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The importance of olfactory and trigeminal event-related potentials (OERPs/TERPs) in the assessment of olfactory function in subjects with chronic rhinosinusitis with nasal polyposis

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Abstract
Objectives: Smell impairment (SI) is a well-known symptom of chronic rhinosinusitis with nasal polyps (CRSwNP). The aim of study was to analyze olfactory and trigeminal event-related potentials (OERPs/TERPs) and psychophysical smell tests in subjects with CRSwNP, and its potential role in clinical practice.
Methods: Prospective study included 57 subjects. Two investigated groups with CRSwNP and one control group. Group I (n = 20) contained subjects without CRSwNP before septoplasty. Group II (n = 18) contained subjects with CRSwNP without therapy. Group III (n = 19) contained subjects with CRSwNP after intranasal corticosteroid therapy. Sniffin stick identification smell test and OERPs/TERPs were performed in all subjects.
Results: According to the psychophysical smell test, SI was detected in 65% of subjects with CRSwNP. In the control Group I (without CRSwNP), the absence of OERPs was 5.0%, whilethe mean absence rate in Groups II, III (with CRSwNP) was 8.1%. The highest percentage of absence of OERPs was registered in Group II (11.1%). Absence of TERPs was detected in an average of 21.6% of CRSwNP subjects. Group III showed the highest percentage of absence of TERPs (32%). In the control Group I, TERPs were absent in 0% of subjects.
Conclusion: CRSwNP significantly impairs olfactory function compared to patients without CRSwNP, Absence of TERPs was detected in an average of 21.6% of CRSwNP subjects versus healthy controls (0%). Presence of TERPs appears to be a predictor of preservation of olfactory function.

Keywords: Chronic rhinosinusitis; Olfactory dysfunction; OERPs; Smell test; Sniffin stick test; TERPs

Highlights:
- We analyzed psychophysical/ electrophysiological smell tests in subjects with CRSwNP.
- According to psychophysical smell tests, smell impairment in subjects with CRSwNP was found in 65%.
- Absence of TERPs was detected in average of 22% of CRSwNP subjects.
- Absence of OERPs was detected in average of 8% of CRSwNP subjects.
- Presence of TERPs appears to be a predictor of preservation of olfactory function.

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Introduction

The sense of smell takes place in our everyday life. As well as being used to detect hazards in the environment, it also has a huge impact on our diet and behaviour. Olfactory dysfunction (OD) is often considered a relatively ordinairy issue, but it can seriously affect an individual's life quality. Interest in olfaction increased dramatically during the Covid-19 pandemic. Complications associated with smell impairment (SI) came to the foreground of general public interest, leading to a dramatic increase in scientific papers on the topic (Červený et al., 2022; Holý et al., 2024a; Pastorkova et al., 2023; Stevenson, 2010; Vodička et al., 2012).

OD has been characterized as conductive and sensory (Červený et al., 2022; Vodička et al., 2012). Conductive OD results from the obstruction of the nasal cavity, e.g., by nasal polyps or post-traumatic changes, which inhibits the access of odorants to the olfactory mucosa. Sensorineural OD develops when the sensory neurons are incapable of transmitting sensory input due to impaired olfactory epithelium, or when it is caused as a result of damage to the central pathways. In addition to aging, the main causes of OD are viral diseases and sinonasal pathologies, defined mostly by sinonasal inflammatory issues (Červený et al., 2022; Dekeyser et al., 2024; Mullol et al., 2020; Rombaux et al., 2007; Vodička et al., 2012).

The most common cause of sino-nasal OD is chronic rhinosinusitis (CRS). OD is a well-established presenting symptom of CRS. OD can also occur in allergic rhinitis but is less common and less severe than in CRS. CRS is described as an inflammatory disorder of the sino-nasal mucosa and is a common medical issue affecting 5–12% of the general population (Biswas et al., 2023; Haxel, 2019; Mullol et al., 2020; Psaltis et al., 2014). The disease is characterized by symptoms of nasal congestion, rhinorrhea, facial pressure, and loss of sense of smell lasting more than three months (Psaltis et al., 2014). In addition to significant health care costs, patients' absence from employment or loss of occupational efficiency, CRS is reported to severely impact the life quality of sufferers (Rosenfeld et al., 2015).

CRS may be categorized as CRS with nasal polyps (CRSwNP) or without nasal polyps (CRSsNP). Curiously, SI is regarded as one of the most distressing features in patients with CRSwNP (Hopkins et al., 2009; Mamiňák et al., 2024). Most research studies have focused only on orthonasal olfactory analysis. However, several others have reported that retronasal odor perception is also affected by CRS (Alobid et al., 2006; Bhattacharyya, 2003; Fokkens et al., 2020; Litvack et al., 2008; Zhao et al., 2021), but less than orthonasal function (Alobid et al., 2006). According to EPOS 2020, CRSwNP type 2 is typically associated with OD (Fokkens et al., 2020). Olfactory impairment in CRSwNP will be mainly due to inflammatory changes (Fokkens et al., 2020). OD occurs in 61% to 83% of individuals with CRSwNP type 2 (Bhattacharyya, 2003; Haxel, 2019; Litvack et al., 2008; Orlandi and Terrell, 2002; Soler et al., 2008). Rhinomanometry and acoustis rhinometry are used to evaluate nasal obstruction (Červený et al., 2022). In general, olfactory examination methods can be divided into psychophysical and objective. Quality of life questionnaires are used to assess olfaction. Among psychophysical tests, the screening odor marker test (OMT) (Vodička et al., 2012) and the globally-used Sniffin's threshold, discrimination, and identification test with a stick (Hummel et al., 1997, 2023; Vodička et al., 2007; Whitcroft et al., 2023) are widely used in the Czech Republic. These are widespread in Europe, including the Czech Republic.

In the USA, the University of Pennsylvania scent identification test (UPSIT) is widely used (Doty et al., 1984). In Japan, the sense of smell is still tested by T&T olfactometry and intravenous odor test using prosultiamine solution (Nakashima et al., 2024).

A new trend in olfaction testing is the use of modern technology. For example, the latest Brazilian type of handheld digital identification olfactory test, the Multiscent-20 Digital Scent Device (DSD-20; Noar), is available at the olfactory laboratory in Dresden, Germany. The patient under examination identifies the odorant directly from a special tablet. On a smartphone, the tested subject then selects a response from four scent options (Nakanishi et al., 2024).

Objective olfactory examination methods are still less frequently used in OD diagnostics and are almost never used in clinical practice. Their main use is in uncooperative persons, in children, in persons with Parkinson's disease, in demyelinating diseases, in post-traumatic OD, in post-covid OD, and in medico-legal problems. In persons with CRS, the use of objective olfactory testing is rarely documented in the literature. Objective olfactory tests include electrophysiological methods – olfactory and trigeminal evoked potentials, as well as magnetic resonance imaging of the olfactory bulb and functional magnetic resonance imaging of the olfactory pathway (Holý and Janoušková, 2024; Holý et al., 2023, 2024b; Hummel et al., 2015; Pellegrino et al., 2016).

The aim of this research was to analyze olfactory event-related potentials (OERPs), trigeminal event-related potentials (TERPs), and the outcomes of psychophysical smell tests in subjects with CRSwNP.

Materials and methods

This prospective single-center study was conducted in accordance with the Declaration of Helsinki. All patients signed an informed consent form.

In the period 5/2022–12/2024, 57 subjects were included in the study. The group of subjects consisted of 17 females and 40 males. The average age was 46 years (range 19–79 years). The results of the Sniffin stick identification test, curves of olfactory event-related potentials (OERPs), and trigeminal event-related potentials (TERPs) were then statistically analyzed.

Participants were divided into three main groups. Control Group I (n = 20, participants without CRS, before septoplasty); Group II (n = 18, subjects with CRSwNP without corticosteroids therapy); Group III (n = 19, subjects with CRSwNP with corticosteroid therapy).

The standardized psychophysical identification Sniffin stick test was used for subjective assessment of olfaction. Normosmia was assessed to have a score of 12–16 points according to the Sniffin Sticks olfactory identification test. A score at or below 11 points can also include patients with anosmia.

For the electrophysiological objective investigation of OERPs/ TERPs, we used clinical olfactometer OL 024 (Burghart, Germany).

The clinical olfactometer gives precisely defined odor stimuli that are necessary to evoke OERPs and TERPs. An 8-channel EEG system (OL 026; Burghart, Holm, Germany) was used to analyze the responses.

OERPs were recorded at the top of the head (EEG, electrode Pz). 2-phenylethanol (50% v/v) was used to selectively activate the olfactory afferents. TERPs were recorded at the top of the head (EEG, electrode Cz). CO_2 gas (50% v/v) was used to selectively activate trigeminal afferents. During the experiment, olfactory and trigeminal stimuli were presented separately. Each stimulus type was repeated 20 times and lasted 250 milliseconds (ms). The interstimulus time interval between each stimulus was 10–20 seconds (Dekeyser et al., 2024; Hopkins et al., 2009).

The result of the examination is a curve of evoked potentials, which has an N1 and P2 wave. The assessment of the presence/absence of the OERPs/TERPs curve is of interest. Then, the latency in milliseconds and the amplitude in microvolts of the N1/P2 peaks are analyzed.

The result of the examination is a curve of evoked potentials, which has an N1 and P2 wave. The assessment of the presence/absence of the OERPs/TERPs curve is of interest. Then, the latency in milliseconds and the amplitude in microvolts (uV) of the N1, P2 peaks are analyzed (Červený et al., 2022; Holý et al., 2024a; Pastorkova et al., 2023).

Inclusion and exclusion criteria

The inclusion criteria of Group I were: minimum age of 18 years, endoscopic intranasal finding with nasal septum deviation and without nasal polyps, and intranasal corticosteroid therapy was not used.

The inclusion criteria of Group II were: minimum age of 18 years, endoscopic intranasal finding with nasal polyps, and intranasal corticosteroid therapy was not used.

The inclusion criteria of Group III were: minimum age of 18 years, endoscopic intranasal finding with nasal polyps, and intranasal corticosteroid therapy was used.

Exclusion criteria for Group I were: age less than 18 years, history of a loss of sense of smell after Covid-19 infection, Parkinson's disease, Alzheimer's disease, multiple sclerosis, and evidence of nasal polyposis.

Exclusion criteria for Group II were: age less than 18 years, history of a loss of sense of smell after Covid-19 infection, Parkinson's disease, Alzheimer's disease, multiple sclerosis, an absence of nasal polyposis, and use of intranasal corticosteroid therapy.

Exclusion criteria for Group III were: age less than 18 years old, history of loss of sense of smell after Covid-19 infection, Parkinson's disease, Alzheimer's disease, multiple sclerosis, an absence of nasal polyposis, and intranasal corticosteroid therapy was not used.

The results of the olfactory tests were then statistically processed. A statistical analysis was performed using IBM SPSS Statistics (version 29.0; SPSS, IBM, Armonk, NY, USA). The data were analyzed using descriptive statistics and the Kruskal–Wallis test; Mann–Whitney *U* test; Fisher exact test; Chi-Square test; *p*-values equal to or less than 0.05 were considered significant.

Results

A subjective smell identification Sniffin Stick test was performed on all enrolled subjects. Table 1 presents the results for each group. The percentage distribution of SI and normosmia in Group I, II, III has been analyzed. SI was most common in the groups with CRSwNP (64.9%), while in control Group I, SI was present in only 35.0% of subjects.

Objective electrophysiological tests of OERPs/ TERPs were performed in all enrolled subjects in Group I, II, III. The mean N1 wave latency of OERPs in milliseconds was significantly shorter in subjects in Group II than in the control Group I, at a significance level of $p = 0.011$ (Table 2). The mean latency of the P2 wave for OERPs in milliseconds was significantly shorter in subjects in Group II than in the control Group I, at a significance level of $p = 0.012$ (Table 3).

The N1/P2 interval of OERPs was evaluated. The mean latency of the N1/P2 interval of OERPs was the shortest in

Table 1. Identification Sniffin Stick test in Group I, II, III. Percentage comparison of smell impairment versus normosmia

Sniffin Stick identification smell test	Normosmia		Smell impairment	
	Count	Row *N* %	Count	Row *N* %
Group I	13	65.0%	7	35.0%
Group II	6	33.3%	12	66.7%
Group III	7	36.8%	12	63.2%
Total	26	45.6%	31	54.4%

Table 2. OERPs – distribution of N1 wave latencies in each Group I, II, III

OERPs latency of N1 wave		Mean	Median	Minimum	Maximum	Absent
Latency (ms)	Group I	432	422	356	600	1 (5.0%)
	Group II	350	338	238	494	2 (11.1%)
	Group III	425	414	189	678	1 (5.3%)
	Total	405	406	189	678	4 (7.0%)

Table 3. OERPs – distribution of P2 wave latencies in each Group I, II, III

OERPs latency of P2 wave		Mean	Median	Minimum	Maximum	Missing
Latency (ms)	Group I	556	533	464	942	1 (5.0%)
	Group II	459	421	305	773	2 (11.1%)
	Group III	531	513	277	797	1 (5.3%)
	Total	518	514	277	942	4 (7.0%)

subjects in Group III and the longest in subjects in control Group I. In contrast to the above statistically significant data for the N1 and P2 latency of the OERPs curves, the differences of the N1/P2 interval between groups I, II, III were not statistically significant ($p > 0.05$).

The absence of OERPs in each group can be seen in Tables 2 and 3. The highest percentage of absence of OERPs was registered in Group II (11.1%).

Comparison of the absence of OERPs: in the control Group I (without CRSwNP) the absence rate was 5.0%, while the mean absence rate in Groups II, III (with CRSwNP) was 8.1%.

The values of OERPs amplitudes in microvolts (μV) did not detect statistically significant differences between groups I, II, III ($p > 0.05$).

In the analysis of the TERPs curves, the values of amplitudes and latencies did not show statistically significant differences between Groups I, II, III ($p > 0.05$).

The N1/P2 interval for TERPs was evaluated. The mean latency of the N1/P2 interval of TERPs was the shortest in subjects in control Group I and the longest in control Group III. Differences between groups were not statistically significant ($p > 0.05$).

The absence of TERPs in each group can be seen in Table 4. Absence of TERPs was detected in an average of 21.6% of CRSwNP subjects. Group III showed the highest percentage of absence of TERPs (32%). In control Group I, TERPs were absent in 0% of subjects.

Table 4. TERPs – distribution of N1/P2 interval latencies in groups I, II, III

TERPs latency of N1/P2 interval		Mean	Median	Minimum	Maximum	Missing
Latency (ms)	Group I	111.05	113.00	37.00	218.00	0 (0%)
	Group II	128.50	112.50	43.00	355.00	2 (11.1%)
	Group III	137.54	148.00	67.00	189.00	6 (32%)
	Total	123.78	125.00	37.00	355.00	8 (14%)

Discussion

Actual psychophysical testing of the olfactory function using simple screening tests identifying odors is standard in the basic diagnostic procedure for SI in CRS (Hummel et al., 2023; Vodička et al., 2012; Whitcroft et al., 2023). The disadvantage of subjective methods is that the subject can influence the outcome of testing. The principle of these psychophysical methods is the presentation of an odorant and the evaluation of its interpretation by the subject. Thus, these methods focus on quantitative rather than qualitative OD (Červený et al., 2022; Corey et al., 1997; Vodička et al., 2007). In Europe, the Sniffin Stick identification test is widely used. In the Czech Republic, the OMT developed by Czech researchers is widespread (Konstantinidis et al., 2008; Vodička et al., 2007, 2012).

In his extensive review study, Haxel states that by performing the UPSIT and the Sniffin´ stick tests, it was ascertained that subjects with CRS and nasal polyposis had a greater chance of postoperative improvement in the sense of smell than subjects with CRS but no nasal polyposis. Improvement of the sense of smell can be achieved in 50% of subjects. However, complete restoration of function is not possible. Normosmia is reported in only 33% of subjects (Haxel, 2019). Previous sinus surgery, longer history of sinus disease, and preoperative normosmia have a negative effect on postoperative olfactory outcome. Olfactory testing in subjects undergoing sinus surgery using the established UPSIT and Sniffin Stick test kits is essential to determine the full extent of a disease and to monitor the effects of surgery (Haxel, 2019). Knížek et al. (2017) presented the results of olfactory evaluation before and after FESS (Functional Endoscopic Sinus Surgery) in a cohort of 51 patients with CRS. The smell test OMT was used for the evaluation. In 25% of the patients there was an improvement in olfactory function, in 55% of patients no change was noted, and in 20% of patients there was a worsening of the sense of smell (Knížek et al., 2017). In the present study, we detected hyposmia in 66.7% of subjects in the untreated CRSwNP group. In subjects with CRSwNP treated with ICS, SI was detected in 63.2%. No statistically significant difference was found here. In contrast, SI was reported in 35.0% in subjects before septoplasty (without CRSwNP). In both our previous studies, SI in control healthy groups was reported in 0% (Holý et al., 2023, 2024a).

In routine medical practice, the quality of life questionnaire is often used to assess olfaction. The SNOT-22, questionnaire of olfactory disorder-negative statements (QOD-NS), and Smell-Qx questionnaire are currently used in routine otorinolaryngology practice. However, quality of life questionnaires were not used in this study (Kovář et al., 2017; Lechner et al., 2025; Schalek et al., 2010; Yuan et al., 2022).

Objective examination of the olfactory function in CRS using electrophysiological methods or functional magnetic resonance imaging of the olfactory pathway is uncommon. This is justified by the fact that these tests are expensive and only some super-specialized olfactory laboratories are equipped with them (Mullol et al., 2020). Worldwide, the assessment of olfactory (OERPs) and trigeminal (TERPs) evoked potentials is a method that is not widely used. As of 2020, this method is also available in the Czech Republic, and it was initially used mainly within research. Since 2024, it has been introduced into the otorhinolaryngology practice (Holý and Janoušková, 2024; Holý et al., 2023, 2024a, b). In the Czech Republic, it was published as the first study of OERPs/TERPs in healthy normosmic subjects, as well as a study in post-covid OD. Research is now underway where the sense of smell is comprehensively compared in CRSwNP subjects (before/after treatment) by subjective and electrophysiological objective methods (Červený et al., 2022; Holý et al., 2024b). In the world literature, use of electrophysiological methods in CRS has been described only sporadically. For example, a Chinese study focused specifically on the importance of the presence of olfactory evoked potentials in subjects with CRS. The presence of OERPs in CRSwNP was found in 41% of the 92 subjects evaluated (Hu et al., 2010). Chinese authors reported that OERPs presence in CRSwNP before surgery may indicate preserved residual olfactory function, which could be a prerequisite for good olfactory recovery after surgery in preoperative anosmic subjects (Hu et al., 2010). In previous studies by Belgian authors, the presence of OERPs ranged between 34% and 36% (Rombaux

et al., 2007). It is noteworthy that the Belgian authors noted the presence of OERPs in the hyposmic subjects, whereas no OERPs which were noted in the anosmic subjects. For future studies, it will be interesting to follow the group of hyposmic subjects with CRS (Rombaux et al., 2007).

In our study, we detected the presence of OERPs in 92% in groups with CRSwNP. The presence of OERPs in the control group without CRSwNP was 95%. In previous studies, we detected the presence of OERPs at a level of 100% in healthy groups (Holý et al., 2023, 2024a).

This value (92%) in our study is higher than in the previous Chinese and Belgian study. Surprisingly, we detected that the average latency of the N1 wave and P2 wave of the OERPs was significantly shorter in the CRSwNP group than in the control group without CRSwNP. In contrast to the above statistically significant data for the N1 and P2 latency of the OERPs curves, the differences of the N1/P2 interval between groups with/without CRSwNP were not statistically significant. We also assume the possible influence of small number bias, because we expected longer latency of OERPs in the CRSwNP group. Instruments for measuring olfactory function can be used to assess trigeminal nerve as well. In our previous study, we established pilot normative TERPs curves for the Czech Republic in healthy probands. The presence of TERPs was detected in 86% of enrolled healthy subjects (Holý et al., 2023). The characteristics of TERPs curves in CRS are rarely discussed in the world literature. For example, In 2009, Rombaux et al. mentioned in their study, that TERPs curves were registered in almost all patients (95%) with no difference in the included groups. In this study, we observed the absence of TERPs curves in 21.6% of subjects with CRSwNP (mean). We detected the presence of TERPs curves in 100% of subjects in the control group. This result may support our thesis that the presence of TERPs appears to be a predictor of preservation of olfactory function.

The relatively small number of subjects included in each group appears to be a limitation of the study.

A detailed analysis of the OERPs/TERPs in the new study is planned for the future. It will focus on the investigation of OD in subjects before/after treatment (biological treatment, FESS), including the examination of taste, which is closely related to the retronasal sense of smell.

Conclusion

Electrophysiological olfactory tests and psychophysical Sniffin Stick identification olfactory tests are valid tests in the assessment of the olfactory function in subjects with CRSwNP. Electrophysiological olfactory tests provide an objective assessment of olfactory dysfunction, which is useful for clinical diagnosis and monitoring treatment efficacy.

The results of the study show that CRSwNP significantly impairs olfactory function, with the untreated form being associated with the highest rate of hyposmia and changes in the electrophysiological responses. CRSwNP has a significant impact on olfactory function, and subjects with untreated CRSwNP have the highest risk of SI.

Absence of TERPs was detected in an average of 21.6% of CRSwNP subjects versus healthy controls (0%). This result may support our presumption that the presence of TERPs appears to be a predictor of preservation of olfactory function.

This research has provided new insights into the impact of chronic inflammatory diseases of the nose and paranasal sinuses on olfactory organ function — and will provide the basis for further studies of treatment strategies for CRSwNP.

Authors' contribution

All authors contributed to the conception and design of the study. All authors have read and agreed to the published version of the manuscript. Conceptualization, *R.H., K.J., P.D., D.Ka., K.M., V.M.* and *J.A.*; validation, *K.J., R.H., L.V., D. Ko., N.P., D.Ka.* and *J.H.*; investigation, *R.H., K.J., N.P., L.V., O.V., E.A.* and *K.M.*; resources, *R.H., K.J., D.Ko., J.H., V.M.* and *J.A.*; data curation, *R.H., K.J., J.V., J.H., N.P., K.M., P.D., O.V.* and *D.Ko.*; writing original draft, *K.J., R.H., O.V., L.V., K.M., J.V., P.D.* and *D.Ka.*; writing review and editing, *R.H., K.J., D.Ka., K.M., S.K., J.V., E.A.* and *J.A.*; visualization, *K.J., R.H., P.D., L.V., O.V., N.P., V.M.* and *J.V.*; supervision, *R.H., J.V., D. Ko, N.P., D.Ka., J.H., V.M.* and *J.A.*; project administration, *R.H., L.V., O.V., K.J.* and *J.H.*; funding acquisition, *R.H., K.J.* and *J.A.*

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Ethical aspects and conflict of interest

The author of this article declares that he/she has no conflict of interest in relation to the topic, development and publication of this article. Neither the creation nor the publication of this article was supported by any pharmaceutical company. This declaration also applies to all co-authors.

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