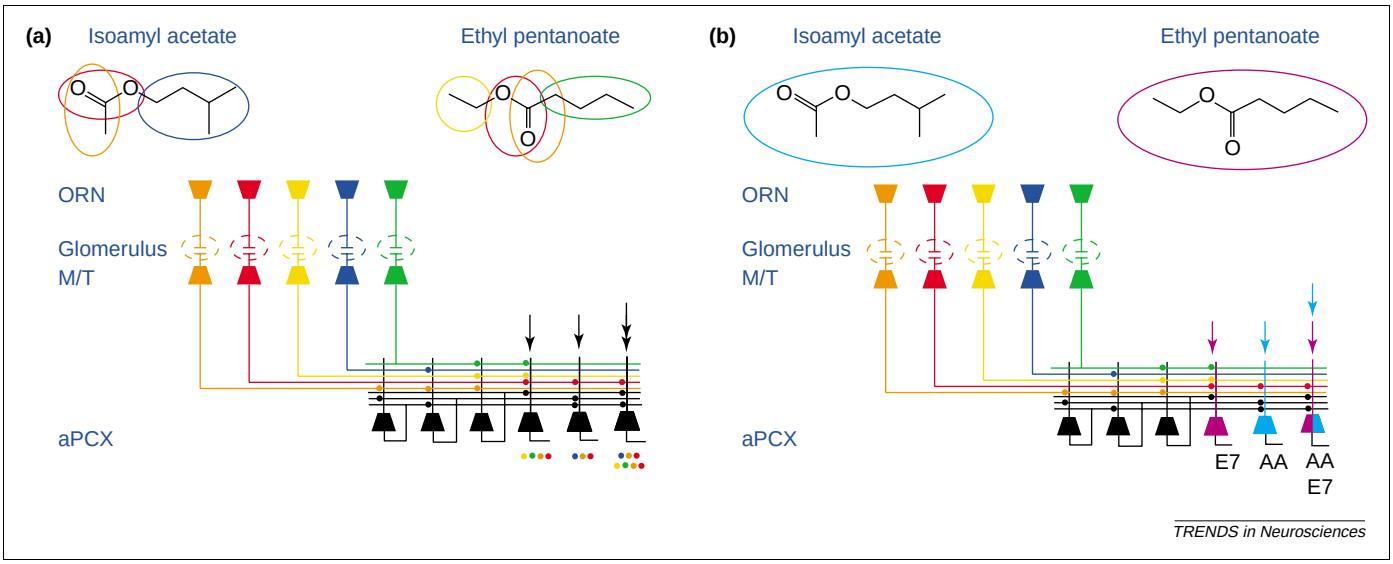

Fig. 3. Recent olfactory sensory physiology is consistent with a view of olfactory bulb mitral cells serving a largely feature-detection role in odor processing and neurons in the anterior piriform cortex (aPCX) serving as synthetic processors, capable of learning unique combinations of feature input associated with specific odors. (a) In response to a novel odor, neurons of the piriform cortex function largely as coincidence detectors for co-active feature input from mitral and tufted (M/T) cells [color-coded for the type of feature input they receive from the olfactory receptor neurons (ORN)]. As coincidence detectors, they might not be efficient at discriminating different odors within their receptive fields. (b) After rapid perceptual learning and plasticity of association and/or afferent synapses, single neurons of the piriform cortex respond to odors as a whole, which allows enhanced discrimination between odors within their receptive fields and allows maintained responsiveness to partially degraded inputs. The odorants in this example are isoamyl acetate (AA) and ethyl pentanoate (E7), although the model also applies to mixtures of multiple odorants.

cortical neurons respond to familiar binary mixtures and components as different, unique odor objects (synthetic coding) [51,52]. That is, in the anterior piriform cortex, habituation to a binary mixture produces little cross-habituation of the components, whereas mitral and tufted cells show strong cross-habituation between mixtures and their components [51,52]. This enhanced discrimination in the piriform cortex is expressed only after at least 50 s of familiarization with the odor or mixture – 10 s of exposure is insufficient [52]. Cortical application of the ACh muscarinic receptor antagonist scopolamine, which disrupts normal piriform cortex synaptic plasticity [45,53], reduces odor discrimination by piriform cortical units to a level similar to that expressed by mitral cells, while having no impact on odor responses themselves [54]. Finally, as already noted, previous experience with an odor can enhance subsequent behavioral discrimination of that odor from similar odors in humans [16,17] and rats [55,56]. In rats, this behavioral olfactory perceptual learning can be disrupted with scopolamine [55] and odor discrimination can be enhanced by the ACh receptor agonist physostigmine [57].

Concluding remarks

Together, these new behavioral and neurophysiological results show a strong synthetic component to odor discrimination that is inconsistent with a highly analytical, feature-detecting system. Cortical synthetic processing has the adaptive advantage of allowing identification of, and discrimination between, a broad range of complex odorants containing novel combinations of features, in addition to allowing recognition of partially degraded familiar inputs. Thus, rapid perceptual learning, based on enduring changes within olfactory cortical regions such as the piriform, and perhaps orbitofrontal, cortex [58–60] plays a crucial, defining role in odor discrimination at both the neural and the behavioral levels.

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