Title: Understanding smell – the olfactory stimulus problem

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PII: S0149-7634(13)00164-4
DOI: http://dx.doi.org/doi:10.1016/j.neubiorev.2013.06.009
Reference: NBR 1791

To appear in:

Received date: 30-7-2012
Revised date: 9-5-2013
Accepted date: 13-6-2013

Please cite this article as: Auffarth, B., Understanding smell – the olfactory stimulus problem, *Neuroscience and Biobehavioral Reviews* (2013), http://dx.doi.org/10.1016/j.neubiorev.2013.06.009.

- For the olfactory system, a topographic organization is disputed.
- However, work on different species suggests a topography in olfaction.
- We compare other modalities such as taste and color vision.
- We discuss the utility of a categorization of smell perception.

Neuroscience and Biobehavioral Reviews x, 1–23 x 2013
DOI: doi:10.1016/j.neubiorev.2013.xx.xxx

Understanding smell — the olfactory stimulus problem

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Summary: The main problem with sensory processing is the difficulty in relating sensory input to physiological responses and perception. This is especially problematic at higher levels of processing, where complex cues elicit highly specific responses. In olfaction, this relationship is particularly obfuscated by the difficulty of characterizing stimulus statistics and perception. The core questions in olfaction are hence the so–called *stimulus problem*, which refers to the understanding of the stimulus, and the *structure–activity* and *structure–odor relationships*, which refer to the molecular basis of smell. It is widely accepted that the recognition of odorants by receptors is governed by the detection of physico–chemical properties and that the physical space is highly complex. Not surprisingly, ideas differ about how odor stimuli should be classified and about the very nature of information that the brain extracts from odors. Even though there are many measures for smell, there is none that accurately describes all aspects of it. Here, we summarize recent developments in the understanding of olfaction. We argue that an approach to olfactory function where information processing is emphasized could contribute to a high degree to our understanding of smell as a perceptual phenomenon emerging from neural computations. Further, we argue that combined analysis of the stimulus, biology, physiology, and behavior and perception can provide new insights into olfactory function. We hope that the reader can use this review as a competent guide and overview of research activities in olfactory physiology, psychophysics, computation, and psychology. We propose avenues for research, particularly in the systematic characterization of receptive fields and of perception.

Key words: olfactory system; olfactory stimulus–problem; structure–activity relationship; structure–odor relationship; odor perception; spatial coding; olfactory receptors; topography; hedonics; basic odors; vertebrate olfaction; insect olfaction.

CONTENTS

1. Introduction

The sense of smell, for millions of years, has played a significant role in the behavior of evolutionary diverse animal species (Hansson and Stensmyr, 2011; McBride, 2007). Although, historically, it was long considered of secondary importance to senses such as vision or hearing (Shepherd, 2004; Le Guérer, 2002), it is now recognized as one of the most prevalent senses in humans and many other animal species and a key determinant of behavior (e.g. Croy et al., 2013; Asahina et al., 2008).

Possibly the most central function of olfaction is to enable animals to discriminate between a wide variety of attractive and repulsive objects, and often it plays a decisive role in species–specific communication. Many behaviors in different animals rely on olfactory cues, such as maternal bonding, mating, foraging, kinship recognition, territorial defense, and modulation of aggressive behavior (c.f. Wyatt, 2010; Sanchez-Andrade and Kendrick, 2009; DeBose and Nevitt, 2008) to name just a few.

A particularly impressive behavioral effect of odorants in humans is the identification of their mother's nipple by her newborn child (Varendi et al., 1994). Other influences are in mate selection (Moshkin et al., 2011), social preferences (Li et al., 2007; Todrank et al., 1995), identification of kinship (Porter et al., 1986; Hold and Schleidt, 1977), and the regulation of emotional responses (Albrecht et al., 2011; Mujica-Parodi et al., 2009; Nakashima et al., 2004). Further, putative sex hormones can trigger hypothalamic responses associated with sexual arousal in humans and affect gender judgment (Kovács et al., 2004; Savic et al., 2001). Recently, it has also been shown that tears reduce sexual arousal in men by a chemical signal (Gelstein et al., 2011).

Some effects of olfactory cues have been claimed to be pheromonal in nature, however, the distinction between odorants, pheromones, and signature mixtures is in many cases contentious, especially in humans (Wyatt, 2009; Doty, 2003). Interestingly, although in humans there is probably not a functional (vomeronasal) organ for pheromones (Trotier, 2011), it is known that pheromones and social cues can mediate their effects over the main olfactory pathway in rodents (Baum, 2012; Liberles and Buck, 2006), and that humans express receptors from the V1R and TAAR families, which are typically associated with social cues and pheromone systems (Keller and Vosshall, 2008). However interesting, such a debate is out of the scope of this article, and we will discuss common olfactory function and effects elicited by olfactory cues, largely concentrating on the main olfactory system, rather than on specific pheromones and their associated systems. Likewise, we will not discuss in detail other chemical senses such as taste or chemesthesis.

It has been emphasized that many components of the biological olfactory system, by which odorant molecules are sensed by receptors and then translated into neural activation patterns underlying odor perception, exhibit consistencies from functional and anatomical perspectives across very diverse species (Kaupp, 2010). These similarities could have their origin either in common evolutionary ancestry or could reflect adaptations to similar environments and constraints. It is probably fair to say (c.f. supplementary figure 1) that the main animal models in olfaction in terms of research activity and influence are humans, rodents (mice and rats), and insects, such as the honeybee (*apis melifera*) and the fruit fly (*Drosophila melanogaster*). Consequently, we concentrate on these animal models in this paper. In insects, because there are only few relays between sensory perception and behavioral responses, and generally the nervous system is less complex than in vertebrates, it has been instrumental in producing many insights about the workings of the olfactory system. Insects are model systems for studying associative learning and memory (Davis and Giurfa, 2012), and could possibly even serve as models of cognitive functions (Menzel, 2012).

Odor detection and perception occur as a result of activation of olfactory receptor neurons (ORNs), which are located in the primary sensory organs, i.e. the nasal epithelium in vertebrates and the antenna in insects. The response profile of each ORN is determined by one functional type of olfactory receptor (OR; Kaupp, 2010). Sensory axons of the same receptor type converge onto single or multiple glomeruli, neuropil structures located in the primary processing center — the olfactory bulb (OB) in vertebrates and the antennal lobe (AL) in insects (Martin et al., 2011; Mori and Sakano, 2011). These axons synapse with output neurons (mitral/tufted cells, short M/T cells, in vertebrates and projection neurons, PNs in insects) and interneurons. These primary sensory organs are reciprocally connected with higher processing centers (Oswald and Urban, 2012; Martin et al., 2011; Hu et al., 2010), a fact which emphasizes their implication in many computational functions.

Smell is not an intrinsic property of odorant molecules, but a perceptual phenomenon that depends on mechanisms which are peculiar to the perceiving biological organism. Therefore, in order to understand the nature of smells, and the processing of the olfactory system, we argue toward adopting a systems approach, which involves the relationships between the physical space, genetic makeup of the organism, physiological activities, and smell perception. The discussion of each of these aspects in this review will include structure–activity and structure–odor relationships, the organization of odor representations at different levels, starting from receptors, and perceptual dimensions of smell. In order to highlight certain features of smell processing, we will sometimes mention parallels to other sensory modalities, especially taste and color vision.

2. Aspects of smell

There are various problems associated with the understanding of the olfactory system. The *stimulus problem* is generally understood as the difficulty to understand stimuli in terms of their meaning (c.f. Herrnstein, 1982). In olfaction, it refers to the impact of physico–chemical odorant properties on physiology and smell perception. More specifically, the relationships between physical properties and physiological activity, and between physical properties and odor perception, have been referred to as *structure–activity* and *structure–odor relationships*, respectively.

Understanding the stimulus is arguably one of the most important issues in olfaction. The poor grasp of the stimulus makes the interpretation of molecular and physiological dimensions difficult, as discussed here. Moreover, perceptual dimensions of smell are far from well–understood. We will discuss measures for odorant molecules, for receptors, physiological activations, and perceptions.

Odor–related spaces are illustrated in fig. 1 and correspond to genetics, the olfactory stimulus, neurophysiology, and cognition. Each receptor has a complicated genetic makeup, which has evolved over millions of years (fig. 1a). Each odorant has a complex structure that can be analyzed and described (fig. 1b). Each odorant triggers one of a possibly unlimited number of activation patterns on the epithelium, the OB/AL, and downstream layers (fig. 1c). These activity patterns give rise to the perception of smell (fig. 1d).

Elucidating the interactions and links between these odor spaces could be pivotal in establishing a systemic concept for the analysis of olfactory function. In order to accomplish this, different approaches are necessary, such as investigating how the brain represents odors, the behavioral importance of smells, their perceptual dimensions, and computational principles.

[Figure 1 about here.]

2.1 *The Stimulus*

In terrestrial animals, odorants are light, volatile molecules, while in aquatic animals, odorants are water soluble. The complexity of smells varies: floral odors can contain dozens of odor components (Raguso, 2008), while more complex smells such as wines and coffees are composed of hundreds (Louw et al., 2009). However, it seems that many complex smells can actually be reduced to the impact of a few molecules (e.g. d'Acampora Zellner et al., 2008).

We return to the stimulus problem. Alexander Bell is quoted as having said in 1914 (after Wise et al., 2000):

> 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 odour of violets and roses up to asafetida. But until you can measure their likeness and differences you can have no science of odour.

Ninety years later, in his review "On the Unpredictability of Odor," Charles Sell concluded that there are no molecular features of the odorant that directly determine perceptive quality and that it "would seem that consistently accurate prediction of odors are not possible for a very considerable time" (Sell, 2006). Further complicating this situation, interactions between physical properties (e.g. Johnson et al., 2005) and between molecules in a mixture can also occur (Rospars et al., 2008).

A particular distinction of smell is its relative lack of intrinsic spatial topology when compared to other sensory modalities (or at least it is not well understood). This means that obvious relations, such as those with the somatosensory, visual, and auditory systems, between stimulus and percept do not exist. In turn, this can be taken to imply a different way of information processing in the olfactory system. We will discuss parallels in subsequent sections and come back to this point at the end of this article.

Molecules can be compared by their shape and by applying distance functions on sets of chemical features derived from known information about the molecules. However, it is not straightforward to develop measures that describe biological processes and make good predictions of perceptual differences. For illustration, some odorants of comparable structure can smell similarly, e.g. guaiacol and vanillic acid; however, the same can also be said for some odorants with completely dissimilar structures, such as benzyladehyde and cyanide. Multiple non–exclusive hypotheses account for these phenomena including (i) differences in early pathways, e.g. differing sets of receptors, determine similarity or differences, (ii) stimulus correlation or learning, or (iii) memory effects, learnt associations (e.g. category membership) driving similarity judgments.

While properties of visual receptive fields can be explained from first principles (e.g. Lindeberg, 2010), in olfaction, the field has moved closer to defining the structural ligand–receptor rules. Investigations underlined the importance of structural similarity of ligands, such as size and volatility (Saito et al., 2009; Hallem and Carlson, 2006; Mori et al., 2006; Leon and Johnson, 2003; Johnson and Leon, 2000). So it is known that small volatile molecules allow for rapid diffusion over short distances, while large and less volatile molecules provide a relatively long signal (Wyatt, 2010). In addition, structural complexity, including length and weight, contribute to the overall complexity of smells and their pleasantness (Kermen et al., 2011; Zarzo, 2011; Joussain et al., 2011).

However, the physico–chemical space is probably highly complex as indicated by recent studies. Several research groups proposed metrics based on larger sets of molecular properties that explained a part of the variance in neuro–physiological data (Chen et al., 2011b; Soh et al., 2011; Saito et al., 2009; Haddad et al., 2008a). Furthermore, the case of enantiomers, molecules that are mirror–symmetric to each other could call for possibly even more complicated molecule descriptors. Enantiomers can produce different activation patterns at receptor, primary processing center, and cortical levels, and produce different odor sensations (Laska and Shepherd, 2007; Saito et al., 2009; Li et al., 2008; Leon and Johnson, 2003).

2.2 *Receptors*

The numbers of functional OR types range from a few dozen in insects to approximately 600–1400 in vertebrates (Kaupp, 2010). Such a high number of independent information channels give olfaction possibly a much higher dimensionality than other modalities.

For comparison, in vision, the retina contains light–sensitive rods and cones; and color vision is mediated by separate classes of cones each tuned to different frequencies of light (De Valois and De Valois, 1993). In hearing, organs in the inner ear distinguish between resonance frequencies (Robles and Ruggero, 2001). In taste, evidence suggests that five basic tastes are sensed by specialized taste receptor cells (reviewed in Yarmolinsky et al., 2009).

The transduction principle of ORs is incompletely understood (Gelis et al., 2012; Lai and Crasto, 2012; Spehr and Munger, 2009), however it is widely accepted that receptors detect regions of volatiles by the presence of specific combinations of physico–chemical properties, known as *odotopes*, in analogy with epitopes, the antigenic determinant of the immune system (Shepherd, 1987). Odorants are detected and thereby encoded, by distinct sets of ORs, and resulting in spike generation by ORNs (Nagel and Wilson, 2011). ORs typically respond to only few odorants (i.e. they have a narrow tuning profile), while some are more broadly tuned (Nara et al., 2011; Saito et al., 2009).

The olfactory subgenome of ORs constitutes one of the largest gene families in the mammalian genome, occupying approximately 1% (Waterston et al., 2002; Venter et al., 2001; Lander et al., 2001). Understanding the functional significance of receptor diversity is advancing by genetic and structural studies (Lagerström and Schiöth, 2008). It is established that genetic variations in the expression of the chemosensory repertoire is of perceptual consequence, where for example, a change in a single OR can result in the loss of perception of androstenone or andostadieonone (Menashe et al., 2007; Keller et al., 2007). In addition, it has been shown that the frequency distribution of OR gene expression is not uniform (Khan et al., 2011) and that expression also varies during development (Nguyen et al., 2010).

Organisms adapt to their environment over evolutionary processes (c.f. Shoval et al., 2012) and reflect the relevance of odorants in their environment, and the role of these odorants in evolutionary history (Nei et al., 2008; McBride, 2007; Stensmyr et al., 2003). Interesting in this context, Nara et al. (2011) observed that odorants recognized by the same ORN tend to share a perceptual quality, such as fishy or minty. Furthermore, some ORNs are specific for animal–associated chemicals.

Different measures of similarity between receptors have been proposed, including measures between gene sequences, such as distances between predicted binding pockets (fig. 1a; Man et al., 2007). ORs can be grouped into different gene families by phylogenetic similarities (Zhang and Firestein, 2002; Glusman et al., 2001). Some of these groups have been named after their evolutionary history, such as class 1, "fish–like," or class 2 ORs, "tetrapod–specific." Saito et al. (2009) confirmed that class I ORs are indeed more hydrophylic than class II ORs in their response profiles. Class 2 ORs constitute as much as 10% of the human OR repertoire and Glusman et al. (2001) emphasize that, even though, class 1 ORs have been considered a relict in higher tetrapods, their low pseudogene fraction suggests that they have a functional significance.

It is not unreasonable to assume that the number of functional genes and a low ratio of pseudogenes are related to the performance in smell–related tasks. By this logic, humans, who possess a low number of functional OR genes and a high proportion of pseudogenes as compared to other vertebrates (Aloni et al., 2006), should have a bad sense of smell. However, surprising to many, Maresh et al. (2008) located more glomeruli in humans than had been previously known to exist in other vertebrate species. Although specific estimates should be treated with caution — Royet et al. (1998) has suggested, based on comparisons across studies, that the number of glomeruli is often underreported — such evidence should actually predict a superior functionality of the human primary processing center relative to other animals, although this could also be taken as indication of differences at molecular and synaptic levels in the OB. As a matter of fact, humans have shown to be excellent at identifying and discriminating odors (Porter et al., 2007).

2.3 *Physiology*

The importance of time dynamics relative to the spatial dimension is an open question (however, please see Stierle et al., 2013; Fukunaga et al., 2012; Nawrot, 2012; Blumhagen et al., 2011; Smear et al., 2011; Verhagen et al., 2007), and physiological studies differ in particular on whether they take time explicitly into account. In the present discussion, we focus on how odors are represented by spatial patterns, because the organization of the spatial domain is a particularly puzzling aspect of olfactory processing. We focus particularly on the primary processing centers, specifically on the olfactory neuropil, the glomeruli, because they have been the object of many studies, and due to their unique input–output relationship that can facilitate our understanding of how lower level features are interpreted and shaped into higher–order representations.

Using different techniques (for reviews see Pain et al., 2011; Galizia, 2009), it has been demonstrated, in insects as well as in vertebrates, that spatial activity patterns at the glomerular level are characteristic of odor identity and intensity (e.g. Johnson and Leon, 2000; Galizia et al., 1999). These patterns are conserved across members of a species (Soucy et al., 2009; Wang et al., 2003; Galizia and Menzel, 2000), and even sometimes across species — despite many species–specific adaptations, for example to host–plants in insects (Carlsson et al., 2011; Dupuy et al., 2010; however Galizia et al., 1999).

We will now discuss systematic relationships in spatial arrangements in the primary processing centers. An assumption often made in decoding neural ensembly activities is that information is represented by the activities of many or even every neuron in the population. Here, we discuss a compromise between this idea, the *distributed population code*, and information storage in single cells (sometimes referred to as *grandmother cells*). This is a localist ensembly storage, where spatial location depends on dimensionality of the input.

It has been established for different brain regions that information is embedded in the spatial structure, and that relative spatial structure is preserved between regions (c.f. Thivierge and Marcus, 2007; Malach et al., 2002). Generally, such an organizing principle, called *topography*, is a common feature observed in mammals as well as in insects (Thivierge and Marcus, 2007).

While especially well–known examples it in the visual (Swindale, 2008) and somatosensory systems (Di Noto et al., 2012) might suggest so, topography is not limited to reflect spatial aspects of the input space (e.g. Humphries et al., 2010). This is best illustrated in taste, while the idea that regions of the tongue are exclusive for certain taste categories has been abandoned, there is evidence for a labeled–line code where, apart from distinct receptor cell types, fiber tracts are responsible for specific gustatory sensations such as salty, savory, or sweet (Yarmolinsky et al., 2009). Additionally, it has recently been found that a spatial map in the gustatory cortex encodes basic taste sensations (Chen et al., 2011a). Similarly, functional studies on the visual cortex of primates suggest the existence of segregated domains for color processing (Valverde Salzmann et al., 2012).

Given the prevalence of the topographic principle, we think it is worthwhile to discuss factors that play a role in the spatial organization of the olfactory system. Although functional implications of a topographic organization in the brain are not clear (e.g. da Costa and Martin, 2010), what makes it exceptionally interesting is that the spatial structure of representations in sensory cortices has been observed in many parts of the brain to locally reflect subspaces of stimuli that are behaviorally or perceptually relevant (Malach et al., 2002).

Thomas Cleland, Christine Linster, and colleagues (Cleland and Sethupathy, 2006; Linster et al., 2005) argued that a two–dimensional geometry (such as the surface of the OB) cannot accommodate the complexities of contrast–enhancement — this projection would result in a fragmented map. Topography in the brain is often complemented by splits and magnifications, among other transformations (Thivierge and Marcus, 2007). In accordance with this, Johnson and Leon (2007) observed that spatial progressions of activation foci in relation to continuous properties on the glomerular layer of the OB tend to be disrupted by unresponsive areas.

Studies on insects and vertebrates repeatedly demonstrated a coarse topographic organization in the olfactory system with respect to overall response profiles (Ma et al., 2012; Soucy et al., 2009; Galizia et al., 2010) (this has been referred to as *tunotopy*), and many studies emphasize an organization by chemical similarity (e.g. Yablonka et al., 2012; Auffarth et al., 2011a; Matsumoto et al., 2010). It therefore seems plausible that lateral processing in the olfactory system makes use of a topographic organization.

There are many factors that have an impact on the spatial organization in the olfactory system. In the moth, the AL is subdivided between the main AL and the macroglomerular complex; generally, in the insect AL, there exists a glomerular topography by PN neuroblast origin, sensilla type, and mushroom body target region (Martin et al., 2011). The main factors in vertebrates and insects are these (c.f. Mori and Sakano, 2011; Brochtrup and Hummel, 2011), of which we discuss iii-vi in more detail: (i) rhinotopy, (ii) genetic factors (axon guidance cone, OR type), (iii) chemotopy, (iv) odotopy, (v) response tuning (tunotopy), and (vi) perceptual features (odor quality and hedonics). While we discuss each of these factors in turn, we particularly focus on chemotopy, odotopy, tunotopy, and perceptual quality and hedonics.

Rhinotopy refers to a spatial order related to the distribution of ORNs at the epithelium (for a detailed discussion see Johnson and Leon, 2007; Miyamichi et al., 2005; Schoenfeld and Knott, 2004; Astic and Saucier, 1986). *Receptor type* and the *genetic identity of the axon guidance cone* are other key factors (Pacifico et al., 2012; Silbering et al., 2011; Bozza et al., 2009).

In olfaction, molecular properties of receptive fields have been called *molecular receptive ranges* (Mori and Shepherd, 1994; Arzi and Sobel, 2011; Murthy, 2011; Khan et al., 2010 review the topic). Many experiments examined glomerular activation patterns in response to a limited set of mono–molecular odorants which varied with respect to certain physico–chemical properties.

Investigated properties which were found to have an outstanding influence on the localization of activation peaks, were molecular length, functional groups, and hydrocarbon structures. From such studies, a modular organization of the glomerular layer has been suggested (c.f. Matsumoto et al., 2010; Johnson and Leon, 2007; Couto et al., 2005) in the sense of functional clusters of glomeruli, which respond to related features.

Our results from a systematic large–scale study of glomerular activity indicated that coding of some molecular properties, including functional groups and chemical bonds, is organized in continuous zones and locally restricted (Auffarth et al., 2011a). Furthermore, the relative spatial locations between representational areas corresponding to odorant categories could be related to chemical similarity (Yablonka et al., 2012; Ma et al., 2012; Auffarth et al., 2011a; Johnson et al., 2004). This principle has been referred to as *chemotopy* or, *spatial progression*, in the case of a spatial shift related to molecular properties. A similar concept is *odotopy*, which refers to a spatial arrangement by odotopes.

We now come to the perceptual and behavioral relevance as a factor in the spatial organization of the olfactory system. Studies in rats and mice have shown that different types of behavior, e.g. defensive behavior toward predators, aversion or attraction to food, can be related to spatial domains in the OB (Mori and Sakano, 2011; Kobayakawa et al., 2007; van der Goes van Naters and Carlson, 2007; Stockinger et al., 2005; Dielenberg and McGregor, 2001). A study by Kobayakawa et al. (2007) suggested that the OB of mice consists of at least two different functional modules, one for innate odor responses and one for (associatively) learned odor responses. In mice and humans the dorsal part of the OB was implicated in innate responses to aversive odorants (Kobayakawa et al., 2007; Rolls et al., 2003). Several studies have found a relationship between differences in behavior and shifts in spatial patterns (Ho et al., 2006; Linster et al., 2002) and, even more, changing locations of glomeruli in mice can result in behavioral impairments, in spite of persistent physiological activations (Adam and Mizrahi, 2010). Similarly, in the AL of female moths, glomeruli in a sexually dimorphic region specialize in odorants that are related to oviposition (Kalberer et al., 2010; Reisenman et al., 2009). In Drosophila, it is known that particular glomeruli mediate appetitive and aversive behavioral responses (Semmelhack and Wang, 2009).

Haddad et al. (2010) showed that the first principal component of activity at the level of the primary processing center in different animal species is highly correlated to approach or withdrawal in animals, or pleasantness in humans, which suggests that the primary processing center separates odors by a hedonic dimension. In several animal models and different levels of the system, there is evidence that perceptual features are related to the spatial topology (Knaden et al., 2012; Auffarth et al., 2011c; Matsumoto et al., 2010; Jefferis et al., 2007). In humans Lapid et al. (2011) showed that spatial offsets on the receptor sheet are correlated with differences in pleasantness. In Drosophila, on the other side, Knaden et al. (2012) did not find such a separation within the first two principal components of signals in the insect antenna.

Knaden et al. (2012) tested Drosophila olfactory preferences in a chemotaxis assay. They found that aversive and attractive odors can be differentiated by the location of the response patterns at the output of the antennal lobe. They observed that aversive odorants elicited clustered activations in the lateral domain of the AL, while attractive odorants elicited clustered activations in the medial domain.

In rats, Auffarth et al. (2011b) and Raman and Gutierrez-Osuna (2009) found indication that some odor categories can be predicted from spatially clustered areas of glomerular activity patterns and in a subsequent computational model, such a clustering was explained in part by structural similarities of odorants (Auffarth et al., 2011c). In the mice OB, Matsumoto et al. (2010) found feature clusters that are associated with odorant categories and behavioral responses.

Simple odorant molecules tend to activate several regions in the OB (e.g. Spors and Grinvald, 2002) and each site of activation consists of multiple glomeruli (e.g. Johnson et al., 1998, 1995). Studies have found different modes of how odorant components are integrated when they are delivered together with other components in a mixture. While some studies argue for a mostly linear integration of mixtures (Lapid et al., 2008; Carlsson et al., 2007; Lin et al., 2006; Belluscio and Katz, 2001), others demonstrate non–linear mixture effects, some concluding that neural responses cannot be decomposed easily into components (Deisig et al., 2010; Rospars et al., 2008; Duchamp-Viret et al., 2003; Joerges et al., 1997; Laing and Francis, 1989).

As we mentioned before, in section 2.1, the effect of natural odorants can often be reduced to few molecules, and from resemblances of activity peaks evoked by mono–molecular and natural stimuli it has been suggested that the olfactory bulb represents odors in perceptual feature maps (Johnson et al., 2010), even though responses to artificial stimuli have been shown to be more sparse (Vincis et al., 2012; Johnson et al., 2010).

Rather than key to some computational function or arising from broader rules, the organization of the OB/AL could be the result of developmental processes by which axons are guided based on chemical cues (Mori and Sakano, 2011; Mombaerts, 2006). However, it is known that ORN type–convergence is at least partly mediated by experience (Imai and Sakano, 2007; Kerr and Belluscio, 2006; Yu et al., 2004; Zou et al., 2004), and that, in the absence of activity cues, glomeruli can contain projections from ORNs of different OR types (Zou et al., 2004). Serizawa et al. (2006) found evidence in the mouse that a correlation of neural activity mediated axonal attraction and repulsion by up– and down–regulation of a set of olfactory axon guidance cues. This indicates that axon sorting could be based on correlated neural activity.

Topography leads to a grouping of units with similar response profiles, and therefore self–organized models have been proposed as a model of map formation. It is known that some parts of cortical maps form independently of the development of functions — spontaneous activity can lead to a high degree correlation between the activity patterns of neighboring neurons — while others are subject to environmental stimulation. Mathematical models based mostly on correlations in the stimulus statistics reflect many properties of these maps (van Ooyen, 2011; Goodhill, 2007). Biologically, such a correlation–based principle could be implicit in the global or local distribution of gradients cues in the axonal guidance process (Serizawa et al., 2006; Ming and Song, 2005).

2.4 *Perception*

The epistemological status of olfaction was disputed during a long time (Le Guérer, 2002) and therefore it is not surprising that literature on perceptual olfactory dimensions is not abundant (however, see the review in Zarzo and Stanton, 2009, and references therein). Although humans recognize smells, they often have problems labeling them linguistically. This problem is called the *tip–of–the–nose phenomenon* (Lawless, 1977) and suggests that olfaction is often an unconscious process (c.f. Sela and Sobel, 2010). Probably this is the reason why defining objects on the basis of their olfactory perception, without recourse to their visual aspect or grasp is not intuitive (c.f. Yeshurun and Sobel, 2010; Stevenson and Wilson, 2007).

Odorants can pass through the nasal passages (the so–called *orthonasal* stimulation) and via the mouth (*retronasal* stimulation). Therefore olfactory and gustatory experiences are often intermingled — odors influence our perception of taste over the retronasal pathway (Mozell et al., 1969) and, conversely, taste influences odor perception (Green et al., 2012).

Olfaction has a special status in the sense that information must pass only two synapses from sensory periphery to brain centers responsible for memory formation and behavior, such as amygdala and hippocampus. Psychological studies demonstrated that smells are associated with emotional arousal (Willander and Larsson, 2007; Bensafi et al., 2002). It is anecdotal wisdom, voiced in Marcel Proust's *à la recherche du temps perdu* that smell can evoke vivid memories from early life. Indeed, experimental evidence shows that olfactory cues tend to bring back memories from earlier in life than visual and verbal cues (Larsson and Willander, 2009). Whereas it is possible that olfactory memory follows a slower decay function, another explanation for the findings of age distribution of memories could be that olfactory experience is highly complex and little redundant and therefore less prone to be extinguished (c.f. Lewandowsky et al., 2009). In fact, it has been observed that in olfactory fear conditioning of rats, extinction occurs on a slower timescale than it does with auditory or visual cues Richardson (2002).

The perceptual character of odors in humans has been described by two different methods: (i) numerical scales of odor relatedness assigned by a panel, such as Dravnieks' panel assessment of odor character (Dravnieks, 1985), and (ii) semantic labeling, such as semantic databases like Acree and Arn (1998). Similarly to the case with physico–chemical properties, the dimensionality of such datasets is quite high.

Analyses on datasets of perceptual odor characterizations commonly show an embedded structure of latent dimensions which explain the perceptual experience or the common effect of odorants. One of the most salient dimensions in these data seems to be pleasantness (Arzi and Sobel, 2011; Yeshurun and Sobel, 2010; Zarzo, 2008). After pleasantness, edibility is one of the crucial sources of variability (Haddad et al., 2008b; Zarzo, 2008; Khan et al., 2007; Mamlouk and Martinetz, 2004).

In order to account for the structure of subjective olfactory experiences, models have been proposed as a way to systematically classify odors by membership to categories. Besides specialized categorization systems, such as the wine aroma wheel (Noble et al., 1984), the beer flavor wheel (Meilgaard, 1982), or Carl Linnæus' for medical plants (Linneus, 1752), different categorizations have been proposed for natural odors (e.g. Zarzo and Stanton, 2006; Mamlouk and Martinetz, 2004; Chastrette et al., 1988; Abe et al., 1990; Crocker and Henderson, 1927; Henning, 1916).

Currently, there is no universally accepted comprehensive system of odor classification. However, work based on a variety of data and statistical and descriptive methodologies is encouraging for endeavors to find such a system. It suggests the existence of groups of odors by perceptual similarity (e.g. Zarzo and Stanton, 2009; Civille and Lawless, 1986), even across cultural boundaries (Chrea et al., 2005). Such categories of human olfactory perception include smoky, camphoraceous, fruity, herbaceous, resinous, earthy, and sweet.

An intriguing idea, analogous to primary colors, is that of *primary* or *basic odors*, components or constituents, from which all remaining odors can be derived. Based on the notion of compositionality, these basic categories can also be called unique or unitary qualities, while mixtures, depending on the number of their constituents, can be referred to as secondary (or binary), tertiary qualities, etc. Such compositionality in olfaction would open commercial applications such as in the perfume industry or in *smellies*, films with accompanying olfactory stimuli. As one of the few to demonstrate this compositionality principle, Weiss et al. (2012) found that *olfactory white* can be produced from the composition of around thirty odorants that spanned the perceptual space.

There is confusion, however, if the principle of compositionality alone is sufficient as a definition for basic qualities. Although the idea of basic categories has guided research in different sensory modalities for a long time, until defined and therefore testable, its usefulness is only limited (Erickson, 2008; Delwiche, 1996).

Henning (1916) proposed his odor prism based on six primary odors. In this case, there is the added principle of orthogonality, which means that these primary categories are independent of each other, so that a primary category is not composable out of the others. Orthogonality is given with colors. As discussed by Delwiche (1996), although red, blue, and green are routinely discussed, there is no unique set of primary colors to compose other colors — any colors of long, medium, and short wavelength could be primary colors in the sense of compositionality and orthogonality. Even though there are cultural differences, there seem to be some universal categories (c.f. Regier and Kay, 2009).

From data on specific anosmia, the selective loss of smell, Amoore (1977) proposed there should be at least 32 basic categories, such as sweaty, spermous, fishy, malty, urinous, and musky. This is a prominent example, for theories where basicness is — explicitly or implicitly — based on physiological mechanisms. We discussed before the case for color; in taste, only recently, evidence for a labeled–line code, as discussed in sections 2.2 and 2.3, has emerged, but still there are inconsistencies such as the apparent lack of a region for sour in the primary gustatory cortex and the sensitivities for calcium and complex carbohydrate (c.f. Tordoff et al., 2012).

Besides the criteria for primary perceptions which we just discussed, others can be distinguished (c.f. Byrne and Hilbert, 2008). Ultimately, if the concept of primary odors is useful or a red herring, remains to be seen.

Apart from humans, it is instructive to look at the behavior of other animals for clues about their perception. In drosophila, olfactory qualities relate to fruits, plants, and microorganisms living on plants; as they prefer to feed on decaying fruits and also choose these for oviposition (reviewed in Hansson et al., 2010). Mandairon et al. (2009) found that their investigation times of smells could be predicted from human pleasantness. They argued that perception of odors in mice and humans is similar because of a prewiring at the receptor level.

Such a common structure of the perceptual space suggests principles which are independent of learning and points to commonalities in natural stimuli statistics. Commonly, objects that are potentially useful for the body tend to smell good; conversely, potentially harmful things smell bad. However, as we can observe with certain kinds of food, this association is subject to associative learning. Examples for acquired food preferences are some types of cheese, coffee, and fermented herring. In fact, the olfactory system developed highly plastic modulatory mechanisms (Sanchez-Andrade and Kendrick, 2009; Wilson et al., 2004), including centrifugal innervation (e.g. Fuentes et al., 2008; Kay and Laurent, 1999; Pager et al., 1972) and adult neurogenesis (Malnic and Armelin-Correa, 2010; Whitman and Greer, 2009). These mechanisms are expected to alter relations between the stimulus and perception throughout the lifespan of an individual, and could serve to adapt olfactory performance to a highly changeable environment.

Many studies found plastic effects in olfactory sensation (e.g. Barkat et al., 2008; Herz et al., 2004; Wilson et al., 2004; Stevenson, 2001a,b), and it was proposed that many perceptual and behavioral odor responses can be explained within a framework of associative learning (Herz and Engen, 1996). The extent of learning–related modulation is illustrated by a recent study where it was found that even responses to androstenone, a putative pheromone, correlate slightly with sexual experience in women (Knaapila et al., 2012).

3. Discussion

The two underlying basic challenges in olfaction are: (i) the *stimulus problem*, (ii) the encoding of saliency and perceptual features. In olfaction, the stimulus, perceptual objects, and behavior are not easy to characterize. In order to gain new insights into olfactory information processing, we propose a perspective inspired by cognitive science: to describe the information the sensory apparatus takes as input, the algorithms it uses to transform that information, the representations those algorithms operate on, and what kinds of representations or behaviors it generates as output. We argued that a deeper understanding of olfaction should involve the stimulus, physiological responses, evolution of olfactory receptors, odor perception, and behavioral relevance.

Studies of the organization in areas downstream from the primary processing centers show a curious picture. With the exception of the honeybee (Martin et al., 2011), they found no apparent spatial bias in connectivity to the piriform cortex and the mushroom body, respectively (Caron et al., 2013; Miyamichi et al., 2011; Ghosh et al., 2011; Sosulski et al., 2011; Choi et al., 2011; Stettler and Axel, 2009; Jefferis et al., 2007). In vertebrates, the non–topographic organization of the piriform cortex and the plastic patterns have been taken to mean that the piriform cortex is de factum not a sensory, but an association cortex (Weiss and Sobel, 2012; Chapuis and Wilson, 2011; Kay, 2011). Conversely, topographic mappings are well documented in vertebrates, from OB output neurons to the amygdala and the AON, respectively (Kay et al., 2011; Miyamichi et al., 2011; Sosulski et al., 2011), and there is indication for such projections in insects, between PNs in the AL to the LH (Jefferis et al., 2007). This suggests that these downstream structures could take the role of primary sensory projection areas.

As mentioned before, there is evidence that the AL (Martin et al., 2011; Hu et al., 2010) as well as the OB (Oswald and Urban, 2012) receive functional centrifugal feedback from higher processing areas. Therefore, even though the speed of olfactory information processing suggests that the basic integration of olfactory signals occurs in a feedforward fashion (Olsen et al., 2010), feedback modulation can regulate physiological responses by motivational context, such as sexual arousal, sleepiness, foraging, or oviposition. Kay and Stopfer (2006) and (Kay and Sherman, 2007) likened the OB to the thalamus, because of its structure and convergence relationships, and argued that the OB is effectively a relevance filter, where separability between behaviorally and ecologically relevant olfactory inputs is increased, and centrifugal modulation could play an important role for such filtering processes.

In both insects and vertebrates, olfactory information has to pass only two synapses from sensory periphery to brain centers responsible for memory formation and behavior. Their inter–areal projections underline that both the OB and the AL are implicated in important functional processes and well–suited to convey behaviorally relevant information to higher stages (c.f. Niewalda et al., 2011; Yoshida and Mori, 2007; Lin et al., 2005).An important mechanism for such a function in vertebrates could be the bulbar sensory modulatory feedback loop with the amygdala (Gutiérrez-Castellanos et al., 2010), which is associated with emotional processing, especially the formation, consolidation, and retention of fear memories (Ledoux, 2012), and evaluation of biological significance (Pessoa and Adolphs, 2010).

It has been argued that the olfactory system is different from other modalities in that information is processed in a synthetic (also called *configural*) rather than analytical (also *elemental*) fashion (c.f. Wilson and Stevenson, 2003). In this account, information is not locally decomposed, but rather broadly processed. While it is plausible that local and global mechanisms could work together to achieve robustness and speed, it should be noted that views on which this position is based have been undergoing recent changes. Arguments for such a position come from (i) descriptions of a combinatorial code at receptor level (Malnic et al., 1999), (ii) the lack of apparent intrinsic dimensionality of the stimulus (c.f. Cleland and Sethupathy, 2006), (iii) synergistic effects in mixture processing (Laing and Francis, 1989), and (iv) evidence for slow integration of olfactory information over time (e.g. Friedrich and Laurent, 2001).

However, as we have discussed, recent data indicate that (i) receptor neurons are typically narrowly tuned (Nara et al., 2011), (ii) there is emerging evidence for a spatial segregation along ecologically–relevant stimulus dimensions (e.g. Knaden et al., 2012; Auffarth et al., 2011b; Matsumoto et al., 2010; Jefferis et al., 2007), (iii) there are elemental as well as configural effects in mixture processing, and both types of mixture effects can be explained by properties of stimuli, receptors, and network integration (e.g. Capurro et al., 2012; Deisig et al., 2010), and lastly (iv) olfactory information processing is surprisingly fast (Szyszka et al., 2012; Shusterman et al., 2011).

Furthermore, evidence from olfactory psychophysical experiments (Laing and Francis, 1989) is in line with the argument for a general capacity limit of the human capacity to process information and store it in short–term memory (STM) (*the magical number 4+-1;* Cowan, 2001). This limit could result from memory rules, such as mutual interference and distinctiveness, or from constraints such as scheduling conflicts and processing strategies. It has been observed that in many circumstances, processing strategies can increase this limit, however, in the olfactory context, it is plausible that such strategies are not well developed. We are not aware, of any test of olfactory STM so far that has controled for sensory differences in the training set (cf. Weiss et al., 2012).

Consequently, it appears that it is consistent with the available data to assume that olfactory processing is similar to other systems in the brain. This is in line with the "system–theoretic" hypothesis, which assumes that information processing in the brain can be explained by a shared set of rules independent of the system (e.g. Kärcher et al., 2012; Melchner et al., 2000; Métin and Frost, 1989).

Given its long evolutionary history, it can be assumed that olfactory processing has been optimized toward high efficiency. Therefore, information–theoretic approaches, possibly from the point of view of optimal coding, could prove insightful for a mechanistic understanding of olfaction. In this context, mathematical models compared the organization of connectivity from the primary processing centers to higher–order centers to a support–vector machine with a random kernel function (Huerta et al., 2004). Interestingly, random projections have been mathematically shown to be a powerful implementation for dimensionality reduction and feature expansion (Ganguli and Sompolinsky, 2012).

The olfactory system has sometimes been taken as a prime example for sparse representations (e.g. Turner et al., 2008). However, as mentioned before, caution should be exercised when talking about sparseness in the olfactory system. There is a need for an extensive characterization of physiological responses in terms of physico–chemical, perceptual, and spatial properties. To start, even though single molecules have also been shown to elicit attractive or aversive behavior (in drosophila Dekker et al., 2006; Stensmyr, 2003), most natural stimuli are mixtures. However, most studies have been using artificial stimuli. Johnson et al. (2010) found that glomerular activations of ecologically relevant odors in awake rats were more focal than those elicited by mono–molecular compounds. Further complicating factors in the interpretation of results are anesthesia and odor concentration. Comparing awake and anesthetized mice and two different concentrations of odorants, Vincis et al. (2012) found that the activated glomerular area evoked by natural odorants at realistic concentrations in awake animals is dense — contrary to the case in anesthetized mice and when making use of a delivery system that gives odorants at lower doses.

There is also a need to perceptually characterize odorants, in particular their hedonic value. In insects, assays and high–throughput methodologies can be applied for measuring odor attractiveness (Steck et al., 2012). Recently, large–scale psychophysics studies have been applied in humans (Keller et al., 2012), and it is to hope that more studies will go in a similar direction.

As we have seen, it can be of value to establish meaningful correspondences between receptors, odorant structure, and physiological and behavioral responses can be established. At some point of the sensory pathway, we would expect the neural responses to reasonably predict behavioral responses and perceptual structure. As we have discussed in section 2.3, there is converging evidence that at the primary processing centers, significant correlations between such measures can already be found.

Such comparisons require an adequate description of odorants, their neural representations, and associated responses in the form of perception or behavior. As we have discussed, the field of olfaction still has a relatively primitive understanding of behavioral and perceptual relevance of stimuli. Moreover, most data still come from artificial settings which might not translate to naturalistic conditions with stimuli in ecologically–relevant concentrations and ratios. Using more biologically–plausible scenarios could be crucial to gaining a deeper understanding of the meaning of olfactory stimuli. *Neuroethological approaches* would take inspiration in natural settings and behaviors, while focusing on tasks that couple sensation and behavior.

Given the active role of the neural networks, particularly in the primary processing centers, shaped by experience and shaping perception, how does the physiological organization discussed in section 2.3 arise? By the simplest model, a measure of ligand similarity and stimulus correlation could serve as the basis for spatial arrangement (e.g. Auffarth et al., 2011c). By this model, odor perception is not the basis of spatial organization, but, on the contrary, would be expected to emerge based on natural stimulus statistics. Experiments with children of different ages suggest that category formation is influenced increasingly with age by cognitive factors (Valentin and Chanquoy, 2012).

We argued that the combined analysis of the stimulus and of biological and computational mechanisms underlying perception and behavior may provide new insight into olfaction and its function. We discussed the organizing principles of smell in terms of physico–chemical properties, genetic makeup of the organisms, physiological activations, and perception. Understanding these structures can help in the generation of models of transformation between them. The aim of this review paper was to promote a systems perspective for understanding smell, thereby facilitating the visualization of steps to fill gaps in the current knowledge. We suggest that the study of the stimulus and the receptors, and the characterization of physiological responses and perceptual properties have the potential to enhance our understanding.

ACKNOWLEDGMENTS

The author thanks the anonymous referees, who made very useful and insightful comments, and gave even concrete suggestions that helped to raise the quality of this article considerably. He further thanks Dr. Timm Lochmann, Dr. Michael Schmuker, Isabelle Peres, and Gundula Meckenhäuser for extensive feedback regarding presentation and discussion. For the critical reading of draft versions that finally resulted in this paper he thanks professors Tony Lindeberg and Anders Lansner, Jan Pieczkowski, Bernhard Kaplan, and David Silverstein. The author apologizes to those colleagues the work of which he has not been able to cover for reasons of coherence of presentation and reasons of space. This work was partly supported by a scholarship from the EC-FP7-PEOPLE sponsored NAMASEN Marie-Curie Initial Training Network (grant n. 264872).

APPENDIX

[Figure 2 about here.]

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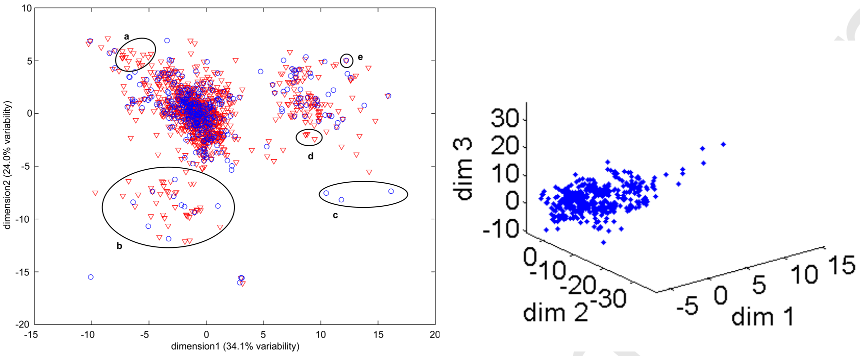
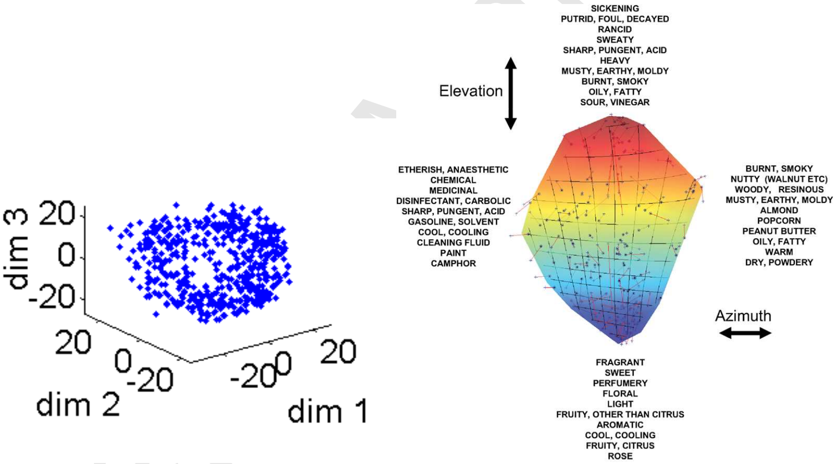


(a) Receptor space (b) Physico–chemical Space



(c) Activation space (d) Perceptual space

Figure 1: **Spaces of smell**. **A** — Isomap projection of receptors similarity based on distances between genetic coding regions of predicted binding pockets. Each dot stands for a receptor in humans (red) and mice (blue). Circles a–d indicate regions where binding sites of either human or mouse are over–represented. Circle e indicates a pair of human–mouse orthologs (MOR27-1 and OR52P1) with identical binding site. Source: Man et al. (2007). **B** — Multidimensional scaling (MDS) projection onto three dimensions of the 32–dimensional matrix of molecular properties proposed by Haddad et al. (2008a). Each point represents an odorant. **C** — MDS projection of Euclidean distances between glomerular odorant response patterns, computed based on data from Leon and Johnson (2006). **D** — MDS projection of odorant perceptual descriptors. Source: Koulakov (2011).

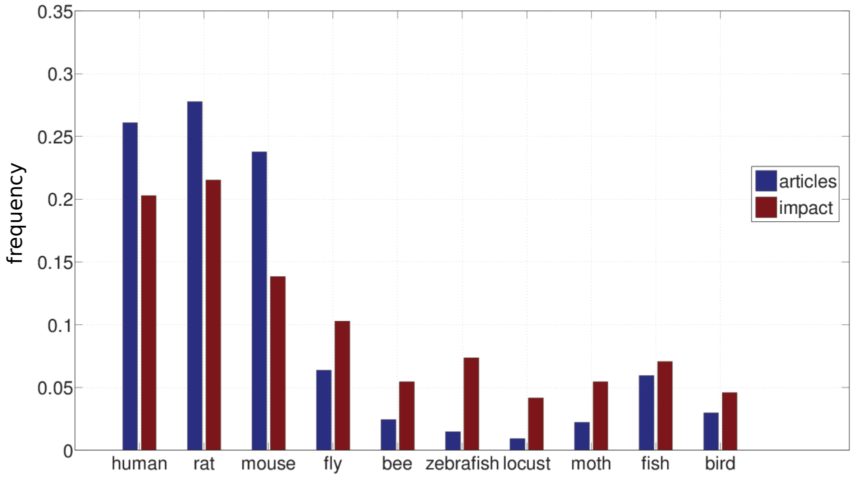


Figure 2: **Informal study of number of scientific articles and scientific impact of different animal models**. This bar chart shows each animal model estimates of the total number of articles and the number of citations. All values for articles and impact each are normalized to percentages of totals over all animals. These results should be taken with a grain of salt, because they depend on the formulation of search terms, connection to google servers, and possibly other factors. It constitutes an attempt to use google scholar to quantify the number of scientific articles for different animal models and the number of citations each. Google scholar was searched for the animal by their English and Latin names in conjunction with the words "olfactory OR olfaction." Citation analysis was conducted using the same search pattern in the software Publish Or Perish (Harzing, 2007) on the basis of google scholar. Impact refers to estimates of the total number of citations within the returned search results of a maximum of 1,000 papers. The results were relatively stable over repetitions. Results included 950,620 scholarly articles matching the terms. 751,653 citations could be taken into account (as of July 2012).