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Review

New ways to understand aroma perception

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Abstract

Orthonasal or retronasal presentation of odorants evokes different responses. To study this phenomenon in depth, a stimulation technique has been developed that allows ortho- or retronasal presentation of chemosensory stimuli, the release of which is precisely controlled. Based on this technique studies have been conducted using psychophysical, electrophysiological, and imaging techniques. In conjunction with clinical data the results clearly suggest that there are differences in the perception of ortho- and retronasal stimuli. The basis for this phenomenon may be found in ideas by Mozell and colleagues with regard to odorant absorption across the mucosa which may determine activation of the olfactory epithelium.

Keywords: Retronasal olfaction; Smell; Psychophysics; Trigeminal; Electrophysiology

Contents

1. Introduction

Aroma stimuli reach the olfactory epithelium usually through two pathways: via the nose, during sniffing, and via the mouth, during eating or drinking (Fig. 1). Three major chemosensory systems are implied in the perception of these stimuli: smell, taste, and trigeminally mediated sensations.

Commonly referred to as "smell", orthonasal olfaction processes olfactory stimuli from the external environment, traveling through the anterior nares towards the olfactory mucosa during nasal inhalation or sniffing. It appears that an infinite number of chemical stimuli can be perceived through orthonasal olfaction, providing information

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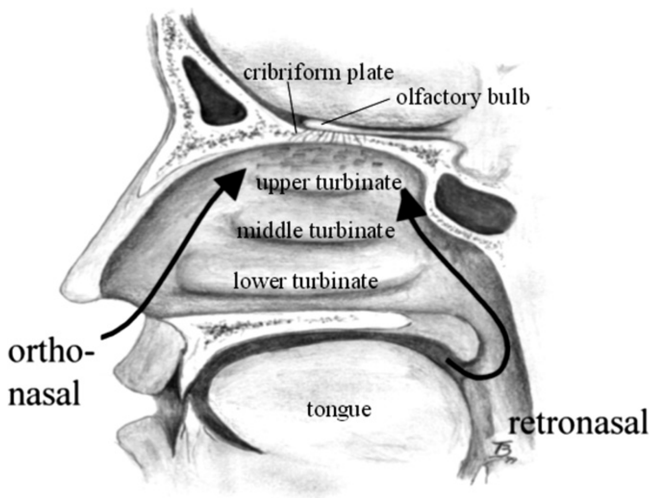

Fig. 1. Schematic drawing of the nasal cavity with the lower, middle, and upper/superior turbinates. The olfactory bulb/peduncle as the first relay station of olfactory processing (it is here where axons from olfactory receptor neurons synapse with mitral cells) is lying in the olfactory sulcus located just above the cribriform plate. The olfactory epithelium is found in the top of the nasal cavity, largely beneath the cribriform plate. Airflow in relation to orthonasal (through the nostrils) or retronasal (from the mouth/pharynx to the nasal cavity) presentation of odors to the olfactory epithelium is indicated by thick arrows. We would like to thank Thomas Beleites for the drawing.

regarding the environment with particular interest in aspects related to food, danger, or social interactions and integration (Spors & Grinvald, 2002).

The second pathway for aroma perception is frequently combines taste and olfactory stimulation. During mastication, odorous molecules are released. During exhalation or swallowing, they reach the nasal cavity through the pharynx, stimulating receptors in the olfactory cleft. This is defined as *retronasal olfaction* which provides major basis for olfaction being related to our quality of life (Hummel & Nordin, 2005). As the odorant source for retronasal stimulation is in the oral cavity or the esophagus/stomach, the range of perceived stimuli is typically food-related. Furthermore, stimuli perceived through this pathway are referred to the mouth (Murphy et al., 1977; Rozin, 1982). Consequently smell – taste confusions have been described frequently. (Murphy & Cain, 1980; Murphy et al., 1977; Rozin, 1982).

1.1. Differences between ortho- and retronasal olfaction

Starting with Rozin's observation of olfaction being a dual system (Rozin, 1982), many studies have focused on qualitative and quantitative comparisons of orthonasal and retronasal olfaction. A number of mechanisms have been identified to explain the results obtained (Heilmann & Hummel, 2004; Heilmann et al., 2002; Homma et al., 2003; King et al., 2006; Landis et al., 2005; Landis et al., 2003; Marian Espinosa Diaz, 2004; Marie et al., 1987; Pfaar et al., 2006; Pierce & Halpern, 1996; Rombaux et al., 2006; Small et al., 2005; Sun & Halpern, 2005).

Differences in *airflow patterns* through the two pathways have been implied to account for ortho and retronasal perceptual differences. This was first suggested by Mozell (Mozell, 1970) in his chromatographic model of olfaction. He hypothesized that the direction of odor movement across the olfactory epithelium could lead to differences in the processing of this signal. Further on, evidence of perceptual differences induced by changes in anatomical compartments of the nose (Damm et al., 2002; Leopold, 1988; Sobel et al., 1999; Zhao et al., 2004) supported the importance of flow characteristics in ortho and retronasal olfaction (see also Raudenbush & Meyer, 2001).

2. Interaction of ortho- and retronasal olfactory stimuli with other sensory modalities

Interaction with other chemical senses also was hypothesized to account for perceptual differences for stimuli experienced orthonasally or retronasally. Burdach and colleagues reported a suppression of retronasal aroma by taste (Burdach et al., 1984). Slotnick et al. reported enhancement of taste aversion in rats only for retronasally presented odors (Slotnick et al., 1997). In addition to this, different brain activation patterns were identified by Small and colleagues for interaction between taste and orthonasally or retronasally presented stimuli (Small et al., 1997; Small et al., 2004). In these two studies, significant deactivation in the orbitofrontal cortex, insula, and anterior cingulate cortex was described for taste-orthonasal stimulus association, while a supra-additive response was registered at the same regions for the combination of taste and retronasal stimuli. It was also pointed out that previous experience with taste-odor association might be responsible for this type of response. In contrast, Sakai et al. (2001) described odor-induced taste enhancement for both orthonasal and retronasal olfaction and reported little functional difference between the two olfactory aspects. Correspondingly, using fMRI, Cerf-Ducastel and Murphy no major differences for brain activation for orthonasal or retronasal delivery of odorous stimuli (Cerf-Ducastel & Murphy, 2001).

As most odorous stimuli have also a trigeminal component (Doty et al., 1978), many studies focused on the *interaction between the trigeminal and the olfactory system* (Cain & Murphy, 1980; Frasnelli et al., 2006; Hummel & Livermore, 2002; Husner et al., 2006; Brand, 2006). Using electrophysiological and psychophysical measures, it was shown that mechanical and trigeminal chemosensory stimuli are perceived differently depending on the site of stimulation with a most accurate perception in the anterior portion of the nasal cavity for chemosensory stimuli, and a higher sensitivity in the posterior portion following mechanical stimulation (Frasnelli et al., 2004). It has been hypothesized that these differences might contribute to the different perception of orthonasal and retronasal olfactory stimuli.

Further, Koza et al. (2005) reported differential *effects of colours* on odor intensity, with specific enhancement when stimuli were presented orthonasally, and suppression when odorous stimuli were presented retronasally. *Texture* did not appear to differentially influence ortho and retronasal odor perception, as suppression of flavor intensity by increased thickness regardless whether the stimuli were presented ortho or retronasally (Bult et al., 2007; Cook et al., 2005; Hollowood et al., 2002; Visschers et al., 2006; Weel et al., 2002). In contrast, odorous stimuli increased the intensities of thickness and creaminess, but only when the odor was presented retronasally (Bult et al., 2007). This enhancement was most pronounced when odor presentation coincided with swallowing.

3. Presentation of chemical stimuli as key to the investigation of differences between ortho- and retronasal function

One important problem in the investigation of these issues relates to the presentation of odorous stimuli. Halpern pointed out that ortho- and retronasal stimuli should reach the olfactory mucosa through the two distinct pathways, without producing additional gustatory or mechanical stimuli (Halpern, 2004). Studies employing liquid or solid stimuli in direct contact to the oral cavity cannot allow direct comparisons to orthonasal olfaction as gustatory, thermal and mechanical sensations from the oral cavity interact with olfactory mediated sensations. To avoid this situation, Halpern and colleagues used liquid extracts of food products as odorants placing them intra-orally in containers to prevent contact between the odorants and the oral mucosa (Halpern et al., 2000; Sun & Halpern, 2001; Sun & Halpern, 2005; Wininger, 1999). Others (Voirol & Daget, 1986) had subjects sniff the head space of an odorous liquid or inhale the same head space through the mouth followed by nasal exhalation (see also Duffy et al., 1999; Homma et al., 2003). However, an important limitation of these method is the unknown odor concentration in the oral cavity and the mechanical stimulation of tongue, palate, and teeth produced by the intra-oral container which is problematic, especially in the context of research indicating that mouth movements enhance retronasal odor perception. Further on, swallowing provides higher intensity ratings than spitting, emphasizing that retronasal olfaction is a dynamic process (Burdach & Doty, 1987; Land, 1996).

The complex interactions following real time aroma release in the oral cavity (mouth and tongue movement, swallowing, saliva level, mucosal adsorption, etc.) and their consequence on retronasal perception have received increased attention in the last years (Buettner et al., 2001; Buettner et al., 2002; Haahr et al., 2004; Hodgson et al., 2003; Hodgson et al., 2005; Pionnier et al., 2004).

4. New approaches to study potential differences between orthonasal and retronasal olfaction – the model

To achieve more defined retronasal stimulation, a new device was developed (Heilmann & Hummel, 2004) which allows the release of odors directly into the epipharynx above the soft palate. This avoids concomitant oral gustatory, thermal and mechanical stimulation, thus permitting the study of ortho or retronasal olfaction in isolation. Specifically, two soft plastic tubes of 3.3 mm outer diameter and 15 cm length are attached to each other so that the openings of the two tubes are 6 cm apart. Tubes are cut from a sterile suction catheter made from soft polyvinyl chloride. The tubes are placed inside the nose under endoscopic control such that the opening of one of the tubes is just beyond the nasal valve (approximately 1.5 cm from the naris) and the opening of the other tube is in the epipharynx (approximately 7.5 cm from the naris). The openings of the two tubes are at approximately the same distance (an estimated 6–9 cm) from the center of the olfactory epithelium (Fig. 1). The tubes are attached to the nose by adhesive tape, so that the "retronasal" tube, ending in the epipharynx, is placed beneath the "orthonasal" tube, ending in the nasal vestibulum.

For stimulus presentation, the tubes are connected to outlets of a computer-controlled air-dilution olfactometer (OM6b; Burghart, Wedel, Germany). This stimulator allows application of rectangular-shaped pulses of chemical stimuli. Mechanical stimulation is avoided by embedding these stimuli into a constant flow of odorless, humidified air of controlled temperature (80% relative humidity, total flow 8 l/min, 36 °C) (Kobal, 1981; Kobal, 1985).

To ascertain that odors presented through the two routes reach the olfactory cleft in a comparable manner, measurements of odor concentrations have been taken in the olfactory cleft. To this end, a thin Teflon™ tube (outer diameter 0.8 mm, inner diameter 0.3 mm) was placed in the olfactory cleft under endoscopical control. The end of this tube of 30 cm length was connected to an "electronic nose" (model DL1000 IS; Sensobi GmbH, Halle, Germany) with a relatively high temporal resolution. Results of these measures in the olfactory cleft indicated that the route of odor administration had no major effect on either time-course or maximum concentration of measured odor concentrations at the level of the olfactory epithelium (Small et al., 2005).

5. Results obtained with that model

In the following results from selected experiments will be described briefly together with a short discussion of the most relevant findings.

Determination of thresholds to ortho- and retronasal stimuli (Heilmann & Hummel, 2004): Considering the contradictory information existing in the literature, a first application of this method aimed to evaluate the perception of odors presented orthonasally and retronasally. As the context of the odor might play a role in possible differences between ortho- and retronasal odor perception (Small et al., 2001) a food-related (chocolate) and a non-food-related (lavander) odor was investigated. Analysis of variance showed a significant effect for the factor "site of stimulation", but not for the factor "odorant". Post-hoc comparisons indicated that orthonasal thresholds for both lavender and chocolate were significantly lower than retronasal thresholds.

These results confirmed work by Voirol and Daget (1986). Their experiments indicated higher thresholds and, accordingly, decreased suprathreshold responsiveness for retronasal presentation of air phase vanillin and citral compared to orthonasal stimulation, but the result was attributed to flow rate differences. On a suprathreshold level Pierce and Halpern (1996) reported a diminished ability of odor identification through the retronasal pathway using the oral presentation of the vapor phase of solid odorous substances. They found odor identification to be significantly better when odors were presented orthonasally during normal breathing. When subjects used velopharyngeal closure as a specific breathing technique (Kobal, 1981) that leveled flow rate differences between the two pathways, retronasal odor identification was still less effective than orthonasal odor identification, but the effect was no longer significant. This confirmed the previous observation of Voirol and Daget (see above) concerning the influence of respiratory parameters in the different perception of orthonasal and retronasal smelling and was subsequently viewed as an argument against the "olfactory duality" claimed by Rozin (1982). However, an important limitation of the study was the relatively small number of items used to assess odor identification abilities, leading to a ceiling effect. Using olfactory threshold measurements, Duffy et al. (1999) reported greater impairment for retronasal than for orthonasal perception in elderly people, but this was correlated to oral conditions that influenced chewing and mouth movements.

The higher thresholds to retronasally presented stimuli seem to be explained by the fact that under natural conditions, the concentration of odorant reaching the olfactory cleft through the retronasal pathway is much higher than during orthonasal perception of odors due to intraoral salivation, warming, and mastication (Burdach et al., 1984).

Cross-modal interactions of texture and aroma perception (Bult et al., 2007; Visschers et al., 2006): During oral processing foods are subjected to a physical process that includes changes in temperature, mechanical deformation and effects caused by saliva such as dilution and enzymatic breakdown of certain food ingredients as, for example, starch (de Wijk et al., 2004). During oral processing nonvolatile compounds responsible for producing basic tastes are able to diffuse into the saliva and subsequently reach the gustatory receptors. Furthermore, during oral processing and after swallowing, volatile aroma compounds are released from the food matrix into the air and are thus able to flow to the olfactory epithelium where they interact with olfactory receptors. During these processes, the different senses interact in a non-linear way and several cross-modal phenomena take place, in which texture and taste influence the perception of the aroma (and vice versa) of a food product (Cook et al., 2003; Cook et al., 2003; Hollowood et al., 2002; Hort and Hollowood, 2004; Lethuaut et al., 2004; Pfeiffer et al., 2005; Rolls, 2005; Stevenson et al., 1999; Weel et al., 2002).

To assess the influence of orthonasal and retronasal stimulation on cross-modal interactions between texture and flavor perception of food, a series of experiments have been conducted. Healthy volunteers were exposed to strawberry aroma pulses delivered by the stimulator described above (Visschers et al., 2006). Just prior to exposure to the aroma, subjects consumed water, custard, or protein gels with different textures without any added aroma. The aroma was delivered as a sequence of aroma pulses, either orthonasally or retronasally. The time between oral consumption of the food, including swallowing, and the exposure to the aroma varied between 0.5 and 6.5 s. It was observed that the intensity of aroma decreased with increasing firmness of the food that was consumed. Aroma pulses delivered 6.5 s after swallowing were perceived as being more intense as compared to aroma pulses delivered immediately after swallowing. In conjunction with late delivery, the effect of cross-modal interactions apparently decreased. Significantly higher odor intensities were reported for the aroma stimuli supplied orthonasally in comparison to retronasal administration. The observed cross-modal effect of texture on aroma intensity was not significantly altered by the mode of aroma delivery, i.e., orthonasal or retronasal stimulus administration. These results suggest that *differences in texture can lead to differences in aroma intensity*. Using the current experimental protocol, however, these cross-modal texture aroma interactions did not depend on orthonasal or retronasal stimulation, which points to a higher-level central-nervous origin of this phenomenon.

Odorous stimuli have also been shown to increase the intensities of thickness and creaminess, but only when the (butter) odor was presented retronasally (Bult et al., 2007). This enhancement was most pronounced when odor presentation coincided with swallowing. Thus, the investigation of multi-modal interactions appears to depend not only on the questions being asked and the odors being used (for example, whether they are contextually congruent with the orally administered texture or not), but also with the time during oral processing, including swallowing, when measurements are being obtained.

Comparison of orthonasal and retronasal perception of odors using functional MR imaging (Small et al., 2005): Imaging techniques allow to investigate differences between ortho- and retronasal olfaction at a central-nervous level (see Fig. 2). Considering intriguing preliminary observations (Small et al., 2001) response patterns to orthonasal and retronasal stimulation were investigated in a fMRI study. Three "non-food" odors, different regarding their physicochemical properties (butanol – hydrophilic, farnesol – lipophilic) and their association with food (chocolate) or non-food (lavender) were delivered both ortho and retronasally.

Collapsed across odorants, significant retronasal activation was found at the base of the central sulcus, corresponding to the primary representation of the oral cavity (Pardo et al., 1997; Yamashita et al., 1999). This may reflect the fact that *retronasal odors are referred to the mouth*.

When analyzing effects for chocolate odor (which was perceived at the same intensity and as pleasant when presented ortho- or retronasally), retronasal presentation of chocolate produced preferential activation in the medial orbitofrontal cortex and in the peri-genual cingulate, superior temporal gyrus, and posterior cingulate cortex. Comparison of orthonasally vs retronasally presented chocolate produced activation in the thalamus, right caudolateral orbitofrontal cortex (OFC) and right hippocampus, frontal operculum bilaterally, temporal operculum/ventral bilaterally, right temporal-parietal operculum at the level of the supramarginal gyrus, left anterodorsal insula and right anterior insula. These results indicate that *the neural processing of an odor may be influenced by route of administration*. Consequently, this observation provides support for Rozin's theory of olfaction as a dual sense modality. The fact that the magnitude of route of delivery effect was greater for a food odor implies that conditioned association differences exist between ortho- and retronasal perception. Its *processing may be related to differential reward circuits for food but not non-food odors* (Berridge, 1996). As sustained by the results of this study, orthonasal olfaction appears to correlate to the anticipatory phase in food reward, whereas retronasal olfaction relates to the consumatory phase, receipt of a reward.

6. Clinical observations in patients with nasal polyposis with regard to ortho- or retronasal presentation of chemosensory stimuli

Considering its contribution to flavor perception and perceptual association with consumption of food, retronasal olfaction has received much interest in a food related context (Shepherd, 2006) which was not mirrored by the clinical community (Guettich, 1961). During the last years, however, a series of clinical studies reported quantitative differences between ortho- and retronasal smelling. Defects in retronasal smelling in the absence of orthonasal deficits have been described by Cowart et al. (Cowart et al., 2003; Cowart et al., 1999) (a list of possible causes of olfactory loss is presented in Table 1). In addition, better retronasal than orthonasal olfactory function, meaning impaired smell with preserved flavor perception, has been reported in patients with nasal polyposis (Landis et al., 2003). This is thought to be related to the presence of mechanical obstruction in the anterior portion of the olfactory cleft (Pfaar et al., 2006).

However, *rare cases of olfactory loss without altered flavor perception in the absence of nasal polyposis have been reported* starting with early descriptions of olfactory dysfunctions as the one of Ogle in 1870. Landis et al. (2005) investigated this clinical observation using psychophysical and electrophysiological approaches. They identified 19 patients with loss of orthonasal olfactory function while flavor perception was virtually not affected. On detailed questioning these patients confirmed that they still enjoyed the pleasures of different tastes during eating and drinking. Following a through clinical workup, excluding the presence of nasal polyps and ascertaining an open olfactory cleft, psychophysical testing revealed normal or slightly altered retronasal olfaction, while orthonasal olfaction was either absent or severely compromised. At an electrophysiological level, in response to orthonasal stimulation there were no detectable olfactory event-related potentials (OERP) or OERP with small amplitudes, while OERP to retronasal stimulation were clearly present in some patients.

These results suggest on a clinical level that orthonasal and retronasal olfaction is processed differently. Routine

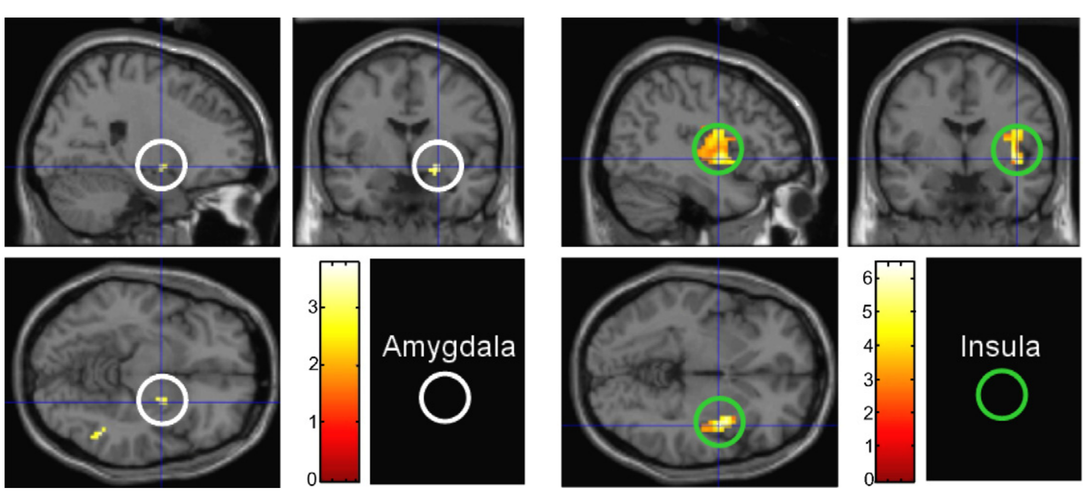

Fig. 2. Results from functional magnetic Resonance Imaging (fMRI) – typical response patterns are shown to orthonasal activation with hydrogen sulfide (H2S) which, among other effects, produced both activation in the amygdala (left; light grey circles) and the insular cortex (right; green circles). The bars indicate the degree of activation from dark red (lowest) to yellow/white (highest degree of activation). (For interpretation of the references in colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Most frequent causes of olfactory loss (from Damm, M., Temmel, A., Welge-Lüssen, A., Eckel, H.E., Kreft, M.P., Klussmann, J.P., et al. (2004). Epidemiologie und Therapie von Riechstörungen in Deutschland, Österreich und der Schweiz. *HNO 52*: 112–120

Cause	Frequency (%)	Specific remarks
Sinunasal (including polyps, chronic sinusitis)	72	Slow decrease of olfactory function over the years; good prognosis; can be treated either surgically or medically
Trauma	5	Typically found after blow to the back of the head
Infection of upper respiratory tract	11	Increased frequency in women above the cage of 50 years
Congenital	1	Frequently noted for the first time during puberty
Idiopathic (unknown)	6	Possible causes: neurodegenerative diseases, e.g. Parkinson's disease
Toxicity (drugs, environmental causes)	2	Olfactory system appears to very resilient to drug effects

clinical testing of retronasal olfaction seems to be of exquisite interest. It is possible with simple test kits that have been validated for such purposes (Heilmann et al., 2002).

7. Conclusion

Psychophysical, electrophysiological and imaging data together with clinical observations point to differences in processing of orthonasal and retronasal olfactory information. The basis for this phenomena may be found in ideas by Mozell and colleagues (Kent et al., 2003; Mozell, 1966; Mozell et al., 1969; Mozell & Jagodowicz, 1973) with regard to odorant absorption across the mucosa which may determine olfactory activation.

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