© Med Sci Monit, 2012; 18(3): CR154-159
PMID: 22367126

WWW.MEDSCIMONIT.COM
Clinical Research

Received: 2011.07.06
Accepted: 2011.12.06
Published: 2012.03.01

Examination of chemosensory functions in patients with dysosmia

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Ling Yang[1ABCDEF], Yongxiang Wei[2ABDG], Wei Zhang[3BEF], Yuanyuan Ren[2BCF], Di Yu[1ABF], Kunyan Li[2BCF], Yichen Guo[2BCF], Jinfeng Zhang[3ABC]

[1] Center Lab of Beijing Tongren Hospital, Capital Medical University, Beijing, China
[2] Department of Otolaryngology-Head and Neck Surgery, Beijing Chaoyang Hospital, Capital Medical University, Bejing, China
[3] Department of Otolaryngology-Head & Neck Surgery, Beijing Tongren Hospital, Capital Medical University, Bejing, China

Source of support: China Natural Scientific Foundation under project No. 30973284, and Capital Medical Development Foundation under project No. 2007-1034

Summary

Background: To examine changes of chemical sensory functions in patients with dysosmia.

Material/Methods: The 272 study subjects included 98 healthy volunteers, 86 subjects with hyposmia and 88 subjects with functional anosmia. Their chemical sensory functions were examined using olfactory event-related potentials (oERPs), trigeminal event-related potentials (tERPs), T&T olfactometer and triple drop method, respectively.

Results: The T&T results showed that the difference between patients and healthy subjects had statistical significance. The oERPs and tERPs results showed that patients with functional anosmia had N1 and P2 waves of prolonged latency and reduced amplitude when compared to healthy subjects with the difference of statistical significance. When compared to healthy subjects, patients with functional anosmia had clear hypogeusia and the difference had statistical significance. For the younger group there was significant difference between healthy subjects and patients in T&T, oERPs and tERPs results.

Conclusions: It is suggested by the apparently concomitant trigeminal nerve dysfunction and hypogeusia in patients with functional anosmia in this study that olfactory and nasal trigeminal function in young patients was clearly decreased. Our study suggests the possible application of oERPs, tERPs and three drops method in clinical diagnosis in Chinese populations and provides scientific evidence for treatment.

key words: **olfaction • gustation • olfactory event-related potentials • T&T olfactometer • trigeminal event-related potentials • three drops method**

Full-text PDF: http://www.medscimonit.com/fulltxt.php?ICID=882520

Word count: 2720
Tables: 3
Figures: –
References: 33

Author's address: Yongxiang Wei, Department of Otolaryngology-Head and Neck Surgery, Beijing Chaoyang Hospital, Capital Medical University, Bejing, China, e-mail: yongxiangwei@126.com

Background

The chemical sensory systems mainly consist of olfactory sensation, gustatory sensation and trigeminal nerves. Although these 3 chemical sensory systems are regulated independently in daily life, they work together collaboratively [1–3]. Regulation of intranasal chemical sensory signals is mainly accomplished through the olfactory nerve and trigeminal nerves [4], while gustatory sensation during eating relies on a high level of integration of the olfactory, gustatory and trigeminal signals [2,5]. Loss or reduction of olfactory and gustatory sensation is the most common type of dysosmia and dysgeusia [6]. Because odor discrimination largely relies on olfactory sensation [7], physicians should not only examine hypogeusia but also investigate potentially concomitant hyposmia when subjects complain about tasteless food. Currently, the common methods used in clinical laboratories include olfactory event-related potentials (oERPs) [8] and T&T olfactometer [9] for olfactory examination, trigeminal event-related potentials (tERPs) [10] for trigeminal nerve examination, and triple drop method for gustatory examination [11]. The purpose of the present study was to exam 272 subjects using the above methods to investigate changes of the chemical sensory functions in patients with dysosmia in a Chinese population.

Material and Methods

Subjects

This retrospective study enrolled 272 subjects, with 98 in a healthy group including 50 men and 48 women of 18–70 years of age and mean age of 40±13 years. The subjects were divided into 3 subgroup: 34 in the younger group (18–35 years of age), 33 in the middle-age group (36–50 years of age), and 31 in the older group (51–70 years of age). The 86 subjects in the hyposmia group including 45 men and 41 women of 14–72 years of age and mean age of 41±15 years; and these were also divided into 3 subgroups: 26 in the younger group, 36 in the middle-age group, and 24 in the older group. The 88 subjects in the functional anosmia group included 43 men and 45 women of 18-71 years of age and mean age of 42±11 years; and these were divided into 3 subgroups: 19 in the younger group, 42 in the middle-age group, and 27 in the older group (Table 1). All healthy volunteers were from the Department of Physical Examination and had no chief complaints of dysosmia and dysgeusia, abnormal nasoendoscopic findings, or other body discomforts or medical history of chemical sensory system disorders. The 174 patients with dysosmia included 91 with chronic sinusitis and nasal polyps, 29 with dysosmia after upper respiratory tract infection, 32 with post-traumatic dysosmia, 6 with congenital anosmia and 16 with dysosmia of unknown causes, and all these subjects were from the outpatient clinic of the Department of Otolaryngology-Head and Neck Surgery between 2007 and 2011. These patients were entered the study consecutively at admission and were allocated into hyposmia group and anosmia group according to clinical diagnostic results. The entire study protocol had been approved by the ethics committee of the hospital and subjects understood these examinations and signed the informed consent forms before initiation of any study-related procedures.

Chemosensory assessment

T&T olfactometer

T&T olfactometer was purchased from Daiichi Pharmaceutical Co. Ltd. (Japan). Standard administration was performed according to the manufacturer's instructions. Briefly, quantitative analysis was based on the dilution time of 5 odorants (rose, scorched, rotten, fruit and stool), each substance at 8 concentrations (10^2~10^5) which represented 8 degrees (–2 to +5). Average odor threshold, which was obtained by dividing the sum of identification threshold for 5 olfactory substances by 5, was used to judge the degree of olfactory injury [9].

oERPs and tERPs

Both exams were performed using published protocols. Phenethyl alcohol was purchased from J&K Chemical Reagent Company (Beijing). The Olfactometer OM6b was purchased from Burghart (Germany). Briefly, the subjects were in the sitting position comfortably, relaxed, and were asked to sit still, to neither blink nor swallow, and to breathe through the mouth. Olfactory and trigeminal stimuli (40%v/v Phenethyl alcohol and 40% v/v CO2, respectively) were infused to the olfactory field of the nasal cavity at a constant temperature and flow rate. The infusion of each gas was repeated for 30 times alternatively (stimulus duration: 250ms, interval: 30s, flow rate: 8L/min). The whole operation was performed in a well ventilated and electrically shielded room. Brain potentials were recorded at Fz, Cz, Pz, C3, and C4, etc. on the scalp according to international standard 10/20 method. Generally, the waveform recorded at Cz was the best. Reference electrodes were placed at the left and right ear lobes (A1 and A2). Stable oERPs and tERPs waveforms were obtained after amplification and filtering. Records contaminated by blinking were excluded. During the examination, white noise of 60 dB was presented via a head phone to mask the interference noise [8,10].

Gustatory function by the triple drop method

Subjective examination of gustatory function was performed using the triple drop method. Sucrose, sodium chloride, citric acid and quinine hydrochloride were purchased from Chemical Reagent Company (Beijing). We prepared solutions of different concentrations of each tastant; the lowest concentrations of sucrose, sodium chloride, citric acid and quinine hydrochloride were 0.19 g/mL, 0.06 g/mL, 0.15 g/mL and 0.0012 g/mL, respectively. The subjects were not allowed to eat 1 h before the examination. When performing the examination, 1 drop of the above solutions and 2 drops of distilled water were placed on the anterior 1/3 of the tongue in randomized order. After closing the mouth, the subjects were asked to identify the taste as sweet, sour, salty, or bitter, and to rinse the mouth with water. Bitterness was tested at the end of the session. If a subject chose the wrong answer, then a higher concentrated solution was used for the next trial. Total score was obtained by the sum of 4 tastents' result [11].

Statistical analysis

All analyses were performed using SPSS12.0. The results of T&T, triple drop method, latencies and amplitude of each

Table 1. Descriptive statistics of T&T olfactometer and Olfactory event-related potentials.

Group		Age	Number	T&T	N1-latencies (ms)	N1-amplitude (uv)	P2-latencies (ms)	P2-amplitude (uv)
Healthy	Young	18–35	34	–1.55±0.59	375±70	–4.59±1.67	565±80	7.42±4.19
	Middle age	36–50	33	–1.16±0.91	434±123	–4.70±2.00	618±138	6.83±3.88
	Old-age	51–70	31	–0.87±0.94	465±96	–4.67±2.52	664±113	6.44±3.20
	Total		98	–1.21±0.86*	423±104*	4.65±2.06*	614±119*	6.91±3.78*
Hyposmia	Young	14–35	26	1.50±2.16	544±200	–4.58±3.99	674±179	6.73±5.76
	Middle age	36–50	36	1.73±2.17	575±224	–3.64±3.51	677±221	4.84±2.75
	Old-age	51–72	24	3.07±2.05	580±146	–3.35±3.30	713±155	6.12±3.60
	Total		86	2.04±2.21*	565±197*	3.91±3.61	684±190*	5.81±4.25
Functional anosmia	Young	18–35	19	5.64±0.26	447±139	–3.98±3.63	597±142	5.41±3.26
	Middle age	36–50	42	5.54±1.67	580±188	–3.01±1.75	701±171	4.93±3.86
	Old-age	51–71	27	5.64±0.21	672±243	–1.75±1.48	791±236	4.62±2.83
	Total		88	5.59±0.49*	571±197*	3.02±2.43*	691±187*	5.00±3.28*

Results are shown as mean ±SD. * P< 0.05.

wave in ERPs were expressed as mean ±SD. Normal distribution test was performed on the data in each group and test of homogeneity of variance was performed on grouping data, then differences in average between different groups were analyzed using one-way ANOVA. The post-hoc multiple comparisons test was employed to analyze the differences between individual groups. Pearson statistics were used for correlation analyses between different tests.

Results

T&T olfactometer

For T&T examination, the results showed that the difference between patients with hyposmia and functional anosmia and healthy subjects had statistical significance (P=0.001, 0.001, respectively). There was a significant difference between the hyposmia group and the functional anosmia groups (P=0.001). For the younger group there were significant differences between healthy subjects and patients with hyposmia and functional anosmia. (P=0.001, 0.001, respectively). The results are shown in Table 1.

oERPs

The result of oERPs showed that there was significant difference in latencies of the N1 peak between healthy subjects and hyposmia group/functional anosmia group (P=0.001, 0.001, respectively), and there was also significant difference in amplitude of N1 wave between healthy subjects and the functional anosmia group (P=0.001). For P2 wave, there was significant difference in latencies between healthy subjects and the hyposmia group/functional anosmia group (P=0.044, 0.043 respectively), and there was also significant difference in amplitude of P2 wave between healthy subjects and the functional anosmia group (P=0.009). For the younger group, there was significant difference in latencies of N1 peak between healthy subjects and patients with hyposmia (P=0.045). The results are shown in Table 1.

tERPs

The result of tERPs showed that there was significant difference in latencies of the N1 peak between healthy subjects and hyposmia group/functional anosmia group (P=0.001, 0.001 respectively). For P2 wave, there was significant difference in latencies between healthy subjects and functional anosmia group (P=0.001), and there was also significant difference between hyposmia group and functional anosmia group (P=0.004). There was significant difference in amplitude of P2 wave between healthy subjects and hyposmia group (P=0.01). For the younger group, there were significant difference in latencies of N1 peak between healthy subjects and hyposmia group/functional anosmia group (P=0.027, 0.003), and there was also significant difference in latencies of P2 peak between healthy subjects and patients with functional anosmia group (P=0.019). The results are shown in Table 2.

Correlations analysis

For correlations between olfactory tests, measures of olfactory function were correlated with parameters of oERPs and T&T. The T&T results were significantly correlated with latencies of N1/P2 (N1r=0.412, P=0.001; P2r=0.250, P=0.001) and amplitudes of N1/P2 peak (N1r=–0.218, P=0.001, P2r=–0.230, P=0.001), indicating that lower T&T result were generally associated with shorter latencies of N1/P2 and higher amplitudes of P2 peak. The oERPs and tERPs was significantly correlated with latencies of N1/P2 (N1r=0.510, P=0.001, P2r=0.309, P=0.001) and amplitudes of N1 peak (N1r=0.321, P=0.001). The trigeminal N1/P2 latencies were earlier than olfactory N1/P2 (P_{N1}=0.001, P_{P2}=0.001), and the trigeminal N1/P2 amplitude were greater than olfactory N1/P2 (P_{N1}=0.001, $P(_{P2}$=0.001).

Table 2. Descriptive statistics of trigeminal event-related potentials.

Group		Age	Number	N1-latencies (ms)	N1-amplitude (uv)	P2-latencies (ms)	P2-amplitude (uv)
Healthy	Young	18–35	34	320±37	–6.82±3.47	476±64	9.36±4.12
	Middle age	36–50	33	343±64	–5.83±2.66	518±100	7.62±2.83
	Old-age	51–70	31	384±96	–5.35±4.45	574±93	6.46±3.79
	Total		98	348±73*	6.02±3.60	521±95*	7.85±3.78*
Hyposmia	Young	14–35	26	426±129	–5.56±7.70	552±117	11.80±7.68
	Middle age	36–50	36	406±129	–5.99±6.24	547±121	9.83±5.52
	Old-age	51–72	24	436±114	–6.01±5.49	597±109	9.45±5.37
	Total		86	421±125*	5.85±6.52	560±117	10.39±6.28*
Functional anosmia	Young	18–35	19	442±101	–6.58±7.75	586±107	10.96±6.20
	Middle age	36–50	42	431±107	–5.11±4.16	601±152	9.61±6.20
	Old-age	51–71	27	551±180	–3.88±2.35	680±175	7.70±5.05
	Total		88	464±135*	5.22±5.15	616±150*	9.50±6.05

Results are shown as mean ±SD. * P< 0.05.

Table 3. Descriptive statistics of triple drop test.

Group		Age	Number	Three drops test
Healthy	Young	18–35	34	36±0
	Middle age	36–50	33	35.97±0.17
	Old-age	51–70	31	35.97±0.18
	Total		98	35.98±0.14
Hyposmia	Young	17–35	26	35.62±1.96
	Middle age	36–50	36	35.63±1.45
	Old-age	51–72	24	35.38±1.55
	Total		86	35.56±1.62
Functional anosmia	Young	18–35	19	35.37±2.29
	Middle age	36–50	42	34.48±5.83
	Old-age	51–71	27	34.81±2.71
	Total		88	34.77±4.40*

Results are shown as mean ±SD. * P< 0.05.

Three drops method

Gustatory function examination showed that there was significant difference between healthy subjects and the functional anosmia group (P=0.036). The results are shown in Table 3.

Discussion

Our T&T result showed significantly decreased olfactory function in comparing patients to healthy subjects,and similar trends were observed in the Ishimaru et al. [9] study. T&T examination is sensitive to the smell loss of Japanese sinusitis/polyposis patients [12] and has been used as a "subjective" examination of olfactory function in Chinese clinics for many years. Our study confirmed it is a reliable method to divide subjects with euosmia from those with anosmia. Up to now, the oERPs test as an "objective" examination of olfactory function has not been widely used in clinical examination in China, but often was used in animal research [13]. Our data showed that postponed latency and reduced amplitude of N1 and P2 waves of oERPs were observed in patients with functional anosmia in this study when compared to healthy subjects; the results demonstrated clear changes in oERPs under dysosmia and suggest a possible application of this method in clinical diagnosis in Chinese populations. Braemerson et al. [14] showed

that patients with dysosmia had prolonged latency and reduced amplitude of oERPs when compared to healthy subjects. Similar trends were observed in our study. Lotsch et al. [15] detected oERPs using phenethanol as a stimulant in 123 subjects and demonstrated the potential to differentiate patients with euosmia from those with anosmia using the oERPs technique in a European population.

Studies have demonstrated a correlation between objective (oERPs) and subjective (T&T) olfactory examination methods. Lower T&T values correlate with shorter latency and higher amplitude of N1 and P2 waves. In a study involving 88 patients with functional anosmia, the T&T values were all greater than 5.5 and oERPs was detectable in 20 patients (detection rate: 22%). The T&T result meant that a portion of patients with anosmia still retained some olfactory function. In this study, the results were interpreted by the following criteria: subjects had normal olfactory function if T&T results were normal and oERPs were detectable at the same time; subjects had functional anosmia if T&T results indicated anosmia and oERPs were undetectable at the same time; subjects might have hyposmia if T&T results indicated hyposmia and oERPs were undetectable, possibly because detection of oERPs was interfered with by blinking movement or hyperactivity of facial muscles during examination; subjects still had olfactory function if T&T results indicated functional anosmia and oERPs were detectable. Ishimaru et al. [9] examined 14 patients using T&T and EOEP methods and observed a T&T value greater than 5.8 in 1 patient with detectable EOEP. Lötsch et al. [15] also observed detectable oERPs in 20% of patients with functional anosmia, a result consistent with ours. This study indicated combined subjective and objective examination would better reflect olfactory function with patients.

Our study findings show that patients with hyposmia or anosmia had reduced amplitude and postponed latency of N1 and P2 waves of tERPs when compared to healthy subjects. Consistent with Hummel's conclusion [16], this observation also suggests that trigeminal nerve functions were affected in European patients with dysosmia. The olfactory and trigeminal pathways are concentrated in identical neural units of the mediodorsal thalamic nucleus. The trigeminal system and olfactory system interact with each other in the central nervous system. It was shown by comparing functional imaging of trigeminal and olfactory conduction that these 2 chemical sensory systems are independent of each other, but are closely interrelated [17–19]. When interaction between these 2 systems at nerve centers in the brain was lost in anosmia, sensitivity of intranasal trigeminal nerves subsequently decreased [20]. Our data show that olfactory and trigeminal function of younger subjects of olfactory dysfunction were clearly decreased to compare with healthy subjects. The olfactory and trigeminal function of patients in the middle-age group and the old-aged group was generally lower than in healthy subjects, but there was no statistical significance. The results were consistent with report by Frasnelli [21,22] who showed that persistent dysosmia decreased sensitivity of the trigeminal nerves. However, such effect was weak or difficult to detect in mostly elderly patients [23]. Sensitivity of intranasal trigeminal nerves could be improved with recovery of olfactory functions [24]. Murphy et al. [25] showed that the latency of N1 and P2 waves of oERPs was 30–70 ms earlier than that of tERPs; in contrast, N1 and P2 amplitudes of tERPs were higher than that of oERPs in an American population. In our study, we observed that the latency and amplitude of tERPs were earlier and higher than that of oERPs, respectively, with differences of statistical significance. The result was comparable with reports by Stuck [26] and Welge-Lussen [27]. This may suggest that the human cerebral cortex responds more slowly to olfactory stimulus than to trigeminal stimulus, and interaction between olfactory system and trigeminal system may take place at the subcortical level. Despite involvement in the perception of chemicals, the intranasal trigeminal system has received relatively little attention compared to the olfactory system in China. This study provides further evidence that tERPs is a sensitive and specific method, and olfactory status could influence sensitivity of the intranasal trigeminal system.

Three drops test comes from Germany; until now this test has not been used in clinical examination in China. Overall, our results show that these tests are feasible in Chinese populations. Some reports indicated that gustatory functions decrease somewhat with aging [11]. We divided the subjects into different subgroups according to age, and there was no significant difference between individual groups. This indicates that decreasing of gustatory function exhibited little or no relationship with age and is in agreement with our previous work [28]. This study demonstrated that patients with functional anosmia manifested significant hypogeusia when compared to healthy subjects. The results were consistent with a report by Landis [1], who examined 107 healthy subjects and 103 patients with dysosmia. They observed that patients with long-term olfactory impairment manifested dysgeusia and suggested that interaction between chemical sensory systems were characterized by mutual attenuation rather than compensation. Vennemann [29] showed that hypogeusia was often accompanied by olfactory impairment, and interaction between chemical sensory systems resulted in simultaneous functional impairment. Kettenmann [30] showed that N1 and P2 waves were very useful in examining the correlation between olfactory and gustatory functions because both of them were generated in the insular cortex. There was close interaction between olfactory and gustatory neural centers [31]. Such interaction possibly took place at the subcortical level and manifested the characteristic of mutual amplification. Clinically, anosmia corresponded with alteration of gustatory threshold [27]. This observation suggests that chemical sensory functions are interrelated and interact with each other. Impairment of 1 sensory function will affect the other 2. Because of continuous and repetitive interactions in daily life, functions of the 3 chemical sensory systems are interrelated [32]. Sudden loss of 1 chemical sensation in patients will lead to the absence of the afferent signals, and further decrease the integrated reaction of the remaining 2 chemical sensory systems [16,23].

Conclusions

Our data show that patients with functional anosmia often had significant trigeminal nerve dysfunction and hypogeusia. Especially in younger patients, demonstrated olfactory and trigeminal function clearly decreased. These findings will be useful for assessing chemosensory function in future work in Chinese populations, particularly when assessing subjects

with olfactory complaints and olfactory disease. Combined examinations of T&T oERPs, tERPs and three drops method will make it possible to reflect the overall chemical sensory functions in subjects systematically, and to provide scientific evidence for early clinical diagnosis and treatment.

REFERENCES:

1. Landis BN, Scheibe M, Weber C et al: Chemosensory interaction: acquired olfactory impairment is associated with decreased taste function. J Neurol, 2010; 257: 1301–8
2. Kirchner A, Landis BN, Haslbeck M et al: Chemosensory function in patients with vagal nerve stimulators. J Clin Neurophysiol, 2004; 21: 418–25
3. Dalton P, Doolittle N, Nagata H et al: The merging of the senses: integration of subthreshold taste and smell. Nat Neurosci, 2000; 3: 431–32
4. Hummel T, Livermore A: Intranasal chemosensory function of the trigeminal nerve and aspects of its relation to olfaction. Int Arch Occup Environ Health, 2002; 75: 305–13
5. Veldhuizen MG, Shepard TG, Wang MF et al: Coactivation of Gustatory and Olfactory Signals in Flavor Perception. Chem Senses. 2010; 35: 121–33
6. Hoffman HJ, Cruickshanks KJ, Davis B: Perspectives on Population-based Epidemiological Studies of Olfactory and Taste Impairment. Ann NY Acad Sci, 2009; 1170: 514–30
7. Wrobel BB, Leopold DA: Clinical assessment of patients with smell and taste disorders. Otolaryngol Clin North Am, 2004; 37: 1127–42
8. Hummel T, Bensafi M, Nikolaus J et al: Olfactory function in children saaessed with spychophysical and electrophysiological techniques. Behavioural Brain Research, 2007; 180: 133–38
9. Ishimaru T, Shimada T, Miwa T et al: Electrically stimulated olfactory evoked potential in olfactory disturbance. Ann Otol Rhinol Laryngol, 2002; 111: 518–22
10. Stuck BA, Weitz H, Hörmann K et al: Chemosensory event-related potentials during sleep- A pilot study. Neuroscience Letters, 2006; 406: 222–26
11. Gudziol H, Hummel T: Normative values for the assessment of gustatory function using liquid tastants. Acta Oto-Laryngologica, 2007; 127: 658–61
12. Kondo H, Matsuda T, Hashiba M et al: A study of the relationship between the T&T olfactometer and the University of Pennsylvania Smell Identification Test in a Japanese population. Am J Rhinol, 1998, 12: 353–58
13. Wei YX, Miao XT, Xian M et al: Effects of transplantating olfactory ensheating cells on recovery of olfactory epithelium after olfactory nerve transection in rats. Med Sci Mornit, 2008; 14(10): BR198–204
14. Brämerson A, Millqvist E, Ydse B et al: Event-related potentials in patients with olfactory loss. Acta Oto-Laryngologica, 2008; 128: 1126–31
15. Lötsch J, Hummel T: The clicial significance of electrophysiological measures of olfactory function, Behavioural Brain Research, 2006; 170: 78–83
16. Hummel T, Barz S, Lötsch J et al: Loss of olfactory function leads to a decrease of trigeminal sensitivity. Chem Senses, 1996; 21: 75–79
17. Boyle JA, Heinke M, Gerber J et al: Cerebral activation to intranasal chemos- ensortrigeminal stimulation. Chem Senses, 2007; 32: 343–53
18. Iannilli E, Gerber J, Frasnelli J et al: Intranasal trigeminal function in subjects with and without an intact sense of smell. Brain Res, 2007; 1139: 235–44
19. Brückmann H, Kobal G, Wiesmann M: Activation of Olfactory and Trigeminal Cortical Areas Following Stimulation of the Nasal Mucosa With Low Concentrations of S(–)-Nicotine Vapor – An fMRI Study on Chemosensory Perception. Human Brain Mapping, 2009; 30: 699–710
20. Hummel T, Iannilli E, Frasnelli J et al: Central processing of trigeminal activation in humans. Ann NY Acad Sci, 2009; 1170: 190–95
21. Frasnelli J, Schuster B, Hummel T: Olfactory dysfunction affects threshold to trigeminal chemosensory sensations. Neurosci Lett, 2010; 468: 259–63
22. Frasnelli J, Schuster B, Hummel T: Interactions between olfaction and the trigeminal system: what can be learned from olfactory loss. Cereb Cortex, 2007; 17: 2268–75
23. Frasnelli J, Hummel T: Olfactory dysfunction and daily life. Eur Arch Otorhinolaryngol, 2005; 262: 231–35
24. Reden J, Mueller A, Mueller C et al: Recovery of olfactory function following closed head injury or infections of the upper respiratory tract. Arch Otolaryngol Head Neck Surg, 2006; 132: 265–69
25. Murphy C, Morgan CD, Geisler MW et al: Olfactory event-related potentials and aging: normative data. Int J Psychophysiol, 2000; 36: 133–45
26. Stuck BA, Frey S, Freiburg C et al: Chemosensory event-related potentials in relation to side of stimulation, age, sex, and stimulus concentration. Clinical Neurophysiology, 2006; 117: 1367–75
27. Welge-Lüssen A, Drago J, Wolfensberger M et al: Gustatory stimulation influences the processing of intranasal stimuli. Brain research, 2005; 1038: 69–75
28. Yang L, Wei YX, Yu D et al: Olfactory and gustatory function in healthy adult Chinese subjects. Otolaryngol Head Neck Surg, 2010; 143: 554–60
29. Vennemann MM, Hummel T, Berger K: The association between smoking and smell and taste impairment in the general population. J Neuro, 2008; l255: 1121–26
30. Kettenmann B, Mueller C, Wille C et al: Odor and taste interaction on brain responses in humans. Chem Senses, 2005; 30: 234–35
31. de Araujo IE, Rolls ET, Kringelbach ML et al: Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. Eur J Neurosci, 2003; 18: 2059–68
32. Shepherd GM: Smell images and the flavour system in the human brain. Nature, 2006; 444: 316–21
33. Boyle JA, Heinke M, Gerber J et al: Cerebral activation to intranasal chemos- ensortrigeminal stimulation. Chem Senses, 2007; 32: 343–53