# Intranasal Volume and Olfactory Function

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# Abstract

The aim of this exploratory study was to identify the volume intranasal segments as they relate to parameters of olfactory function. Fifty healthy male volunteers (age range 22–59 years, mean age 28.5 years) were included. Olfactory function was measured by lateralized phenyl ethyl alcohol odor thresholds and odor discrimination, and by bilateral odor identification. Magnetic resonance imaging of the nasal cavity was performed immediately following olfactometry. To correlate the results of olfactometry with intranasal volume, each nasal cavity was divided into 11 segments. Significant correlations were found between the odor thresholds and volumes of the anterior part of the lower and upper meatus of the right nasal cavity. These results reveal that two nasal segments are important for inter-individual differences of odor thresholds in healthy subjects: (i) the segment in the upper meatus below the cribriform plate and (ii) the anterior segment of the inferior meatus. The latter finding is of special interest for nasal surgery, which allows modification of this volume through resection of the inferior turbinate and/or septoplasty.

# Introduction

Shape and volume of the nasal cavity influence olfactory function (Masing, 1967; Youngentob *et al.*, 1986; Keyhani *et al.*, 1997). They have a strong impact on intranasal airflow (Scherer *et al.*, 1989; Kelly *et al.*, 2000) and thus on the number of odorant molecules transported to the olfactory epithelium (Tonosaki and Tucker, 1985; Hornung *et al.*, 1987; Keyhani *et al.*, 1997). Several studies have focused on the relationship between the intranasal airflow and olfactory function (Youngentob *et al.*, 1986; Eccles *et al.*, 1989; Hornung *et al.*, 1997; Damm *et al.*, 2000).

Only two studies have quantitatively investigated correlations of human olfactory function and nasal volumetrics (Leopold, 1988; Hornung and Leopold, 1999). Leopold studied the relationship between bilateral human olfaction and nasal anatomy in 34 hyposmic patients. Olfactory function was assessed with an odor identification test (odorant confusion matrix, OCM), and nasal anatomy was evaluated using computed tomography (CT). Leopold identified three areas influencing olfaction. These areas were located beneath and anterior to the cribriform plate, and in the space in the posterior portion of the nose and below the cribriform plate. In a later study (Hornung and Leopold, 1999) unilateral measurements confirmed the findings of the first study. To date, however, no data are available about nasal anatomy and olfactory function in subjects without nasal pathology. The aim of the present exploratory study was to identify intranasal volumes that are related to olfactory function in normosmic subjects.

# Materials and methods

#### Study design

The current exploratory study was performed as an open trial in healthy subjects. Analysis of intranasal volumes was observer-blinded.

#### Subjects

The study was performed according to the ethical principles for medical research involving human subjects (World Medical Association, 2000). Informed written consent was obtained following oral and written explanation of aims and potential risks of the study. Fifty healthy volunteers (mean age 28.5 years, range 22–59 years) participated. To exclude gender as a possible source of variation in olfactory function, only male subjects were recruited (Doty, 1986).

#### Procedure

The following procedures were performed in all subjects in chronological order: (i) medical history; (ii) self-assessment of olfactory sensitivity and nasal ventilation; (iii) active anterior rhinomanometry; (iv) psychophysical measurements of olfactory function (odor detection thresholds, odor discrimination, odor identification); and (v) anatomical measures using magnetic resonance imaging (MRI). To minimize the potential effects of variations in nasal airway congestion on olfactory function, 0.15 mg oxymetazoline (Nasivinetten<sup>®</sup>, Merck Darmstadt, Germany) (Hummel et al., 1998b) were administered to each nostril after the history was recorded and self-assessments had been made (Kayser, 1895; Hasegawa and Kern, 1977; Eccles, 2001). Oxymetazoline was shown to have little or no influence on olfactory function in healthy subjects (Hummel et al., 1998b; Temmel et al., 1999). Rhinomanometry, olfactometry and MRI were performed sequentially, with breaks of <5 min between tests (duration of all measurements  $\sim 2$  h). This tight schedule was thought to be necessary as olfactory function appears to exhibit a certain day-to-day variability, and can even show fluctuations within a single day (Stevens et al., 1988; Lotsch et al., 1997) [see also (Kendal-Reed et al., 2001)].

#### Medical history

A detailed history ascertained the absence of diseases with potential impact on olfaction, including major head trauma, nasal or sinusoidal disease, neural or endocrinological disorders, or previous nasal surgery. All subjects were in excellent health; none of them reported significant olfactory dysfunction. Normosmia was verified by means of the 'Sniffin' Sticks' test (Hummel *et al.*, 1997; Kobal *et al.*, 2000).

#### Ratings of olfactory sensitivity and nasal ventilation

Ratings of olfactory sensitivity and nasal ventilation were obtained using visual analogue scales (VAS) of 10 cm length (left-hand end: 'no olfactory sensitivity' or 'totally blocked nasal airways', respectively; right-hand end: 'extremely high olfactory sensitivity' or 'extremely easy nasal breathing', respectively).

#### Active anterior rhinomanometry

A computer-aided rhinomanometer (Rhinodat K, Heinemann, Hamburg, Germany) was used for measurements of the nasal flow, with a tight-fitting facemask and integrated flow meter. The inspiratory airflows in cm<sup>3</sup>/s at 150 Pa (measured 10 min after decongestion) were subsequently submitted to statistical analysis.

### Measures of olfactory function

Olfactory function was evaluated using the 'Sniffin' Sticks' test battery (Hummel *et al.*, 1997; Klimek *et al.*, 1998; Kobal *et al.*, 2000). This test is based on odor-dispensing devices similar to a felt-tip pen. For odor presentation, the cap was

removed by the experimenter for  $\sim 3$  s and the tip of the odorized pen was placed  $\sim 2$  cm in front of either nostril.

Phenyl ethyl alcohol (PEA) odor thresholds and odor discrimination were measured separately for the left and right nostril. Each nostril was sealed with Micropore® tape (3M, Minneapolis, MN). The sequence of the lateralized measurements was randomized across all participants. Odor identification was measured bilaterally. Subjects might have remembered the odor labels when left and right sides would have been tested sequentially, which, in turn, would have impacted on the test results.

PEA odor thresholds were assessed using a singlestaircase, triple forced-choice procedure (Hummel *et al.*, 1997; Ehrenstein and Ehrenstein, 1999). Sixteen dilutions were prepared in a geometric series starting at a 4% solution (dilution ratio 1:2 in propylene glycol). At each trial, three pens were presented in a randomized order, two of which contained the solvent only, the other containing the odorant at a certain dilution. The subject's task was to detect the odor-containing pen, which was color-coded. Subjects were blindfolded to prevent visual identification of this pen. Triplets were presented at intervals of 20 s. Reversal of the staircase was triggered when the odor was correctly identified in two successive trials. Threshold was defined as the mean of the last four out of seven staircase reversal points. The subjects' scores ranged between 0 and 16.

In the odor discrimination task, triplets of pens were presented in a randomized order. Two of them contained the same odorant, while the third contained a different odorant [for individual odors see Hummel *et al.* (Hummel *et al.*, 1997)]. Subjects had to find out which of the three odor-containing pens smelled differently. Presentation of triplets was separated by 20-30 s. The interval between presentations of individual pens of a triplet was ~3 s. The score was determined as the sum of all correct discriminations; as 16 triplets were tested in total, scores ranged from 0 to 16. The pen with the target odor was color coded for each triplet. Accordingly, as with assessment of odor thresholds, subjects were blindfolded to prevent visual identification of this pen.

Odor identification was assessed by means of 16 common odorants. Using a multiple choice task, identification of individual odorants was performed from a list of four descriptors each. The interval between odor presentations was 20–30 s. The descriptors used were identified during validation of this test (Hummel *et al.*, 1997). Specifically, the odor of each individual descriptor is known by >90% of healthy subjects. The subject's score was determined as the sum of all correct identifications, thus allowing ranges between 0 and 16.

#### Anatomical measures using MRI

*MRI*. MRI was performed on a 1.5 T scanner (Gyroscan 1.0-NT, Philips Medical Systems, Eindhoven, The Netherlands). Immediately following olfactometry, T2-weighted

turbo spin echo sequences were obtained in the head coil, with a repetition time of 3000 ms and an echo time of 100 ms in transverse and coronal planes. Slice thickness was 4 mm, with a 0.4 mm intersectional gap. The acquisition matrix was  $256 \times 256$  pixel, and the field of view was 230 mm. Scan percentage was set to 90% of the phase encoding profiles, resulting in a spatial resolution of  $0.9 \times$ 1.0 mm. The obtained images were transferred to an IBMcompatible workstation. Measurements were done with reference to a caliper. Final volumetric data were calculated with correction for the intersectional gap of 10% between slices. All pixels of one region in one slice were summed up and the sum of the slices were corrected by 10%. No contrast agent was administered. Subsequently to the measurements of the nasal airways, MRI scans of the head were performed to exclude the possible presence of pathologies in the cranium (T1-weighted transversal, Flair transversal, T2-3D transversal).

Image analysis. The MRI scans were transferred to an IBM-compatible workstation and converted to a tagged image file format (TIFF) for digital processing. All data were computed in Image Pro Plus® 1.3 (Media Cybernetics, Silver Spring, MD). This software allows semiautomatic measurement of a region of interest (ROI) (Figure 1). A grid was superimposed on the scans, which divided each nasal cavity into ~80 areas of 10 square pixels each. To contrast the border between air and mucosa, the image was transformed to a two-color bitmap level. For validation of this approach we investigated differences between areas measured on 256 grayscale original images and bitmap level images. Differences between these two approaches were <1%.

Nasal segments. To correlate olfactory function and nasal volumes, the nasal cavity was subdivided into 22 segments (11 segments for the left and 11 segments for the right cavity). Segmentation of the nasal cavity was made similar to suggestions by Leopold, Hong and others (Hong et al., 1998; Hornung and Leopold, 1999; Leopold, 1988). Borders of the presently used segments were non-overlapping; these borders were aligned with respect to the grid mentioned above. Segmentation into  $2 \times 11$  volumes was orientated on anatomical landmarks, e.g. the nasal meatus, the turbinates and the nasal septum. The following four regions (A-D) were distinguished in anterior-posterior direction (Figure 2): region A, 'outer nose': beginning at the tip of the nose, ending at the maxillary aperture; region B, 'anterior nasal cavity': beginning at the aperture of the maxilla, ending at the geometrical midline of the nasal cavity; region C, 'posterior nasal cavity': beginning at the geometrical midline, ending with the nasal septum; region D, 'nasopharynx': beginning at the end of the septum, ending at dorsal pharyngeal mucosa. In the rostro-caudal direction the nasal cavity was divided into three segments (1-3), using turbinates, the floor and the roof of the nasal cavity as markers;



**Figure 1** Example for analysis of MRI scans. Screen print during digital image analysis performed in Image Pro Plus®. The original MRI scan is shown in the background (window A). In the center image (window B), the original scan is shown as at bitmap level with clear contrasts between air (white) and mucosa (black). The region of interest (ROI) was outlined and the number of pixels in this area was counted (see white arrow, pointing towards gray-shaded area in anterior portion of the nasal cavity).

borders were marked with parallel lines: segment 1, 'lower meatus': from the hard palate to the MR slice (transversal orientation) where the middle turbinate becomes visible; segment 2, 'middle meatus': from the upper border of segment 1 to the MR slice (transversal orientation) where the anterior insertion of the middle turbinate is still visible; segment 3, 'upper meatus': reaching from the upper border of segment 2 to a line through the top of the roof of the nasal cavity.

#### Statistical methods

For statistical analyses, SPSS® for Windows<sup>™</sup> was used (Statistical Package for the Social Sciences, Version 10.0, SPSS Inc. Chicago, IL). Normal distribution of the data was checked with the Kolmogorov–Smirnov test. According to the exploratory character of the study, the relation between olfactory function and volumetric measures of the nasal cavity was evaluated using correlational analyses (Pearson). The alpha-level was set at 0.05.

#### Results

Descriptive statistics of the acquired parameters are presented in Tables 1 and 2.

Subjects' self-assessment of olfaction, as well as of



Figure 2 Segmental model of the nasal cavity. The segmental model divides each nasal cavity into 11 regions (region D3 was not used for analysis). A = outer nose; B = anterior nasal cavity; C = posterior nasal cavity; D = pharynx; 1 = inferior meatus; 2 = middle meatus; 3 = superior meatus.

Table 1	Descriptive statistics of ratings of olfactory	/ sensitivity and nasal fl	ow, respectively,	, results of rhinomanomet	tric and olfactory testing in	50
subjects						

	Mean	SEM	Minimum	Maximum
Subjects ratings on VAS (%)				
Ratings of olfactory sensitivity	69.2	2.7	18	100
Ratings of right nasal airflow	61.9	2.9	14	100
Ratings of left nasal airflow	62.2	2.7	13	100
Inspiratory air-flow (at 150 Pa/cm <sup>3</sup> /s)				
Right nasal cavity	270.8	19.8	25	618
Left nasal cavity	265.9	20.9	69	810
Olfactory function				
Odor threshold right	9.9	0.5	3.5	15.3
Odor threshold left	8.8	0.5	0.0	14.4
Odor discrimination right	12.2	0.3	5.0	16.0
Odor discrimination left	11.5	0.4	5.0	16.0
Odor identification (bilateral)	12.9	0.3	8.0	16.0

PEA odor thresholds are in dilution steps; odor discrimination: number of odors correctly identified; odor identification: number of odors correctly identified.

bilateral nasal airflow, was relatively high (olfaction, mean 69.2%; right nasal airflow, mean 61.9%; left nasal airflow 62.2%), as would have been expected since inclusion criteria were normosmia and no nasal or sinus disease. These findings were confirmed by anterior rhinomanometry, which revealed inspiratory airflow at 150 Pa of 270.8 cm<sup>3</sup>/s in the right nasal cavity and 265.9 cm<sup>3</sup>/s in the left nasal cavity,

respectively. Olfactory function was above or within normal limits, resulting in a mean of odor identification of 12.9, threshold right 9.9, threshold left 8.8, discrimination right 12.2, discrimination 11.5 (see Table 1). The slightly better scores for the right nostril throughout all tests may underlie a dominance of the right hemisphere of the brain and the successive olfactory bulb.

Region	Right nose (mm <sup>3</sup> )				Left nose [mm <sup>3</sup> ]			
	Means	SEM	Minimum	Maximum	Means	SEM	Minimum	Maximum
A: outer nose								
1: lower meatus	2193.3	142.7	213.4	4840.0	2118.9	115.4	294.8	3934.7
2: middle meatus	918.9	116.7	13.2	3241.7	836.1	109.8	19.8	3614.6
3: superior meatus	221.6	30.6	9.9	708.4	166.4	22.7	7.9	630.3
B: anterior nasal cavity: a	nterior nasal	cavity						
1: lower meatus	2112.3	131.5	385.0	4479.2	1911.3	122.1	81.4	4239.4
2: middle meatus	1283.5	163.5	0 <sup>a</sup>	5717.8	904.6	113.7	16.5	3609.1
3: superior meatus	198.3	29.8	7.9	878.9	114.8	17.3	0*	442.2
C: posterior nasal cavity:	posterior nas	al cavity						
1: lower meatus	3397.4	173.2	874.5	6966.3	3396.0	185.8	870.1	6912.4
2: middle meatus	1352.2	170.9	16.5	5421.9	963.8	139.4	47.3	3567.3
3: superior meatus	110.9	22.0	3.9	757.9	68.9	14.3	0*	476.3
D: pharynx: pharynx								
1: lower meatus	2132.9	162.3	407.0	4721.2	2030.0	154.8	380.6	3997.4
2: middle meatus	629.2	254.0	233.2	1631.3	587.6	234.4	180.4	1713.8

Table 2 Descriptive statistics of volumes of nasal segments measured in 50 subjects

<sup>a</sup>No measurable air volumes were observed in axial MRI scans in two subjects in the segment A2, in three subjects in the segment B3 and in two subjects in the segment C3. The comparison to coronal MRI scans revealed that partial volume effects above and below the turbinates were responsible for this finding in these subjects.

Values of the descriptive statistics of segmental nasal volumes are depicted in Table 2. Volumes of the right nasal segments are slightly larger than those of the left, which might contribute to the better performance of the right nostril in olfactometry. Largest volumes were found in the lower meatus, decreasing gradually to the superior meatus.

Correlational analyses were performed separately for structural and functional measures of the left and the right part of the nose with the exception of odor identification scores, which had been obtained bilaterally.

The results of the correlational analysis are depicted in Table 3. For the right part of the nose only, significant correlations were found between PEA odor thresholds and areas B1 (anterior nose, inferior meatus; r = 0.31, P < 0.027), and B3 (anterior nose, upper meatus; r = 0.38, P < 0.012), respectively (Figure 3). No significant correlations were found between nasal volumetrics in the left part of the nose and measures of odor discrimination, respectively.

Odor identification scores (Figure 4) exhibited a correlation to the left (r = 0.39, P = 0.012) and the right (r = 0.38, P = 0.02) area C3, which indicates an area in the posterior portion of the nose in the upper meatus. However, when outliers were removed the correlations were no longer significant.

## Discussion

To our knowledge, this is the first study that identified nasal volumes of significance for olfactory function (assessed by PEA odor detection thresholds, odor discrimination and odor identification) in healthy subjects using correlations between functional analyses and MRI-based volumetric

 Table 3
 Correlations between volumes of airway segments and results of olfactometry

Airway segment	Odor thr	esholds	Odor discrimi	nation	Odor identification
	Right sid	e Left side	Right sid	de Left side	Bilateral
A1RE B1RE C1RE D1RE A2RE B2RE C2RE D2RE A3RE B3RE C3RE	-0.01 0.31 <sup>a</sup> -0.04 0.02 0.25 0.24 0.26 0.15 0.21 0.38 <sup>a</sup> 0.17	-0.08 0.20 0.12 -0.09 0.01 0.05 0.08 -0.29 -0.15 0 0.13	-0.19 0.22 0.08 -0.19 0.24 0.22 0.08 0.27 0.24 0.17 0.13	-0.10 0.01 0.137 0.06 0.10 0.04 0.01 -0.16 -0.15 0.12 0.07	-0.16 -0.16 0.01 0.02 0.02 0.10 0.20 0.02 -0.20 0.21 0.38 <sup>b</sup>
A1LI B1LI C1LI D1LI A2LI B2LI C2LI D2LI A3LI B3LI C3LI	-0.13 0.11 -0.06 0.06 0.15 0.25 0.28 -0.19 0.19 0.33 <sup>a</sup> 0.19	-0.01 0.22 0.19 -0.01 -0.02 0.15 0.20 -0.42 0.05 0.11 0.14	-0.25 0.01 0.02 -0.15 0.11 0.09 0.06 -0.14 0.21 0.13 0.03	-0.06 0.01 0.12 0.01 0.12 0.15 -0.266 -0.10 -0.11 -0.06	-0.13 0.11 0.10 0.02 0.07 0.16 0.23 0.13 -0.07 0.09 0.392 <sup>b</sup>

Results using Pearson's correlation test ( $n \ge 47$ ).

 ${}^{a}P \le 0.05$ .  ${}^{b}Correlations were no longer significant when outliers were removed (see Figure 4).$ 



**Figure 3** Correlation between right-sided PEA thresholds (in dilution steps) and intranasal volumes in right-sided areas B1 (anterior nasal cavity, inferior meatus: r = 0.31, P < 0.027) and right-sided B3 (anterior nasal cavity, upper meatus: r = 0.38, P < 0.012). Note the different scaling of the *Y*-axes.



**Figure 4** Odor identification scores (number of correctly identified odors) plotted against left- and right-sided volumes C3 (posterior portion of the nose, upper meatus; see Figure 2). When outliers were removed the correlation was no longer significant.

measures. Results of this exploratory study indicated that PEA odor threshold, but not odor discrimination or odor identification ability, is correlated with certain volumes in the anterior portion of the nasal cavity.

The correlations of the right PEA threshold with area B3 is consistent with the significance of inflammatory processes for olfactory function. Considering (i) that area B3 encompass a large portion of the olfactory epithelium (von Brunn 1892; Leopold et al., 2000) and (ii) that the average volume of area B3 is only 198 mm<sup>3</sup>, it is easily conceivable that minute changes of mucosal thickness (e.g. mucosal edema by vasodilatation or inflammation) may lead to drastic changes in olfactory abilities. In terms of the therapy of olfactory dysfunction due to inflammation with selfadministered nasal sprays, it also becomes clear that only small, if not negligible, amounts of corticosteroids reach the assumed site of action. In fact, it has been shown repeatedly that only small quantities of nasally applied sprays reach the area above the middle turbinate (Hardy et al., 1985; Newman et al., 1987; McGarry and Swan, 1992). While this can be improved by the administration of sprays in 'headdown forward' position (Mott and Leopold, 1991), systemic steroids are usually more effective than locally administered steroids (Mott and Leopold, 1991; Ikeda *et al.*, 1995).

The correlation of PEA thresholds with area B1 (anterior nose, inferior meatus) indicated that this olfactory function might be modified by the volume of the anterior part of the nasal cavity. Specifically, the present data suggest that odor thresholds are affected by inter-individual differences in volumes of the inferior meatus remote from the olfactory cleft. From a clinical point of view this finding is extremely interesting. It helps to explain results from previous studies showing that postoperative olfactory function (Ophir *et al.*, 1986; Damm et al., 2002) is changed by surgery which alters spaces in the inferior meatus (e.g. septoplasty, partial inferior resection of turbinates). However, this interaction should be evaluated by a new experiment using the methods presented here for anatomical measurements and odor threshold and identification to evaluate the intra-individual changes before and after nasal surgery.

Correlations were not found for odor discrimination or odor identification, both of which are suprathreshold tests of olfactory function. Importantly, the presently obtained tests of olfactory function (PEA threshold, odor discrimination and odor identification) have a similar test-retest reliability (Hummel et al., 1997). One possible explanation for this discrepancy may be that nasal airflow has a weaker impact on 'higher' olfactory functions such as odor discrimination (Zatorre and Jones-Gotman, 1991; Hummel et al., 1998a). Functions like odor discrimination appear to involve cognitive factors to a greater degree than odor thresholds. In turn, odor thresholds appear to be more closely related to peripheral olfactory input (Jones-Gotman and Zatorre, 1988; Hornung et al., 1998) [but see also (Doty et al., 1994)]. Thus, other than odor thresholds, odor discrimination and odor identification seem to be less directly dependent on the physical conditions that accompany odorous stimulations. This may partly depend on cognitive processes involved in the discrimination or identification of odors.

How do the present results in healthy volunteers compare to previous work in subjects with olfactory disorders? While only looking at areas above the middle turbinate, Leopold (Leopold, 1988) identified three regions to be most important for non-lateralized measurements of olfactory function, namely (i) 'the space anterior to, and no more than 5 mm below, the cribriform plate' (region 1, Figure 5b); (ii) 'the space between 10 and 15 mm below the cribriform plate' (region 8, Figure 5b); and (iii) 'the space posterior to and between 10 and 15 mm below the cribriform plate' (region 9, Figure 5b). The first of the three regions exhibits considerable overlap with area B3 identified in the present study to be of importance to PEA thresholds (see Figure 5a,b). It is important to note, though, that the volume of Leopold's region 1 correlated negatively with the OCM. The second



Figure 5 Comparison between our material (A) and the results of Leopold (Leopold, 1988) (B). The highlighted areas show the regions influencing the olfactory function.

area identified by Leopold was a volume which would have accounted in the present investigation for a portion of segment C2, and the third region for a portion of segment D2, respectively. Hornung and Leopold (Hornung and Leopold, 1999) evaluated CT scans of 19 subjects presenting with olfactory dysfunction, largely confirming the results of the previous study by Leopold (Leopold, 1988). In addition to previous work, Hornung and Leopold reported numerous and complex interactions between different volumes of the nasal cavity, indicating that 'the relationship between olfactory ability and nasal structure is complex and that changing a structure in one part of the nose far removed from the olfactory area can have dramatic effects on olfactory ability'.

Thus, previous and present studies indicate that the volume in the upper meatus is a major determinant of olfactory function, both in subjects with sino-nasal disease (SND) and healthy volunteers. However, Leopold's region 1 (Leopold, 1988) may reach special significance in SND subjects. In addition, in line with findings of Hornung and Leopold (Hornung and Leopold, 1999), the present study identified an area in the anterior nose (B1, the lower meatus) as a determinant of olfactory function. The lower meatus has also been shown to be involved in respiratory hyposmia (Bonfils *et al.*, 1999).

Although the results of previous work and the present data exhibit numerous similarities and support each other in many ways, it should be noted that the decongestant oxymetazoline was used in the present study to minimize potential effects of, for example, the nasal cycle (Kayser, 1895; Hasegawa and Kern, 1977). While there is evidence that oxymetazoline has little effect on olfactory function (Hummel et al., 1998b) [compare (Temmel et al., 1999)], it may be that oxymetazoline may have a differential influence on the volumes of the 22 defined areas in the nasal cavity, also depending on their functional state (Williams and Eccles, 1992). Thus, while it appeared necessary to reduce possible effects of mucosal congestion, it must be kept in mind that this manipulation certainly had a strong effect on the correlations obtained. In other words, the described significance might change in relation to the use of oxymetazoline.

Although not focused on in the present investigation, it was interesting to note that there was no significant correlation between rhinomanometric measures and intranasal volumes. While the reasons for this finding are unclear, it may be that the rhinomanometric measures would correlate to the diameter of the smallest area of the nasal cavity (Adema and Motserrat, 1982), which was not obtained in this investigation.

It is difficult how to explain the different outcomes for the right and left nostrils. One possible explanation might be hemispheric dominancy in relation to olfactory function (Zatorre and Jones-Gotman, 1990; Zatorre et al., 1992; Hummel et al., 1995; Doty et al., 1997). In terms of laterality, the present results partly contradict the findings of Hong et al. (Hong et al., 1998), who found correlations only between left-sided anatomic structures and both right and left sense of smell. Their study, however, did not actually measure olfactory ability, but the patients estimated their sense of smell as excellent, diminished or absent, and two otolaryngologists and three neuroradiologists assessed radiological findings. This might explain different results in the qualitatively measured study to the present quantitatively evaluated study. In this context, it may be interesting to note that the right nasal cavity was found to be wider than the left nasal cavity [factor side: F(1,47) = 6.0, P = 0.018].

This difference may have had a major effect on the statistical significance of the shown results. It may also partly explain the differences between the findings of Hong *et al.* and this paper.

Taken together, it appears as if nasal volumes of significance to olfactory function are similar in subjects with olfactory dysfunction and healthy volunteers. Intranasal volumes below the cribriform plate and in the anterior, lower meatus appear to be especially important to the sense of smell. Future studies will specifically investigate these correlations.

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#### References

- Adema, J.M. and Montserrat, J.M. (1982) Olfacto-rhinomanometry. Int. Rhinol., 20, 21–28.
- Bonfils, P., Corre, F.L. and Biacabe, B. (1999) Semiologie et etiologie des anosmies: a propos de 306 patients. Ann. Otolaryngol. Chir. Cervicofac., 116, 198–206.
- Damm, M., Eckel, H.E., Streppel, M., Jungehülsing, M. and Stennert,
   E. (2000) Abhängigkeit des uni- und bilateralen Riechvermögens von der nasalen Strömung bei Patienten mit chronischer Rhinosinusitis. HNO, 48, 436–443.
- Damm, M., Eckel, H.E., Jungehülsing, M. and Hummel, T. (2002) Olfactory changes at threshold and suprathreshold levels following septoplasty with partial inferior turbinectomy. Ann. Otol. Rhinol. Laryngol., in press.
- **Doty, R.L.** (1986) *Gender and endocrine-related influences upon olfactory sensitivity.* In Meiselman, H. and Rivlin, R.S. (eds), Clinical Measurement of Taste and Smell. MacMillan, New York, pp. 377–413.
- Doty, R.L., Smith, R., McKeown, D.A. and Raj, J. (1994) Tests of human olfactory function: principle component analysis suggests that most measure a common source of variance. Percept. Psychophys., 56, 701–707.
- **Doty, R.L., Bromley, S.M., Moberg, P.J.** and **Hummel, T.** (1997) *Laterality in human nasal chemoreception*. In Christman, S. (ed.), Cerebral Asymmetries in Sensory and Perceptual Processing. North Holland Publishing, Amsterdam, pp. 497–542.
- Eccles, R. (2001) Nasal airflow. Chem. Senses, 26, 730.
- Eccles, R., Jawad, M.S.M. and Morris, S. (1989) Olfactory and trigeminal thresholds and nasal resistance to airflow. Acta Otolaryngol. (Stockh.), 108, 268–273.
- Ehrenstein, W.H. and Ehrenstein, A. (1999) Psychophysical methods. In Windhorst, U. and Johansson, H. (eds), Modern Techniques in Neuroscience Research. Springer, Berlin, pp. 1211–1241.
- Hardy, J.G., Lee, S.W. and Wilson, C.G. (1985) Intranasal drug delivery by spray and drops. J. Pharmacy Pharmacol., 37, 294–297.
- Hasegawa, M. and Kern, B. (1977) *The human nasal cycle*. Mayo Clin. Proc., 52, 28–34.
- Hong, S.C., Leopold, D.A., Oliverio, P.J., Benson, M.L., Mellits, D., Quaskey, S.A. and Zinreich, S.J. (1998) Relation between CT scan

- Hornung, D.E. and Leopold, D.A. (1999) *Relationship between uninasal anatomy and uninasal olfactory ability*. Arch. Otolaryngol. Head Neck Surg., 125, 53–58.
- Hornung, D.E., Youngentob, S.L. and Mozell, M.M. (1987) Olfactory mucosa/air partitioning of odorants. Brain Res., 413, 147–154.
- Hornung, D.E., Chin, C., Kurtz, D.B., Kent, P.F. and Mozell, M.M. (1997) *Effect of nasal dilators on perceived odor intensity*. Chem. Senses, 22, 177–180.
- Hornung, D.E., Kurtz, D.B., Bradshaw, C.B., Seipel, D.M., Kent, P.F., Blair, D.C. and Emko, P. (1998) *The olfactory loss that accompanies an HIV infection*. Physiol. Behav., 15, 549–556.
- Hummel, T., Pauli, E., Schuler, P., Kettenmann, B., Stefan, H. and Kobal, G. (1995) *Chemosensory event-related potentials in patients with temporal lobe epilepsy*. Epilepsia, 36, 79–85.
- Hummel, T., Sekinger, B., Wolf, S.R., Pauli, E. and Kobal, G. (1997) 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem. Senses, 22, 39–52.
- Hummel, T., Mohammadian, P. and Kobal, G. (1998a) Handedness is a determining factor in lateralized olfactory discrimination. Chem. Senses, 23, 541–544.
- Hummel, T., Rothbauer, C., Pauli, E. and Kobal, G. (1998b) Effects of the nasal decongestant oxymetazoline on human olfactory and intranasal trigeminal function in acute rhinitis. Eur. J. Clin. Pharmacol., 54, 521–528.
- Ikeda, K., Sakurada, T., Suzaki, Y. and Takasaka, T. (1995) Efficacy of systemic corticosteroid treatment for anosmia with nasal and paranasal sinus disease. Rhinology, 33, 162–165.
- Jones-Gotman, M. and Zatorre, R.J. (1988) Olfactory identification deficits in patients with focal cerebral excision. Neuropsychologia, 26, 387–400.
- Kayser, R. (1895) Die exacte Messung der Luftdurchgängigkeit der Nase. Arch. Laryngol., 3, 110–115.
- Kelly, J.T., Prasad, A.K. and Wexler, A.S. (2000) Detailed flow patterns in the nasal cavity. J. Appl. Physiol., 89, 323–337.
- Kendal-Reed, M., Walker, J.C. and Morgan, W.T. (2001) Investigating sources of response variability and neural mediation in human nasal irritation. Indoor Air, 11, 185–191.
- Keyhani, K., Scherer, P.W. and Mozell, M.M. (1997) A numerical model of nasal odorant transport for the analysis of human olfaction. J. Theor. Biol., 186, 279–301.
- Klimek, L., Hummel, T., Moll, B., Kobal, G. and Mann, W.J. (1998) Lateralized and bilateral olfactory function in patients with chronic sinusitis compared with healthy control subjects. Laryngoscope, 108, 111–114.
- Kobal, G., Klimek, L., Wolfensberger, M., Gudziol, H., Temmel, A., Owen, C.M., Seeber, H., Pauli, E. and Hummel, T. (2000) Multicenter investigation of 1,036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. Eur. Arch. Otorhinolaryngol., 257, 205–211.

- Leopold, D.A. (1988) The relationship between nasal anatomy and human olfaction. Laryngoscope, 98, 1232–1238.
- Leopold, D.A., Hummel, T., Schwob, J.E., Hong, S.C., Knecht, M. and Kobal, G. (2000) Anterior distribution of human olfactory epithelium. Laryngoscope, 110, 417–421.
- Lotsch, J., Nordin, S., Hummel, T., Murphy, C. and Kobal, G. (1997) Chronobiology of nasal chemosensitivity: do odor or trigeminal pain thresholds follow a circadian rhythm? Chem Senses, 22, 593–598.
- Masing, H. (1967) Experimentelle Untersuchungen über die Strömung im Nasenmodell. Arch. Klin. Exp. Ohren-, Nasen- Kehlkophheilk., 189, 59–70.
- McGarry, G.W. and Swan, I.R. (1992) Endoscopic photographic comparison of drug delivery by ear-drops and by aerosol spray. Clin. Otolaryngol., 17, 359–360.
- Mott, A.E. and Leopold, D.A. (1991) Update in otolaryngology I: disorders in taste and smell. Med. Clin. N. Am., 75, 1321–1353.
- Newman, S.P., Moren, F. and Clarke, S.W. (1987) Deposition pattern from a nasal pump spray. Rhinology, 25, 77–82.
- **Ophir, D., Gross-Isseroff, R., Lancet, D.** and **Marshak, G.** (1986) *Changes in olfactory acuity induced by total inferior turbinectomy*. Arch. Otolaryngol. Head Neck Surg., 112, 195–197.
- Scherer, P.W., Hahn, I.I. and Mozell, M.M. (1989) The biophysics of nasal airflow. Otolaryngol. Clin. N. Am., 22, 265–278.
- Stevens, J.C., Cain, W.S. and Burke, R.J. (1988) Variability of olfactory thresholds. Chem. Senses, 13, 643–653.
- Temmel, A.F., Quint, C., Toth, J., Herneth, A. and Hummel, T. (1999) Topical ephedrine administration and nasal chemosensory function in healthy human subjects. Arch. Otolaryngol. Head Neck Surg., 125, 1012–1014.
- Tonosaki, K. and Tucker, D. (1985) *Responsiveness of the olfactory* receptor cells in dog to some odors. Comp. Biochem. Physiol. A, 81, 7–13.
- von Brunn, A. (1892) Beiträge zur mikroskopischen Anatomie der menschlichen Nasenhöhle. Arch. Mikr. Anat., 39, 632–651.
- Williams, R.G. and Eccles, R. (1992) Nasal airflow asymmetry and the effects of a topical nasal decongestant. Rhinology, 30, 277–282.
- **World Medical Association** (2000) *World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects.* J. Am. Med. Assoc., 284, 3043–3045.
- Youngentob, S.L., Stern, N.M., Mozell, M.M., Leopold, D.A. and Hornung, D.E. (1986) Effect of airway resistance on perceived odor intensity. Am. J. Otolaryngol., 7, 187–193.
- Zatorre, R.J. and Jones-Gotman, M. (1990) Right-nostril advantage for discrimination of odors. Percept. Psychophys., 47, 526–531.
- Zatorre, R.J. and Jones-Gotman, M. (1991) Human olfactory discrimination after unilateral frontal or temporal lobectomy. Brain, 114, 71–84.
- Zatorre, R.J., Jones-Gotman, M., Evans, A.C. and Meyer, E. (1992) Functional localization and lateralization of human olfactory cortex. Nature, 360, 339–340.

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