Physicochemical influence on odor hedonics
Where does it occur first?

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We recently reported data showing that, while human olfactory pleasantness is modulated by semantic knowledge of smells, the physicochemical aspects of odorant molecules are prominent determinants of odor hedonic valence, especially in children and seniors, two age groups characterized by either low level of (children) or weak access to (seniors) odor semantic knowledge. Here, we present additional data from a human and an animal study, confirming that odorant structure predicts odor pleasantness and suggesting that this influence may be already engraved at receptor level.

Any environmental volatile molecule displaying certain properties (i.e., appropriate polarity, water solubility, vapor pressure, etc.) may be detected and discriminated by our olfactory receptors in the nasal cavity. Once odorant molecules and olfactory receptors bind, transduction can occur, and information is transmitted via the olfactory nerve to the olfactory bulb and via the lateral olfactory tract to primary and secondary olfactory cortices. One important aspect of olfaction is its salient affective dimension. Firstly, a particular odor can provide an early warning system against toxic substances (spoiled or toxic food, industrial pollutants), enabling such dangerous substances to be avoided. Secondly, olfaction plays a major role in hedonic pleasure. Positive affects evoked by food or flowers demonstrate how olfaction can make our life more pleasant. The origin of these olfactory affects is debated between two theories.

According to the first notion, odor hedonic valence is shaped by experience and learning. Humans, like other mammalian fetuses, are capable of olfactory learning in utero. Later on, during the first weeks of development, olfactory preferences can be modified by classical conditioning. In adulthood, olfactory effects are modulated by various factors including early exposure or even the context in which the stimulus is perceived (including verbal cues).

The second theory argues that odor hedonic valence can be predicted from the physicochemical properties of odorant molecules. In the visual and auditory modalities, perception can be predicted from the physical properties of the stimuli. In olfaction, it is agreed that physicochemical features of odorant molecules determine the olfactory percept (for example, esters smell fruity), but the rules governing such relationships remain to be determined. One obstacle to understanding is the high dimensionality of features describing both molecules and percepts. Using psychophysics, Khan and colleagues applied Principal Component Analysis (PCA) to a large set of molecules to reduce dimensionality in both odor percepts and physicochemical descriptors. Hedonics emerged as the primary axis of odor perception and more interestingly, the primary axis of physicochemical properties reflected the primary axis of odor perception, which was highly correlated with pleasantness. This model, in humans, allowed the hedonic valence of novel molecules to be predicted from their physicochemical properties alone, and was
successfully applied in mice, suggesting conservation across species.\(^\text{11}\)

Recently, we suggested that both types of determinant (“learning-type” and “physicochemical-type”) may interact in humans: semantic knowledge of smells influences prewired hedonic processing.\(^\text{1}\) Practically, we showed that children and seniors, two age groups characterized by either low level of (children) or weak access to (seniors) odor semantic knowledge, were more influenced by physicochemical properties than were young adults. Taken together, these findings suggest that hedonic processing of smell involves both prewired and learned components. Downstream of basic odorant encoding driven by physicochemistry, semantic knowledge is acquired, which in turn modulates olfactory affects.

At the neural level, however, one major issue in olfaction research is to know whether molecular features already influence odor pleasantness at the first level of processing, namely the receptor level. The present addendum seeks to provide some elements of response to this question. To this end, we used a dataset from a published study, consisting of single olfactory receptor neuron (ORN) responses to 20 different odorants (Fig. 1A), recorded in frog olfactory epithelium.\(^\text{12}\) Moreover, we performed a psychophysical experiment whereby human participants (n = 15; mean age: 32 ± 10 years; students or employees at the University of Lyon, France) were asked to rate the pleasantness and intensity of the same odorants on a scale from 1 (not at all intense, pleasant) to 9 (very intense, pleasant).

To reduce dimensionality in single cell responses, a PCA was carried out on the ORN dataset (a data matrix with 20 columns for the 20 odorants, and 60 lines
for the responses of 60 olfactory cells expressed in firing rates), using SYSTAT 7 software. The same analysis was performed with the physicochemical properties of odorant molecules (as in ref. 10). We looked for a correlation between the first principal component of the PCA on the ORN dataset (“ORN-PC1”, explaining maximum data variance) and the first principal component of the PCA run on odorant physicochemical properties (“molecular-PC1”).

Results revealed a significant correlation between ORN-PC1 and molecular-PC1 (r = -0.64, p = 0.002) (Fig. 1B). Moreover, molecular-PC1 also correlated significantly with odor pleasantness (r = -0.61, p = 0.003) (Fig. 1C) but not with odor intensity (r = 0.23, p = 0.32) (Fig. 1D) confirming that, for the current data set, molecular-PC1 did indeed reflect odor pleasantness. The exact meaning of molecular-PC1 is unclear: it is a composite physicochemical dimension that includes several parameters. Psychophysical studies, however, suggest molecular weight (MW) as a prominent factor in odor pleasantness.10,13,14 In line with this, a significant correlation was found in the present data between MW and molecular-PC1 (r = -0.99, p < 0.00001) (Fig. 1E) and between MW and odor pleasantness (r = 0.57, p = 0.008) (Fig. 1F), reflecting the notion that light-weight compounds are more aversive. In agreement with the above, a significant correlation between ORN-PC1 and MW was also found (r = 0.69, p = 0.0007) (Fig. 1G).

In conclusion, these findings show that odorant physicochemical properties predict both ORN activation in frog and odor pleasantness in humans. While further work is needed to explore a direct link between olfactory preference based on the physical properties of the molecules and ORN response in the same species, the present results strengthen the hypothesis that (1) the olfactory system decodes odor valence from molecular properties and (2) this encoding may already operate at the level of the olfactory epithelium.

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