Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Neurobiology

# Measuring smells

Rafi Haddad[1,2], Hadas Lapid[1,2], David Harel[2] and Noam Sobel[1]

Olfaction consists of a set of transforms from a physical space of odorant molecules, through a neural space of information processing, and into a perceptual space of smell. Elucidating the rules governing these transforms depends on establishing valid metrics for each of the three spaces. Here we first briefly review the perceptual and neural spaces, and then concentrate on the physical space of odorant molecules. We argue that the lack of an agreed-upon odor metric poses a significant obstacle toward understanding the neurobiology of olfaction, and suggest two alternative odor metrics as possible solutions.

**Addresses**
[1] Department of Neurobiology, The Weizmann Institute of Science, Israel
[2] Department of Computer Science and Applied Mathematics, The Weizmann Institute of Science, Israel

Corresponding author: Haddad, Rafi (rhaddad@weizmann.ac.il) and Sobel, Noam (noam.sobel@weizmann.ac.il)

**Current Opinion in Neurobiology** 2008, **18**:438–444

This review comes from a themed issue on
Sensory systems
Edited by Tony Movshon and David P. Corey

Available online 3rd October 2008

0959-4388/$ – see front matter


**DOI** 10.1016/j.conb.2008.09.007

*What was required was a perfume penetrating enough to obscure the bouquet of rutting goat, yet not so overpowering that is called undue attention to itself: there was little to be gained by moving from one extreme to another on the olfactory scale*

*Jitterbug Perfume*
Tom Robbins

## Introduction

An *olfactory scale*, complete with the notion of units (*Alobars*), was a trivial assumption for Tom Robbins in *Jitterbug Perfume* [1], yet it has eluded both the perfumers practicing the creation of scents, and the scientists studying the mechanisms of their perception. The notion of probing neural coding in a sensory space not bound by a metric is puzzling. Imagine studying the neurobiological mechanisms of color vision without knowing that the color *orange* is a reflection of a stimulus at ~620 nm, red at ~700 nm, and blue at ~450 nm. Moreover, imagine studying such a system without a predictive framework that allows you to assume that orange *looks* more like red than like blue... Such is the current plight of olfaction research.

In studying sensory coding we are probing a transform from an olfactory physicochemical space, through an olfactory neural space, into an olfactory perceptual space. Elucidating the rules of these transforms depends on obtaining valid metrics for each of those spaces. Here we will briefly comment on the two latter spaces, and then concentrate on the notion of the olfactory physicochemical metric space as a necessary component toward understanding olfactory coding.

## Olfactory perceptual space

Perceptual spaces order odors such that distance in the space confers similarity: odors near one another in the spaces are expected to smell similar, and odorants distant from one another are expected to smell dissimilar. Initial efforts to develop a perceptual space assumed boundaries defined by odor primaries, namely a small set of odors from which all odor percepts could be composed [2–4]. This approach, however, failed to predict olfactory experience, and as the number of potential primaries grew, the strategy shifted from searching for individual odor primaries to searching for perceptual axes, along which these odorants may lay, and then use these axes to define a space. In practice, this amounted to applying various scaling methods to either similarity scores obtained from odorant comparisons [5–9], or to verbal descriptors applied to odorants [10–12,13••]. In contrast to the intuition of many, such verbal measures obtained from humans are highly reliable and stable across time and location [9,14], and spaces derived from such descriptors have been validated using the above-noted criteria whereby distance in the space predicted perceptual similarity. Such a perceptual space recently developed in our lab can be actively navigated by going to the *odor space* at www.weizmann.ac.il/neurobiology/worg. Whereas many studies have converged to suggest that the principal axis of these spaces, and hence of human olfactory perception, is odor pleasantness [15–22], there has been only minimal exploration of higher order axes within these perceptual spaces.

## Olfactory neural space

Olfactory neural spaces can be generated from neural responses obtained by a variety of methods in a variety of species [23–29,30•]. The most comprehensive of these efforts to measure the neural response to odors has given rise to an extensive database of odorant-induced activity, as measured with [$^{14}$C]-2-deoxyglucose on the surface of the rat olfactory bulb [31]. This database can be navigated at http://leonserver.bio.uci.edu/. The results of such measurements can then be used to formulate an olfactory space where, again, the concept of similarity serves as a

guiding principal: odorants that generate similar neural responses are proximal within such a space, and odorants that generate divergent neural responses are distant within the space [32,33]. Ideally, such spaces are then further linked to behavior or perception [34•,35–39].

## Comparing the spaces

As previously noted, elucidating olfactory coding depends on comparing three spaces: the physicochemical, neural, and perceptual. Although there are various ways to measure the physicochemical aspects of a molecule, none of these have given rise to an agreed-upon metric that can serve to compare one odorant molecule to another, or a molecule to its ensuing neural activity and percept. Here we will review several approaches to this problem, concentrating on what we think may be the more promising toward an agreed physicochemical odor space.

## Measuring odor quantity

Odor magnitude is odor concentration that can be controlled to a reasonable extent by odorant-generating devices known as olfactometers [40–42], and measured with analytical instruments such as photoionization detectors. The ability to control and measure odor concentration allowed uncovering the mostly simple relations between the physical, neuronal, and perceptual in this realm, whereby increases in concentration lead to increases in firing rate at the receptor [43,44] and spatial extent of activity in the bulb [45–47], as well as increases in perceived intensity. The latter can be captured by a simple logarithmic power function [48] with a slope of less than 1; that is, successive increases in stimulus concentration produce successively smaller increases in perceived intensity. The degree of this compression (i.e. the slope parameter) is odorant specific, reflecting the odorants' solubility in water [49]. Thus, the ability to measure and control the olfactory stimuli gave rise to a rule relating the physical property to neural representation, and to perception.

## Measuring odor quality

Whereas the physicochemical properties that determine odorant quantity are clear, the rules linking such properties to odor quality remain unknown. A first significant attempt at solving this problem, also referred to as the structure-to-odor response (SOR), was conducted by Amoore [50]. Amoore identified benzaldehyde as a prototypical molecule for an *almond* odor note, and then successfully predicted the *almondness* of other molecules on the basis of their three-dimensional structural fit to the reference molecule. This initial study was followed by a myriad of SOR efforts (comprehensively reviewed in [51]). These studies identified several molecular properties, such as molecular weight, length, bond type, electron donor, functional groups, and others [16,52], each of which had a somewhat predictable influence on subsets of odor qualities. However, all these models performed relatively poorly when novel odorants were evaluated [53]. Consequently, in probing the neurobiology of olfaction, researchers had gravitated toward using the practical approach of selecting odorants that differed in only one specific attribute (in most cases the number of carbon atoms). Although this approach has proved to be valuable to some extent [51], it is certainly inadequate for comparing any two randomly selected odorants. To summarize, to date there is no agreed-upon olfactory metric that enables universal odorant comparison.

## Generating an olfactory physicochemical metric

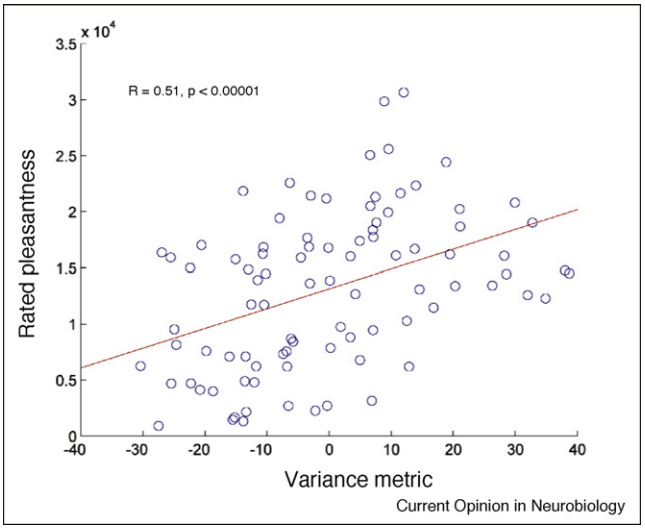
To measure and control olfactory stimuli qualitatively we need to identify the molecular features that govern the biological interaction. However, given the vast number of molecular features and the diversity of olfactory receptors across species, it is improbable that one particular molecular feature will dominate this interaction. In other words, it is improbable that a single physicochemical feature will influence an olfactory perceptual or neural axis in the way that the single physical features of wavelength or frequency dominate the perceptual axes of color and pitch in vision and audition. One possible bypass of this problem is to represent each odorant by a very large number of molecular descriptors, albeit captured in a single value. Here we describe two separate efforts we have made in this direction.

## A physicochemical odor metric that predicts olfactory perception

Single odorants may have many physicochemical features, and one expects these features to present themselves at various probabilities within the world of molecules that have a smell. These probabilities can be captured and represented by applying methods of statistical dimension-reduction to detailed molecular descriptions of odorants. To this end, in Khan *et al.* [13••] we used structural chemistry software (Dragon: http://www.talete.mi.it) to obtain 1664 molecular descriptors for more than 1500 odorants. We then applied principal components analysis (PCA), a well-established method for dimension-reduction that generates an orthogonal basis set for the profile space, in which each successive dimension has the maximal possible variance. Hence, the first principal component (PC), that can be considered as the first new feature or dimension, is the 'best' one-dimensional reflection of the data. Thus, PC1 of the 1664 molecular features of the ~1500 odorants can be used as a physicochemical metric for olfaction, where every odorant can be assigned a PC1 score.

The striking outcome of this exercise was that it revealed a significant correlation between the primary dimension (PC1) of physicochemical space and the primary dimension of perceptual space, namely odorant pleasantness. This correlation allowed us to predict the pleasantness of

**Figure 1**




The correlation between the variance metric (first principle component of molecular structure) and the estimated pleasantness of 90 different odorants as assessed by 20 subjects (note that these are not the same odorants used in Khan *et al*. [13••]).

odorants we had never smelled before (and that were not part of the model-building set), on the basis of their physicochemical structure alone (Figure 1). The main significance of this was not in identifying pleasantness as the primary dimension of olfactory perception (a notion well established [15–22]), nor in the ability to predict perceptual properties from structure (a feat previously achieved [51], albeit rarely for novel odorants not part of the model-building set), but rather in finding that the primary dimension of perception had a privileged link to PC1 of structure. In other words, the single optimal axis for explaining the variance in the physicochemical data was the best predictor of odor pleasantness. That this perceptual dimension is the best correlate of the most discriminating physicochemical measures suggests that, as with other senses, the olfactory system has evolved to exploit a fundamental regularity in the physical world.

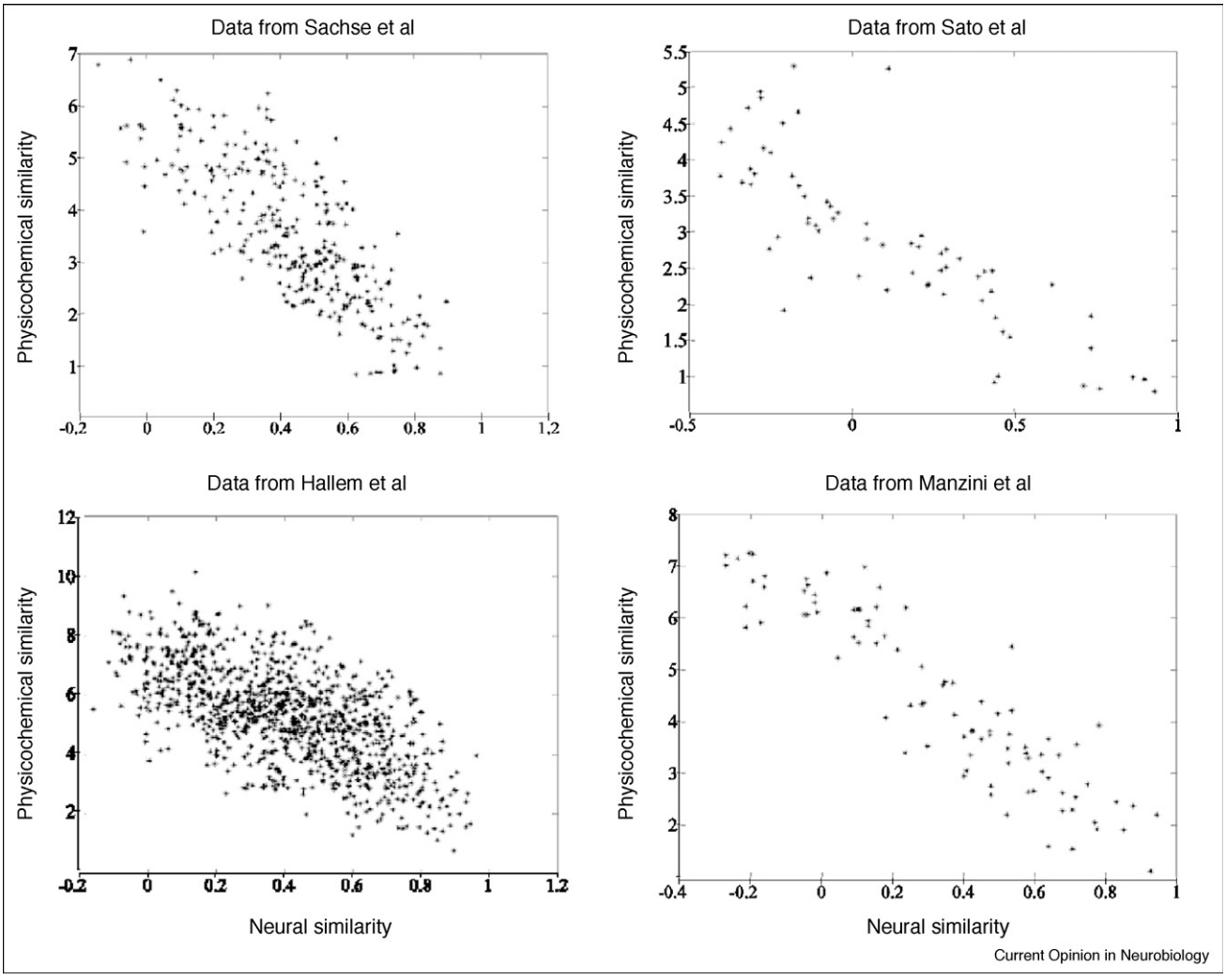
## A physicochemical odor metric that predicts neural response patterns

The above PC1 of physicochemical space is a single axis. However, it is multidimensional in the sense that 1664 known features contributed to it with known weights. In other words, we can represent each odorant as a single value reflecting its PC1 score, or we can represent each odorant as a vector of 1664 values. When using the former approach, the distance between two odorants is the difference in PC1 values. When using the latter approach, one can compute the distance between any two odorants by the square root of the sum of squares of the differences between the descriptors (Euclidean distance). To ask whether such a metric can be used to predict neural activity in the olfactory system, in Haddad *et al*. [54••] we revisited nine previously published datasets and analyzed a novel dataset, for which we knew the odorants used but did not know the neural response. These datasets consisted of different olfactory neurons (e.g. receptors; glomeruli), different model systems (e.g. fly; rat), different neuronal response measurement techniques (e.g. imaging; electrical recording), and odorants varying along different feature types (e.g. carbon chain-length; functional group). We found that this multidimensional metric generated predictions of neural activity that were not only statistically significant, but were also significantly better at accounting for neural responses than the particular metric used in each specific study (e.g. carbon chain-length) (Figure 2). In other words, this approach enabled us to use odorant structure in order to predict odorant-induced neural activity in nonhuman animals. Thus, it provided a generic method for comparing any number of structurally diverse odorants without predetermining the particular features important for each species. Moreover, the applicability of this metric across the different species tested, suggests that odor space is conserved across organisms [55••].

## The relation between the two proposed physicochemical metrics

We have presented two metrics; both on the basis of representing odorants using a very large number of molecular descriptors. The first metric, on the basis of the first PC of these descriptors (the axis best explaining their variance), enabled the prediction of perceptual attributes (pleasantness). We will call this the *variance metric*. The second metric, on the basis of Euclidean distances between odorants in the 1664 physicochemical space, enabled the prediction of odorant-induced neuronal response patterns. We will call this the *distance metric*. To probe the relation between these two metrics, we tested whether the variance metric that predicted perception in humans could similarly predict neural activity in other animals. In four out of eight datasets tested, we found a significant correlation between the variance metric and PC1 of neuronal response. That no correlation was found in the remaining four datasets may be explained by the relatively small size of these datasets combined with the sensitivity of the PCA method to noise. In turn, in cases where the number of neurons sampled or the noisiness of the measuring process renders the variance metric inaccurate, the distance metric that is on the basis of the full 1664-representation is less likely to err. Consistent with this, the distance metric indeed predicted neural response distances in all eight datasets we analyzed. Conversely, one can hypothesize a case where the distance metric will be less accurate than the variance metric. For example, if the direction of maximal variability of a set of odorants in the physicochemical space and in the perceptual space is similar yet the internal distance between these odorants in the two spaces is different (see Figure 3 for an illustration). This situation may be consistent with a

**Figure 2**




Correlation plots of four unrelated datasets [78,79••,80,81]. Each point in the graphs represents the distances between two odorants in both the neural space (difference in neural activity) and the distance metric (the metric used is the optimized metric described in Haddad *et al*. [54••]).

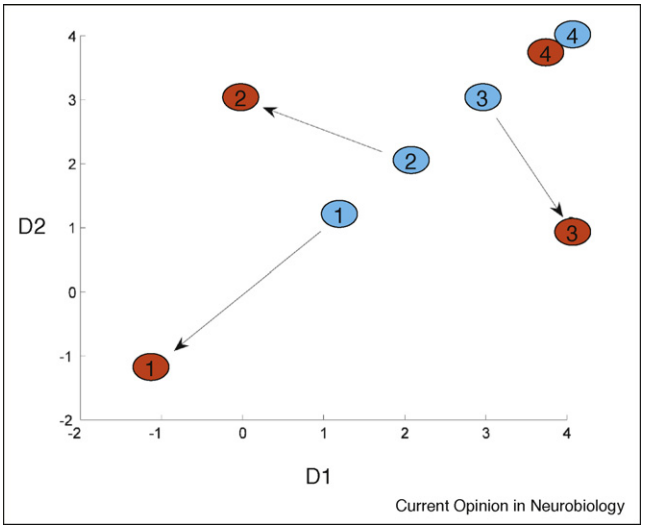
remapping from structural to perceptual that may occur at a the cortical level [56•,57].

## Electronic measurements of odors

A hidden assumption of the above-described physicochemical spaces is that they accept the general framework regarding olfactory transduction, referred to as the odotope approach [58–60]. Specifically, they assume that different olfactory receptors have different affinities to specific molecular structural physicochemical properties, and that the differential activation of these receptors gives rise to a spatiotemporal pattern of activity that reflects the odor. Despite a preponderance of evidence favoring this general framework, an alternative framework suggesting that olfactory receptors measure the molecular vibrational frequencies of molecules has been considered [61–63]. In the context of an olfactory metric, this vibrational approach is of course very appealing, because in its simplest form it would provide a single axis (vibrational frequency) that could serve to predict both perception and neural activity in the olfactory system. Some psychophysical tests of this theory, however, fail to support it [64]. Full consideration of this issue is beyond the scope of this manuscript, but regardless of how olfactory receptors do their business, this issue raises the possibility of generating an olfactory metric using an external odor measurement device, regardless of the device's mode of action. For example, we can use the values reported by mass spectrography (MS), gas chromatography (GC), IR spectra or Raman spectra, and most recently, electronic noses (eNose).

*eNoses* are analytic devices that are playing an increasing role as general-purpose odor analyzers [65]. eNoses are

**Figure 3**




An example for a case where the distance metric will be less accurate than the variance metric. The blue dots are four odorants plotted in 2D (e.g. perceptual space). The red dots are the same odorants in a different 2D representation (e.g. neuronal space), where two odorants have shifted considerably (dots 2 and 3). The axis of maximum variability of the odorants in the two representations remains similar (the main diagonal). Thus, the variance metric will provide a good fit within both spaces. However, the pair wise distances between odorants in the two representations differ considerably. Thus, the distance metric may fail to find a relation in one of the spaces.

cheaper than GCs, and are easier to use. The main component of an eNose is an array of nonspecific chemical sensors. An analyte stimulates many of the sensors in the array and elicits a characteristic response pattern. The sensors inside eNoses can be made of a variety of technologies, but in all cases a certain physical property is measured and a set of signals is generated. The stages of the recognition process are similar to those of biological olfaction, where a sensor responds to more than one odorant and one odorant activates more than one sensor. Together, the set of activated sensors and their signals characterize the odor. Different eNoses can be mapped onto one another [66] and used for odor classification [67–69] including classification of odor mixtures [70,71].

Initial efforts have been made to link eNose measurements to olfactory perception [72] and activity in olfactory receptor neurons [73]. If these links are substantiated, an eNose odor space can serve as a key tool to elucidating coding in olfaction [74]. This will hold true only if researchers agree on a particular eNose and a particular analysis, in order to allow comparisons across time and location.

## Conclusions

Our approach to generating and testing olfactory spaces was in fact quite fashionable in the late 1960s and early 1970s [8,16,19,75,76]. However, the limited computational powers commonly available at that time limited the scope of these efforts. For example, the efforts to generate physichochemical spaces typically used less than 20 molecular descriptors, and the efforts to generate perceptual spaces typically used only a few tens of odorants. The limited applicability of such efforts rendered this approach obsolete. The current availability of structural chemistry software offering thousands of molecular descriptors, combined with modern computational approaches such as PCA, and modern computing, together have allowed us to generate spaces consisting of thousands of odorants each described by thousands of molecular physicochemical descriptors and hundreds of verbal perceptual descriptors. These efforts have generated meaningful spaces, capable of predicting perception [13••], and neural responses [54••] to novel odorants. It is noteworthy that the increase in number of physicochemical descriptors represents more than merely an increase in power, but rather a shift toward describing the relevant space much in the way the mammalian olfactory system itself has tackled this task, with more than a thousand receptor types [77].

To conclude, Galileo said: 'Count what is countable, measure what is measurable. What is not measurable, make measurable'. Here we have highlighted two proposed odor metrics. Whether it is these metrics, some refined version of them, or some new metric, that end up deemed representative of the world of odor, the availability of such a metric remains a crucial must if we are to elucidate the neurobiology of olfaction.

## Acknowledgements

Authors RH and NS are supported by an FP7 Ideas Grant 200850 from the European Research Council. Author DH is supported by The John von Neumann Minerva Center for the Development of Reactive Systems of the Weizmann Institute of Science. We thank Arak Elite.

## References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Robbins T: *Jitterbug Perfume*. Bantam; 1984.
2. Henning H: *Der geruch*. Leipzig: Barth; 1916.
3. Amoore JE: **Evidence for the chemical olfactory code in man**. *Ann N Y Acad Sci* 1974, **237**:137-143.
4. Guillot M: **Anosmies partielles et odeurs fondamentales**. *CR Acad Sci* 1948, **226**:1307-1309.
5. Moskowitz HR, Gerbers CL: **Dimensional salience of odors**. *Ann N Y Acad Sci* 1974, **237**:1-16.
6. Woskow MH: **Multidimensional scaling of odors**. In *Theories of Odor and Odor Measurement.* Edited by Tanyolac N. Robert College; 1968:147-191.
7. Stevens DA, Oconnell RJ: **Semantic-free scaling of odor quality**. *Physiol Behav* 1996, **60**:211-215.
8. Schiffman SS: **Contributions to the physiochemical dimensions of odor: a psychophysical approach**. *Ann N Y Acad Sci* 1974, **237**:164-183.

9. Dawes PJD, Dawes MT, Williams SM: **The smell map: commonality of odour perception confirmed**. *Clin Otolaryngol* 2004, **29**:648-654.

10. Mamlouk, A.M.: **Quantifying Olfactory Perception**. University of Lubeck, Institute for Signal Processing, Lubeck, Germany. The thesis is available online at: http://www.inb.uni-luebeck.de:8084/publications/pdfs/Mada02.pdf.

11. Mamlouk AM, Chee-Ruiter C, Hofmann UG, Bower JM: **Quantifying olfactory perception: mapping olfactory perception space by using multidimensional scaling and self-organizing maps**. *Neurocomputing* 2003, **52–54**: 591-597.

12. Chee-Ruiter CWJ, Bower JM: **Representing odor quality space: a perceptual framework for olfactory processing**. In *Proceedings of the Sixth Annual Conference on Computational Neuroscience: Trends in Research, 1998: Trends in Research, 1998 Table of Contents*. 1998:591-598.

13. •• Khan R, Luk C, Flinker A, Aggarwal A, Lapid H, Haddad R, Sobel N: **Predicting odor pleasantness from odorant structure: pleasantness as a reflection of the physical world**. *J Neurosci* 2007, **27**:10015-10023.

This study describes a systematic link between an odor molecular structure and its perceived pleasantness, suggesting that olfactory pleasantness is partly written into nature much like visual color and auditory pitch.

14. Dravnieks A: **Odor quality: semantically generated multidimensional profiles are stable**. *Science* 1982, **218**:799-801.

15. Richardson JT, Zucco GM: **Cognition and olfaction: a review**. *Psychol Bull* 1989, **105**:352-360.

16. Schiffman SS: **Physicochemical correlates of olfactory quality**. *Science* 1974, **185**:112-117.

17. Godinot N, Sicard G: **Odor categorization by human-subjects — an experimental approach**. *Chem Senses* 1995, **20**:101.

18. Berglund B, Berglund U, Engen T, Ekman G: **Multidimensional analysis of 21 odors**. *Scand J Psychol* 1973, **14**:131-137.

19. Schiffman S, Robinson DE, Erickson RP: **Multidimensional-scaling of odorants — examination of psychological and physiochemical dimensions**. *Chem Senses Flavour* 1977, **2**: 375-390.

20. Steiner JE: **Human facial expressions in response to taste and smell stimulation**. *Adv Child Dev Behav* 1979, **13**:257-295.

21. Soussignan R, Schaal B, Marlier L, Jiang T: **Facial and autonomic responses to biological and artificial olfactory stimuli in human neonates: re-examining early hedonic discrimination of odors**. *Physiol Behav* 1997, **62**:745-758.

22. Engen T: *The Perception of Odors*. New York: Academic Press; 1982.

23. Johnson BA, Woo CC, Leon M: **Spatial coding of odorant features in the glomerular layer of the rat olfactory bulb**. *J Comp Neurol* 1998, **393**:457-471.

24. Meister M, Bonhoeffer T: **Tuning and topography in an odor map on the rat olfactory bulb**. *J Neurosci* 2001, **21**: 1351-1360.

25. Mori K, Nagao H, Yoshihara Y: **The olfactory bulb: coding and processing of odor molecule information**. *Science* 1999, **286**:711-715.

26. Manzini I, Brase C, Chen TW, Schild D: **Response profiles to amino acid odorants of olfactory glomeruli in larval *Xenopus laevis***. *J Physiol* 2007, **581**:567-579.

27. Hallem EA, Carlson JR: **The odor coding system of *Drosophila***. *Trends Genet* 2004, **20**:453-459.

28. Galizia CG, Sachse S, Rappert A, Menzel R: **The glomerular code for odor representation is species specific in the honeybee *Apis mellifera***. *Nat Neurosci* 1999, **2**:473-478.

29. Laurent G: **Olfactory processing: maps, time and codes**. *Curr Opin Neurobiol* 1997, **7**:547-553.

30. • Davison IG, Katz LC: **Sparse and selective odor coding by mitral/tufted neurons in the main olfactory bulb**. *J Neurosci* 2007, **27**:2091.

This study used more than 300 odorants to probe olfactory mitral cell responses. It provides insight on the relationship between odor structure and neural response.

31. Johnson BA, Woo CC, Hingco EE, Pham KL, Leon M: **Multidimensional chemotopic responses to *n*-aliphatic acid odorants in the rat olfactory bulb**. *J Comp Neurol* 1999, **409**:529-548.

32. Doving KB: **Odorant properties correlated with physiological data**. *Ann N Y Acad Sci* 1974, **237**:184-192.

33. Duchamp A, Revial MF, Holley A, Leod P: **Odor discrimination by frog olfactory receptors**. *Chem Senses* 1974, **1**:213-233.

34. • Youngentob SL, Johnson BA, Leon M, Sheehe PR, Kent PF: **Predicting odorant quality perceptions from multidimensional scaling of olfactory bulb glomerular activity patterns**. *Behav Neurosci* 2006, **120**:1337-1345.

Together with Ref. [55••] this study demonstrates how odors that elicit similar neural response tend to elicit similar behavior. This specific study used odors that differ from each profoundly and thus the observed behavior could not be simply predicted from the differences in odor structure.

35. Kent PF, Youngentob SL, Sheehe PR: **Odorant-specific spatial patterns in mucosal activity predict perceptual differences among odorants**. *J Neurophysiol* 1995, **74**:1777-1781.

36. Kent PF, Mozell MM, Youngentob SL, Yurco P: **Mucosal activity patterns as a basis for olfactory discrimination: comparing behavior and optical recordings**. *Brain Res* 2003, **981**:1-11.

37. Cleland TA, Morse A, Yue EL, Linster C: **Behavioral models of odor similarity**. *Behav Neurosci* 2002, **116**:222-231.

38. Linster C, Johnson BA, Yue E, Morse A, Xu Z, Hingco EE, Choi Y, Choi M, Messiha A, Leon M: **Perceptual correlates of neural representations evoked by odorant enantiomers**. *J Neurosci* 2001, **21**:9837-9843.

39. Ho SL, Johnson BA, Chen AL, Leon M: **Differential responses to branched and unsaturated aliphatic hydrocarbons in the rat olfactory system**. *J Comp Neurol* 2006, **499**:519-532.

40. Bodyak N, Slotnick B: **Performance of mice in an automated olfactometer: odor detection, discrimination and odor memory**. *Chem Senses* 1999, **24**:637-645.

41. Kobal G, Hummel C: **Cerebral chemosensory evoked potentials elicited by chemical stimulation of the human olfactory and respiratory nasal mucosa**. *Electroencephalogr Clin Neurophysiol* 1988, **71**:241-250.

42. Johnson BN, Sobel N: **Methods for building an olfactometer with known concentration outcomes**. *J Neurosci Methods* 2007, **160**:231-245.

43. Duchamp-Viret P, Chaput MA, Duchamp A: **Odor response properties of rat olfactory receptor neurons**. *Science* 1999, **284**:2171-2174.

44. Duchamp-Viret P, Duchamp A, Chaput MA: **Peripheral odor coding in the rat and frog: quality and intensity specification**. *J Neurosci* 2000, **20**:2383-2390.

45. Rubin BD, Katz LC: **Optical imaging of odorant representations in the mammalian olfactory bulb**. *Neuron* 1999, **23**:499-511.

46. Spors H, Grinvald A: **Spatio-temporal dynamics of odor representations in the mammalian olfactory bulb**. *Neuron* 2002, **34**:301-315.

47. Johnson BA, Leon M: **Modular representations of odorants in the glomerular layer of the rat olfactory bulb and the effects of stimulus concentration**. *J Comp Neurol* 2000, **422**:496-509.

48. Stevens SS: **On the psychophysical law**. *Psychol Rev* 1957, **64**:153-181.

49. Cain WS: **Odor intensity. Differences in exponent of psychophysical function**. *Percept Psychophys* 1969, **6**: 349.

50. Amoore JE: **Stereochemical and vibrational theories of odour**. *Nature* 1971, **233**:270-271.

51. Rossiter KJ: **Structureminus signOdor relationships**. *Chem Rev* 1996, **96**:3201-3240.

52. McGill JR, Kowalski BR: **Intrinsic dimensionality of smell**. *Anal Chem* 1977, **49**:596-602.

53. Sell CS: **On the unpredictability of odor**. *Angew Chem Int Ed* 2006, **45**:6254-6261.

54. •• Haddad R, Khan R, Takahashi YK, Mori K, Harel D, Sobel N: **A metric for odorant comparison**. *Nat Methods* 2008, **5**:425-429.
This study provides a metric for organizing odorants in a multidimensional space. This metric enables measuring distances between any two odorants so that close odorants will elicit similar neural response. This metric is shown to be applicable across different species and thus suggests that odor space is conserved across species (has also been shown in Ref. [55••]).

55. •• Kreher SA, Mathew D, Kim J, Carlson JR: **Translation of sensory input into behavioral output via an olfactory system**. *Neuron* 2008, **59**:110-124.
This study measured the response profiles of olfactory receptors in *Drosophila* larva and showed that the activity of small number of receptors correlates with the strength of the behavioral response and that odor spaces is conserved across larva and adult *Drosophila*.

56. • Gottfried JA, Winston JS, Dolan RJ: **Dissociable codes of odor quality and odorant structure in human piriform cortex**. *Neuron* 2006, **49**:467-479.
This work suggests that there are two regions for odor coding in the piriform cortex, whereby posterior regions encode quality (but not structure) and anterior regions encode structure (but not quality).

57. Wilson DA: **Rapid, experience-induced enhancement in odorant discrimination by anterior piriform cortex neurons**. *J Neurophysiol* 2003, **90**:65-72.

58. Buck LB: **Information coding in the vertebrate olfactory system**. *Annu Rev Neurosci* 1996, **19**:517-544.

59. Axel R: **The molecular logic of smell**. *Sci Am* 1995, **273**: 154-159.

60. Firestein S: **How the olfactory system makes sense of scents**. *Nature* 2001, **413**:211-218.

61. Brookes JC, Hartoutsiou F, Horsfield AP, Stoneham AM: **Could humans recognize odor by phonon assisted tunneling?** *Phys Rev Lett* 2007, **98**:38101.

62. Wright RH: **Odor and molecular vibration: neural coding of olfactory information**. *J Theor Biol* 1977, **64**:473-502.

63. Turin L: **A spectroscopic mechanism for primary olfactory reception**. *Chem Senses* 1996, **21**:773-791.

64. Keller A, Vosshall LB: **A psychophysical test of the vibration theory of olfaction**. *Nat Neurosci* 2004, **7**:337-338.

65. Gardner JW, Bartlett PN: **Electronic noses. Principles and applications**. *Meas Sci Technol* 2000, **11**:1087.

66. Shaham O, Carmel I, Harel D: **On mapping between electronic noses**. *Sens Actuators B: Chem* 2005, **106**:76-82.

67. Dutta R, Hines EL, Gardner JW, Boilot P: **Bacteria classification using Cyranose 320 electronic nose**. *Biomed Eng Online* 2002, **1**:4.

68. Turner AP, Magan N: **Electronic noses and disease diagnostics**. *Nat Rev Microbiol* 2004, **2**:161-166.

69. Mandenius CF: **Electronic noses for bioreactor monitoring**. *Adv Biochem Eng Biotechnol* 2000, **66**:65-82.

70. Carmel I, Sever N, Harel D: **On predicting responses to mixtures in quarz microbalance sensors**. *Sens Actuators B: Chem* 2005, **106**:128-135.

71. Carmel I, Harel D: **Mix-to-mimic odor synthesis for electronic noses**. *Sens Actuators B: Chem* 2007, **125**:635-643.

72. Burl MC, Doleman BJ, Schaffer A, Lewis NS: **Assessing the ability to predict human percepts of odor quality from the detector responses of a conducting polymer composite-based electronic nose**. *Sens Actuators: B Chem* 2001, **72**:149-159.

73. Haddad R, Carmel L, Sobel N, Harel D: **Predicting the receptive range of olfactory receptors**. *PLoS Comput Biol* 2008, **4**:e18.

74. Harel D, Carmel L, Lancet D: **Towards an odor communication system**. *Comput Biol Chem* 2003, **27**:121-133.

75. Amoore JE, Venstrom D: **Correlations between steriochemical assessments and organoleptic analysis of odourus compounds**. In *Olfaction and Taste II.* Edited by Hayashi T. Pergamon Press; 1967:3-17.

76. Amoore JE, Palmieri G, Wanke E: **Molecular shape and odour: pattern analysis of PAPA**. *Nature* 1967, **216**:1084-1087.

77. Buck L, Axel R: **A novel multigene family may encode odorant receptors: a molecular basis for odor recognition**. *Cell* 1991, **65**:175-187.

78. Manzini I, Peters F, Schild D: **Odorant responses of *Xenopus laevis* tadpole olfactory neurons: a comparison between preparations**. *J Neurosci Methods* 2002, **121**:159-167.

79. •• Hallem EA, Carlson JR: **Coding of odors by a receptor repertoire**. *Cell* 2006, **125**:143-160.
This is the first large-scale profiling of olfactory receptor neurons using more than 100 odorants. This dataset can be used to unravel the relationship between odor structure and neural response as was done in Refs. [54••,73].

80. Sato T, Hirono J, Tonoike M, Takebayashi M: **Tuning specificities to aliphatic odorants in mouse olfactory receptor neurons and their local distribution**. *J Neurophysiol* 1994, **72**:2980-2989.

81. Sachse S, Rappert A, Galizia CG: **The spatial representation of chemical structures in the antennal lobe of honeybees: steps towards the olfactory code**. *Eur J Neurosci* 1999, **11**:3970-3982.