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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