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The perceptual logic of smell

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Mammals have ~1000 different olfactory receptor subtypes, each responding to a number of different odorants, and each odorant activating a number of different receptor subtypes. These molecular and anatomical underpinnings of olfaction imply a perceptual structure of very high dimensionality that relies on combinatorial coding. In contrast to this expectation, the study of olfactory perception reveals a structure of much lower dimensionality. Moreover, a low-dimensionality approach to olfaction enabled derivation of perception-based structural metrics for smell. These metrics provided meaningful predictions of odorant-induced neural activity and perception from odorant structure alone. Based on this low functional dimensionality, we speculate that olfaction likely does not functionally rely on 1000 different receptor subtypes, and their persistence in evolution may imply that they have additional roles in non-olfactory functions such as in guidance of embryogenesis and development.

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Exactly one hundred years ago, Alexander Graham Bell asked: ''Can you measure the difference between one kind of smell and another? It is very obvious that we have very many different kinds of smells, all the way from the odor of violets and roses up to asafetida. But until you can measure their likenesses and differences you can have no science of odor'' [1].

At the heart of Bell's statement is a quest for a formulated link between odor structure and odor perception. Whereas we argue that formulating such a link must start with measurements of perception, recent research in olfaction has rather concentrated on the underlying molecular and systems-level brain organization subserving the sense of smell. This has taught us a lot about olfaction, but has not answered Bell's question. Here we will first briefly highlight the key principals in molecular and systems-level brain organization of olfaction. Next, we will outline a theoretical approach that argues that the structure of perception holds in it the structure of stimulus space and the structure of neural space. With this theory in mind, we apply dimensionality reduction techniques to olfactory perceptual data, and link the perceptual dimensions we identify to odorant structural dimensions. This generated an olfactory metric that links odorant structure to odorant perception, thus providing a solution to Bell's query. Finally, we will consider implications of this solution regarding the underlying brain organization of olfaction and beyond.

The molecular logic of smell

Mammalian olfaction relies on a stereotyped neuroanatomy consisting of a receptive surface termed the olfactory epithelium in the nose, which projects to the olfactory bulb in the brain, that in turn projects to extensive cortical substrates. In the late 1980s and early 1990s, a surge in olfaction research centered on intensive exploration into the molecular mechanisms of olfactory transduction in olfactory epithelium in the nose. The picture that emerged from this effort was summarized in a 1995 review entitled ''The molecular logic of smell'' by Richard Axel [2], and the basic principals outlined then have mostly survived the test of time [3••]. Initial evidence implied that olfactory transduction occurs at the ciliated endings of millions of olfactory receptor neurons that line the olfactory epithelium, and that it relies on a second-messenger cascade [4], suggesting commonality with visual transduction [5]. Buck and Axel (1991) finally identified the gene family that encodes for olfactory receptors [6], and these were indeed 7-transmembrane G-protein coupled second-messenger receptors. Here, a cascade of events that starts with odorant binding culminates in the opening of cross-membrane cation channels that depolarize the cell. However, unlike visual transduction that largely relies on two sensor types, one of which comes in three flavors (RGB), mammalian olfaction relies mostly on one sensor type that comes in ~1000 flavors (a small number of an additional type of receptor called trace amine-associated receptors, or TAARs, also plays a role in olfaction [7•]). In other words, a good few percent of the mammalian genome is devoted to encoding olfactory receptor subtypes. In vitro studies implied that each receptor subtype responds to several different odorants, and each odorant activates several different receptor subtypes [8]. The binding affinity of a given odorant to a given receptor subtype likely reflected specific structural aspects of the odorant [9]. Moreover, each olfactory sensory neuron typically expresses only one of these receptor subtypes. Whereas only minimal

spatial order was identified in the expression pattern of these receptor subtypes in the epithelium, all receptors of a common subtype then converge onto one of two mirror locations on the olfactory bulb, termed glomeruli [10]. This implied an appealing solution for olfaction where the brain would ''read out'' a map of olfactory receptor subtype activation off the surface of the olfactory bulb [11,12•,13]. Given that each receptor subtype responds to several different odorants, and each odorant activates several different receptor subtypes, the combinatorial repertoire of such a map is enormous. Moreover, the dynamic development of the neuronal response adds a temporal component to the representation [14], culminating in a spatiotemporal code for olfaction at the olfactory bulb. That said, given that the projections from olfactory bulb to olfactory cortex seem largely disordered, how the brain reads this spatiotemporal representation remains unclear. The primary notion holds that this link from bulb to cortex remains highly plastic, completely based on associative learning, which may form the basis for olfactory perception in olfactory cortex [15,16•,17].

After achieving the above detailed molecular understanding of olfaction, it was largely assumed that a formulated link between odor structure and odor perception would soon follow. All that was needed was the admittedly painstaking task of independently expressing each receptor subtype in a dish, and then challenging it with batteries of odorants in order to characterize its receptive range. This, however, did not occur. Olfactory receptors proved highly resistant to expression in hetrologus tissue. Only recently has this technical limitation been partially overcome, allowing a slow but steady deorphaning of olfactory receptor subtypes [18,19]. One of the best-characterized cases is that of a receptor named OR7D4, which responds to the odorant androstenone. Androstenone psychophysics are rather unusual. Whereas most of the population perceives it as a sweaty and rather unpleasant smell, a proportion of the population perceives it as very mild and pleasant, and an additional proportion cannot smell it at all, and are referred to as ''androstenone anosmic''. Such anosmic individuals indeed had particular variants of OR7D4 [20]. Similarly, the receptors OR11H7P and OR10G4 respond to isovaleric acid and guaiacol respectively, and indeed, polymorphisms in each alter human perception of their respective ligands [19,21]. Together, these studies confirm that an individual's OR gene repertoire influences their olfactory perception. Despite all this, a comprehensive predictive framework linking odorant structure to odorant perception remains lacking. In other words, despite this molecular understanding, no scientist or perfumer can look at the structure of a novel compound and predict its odor, or smell a novel odor and predict its structure. Notably, a debated alternative theory regarding the molecular events at the heart of olfactory transduction proposes that olfactory receptors are not primarily selective for the physicochemical shape of odorants but rather for their intramolecular vibrations [22]. Although recent evidence implies that a molecule's vibrational mode may have an impact on its ultimate odor [23,24], the mechanisms of this remain poorly understood.

The anatomical logic of smell

Initially, research on peripheral events in olfaction centered on potential structural factors in the nose that may contribute to odorant discrimination and classification. The above detailed discovery of the olfactory receptors diverted attention from such structural factors, yet they remain potentially impactful for olfactory perception. The influence of such anatomical considerations was summarized in a 2005 review entitled ''The anatomical logic of smell'' by Schoenfeld and Cleland [25], and the basic principals outlined then have also mostly survived the test of time. A mucus membrane protects the olfactory epithelium, and different odorants will sorb to and cross this membrane at different rates [26]. Thus, one can classify odorants by sorption, allowing for high-sorption or low-sorption odorants. These odor-specific differences in sorption are tightly linked to solubility in water, but reflect additional factors as well. Specific odorant sorption rates then interact with nasal airflow rates to produce different odorant dispersion patterns on the olfactory epithelium. Given that nasal airflow in long-nosed macrosmatic mammals such as rodents is mostly laminar, if a high-sorption odorant is sniffed at low nasal airflow, it will mostly sorb at the initial phase of the flow path. In contrast, the same odorant at high nasal airflow will be more uniformly distributed and sorbed along the flow path. In turn, a low-sorption odorant at low nasal airflow will also be relatively uniformly distributed and sorbed along the flow path, yet the same low-sorption odorant at high nasal airflow will disperse with minimal sorption all together. Thus, the combination of nasal structure, nasal airflow, and odorant sorption together potentially give rise to a chromatographic-like component in olfactory transduction [26,27••]. Although some studies have questioned this model [28], others support it, finding that rodents adjust sniff parameters to optimize perception as a function of sorption [29]. Moreover, humans often have different airflow in each nostril, and this combines with odorant sorption to generate different olfactory perception in each nostril [30]. In other words, nasal anatomy combines with sampling strategy to form a strong force in olfactory perception [31]. Clearly, the impact of such a mechanism would be greater if receptor subtypes would be ordered rather than disordered along the epithelial surface, and several lines of evidence imply that this is indeed the case [32]. All that said, despite the combined molecular and anatomical understanding of the system, Bell's challenge remains largely unmet.

The perceptual logic of smell

''Thus, even if in their qualities our sensations are only signs whose specific nature depends completely upon our

make-up or organization, they are not to be discarded as empty appearances. They are still signs of something — something existing or something taking place — and given them we can determine the laws of these objects or these events. And that is something of the greatest importance!'' Hermann Helmholtz (1878) [33].

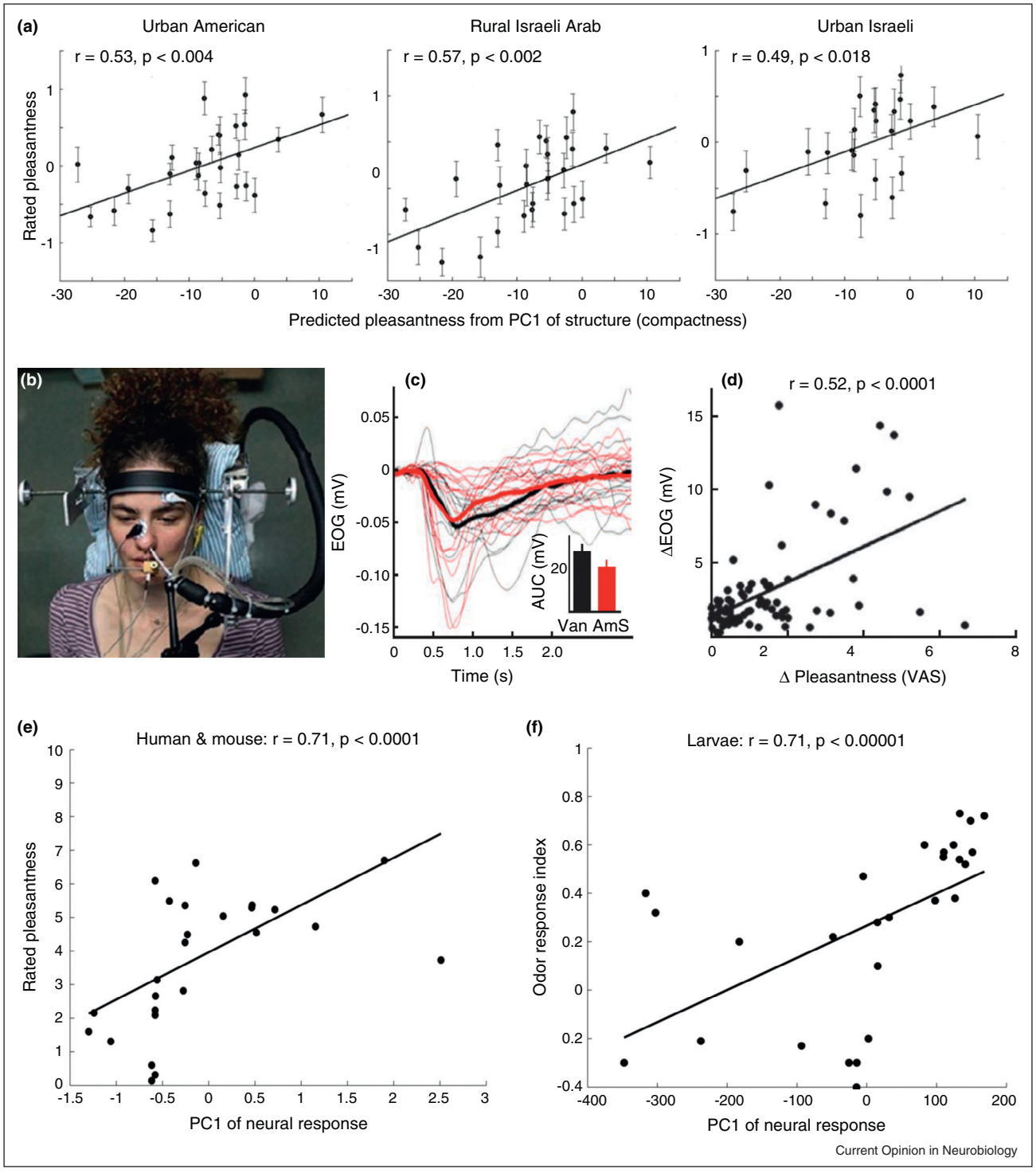
What Helmholtz is telling us is that by studying olfactory perception we may gain important insight into the organization of the physical world of odor (''the laws of these objects'') and the biological world of olfaction (''the laws ... of these events''). With such thinking in mind, several pioneers of olfaction concentrated on quantifying olfactory perception during the 1970s–1980s. This direction has recently reemerged, yet now with the help of modern statistical methods, and modern tools for odorant chemical characterization [23,34–43]. Our own efforts in this direction started with reanalysis of a previously collected dataset, namely the Atlas of Odor Character Profiles amassed by Andrew Dravnieks and colleagues in the 1980s [44]. This text contains numerical ratings provided by ~150 ''experts'' who rated 138 monomolecular odorants along 146 verbal descriptors (e.g. ''flowery''; ''tar like''; ''almond like''; ''sickening''; etc.). We hypothesized that the functional dimensionality of this data is lower than its apparent dimensionality of 146, and therefore applied principal components analysis (PCA). PCA takes data consisting of N points in an M-dimensional space (e.g. 138 odorants in the 146-dimensional odor descriptor space) and finds a rotation matrix that rotates the N points onto a new M-dimensional space such that the new dimensions, called principal components (PCs), successively explain a maximal portion of the variance. Thus PC1 explains the most variance of any linear transform applied to the original data space, PC2 explains the biggest amount of the remaining variance, and so on. The application of PCA to the Atlas of Odor Character Profiles uncovered two important facts: First, a small number of PCs explained the majority of variance in the data, with ~30% of the variance explained by the first PC (PC1) alone. In other words, in contrast to the notion of a high-dimensional percept, this implied a low-dimensional olfactory percept dominated by one perceptual axis. Second, and consistent with numerous previous studies [45], the primary dimension of olfactory perception (PC1) reflected odorant *pleasantness*, that is, an axis ranging from very unpleasant to very pleasant [39]. The primacy of this perceptual axis is further borne out in its mapping onto activity patterns in the human olfactory epithelium [46]. Moreover, it is likely not limited to human olfaction alone, as evidenced in the identification of receptors that are specific for aversive odors in rodents [7•], identification of aspects on the rodent olfactory bulb that are innately tuned to aversive odorants [47], and identification of valence as a coding axis in the fly brain [48].

Next, we used modern analytical chemistry software to obtain ~1600 chemical descriptors for each of ~1500 odorant molecules. Again, hypothesizing that the functional dimensionality of this data is lower than its apparent dimensionality of ~1600, we applied PCA, and again characterized a small number of PCs that explained a large proportion of the variance in the data. Moreover, PC1 of odorant structure, which also explained ~30% of the variance, was strongly influenced by molecular size and compression, and we tentatively refer to it as *compactness*. We next asked whether any of the PCs of perception were correlated with any of the PCs of structure. Strikingly, we identified such a privileged correlation between PC1 of perception (*pleasantness*) and PC1 of structure (*compactness*) [39]. In other words, the primary dimension of olfactory perception is linked to a fundamental physical regularity in nature [37,39]. This link allowed us to develop an algorithm that cross-culturally successfully predicts a modest but significant portion of odorant pleasantness from odorant structure alone [39] (Figure 1a).

Whereas the above is consistent with Helmholtz's view on perception as a window to understanding odorant structure, what about perception as a window to understanding neurobiology of olfaction? Given that PC1 of odorant structure also predicted behavior in mice [49], we next asked whether it is reflected in animal neural activity. We collected neural response data from 12 published data sets using seven species [50]. Neural recordings are multidimensional in space and time, and again assuming that functional dimensionality is lower than apparent dimensionality, we applied PCA. Again, we found that a small number of PCs explained the majority of the variance in neural activity. Moreover, we found that PC1 of neural activity, which explained ~25% of the variance, reflected overall neural response magnitude. In other words, in contrast to the notion of a high-dimensional combinatorial neural code underlying olfaction, this implied that a simple neural code may underlie much of olfactory computation. We next asked whether this axis of neural activity is related to olfactory perception. We found that PC1 of neural activity was related to PC1 of odorant perception, which we recall is related to PC1 of odorant structure [50]. In other words, the primary dimension of odorant structure (*compactness*) is coded in the primary dimension of odorant-induced neural activity (total neural response) that is reflected in the primary dimension of olfactory perception (*pleasantness*). These relations allowed us to generate modest but significant predictions across odorant structure, odorant-induced neural activity, and odorant-induced perception (Figure 1b–f).

In the above analyses we represented each odorant with a single value reflecting its structure. We arrived at this value by first generating a multidimensional representation of the odorant across ~1600 structural features, and then reducing this to a single value with PCA. This single value, namely projection on PC1, or *compactness*, proved to

Figure 1



Predicting odor perception and odorant-induced neural activity from odorant structure. **(a)** An odorant metric based primarily on PC1 of odorant structure serves to predict odorant pleasantness across cultures [39]. Each dot is an odorant. **(b)** A non-invasive stereotactic device allows recording an odorant-evoked response directly from the human epithelium [46]. **(c)** Individual and average responses to the odorants vanillin and ammonium sulfide in human subjects [46]. **(d)** The difference in pleasantness across 18 odorants predicted the difference in neural response at the epithelium of human subjects [46]. Each dot is a comparison of two odorants. **(e)** PC1 of neural response measured in human and mouse olfactory receptors in a dish predicted pleasantness of the odors as estimated by human raters [50]. Each dot is an odorant. **(f)** PC1 of neural response predicted the behavior of approach or withdrawal in larvae [50]. Each dot is an odorant.

be a reasonably useful olfactory metric in that it allowed us to compare between odorants and their induced perception and neural activity. PCA, however, is not the only way to represent a multidimensional odorant structure. For example, the single chemical variable of ''molecular complexity'' successfully predicted the number of discreet olfactory notes, or perceptual complexity attributed to an odorant [38]. Alternatively, a single value reflecting a molecules vibrational spectra predicted responses in olfactory receptors of flies [23]. Another alternative is to continue representing each odor using many structural features (e.g. ~1600), and then compute the distance between any two odorants by the square root of the sum of squares of the differences between the descriptors. This is referred to as Euclidean distance. We found that Euclidean distance effectively predicted the difference in neural response induced by any two odorants [41]. Moreover, using this approach one can optimize the number of features needed, that is, ask which of the ~1600 physicochemical features we modeled are most important in the olfactory response. This allowed derivation of various optimized descriptor lists that further improved predictions, albeit in a species-specific manner [18,41].

All of the above constitutes an initial effort to generate a metric space for olfaction, but has this brought us any closer to answering Bell's question posed at the outset? Whereas the above efforts were all using monomolecular odorants, the real olfactory world that contains rose, violet, and asafetida, is made of mixtures often containing hundreds of components. How can one apply a single metric value to such mixtures? We tested two alternatives: one was comparing between mixtures by conducting all the pairwise Euclidian comparisons between all molecular components in both mixtures (Figure 2a), and the other was to first generate a single vector reflecting the mixture (e.g. by normalized summation), and then compare the single vectors (Figure 2b). We compared the single vectors by measuring the angle between them, generating what we refer to as the ''angle distance metric''. We found that only the latter approach provided valid predictions of odorant mixture perceptual similarity based on odorant mixture structure [40] (Figure 3a). This is consistent with the view of how the mammalian brain treats odors: synthesizing a singular odor percept for an odorant-mixture rather than analytically extracting individual odorant features reflecting mixture components [16]. The above outcome had two implications: First, the averaging involved in the metric calculation implied that as one adds more and more components that span olfactory space to each of two mixtures, these mixtures should smell more and more similar to each other, despite sharing no components in common. This trend continues to a point where all mixtures are predicted to smell the same. We called this point *olfactory white*, and obtained experimental data to support its existence [51]. A second implication of this result is that it allowed answering Bell's question. We computed the distances between rose, violet, and asafetida, and per Bell's challenge, accurately predicted their ''likenesses and differences'' (Figure 3b). To conclude this path, we used perception to generate physicochemical metrics for smell. These metrics predicted modest but significant portions of perception and neural activity. The current best-performing metric is the one we refer to as the ''angle distance metric'' [40], yet this is likely not the final step in the evolution of these metrics. For example, the current metric does not account for component concentrations and intensities within a mixture, and this remains a critical necessary step for olfactory metrics in the future.

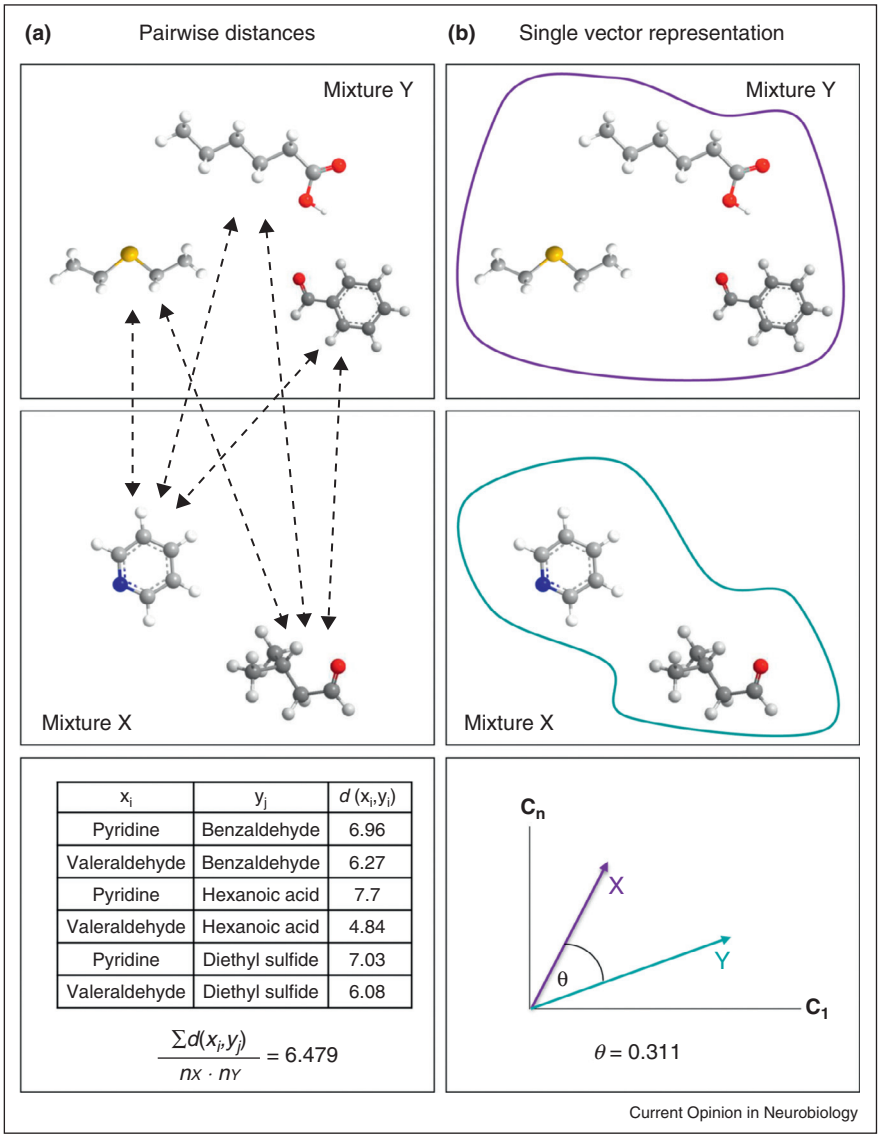
Implications of the perceptual logic of smell

A recurrent theme in the current understanding of olfaction is its multidimensionality, which follows from the enormous combinatorial repertoire provided by the system. Indeed, given ~1000 receptor subtypes, each responsive to a number of different odorants, and each odorant activating a number of different receptor subtypes, olfactory perceptual space is potentially ~1000-dimensional. We find that this multidimensionality, however, is not borne out in perception or behavior. This is not limited to human olfaction, where the one dimension of odorant pleasantness explains a significant portion of perceptual variance. For example, flies have notorious olfactory capabilities. Unwrap a sandwich in the middle of the desert, and a fly will show up. This implies incredible olfactory detection, discrimination (sandwich from not sandwich), and spatial localization, yet all this is achieved with only ~60 olfactory receptor subtypes [52]. As far as we know, flies do not have an inordinately high number of specific anosmias, and will typically perform any olfactory discrimination task in the lab, and again, all this with only ~60 receptor subtypes. So why do mammals need 1000?

Moreover, in a critical study, Fleischmann *et al.* (2008) used a genetic manipulation to generate mice that express a single receptor subtype in more than 95% of their receptor neurons [53]. Whereas the combinatorial-driven view would predict that such mice would have a very limited olfactory repertoire, in practice these mice could smell almost anything. In fact, they were primarily impaired at higher-order olfactory tasks such as olfactory memory, and had only one striking basic olfactory disability, and that was total anosmia for the odorant acetophenone, which happens to be the known ligand for the receptor subtype that these mice over-expressed. If mouse olfaction depends on the relative contributions of 1000 different receptor subtypes, than why was this mouse not horribly impaired at basic olfactory processing?

With all this in mind, the study of olfactory perception has brought us to ask whether non-olfactory forces may have played a role in maintaining the olfactory receptor repertoire. In other words, because we think olfaction is much

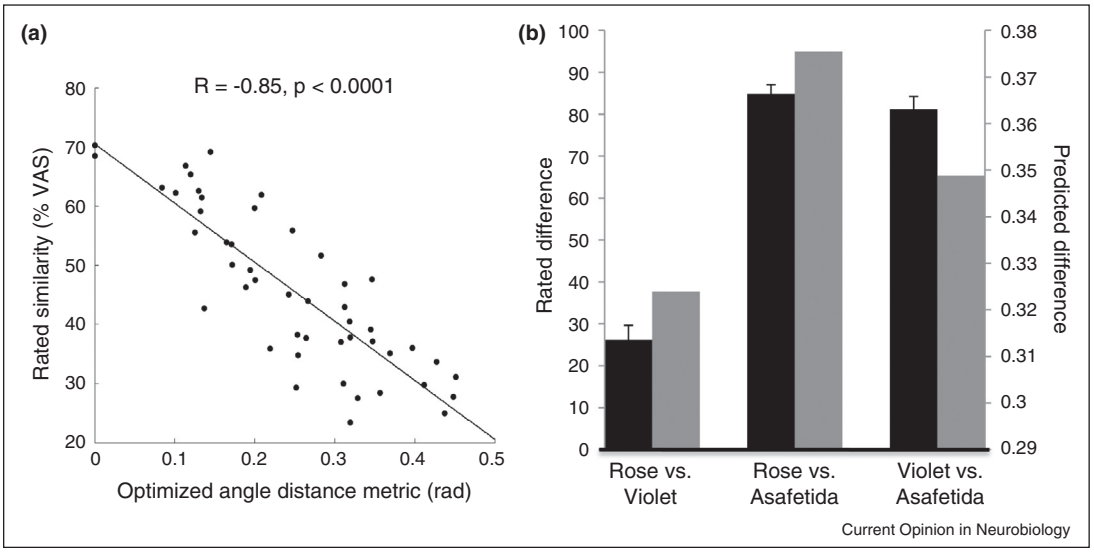
Figure 2



Modeling odorant mixtures as singular objects rather than component amalgamations. The top panels represent one mixture (Y) made of 3 mono-molecular components and the bottom panels represent a different mixture (X) made of 2 mono-molecular components. The distance between X and Y can be calculated as **(a)** the mean of all pairwise distances between all the components of X and Y. **(b)** Alternatively, one can represent both X and Y as single vectors reflecting the sum of their components, and define the distance between them as the angle between these two vectors within a physicochemical space of n dimensions. Only the latter approach predicted mixture perceptual similarity [40].

simpler than implied by its molecular underpinnings, could it be that these underpinnings are also serving some other function. This has of course been proposed before. Perhaps the biggest mystery of biology is that of the specificity in cell migration and assembly during development, and especially during embryogenesis. In a theory dubbed ''the area code hypothesis'', William Dreyer and colleagues first hypothesized that this process relies on a molecular-addressing code that functions much like the country, area, regional, and local portions of the telephone dialing system. Given that the complexity of the information required to code cells for the construction of entire organisms is so enormous, they hypothesized that the code must make combinatorial use of members of large multigene families. They later identified the olfactory receptor genome as a primary candidate for this role [54]. This notion is consistent with growing recent evidence for expression of olfactory receptors in non-chemosensory tissue [55,56], and can also be seen as consistent with the above results of Fleischmann *et al.* (2008): the mice that over-expressed one receptor subtype were not significantly impaired at olfaction, they had

Figure 3



Answering Bell's question: predicting the ''likenesses and differences'' of rose, violet, and asafetida. **(a)** Performance of the optimized angle distance model. Each dot represents a comparison between two mixtures (ranging in size from 4 to 40 components) tested in 24 subjects. The model provided a strong prediction of mixture perceptual similarity from mixture structure alone [40]. **(b)** Bell's question: Predicting the perceptual difference between rose, violets, and asafetida. We bought rose and violet perfumes from a local perfumer, and asafetida at a local spice market. We modeled the odorants based on their primary constituents in the published record (gray bars). Ten subjects then rated pairwise similarity (black bars). The angle-distances between the three odorants were in strong agreement with perception: rose and violet are similar to each other, and both are dissimilar from asafetida, yet violet is closer to asafetida than rose.

impaired cognition possibly following impaired neurodevelopment. Indeed, in an additional study of mice over-expressing primarily one receptor subtype, the mice then experienced seizures when exposed to the cognate odorant [57•]. These seizures were not a reflection of increased receptor responses at the epithelium, but rather the outcome of altered functional organization in the olfactory bulb or beyond, again consistent with the notion of a role for olfactory receptors in neurodevelopment. This view is also consistent with the impaired olfaction typically observed in neurodevelopmental disease [58]. In conclusion, we argue that the perceptual logic of smell has taught us that olfaction is of lower dimensionality and simpler than it first appears. The simplicity of olfactory perception implies that the complexity of the olfactory genome may hold secrets for more than understanding olfaction alone.

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