Patients with olfactory loss exhibit pronounced adaptation to chemosensory stimuli: an electrophysiological study*

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Abstract

Background: Pronounced chemosensory adaptation affects many patients with olfactory loss. The study aimed to investigate adaptation to olfactory and trigeminal nasal stimuli in patients with olfactory loss in comparison to controls using electrophysiological measures.

Methodology: Thirty-four patients with olfactory loss (mean age ± SD = 59 ± 16 years) and 17 healthy volunteers (mean age ± SD = 50 ± 14 years) were recruited. Sniffin' sticks test was used for evaluation of olfactory function and EEG-derived chemosensory event-related potentials were recorded. Intranasal stimuli were presented using high-precision, computer-controlled stimulators based on the principles of air-dilution olfactometry. Data were analyzed in two different approaches according to the relatively short or long inter-stimulus interval. A decreased peak amplitude or a prolonged latency was considered as an expression of adaptation.

Results: The majority of participants (88%) responded reliably to chemosensory stimulation. Patients with olfactory loss exhibited pronounced olfactory and trigeminal adaptation within the long-term design, without such effects in healthy controls. Odor sensitivity correlated with both olfactory and trigeminal amplitude changes: the worse the olfactory sensitivity, the more pronounced chemosensory adaptation.

Conclusions: The results help to explain the patients' complaints in terms of the fast adaptation towards chemosensory stimuli, for example during eating and drinking. The differences in adaptation in patients with olfactory loss and healthy controls could serve as a clinical criterion to gauge olfactory dysfunction.

Key words: adaptation, EEG, olfactory, trigeminal

Introduction

In the clinical context, patients with olfactory loss frequently report a fast decline in odor intensity after perceiving the very first sniff [1,2]. Such desensitization diminishes the chance of avoiding hazardous situations (e.g. gas leakage), dwindles the food pleasantness, and reduces their quality of life. For example, with reference to eating and drinking, when patients have breakfast and eat a croissant, they experience the flavor of the croissant with the first bite. Then they adapt really fast so that the second bite is more or less without aroma. This can be tantalizing! However, this phenomenon has gone unnoticed in research for a long time. Recently a study measured the trajectory of turning points in the odor threshold test suggesting that people with lower olfactory ability declined faster than those with better olfactory function [1]. This might be a good start to listen to the patient's complaints more carefully and provide an important perspective for clinical practice on olfaction.

A recent review clarified the term "adaptation" to odors as a decrease of responses on the neural level due to repetitive exposure, which leads to behavioral "habituation" as a change in perceptual intensity [2]. The electroencephalographic (EEG) technique is a promising approach to evaluate brain responses to chemosensory stimuli, serving as an objective diagnostic tool for olfactory dysfunction [3,4]. Its high temporal resolution is es-

pecially suited to evaluate desensitization [5]. Numerous studies have investigated olfactory/trigeminal adaptation in healthy populations, most of them suggesting decreased amplitudes and unchanged latencies of olfactory or trigeminal event-related potentials (OERP and TERP) after repetitive stimulation [6–8], suggesting an effect of adaptation.

Even in the absence of olfactory function, some individuals could respond to odorous stimuli utilizing the EEG technique. When using ERP to investigate olfactory loss, relatively long inter-stimulus intervals (ISI, approximately 30 seconds) are commonly applied. Using such designs, compared to normosmic controls patients with olfactory loss exhibit lower amplitudes and longer latencies of OERP [9,10]. For TERP, Frasnelli and colleagues reported smaller P2 and N1P2 amplitudes in patients with acquired anosmia but no such differences in isolated congenital anosmia [11,12]. Olfactory adaptation is important to filter non-informative odors, but a very fast adaptation affects people's daily life, especially in patients with olfactory loss [2]. Olfactory adaptation could serve as a discriminative parameter between patients and healthy populations in the clinical context. However, so far studies focusing on adaptation in patients with olfactory loss are still scarce.

Considering the complaints of hyposmic patients in terms of a rapid adaptation to odors, the present study aimed to investigate this symptom using ERP to olfactory and trigeminal stimuli as a technique with high temporal resolution. The interest in this question also came from the idea of the possibility to explore a potential clinical tool to quantitatively gauge this symptom.

Materials

Participants

Thirty-four patients with olfactory loss (mean age ± SD = 59±16 years; cause of olfactory loss: trauma - n=5, idiopathic cause - n=6, infections - n=20, chronic rhinosinusitis - n=3) and 17 healthy volunteers (mean age ± SD = 50 ± 14 years) were included in the study. The patients were recruited from the Smell & Taste Clinic, Department of Otorhinolaryngology, University Hospital of Dresden, Germany. Healthy controls were recruited via word-of-mouth or flyers distributed in the area of the University Hospital. Inclusion criteria were: (i) voluntary participation; (ii) > 18 years old; (iii) good general health; (iv) healthy participants were required to have a normal sense of smell; (v) patients with olfactory loss were required to report that they had at least a residual ability to smell. Exclusion criteria were (i) <18 years old; (ii) pregnancy; (iii) people with related conditions in the field of otolaryngology, and (iv) smokers. Following detailed information on aims and risks of the study, all participants signed written consent and completed a medical history questionnaire, including information on routine medication intake and previous and pre-existing medical conditions. The Ethics Committee at the Medical Faculty Carl Gustav Carus of the Technische Universität Dresden approved this study.

Olfactory function assessment

Olfactory function was measured by the "Sniffin' sticks" test (SST) which is based on reusable pen-like devices [13]. SST contains three subtests: odor threshold, discrimination, and identification. The odor threshold test consists of 48 pens, 16 of which contain the odor of phenyl ethyl alcohol (PEA, a rose-like odor) in different concentrations. Participants need to select the scented one in a triplet alone with the other two odorless sticks. Applying a single staircase procedure where two continuous positive or one negative reaction triggers the reversal of the staircase, the final score was calculated using the average of the last of four staircase reversals (7 reversals in total), ranging from 1 to 16. The odor discrimination test includes 48 scented pens presented as triplets where two of them smell the same and the third one smells differently. Participants have to select the one with a different smell. The score is the sum of correct responses, ranging from zero to 16. The identification test is based on 16 odorous pens. Following the odor presentation, participants need to identify the smell from a list of four verbal options. For this test, the sum score of correct answers ranges from 0 to 16. The composite TDI score is the sum of scores for odor threshold, discrimination, and identification scores, ranging from 1 to 48, with a higher score suggesting better olfactory function.

Stimuli

Chemosensory stimuli were generated using a computer-controlled olfactometer (OM6b, Burghart MT, Wedel, Germany), which is capable of delivering brief odor pulses embedded in constant airflow. We used PEA (40%, v/v) as a selective stimulant for OERP and carbon dioxide (CO_2, 50%, v/v) as a selective stimulus for TERP [4]. Each stimulus presentation lasts 250 ms. These two types of stimuli were embedded into a constant flow of warmed (36°C) and humidified (80% relative humidity) air so as not to irritate the nasal mucosa and delivered at a flow of 7 l/min. A Teflon tube (4 mm inner diameter) was used to deliver the odors. Both PEA and CO_2 were presented three times in a row (Figure 1). The ISI between the stimuli of each triplet was 4 seconds, and the inter-series interval between the triplets was 30 seconds (compare Hummel et al. [5]). After presenting PEA, the same procedure was followed with CO_2. A total of 142 trials were presented where trials 2 to 64 were recorded for PEA and 65 to 145 for CO_2, with the first two trials as dummy stimuli. The longer CO_2 stimuli was because of the expected larger number of artifact-contaminated responses to trigeminal stimuli, so that fewer stimuli would be available for averaging.

Data were analyzed in two different ways according to the relatively short or long ISI: To examine the effects of a relatively "long-term" (LT) adaptation, we divided the data into 3 groups, using averages for stimuli 2-22 as LT class 1, averages for stimuli 23-43

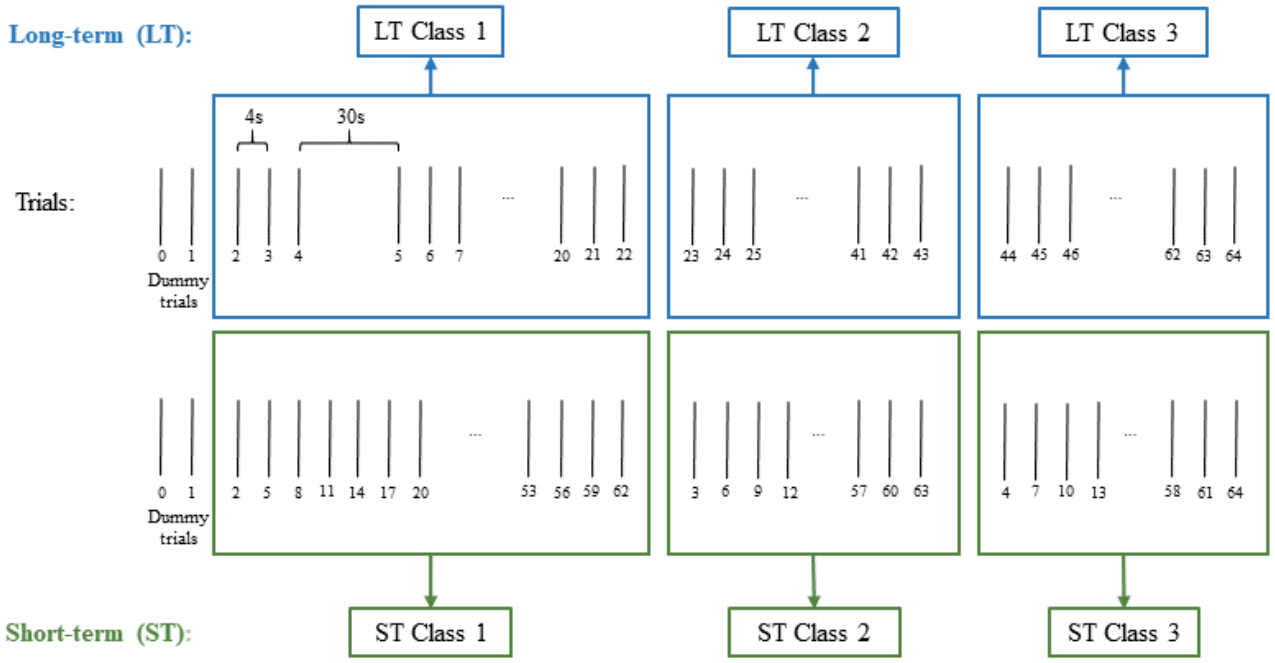

Figure 1. The design of long-term and short-term classes for PEA. The inter-stimulus interval between the stimuli of each triplet was 4 seconds, and the inter-series interval between the triplets was 30 seconds. Long-term class 1 included trials 2-22; class 2 included trials 23-43 and class 3 included 44-64. Short-term class 1 included the first stimulus of all triplets; the second stimulus for class 2 and the third stimulus for class 3.

as LT class 2, and averages for stimuli 44-64 as LT class 3 for PEA. Similar division was applied for LT classes for CO_2 (class 1: stimuli 65-91, class 2: stimuli 92-118 and class 3: stimuli 119-145). We also conducted a second analysis to investigate the "short-term" (ST) effects of adaptation separately for PEA and CO_2. Because stimuli were presented as triplets with short inter-stimulus trials, we averaged all responses to the first stimulus of these groups of 3 stimuli as ST class 1, responses to the second stimulus as ST class 2, and responses to the third stimulus as ST class 3.

Procedure

The study was conducted in a quiet, air-conditioned room, including a medical history, the "Sniffin' sticks" test, and an electroencephalogram all performed consecutively during a single appointment. During the recordings, participants sat in a comfortable chair and performed a simple visual tracking task to minimize head movements and maintain vigilance [4]. To mask switching clicks of the olfactometer associated with stimulus presentation, participants wore headphones that provided white noise (~50 dB). They were also instructed to breathe via the mouth and try not to blink during recording.

EEG recording and preprocessing

EEG was recorded using a 16-channel EEG amplifier (Schabert, Röttenbach, Germany), from 3 midline positions (Fz, Cz, Pz) and Fp2 (to control vertical eyeblinks) according to the 10/20 system referenced against linked earlobes (A1 + A2). Each recording started 500 ms before stimulus onset and continued for 1500 ms after the onset of the stimulation. The sampling frequency was 250 Hz.

We used the software of EPEvaluate 4.2.2 (Kobal, Erlangen, Germany) to preprocess EEG signals. The signal was filtered offline (low pass 15 Hz) and visually inspected for motor and eye-blinking artifacts (records contaminated by blink artifacts of an amplitude > 50 µV were excluded [14]). A trained researcher (ZL) identified the P1, N1, and P2 peaks of each ERP, obtaining the stimulus latencies, base-to-peak amplitudes for P1, N1, and P2 components as well as peak-to-peak N1-P2 amplitudes for each electrode. Overall, for each long- or short-term class a mean number of 16 trials for PEA and 18 trials for CO_2 were used for averaging both olfactory and trigeminal responses per subject. An estimate of 20% of artifact-contaminated trials in relation to olfactory stimulation and 32% for trigeminal stimulation were excluded. The numbers of remaining ERP were comparable between patients and controls ($p>0.25$). Given that fewer stimuli are sufficient to produce reliable chemosensory event-related potentials components [15], the number of recordings in the present study should be sufficient.

Data analysis

We utilized SPSS v28.0 (IBM, Armonk, NY, USA) for data analysis. Descriptive statistics of demographic information were acquired

Table 1. Descriptive statistics between patients and controls (mean ± SD).

	Patients n=34	Healthy controls n=17
Age (years)	59 ± 16	50 ± 14
Gender ratio (M:W)	13:21	7:10
Duration of illness (months)	8.89 ± 11.67	N/A
range	0.25-43	
TDI score	21.74 ± 6.77	34.62 ± 2.73
Odor threshold	2.65 ± 2.23	7.15 ± 2.21
Odor discrimination	9.79 ± 3.05	13.76 ± 2.59
Odor identification	9.29 ± 3.02	13.71 ± 2.29

M=Men, W=Women, N.A.=Not Applicable

from patients and controls. The gender ratio was estimated by Chi-square analysis. Separately for the peak amplitudes and latencies, repeated measures ANOVA analyses were utilized where Class was the within-subject factor and Group (patients vs. controls) the between-subjects factor followed by Bonferroni corrected pairwise comparisons, with separated LT classes (class 1 vs. class 3) and ST classes (class 1 vs. class 2) to minimize the expectation effect and Pz, Cz, and Fz electrodes. ST class 3 was not included because it is the response to the last stimulus of a series that are typically contaminated by the expectation towards the stimuli. With that, the last stimulus receives a certain meaning reflected in the brain responses, which would conflict with the aim of our investigation focused on adaptation [16]. LT class 2 was not included because in this part of the study we focused on the difference between responses to stimuli presented early during the session and those later in the session. A decreased amplitude or a prolonged latency in the latter class was considered as adaptation. Pearson's correlation analysis was used to investigate the relationship between olfactory function and changes between classes (calculated as results for LT class 1 minus class 3, and results for ST class 1 minus class 2) focused on the Pz electrode for OERP and Cz for TERP because recordings at Pz have been reported to provide the best signal-to-noise ratio for OERP, and the Cz electrode for TERP [4]. A p-value below 0.05 denoted significance.

Results

Eighty-eight percent of the patients and controls exhibited event-related responses to olfactory and trigeminal stimuli (averaged responses in Supplementary data Appendix 1). There were no significant differences in age and gender distribution between patients and healthy controls (p>0.05, Table 1).

Responses to long-term OERP

For amplitudes, repeated measures ANOVA analysis revealed a significant main effect of LT "class" ($F[1, 42]=13.75$, $p<0.001$) for N1P2 amplitudes on the Pz electrode. Pairwise comparison showed that N1P2 amplitudes in LT class 1 were larger than in LT class 3 ($p<0.001$). Similar results were found for recordings at Cz and Fz electrodes (all $p<0.05$). We found an interaction between factors "class" and "group" ($F[1, 43]=5.11$, $p=0.029$) on the Fz electrode, suggesting that, only in patients, the N1P2 amplitude in LT class 1 was larger than in LT class 3 (Figure 2, $p<0.001$). Similar Bonferroni corrected pairwise comparisons showed this LT class difference only in the patient group on the Pz electrode with a trend-like significant interaction ($p=0.07$). There were no significant differences related to latency.

Responses to long-term TERP

Similar to OERP, for trigeminal stimulation we found a significant main effect of LT "class" ($F[1, 43]=11.39$, $p=0.002$) for N1P2 amplitudes on the Pz electrode, showing that N1P2 amplitudes in LT class 1 were larger than LT class 3 ($p=0.002$). Similar main effects were found for Cz and Fz electrodes (all $p<0.05$) as well. In addition, Bonferroni corrected pairwise comparisons showed this LT class difference only in the patient group on all electrodes ($p<0.05$), although the interaction between "class" and "group" was non-significant ($p>0.05$). For latency, no main effect of "class" was found, while a group difference was observed in all peaks and electrodes, suggesting that, overall, patients had shorter latencies than healthy controls (all $p<0.05$).

Responses to short-term OERP

We found a main effect of ST "class" in P2 peak for latency ($F[1, 43]=4.23$, $p=0.046$), as well as on Cz and Fz electrodes (all $p<0.05$), suggesting ST class 1 had shorter latencies than ST class 2. No difference in amplitude in all peaks or electrodes was found (all $p>0.05$).

Responses to short-term OERP

On the Cz electrode, we found a significant interaction between factors ST "class" and "group" ($F[1, 40]=6.16$, $p=0.017$), showing in the patient group that P2 amplitudes for ST class 2 were larger than for ST class 1 ($p<0.001$). The main effects of ST class were found for Pz and Fz electrodes showing larger P2 amplitudes in ST class 2 compared to ST class 1 (all $p<0.05$). For N1P2 amplitudes at position Fz there was an interaction between factors ST "class" and "group" ($F[1, 43]=8.77$, $p=0.005$) suggesting that, in patients, the N1P2 amplitude in ST class 2 was larger than in ST class 1 ($p<0.001$). A group difference was observed for P2 latencies for Cz and Fz electrodes, suggesting that patients had shorter P2 latencies than healthy controls (all ps<0.05). No other differences in amplitudes or latencies were found (all $p>0.05$).

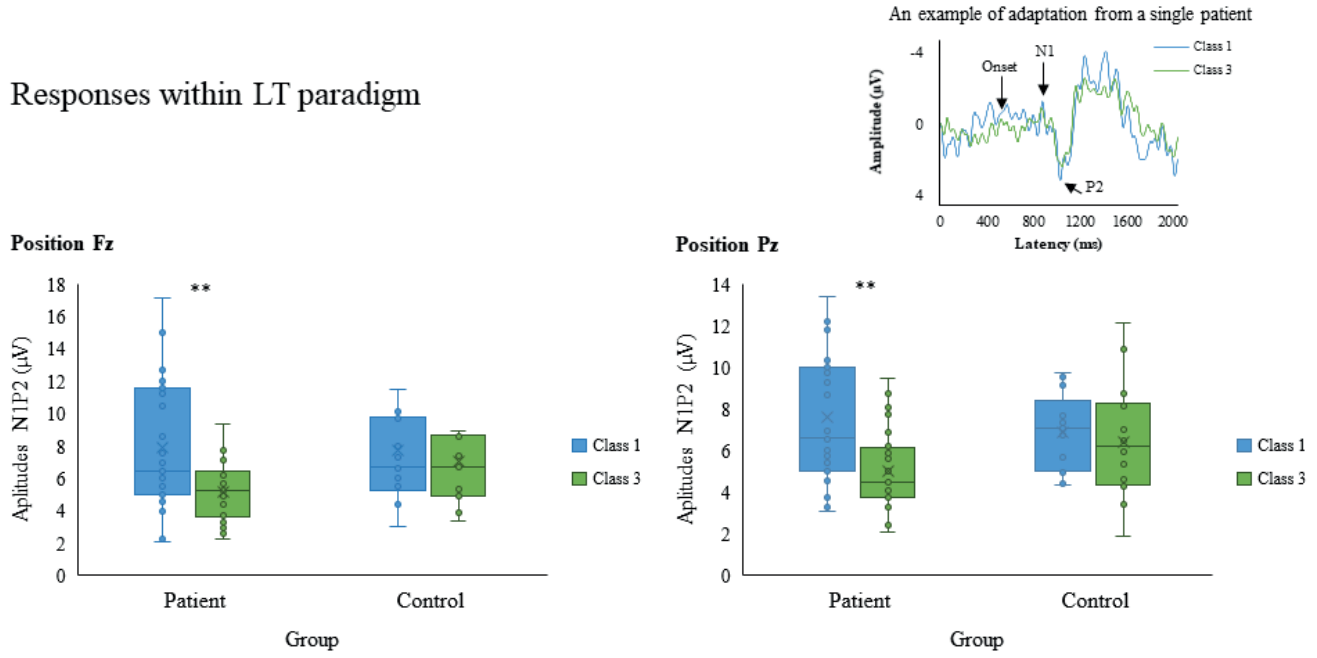

Figure 2. Pronounced adapted N1P2 amplitudes on Fz and Pz electrodes in patients with olfactory loss according to long-term olfactory stimulation. **p < 0.001 in the pairwise comparison.

Correlation analysis

For OERP, the odor threshold correlated with the LT N1P2 amplitude change between class 1 and 3 (r=-0.40, p=0.008, Figure 3A) on the Pz electrode suggesting that the lower the odor sensitivity, the more pronounced the decrease of the N1P2 amplitude from LT class 1 to LT class 3 to odorous stimuli. Subgroup analysis suggested that OERP correlated with odor threshold in healthy controls (r=-0.64, p=0.02). For TERP, the odor threshold correlated with ST P2 amplitude change between ST class 1 and ST class 2 (r=-0.33, p=0.035, Figure 3B) on the Cz electrode. This suggested that the lower the odor sensitivity, the more pronounced the decrease of the P2 amplitude from ST class 1 to ST class 2 to trigeminal stimuli.

Discussion

We found that: (i) patients exhibited pronounced long-term and short-term olfactory/trigeminal adaptation compared with healthy controls, (ii) that patients showed enhanced short-term trigeminal responses, and (iii) odor threshold correlated with the change of amplitudes of OERP and TERP suggesting that individuals with lower sensitivity showed more pronounced adaptation.

With repeated exposure to the olfactory or trigeminal stimuli, the amplitudes of responses decreased within the long-term design, which is in line with previous studies [5,6,8]. Moreover, only patients exhibited pronounced long-term adaptation in the present study. This confirms work by Chen and colleagues who demonstrated olfactory adaptation in patients with olfactory dysfunction which has been hypothesized to be associated with the number or function of olfactory receptor neurons [1,17]. Previous studies with patients with olfactory loss following head trauma or viral infections of the upper respiratory tract suggested a decreased number of olfactory receptor neurons [1,18,19]. One hypothesis is that the lower number of receptors could be occupied quickly and completely by odorants after the first sniff leading to faster adaptation towards odors. The smaller number of neurons probably does not allow for fast recovery from olfactory adaptation compared to normosmic people, resulting in marked adaptation in patients.

Interestingly, patients exhibited increased neural activity response to ST trigeminal stimulation. Moreover, patients processed the stimuli faster than healthy controls regardless of the long- or short-term trigeminal stimulation. This is difficult to explain because it contradicts previous studies showing that patients have lower amplitudes and longer latencies than controls [4,20]. One hypothetical interpretation could be that an enhanced peripheral activation compensates for the decreased central responses. In fact, patients with congenital or acquired anosmia had similar or smaller central but larger peripheral trigeminal activation than controls [11,12]. Frasnelli and colleagues discussed a dynamic model between the olfactory and trigeminal systems [21], where the primary trigeminal activation is increased on a mucosal level in patients with olfactory loss. Without the central nervous amplification of the trigeminal activation that is found in healthy people, the enhanced peripheral responses in anosmic people may compensate the missing central nervous

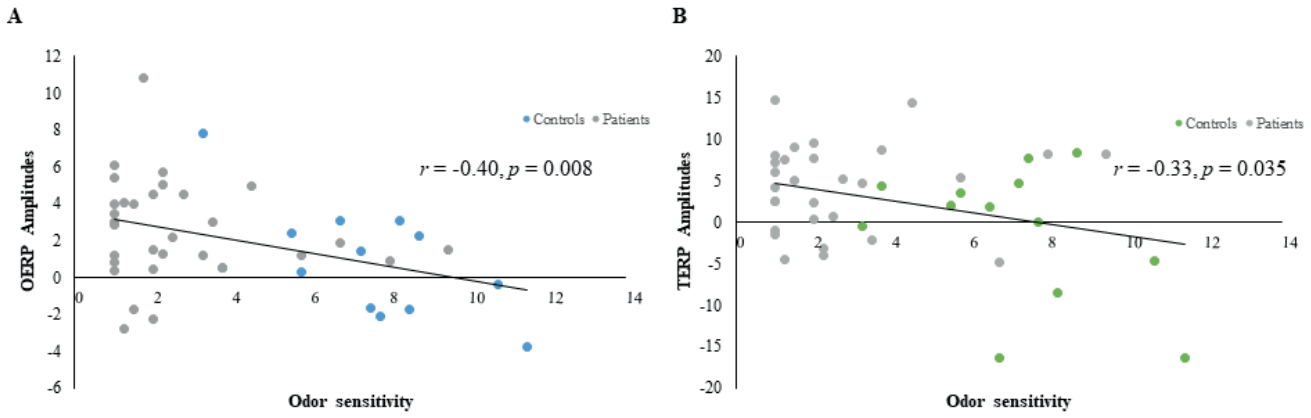

Figure 3. (A) Correlations between odor sensitivity and the change of N1P2 amplitudes of olfactory event-related potentials (OERP) on Pz electrode, and (B) trigeminal event-related potentials (TERP) on Cz electrode. OERP amplitude changes relate to LT class 1 - LT class 3; TERP Amplitudes changes relate to ST class 1 - ST class 2. The line refers to the trend of the whole sample.

amplification. The hypothesized compensatory mechanism in the present study certainly needs more future study to prove. Odor thresholds correlated with amplitude changes of both OERP and TERP, indicating that the lower the odor sensitivity the more pronounced the adaptation for both, olfactory and trigeminal stimuli. A recent study suggested a similar relationship between TDI scores and N1 amplitudes for OERP in patients with idiopathic olfactory loss [10]. In addition, better olfactory function also correlated with increasing N1P2 amplitude of trigeminal responses [22]. The present results extended these relationships, and confirmed our previous findings [1,2] that patients had more pronounced olfactory adaptation than controls. In addition, considering that thresholds may relate more closely to peripheral functions of the olfactory system than to central nervous functions [23,24], these correlations seem to indicate that the rapid adaptation in patients with olfactory loss is more related to lesions at the level of the mucosa than to changes at a central level of processing.

One limitation of the present study was the relatively small sample size which probably was one of the reasons for trends towards significant findings for some of the recorded parameters although differences were found in pairwise comparisons. This should be addressed by larger sample sizes in future studies.

Conclusion

Results from the present study suggest marked olfactory and trigeminal adaptation in patients with olfactory dysfunction compared to healthy controls in relation to long-term design. This could be used as a parameter to describe more subtle complaints of patients with olfactory dysfunction in the clinic. Odor sensitivity correlated with parameters from OERP and TERP, suggesting that people with lower odor sensitivity have more pronounced olfactory or trigeminal adaptation which possibly originates at a mucosal level.

Authorship contribution

ZL analyzed, interpreted the data, and wrote the manuscript; RS ran the study, interpreted the data, and wrote the manuscript; TH designed and ran the study, analyzed and interpreted the data, and wrote the manuscript. All authors critically reviewed the manuscript before submission.

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Conflict of interest

The authors declare no competing financial interests.

References

1. Chen B, Haehner A, Mahmut MK, Hummel T. Faster olfactory adaptation in patients with olfactory deficits: An analysis of results from odor threshold testing. Rhinology. 2020;58(5):1–6.
2. Pellegrino R, Sinding C, de Wijk RA, Hummel T. Habituation and adaptation to odors in humans. Physiol Behav. 2017;177:13–9.
3. Rombaux P, Huart C, Mouraux A. Assessment of chemosensory function using electroencephalographic techniques. Rhinology. 2012;50(1):13–21.
4. Hummel T, Kobal G. Methods and frontiers in chemosensory research. In: Simon SA, Nicolelis MAL, editors. Olfactory event-related potentials. Boca Raton (FL): CRC press; 2001. p. 429–64.
5. Hummel T, Gruber M, Pauli E, Kobal G. Chemo-somatosensory event-related potentials in response to repetitive painful

chemical stimulation of the nasal mucosa. Electroencephalogr Clin Neurophysiol Evoked Potentials. 1994;92(5):426–32.
6. Flohr ELR, Boesveldt S, Haehner A, Iannilli E, Sinding C, Hummel T. Time-course of trigeminal versus olfactory stimulation: Evidence from chemosensory evoked potentials. Int J Psychophysiol. 2015;95(3):388–94.
7. Scheibe M, Opatz O, Hummel T. Are there sex-related differences in responses to repetitive olfactory/trigeminal stimuli? Eur Arch Oto-Rhino-Laryngology. 2009;266(8):1323–6.
8. Croy I, Maboshe W, Hummel T. Habituation effects of pleasant and unpleasant odors. Int J Psychophysiol. 2013;88(1):104–8.
9. Brämerson A, Millqvist E, Ydse B, Larsson C, Olofsson JK, Bende M. Event-related potentials in patients with olfactory loss. Acta Otolaryngol. 2008;128(10):1126–31.
10. Liu J, Pinto JM, Yang L, Yao L, Miao X, Wei Y. Evaluation of idiopathic olfactory loss with chemosensory event-related potentials and magnetic resonance imaging. Int Forum Allergy Rhinol. 2018;8(11):1315–22.
11. Frasnelli J, Schuster B, Hummel T. Interactions between olfaction and the trigeminal system: What can be learned from olfactory loss. Cereb Cortex. 2007;17(10):2268–75.
12. Frasnelli J, Schuster B, Hummel T. Subjects with congenital anosmia have larger peripheral but similar central trigeminal responses. Cereb Cortex. 2007;17(2):370–7.
13. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin'sticks": olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold.' Chem Senses. 1997;22(1):39–52.
14. Tateyama T, Hummel T, Roscher S, Post H, Kobal G. Relation of olfactory event-related potentials to changes in stimulus concentration. Electroencephalogr Clin Neurophysiol - Evoked Potentials. 1998;108(5):449–55.
15. Rombaux P, Mouraux A, Bertrand B, Guerit J, Hummel T. Assessment of olfactory and trigeminal function using chemosensory event-related potentials. Neurophysiol Clin. 2006;36(2):53–62.
16. Thaploo D, Zelder S, Hummel T. Olfactory Modulation of the Contingent Negative Variation to Auditory Stimuli. Neuroscience. 2021;470:16–22.
17. Stevens JC, Cain WS, Schiet FT, Oatley MW. Olfactory adaptation and recovery in old age. Perception. 1989;18(2):265–76.
18. Lee VK, Nardone R, Wasco F, Panigrahy A, Zuccoli G. Delayed activation of the primary orbitofrontal cortex in post-traumatic anosmia. Brain Inj. 2016;30(13–14):1737–41.
19. Finlay JB, Brann DH, Abi-Hachem R, et al. Persistent post-COVID-19 smell loss is associated with inflammatory infiltration and altered olfactory epithelial gene expression. bioRxiv. 2022;2022.04.17.488474.
20. Hummel T, Barz S, Lötsch J, Roscher S, Kettenmann B, Kobal G. Loss of olfactory function leads to a decrease of trigeminal sensitivity. Chem Senses. 1996;21(1):75–9.
21. Frasnelli J, Hummel T. Interactions between the chemical senses: Trigeminal function in patients with olfactory loss. Int J Psychophysiol. 2007;65(3):177–81.
22. Rombaux P, Mouraux A, Keller T, Hummel T. Trigeminal event-related potentials in patients with olfactory dysfunction. Rhinology. 2008;46(3):170–4.
23. Hedner M, Larsson M, Arnold N, Zucco GM, Hummel T. Cognitive factors in odor detection, odor discrimination, and odor identification tasks. J Clin Exp Neuropsychol. 2010;32(10):1062–7.
24. Lötsch J, Reichmann H, Hummel T. Different odor tests contribute differently to the evaluation of olfactory loss. Chem Senses. 2008;33(1):17–21.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Appendix 1: The averaged responses (mean ± SD) of olfactory and trigeminal stimulation in patients and controls.

OERP	Patient (n=31)				Control (n=14)			
	LT Class 1	LT Class 3	ST Class 1	ST Class2	LT Class 1	LT Class 3	ST Class 1	ST Class2
Pz Amplitude								
P1	0.17±4.25	0.85±2.16	0.40±3.70	-0.72±5.46	-0.64±5.44	-0.98±3.25	-2.23±6.58	-0.32±4.86
N1	-3.80±4.92	-2.63±2.41	-2.63±3.87	-3.13±3.85	-5.30±6.33	-4.15±4.47	-5.47±7.09	-4.33±6.37
P2	3.81±4.49	2.41±2.07	3.12±4.36	2.42±4.04	3.81±4.49	2.25±3.59	0.47±7.14	2.33±6.82
N1P2	7.60±3.57	5.03±1.87	5.82±3.06	5.49±2.38	6.83±1.88	5.96±2.40	5.94±2.70	6.66±4.66
Pz Latency								
P1	451.70±74.81	473.38±72.22	448.95±71.18	475.10±87.75	451.91±63.16	470.86±66.38	451.91±65.76	481.14±93.73
N1	504.43±75.12	534.19±72.67	501.72±78.52	532.04±92.90	518.19±63.32	522.76±64.54	508.57±69.01	535.33±80.22
P2	617.76±85.37	649.16±93.30	616.95±96.82	648.69±106.82	631.81±66.31	640.47±89.30	623.81±66.07	661.43±86.68
Cz Amplitude								
P1	1.11±4.23	1.07±2.89	1.17±4.66	0.42±4.96	1.12±3.30	-0.33±3.12	-0.76±3.38	0.12±3.12
N1	-3.11±4.65	-2.84±2.98	-2.69±5.07	-2.98±4.67	-4.48±3.78	-3.92±3.78	-4.27±3.51	-3.94±3.81
P2	4.28±4.21	2.92±2.50	3.14±4.77	3.68±6.05	3.51±7.10	3.15±4.02	3.14±4.77	3.68±6.05
N1P2	7.89±4.06	5.14±1.72	5.80±2.99	5.82±2.82	7.74±3.94	7.07±3.41	5.22±3.17	5.98±2.40
Cz Latency								
P1	454.67±73.61	474.02±72.59	448.17±72.33	477.46±85.33	450.86±66.41	468.95±64.28	449.43±64.07	484.57±95.42
N1	507.14±75.16	536.00±72.98	502.67±79.02	535.61±90.93	517.43±62.72	525.05±64.90	505.90±68.58	542.00±84.44
P2	618.75±86.84	649.94±93.61	618.02±95.09	648.56±111.09	632.48±65.43	640.86±90.22	620.57±65.28	664.10±87.33
Fz Amplitude								
P1	-0.69±5.78	0.37±2.55	-0.66±4.97	-0.76±5.72	0.45±3.15	-1.03±3.05	-1.13±5.32	-0.41±3.35
N1	-3.79±3.19	-3.32±2.52	-4.48±5.24	-4.23±5.14	-4.30±3.61	-4.06±3.31	-5.03±5.94	-5.21±6.35
P2	3.30±6.30	1.63±2.42	1.34±6.08	1.40±5.38	1.78±3.71	1.95±3.12	0.82±5.30	2.78±4.64
N1P2	7.89±4.06	5.14±1.72	5.82±2.93	5.63±2.75	7.74±3.94	7.07±3.41	5.73±1.68	5.67±2.65
Fz Latency								
P1	452.53±74.64	473.38±71.34	448.95±69.77	476.09±87.89	449.62±65.62	470.29±66.48	449.81±65.33	483.71±98.78
N1	506.88±75.08	533.59±72.02	505.25±78.07	535.74±89.49	520.76±64.26	525.43±65.09	508.00±69.54	541.81±84.71
P2	620.13±86.69	650.49±94.31	617.89±95.74	650.15±113.27	632.95±68.21	640.76±85.40	620.76±67.57	663.72±87.21

TERP	Patient (n=31)				Control (n=14)			
	LT Class 1	LT Class 3	ST Class 1	ST Class2	LT Class 1	LT Class 3	ST Class 1	ST Class2
Pz Amplitude								
P1	0.74±2.82	0.94±2.65	1.07±2.63	1.55±3.51	1.94±4.43	0.91±2.60	0.65±3.66	2.77±5.47
N1	-4.27±4.05	-3.01±3.13	-3.03±3.47	-2.48±4.00	-2.89±4.13	-2.24±2.48	-3.03±3.43	-0.81±5.28
P2	7.80±6.10	6.38±4.26	5.41±3.98	9.52±7.10	8.28±7.56	6.41±4.92	6.78±6.98	9.84±3.86
N1P2	12.07±5.87	9.38±4.22	8.44±4.07	12.01±6.15	11.17±6.49	8.65±3.87	9.82±4.76	10.65±6.68
Pz Latency								
P1	448.47±64.48	437.72±55.77	440.77±60.52	432.69±66.34	479.05±67.09	483.14±79.52	479.52±68.64	470.76±98.40
N1	508.86±64.55	493.16±51.48	494.49±59.21	493.50±64.61	546.00±65.75	538.67±81.82	540.67±66.88	523.62±90.57
P2	650.75±77.17	639.27±53.79	631.70±77.17	652.52±80.20	688.57±57.96	695.24±72.56	681.14±61.05	684.67±80.10
Cz Amplitude								
P1	0.49±4.32	-0.05±5.08	0.15±3.28	1.74±4.05	1.94±2.56	1.35±1.91	1.68±3.37	1.31±3.91
N1	-5.71±4.58	-4.47±4.90	-4.65±3.85	-3.85±4.83	-3.27±3.89	-2.77±1.98	-2.76±3.34	-2.72±4.50
P2	7.04±6.29	5.43±6.02	5.66±4.88	9.83±6.15	8.71±5.15	7.49±4.88	9.46±8.80	8.39±3.95
N1P2	12.43±5.73	9.98±5.29	9.56±4.76	11.67±6.80	11.97±5.05	10.27±4.14	12.64±7.09	12.07±6.21
Cz Latency								
P1	444.69±65.47	433.50±56.42	437.33±61.26	430.11±63.42	478.00±65.50	476.95±83.80	473.52±74.32	468.00±93.64
N1	509.85±65.48	491.44±52.42	495.66±57.83	495.05±64.41	542.95±65.79	534.38±84.92	532.95±73.37	524.38±86.70
P2	650.75±72.45	640.34±53.76	630.88±74.62	652.52±77.05	690.57±57.53	696.00±71.26	683.81±68.19	686.19±78.69
Fz Amplitude								
P1	1.59±4.09	0.93±3.83	0.44±3.70	3.08±5.47	1.61±4.89	0.45±3.80	1.10±5.80	1.68±3.82
N1	-3.85±3.80	-3.65±3.59	-4.02±4.44	-1.82±4.95	-3.25±5.59	-3.42±3.09	-3.82±5.83	-2.04±4.87
P2	6.12±5.65	4.74±4.07	3.56±5.23	8.80±4.91	7.62±7.65	5.25±5.03	6.26±9.26	7.10±4.58
N1P2	9.97±5.08	8.39±3.85	7.58±3.58	10.62±5.08	10.86±6.09	8.66±3.35	10.08±5.96	9.14±4.62
Fz Latency								
P1	445.50±65.48	435.66±54.78	435.05±61.25	431.05±63.95	474.48±67.93	478.38±79.65	477.81±69.64	464.48±96.07
N1	508.13±67.25	491.66±51.63	490.75±60.44	495.66±65.51	536.67±65.51	534.48±83.11	536.67±67.49	518.76±87.96
P2	651.48±75.45	643.87±57.78	633.29±76.34	653.16±78.09	695.90±57.75	698.95±71.49	681.24±58.95	688.48±79.56

Abbreviations: OERP=Olfactory event-related potential; TERP=Trigeminal event-related potential; LT=Long-term; ST=Short-term