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Trigeminal event-related potentials in patients with olfactory dysfunction*

Ph. Rombaux[1], A. Mouraux[2], T. Keller[3], T. Hummel[4]

[1] Department of Otorhinolaryngology, Cliniques Universitaires Saint Luc, Brussels, Belgium
[2] Readaptation Unit (READ), Université catholique de Louvain, Brussels, Belgium
[3] Acomed Statistik, Leipzig, Germany
[4] Smell & Taste Clinic, Department of Otorhinolaryngology, University of Dresden Medical School, Germany

SUMMARY

Objective: *There are mutual interactions between the olfactory and trigeminal systems. The purpose of this study was (1) to assess trigeminal sensitivity using chemosensory event-related potentials (CSERPs) in patients with olfactory dysfunction and (2) to evaluate whether trigeminal ERPs were different with regard to the presence or absence of olfactory ERPs.*

Materials and Methods: *Prospective study of 60 patients who presented with olfactory dysfunction (postinfectious olfactory loss: n = 19, posttraumatic olfactory loss: n = 28, and olfactory loss due to idiopathic, or toxic causes: n = 13). All patients were extensively evaluated with an orthonasal olfactory test based on the "Sniffin' Sticks". In addition, chemosensory ERPs were recorded in response to olfactory and trigeminal stimulation.*

Results: *Olfactory / trigeminal ERPs were recorded in 25 / 60 patients, respectively. Patients with no detectable olfactory ERPs, considered as severely affected, demonstrated an altered trigeminal sensitivity as indicated by an increase in P2 latencies and a decrease in both, P2 and N1-P2 amplitudes compared to patients with detectable olfactory ERPs. A regression analysis showed a negative relation between P2 latencies and the "Sniffin' Sticks" score ($r = -0.46$, $p < 0.001$).*

Conclusions: *Patients with severe olfactory dysfunction demonstrated decreased trigeminal sensitivity as indicated by electrophysiological measures. This study supports the idea of interactions between the chemical senses. Whether altered responses to trigeminal stimulation may be used as a prognostic measure related to recovery from olfactory loss remains to be demonstrated.*

Key words: smell, olfaction, trigeminal and olfactory event-related potential, orthonasal testing

INTRODUCTION

Most odourants activate the olfactory and the trigeminal systems so that, typically, input from both systems contributes to the perception of odours [(1)]. While olfactory receptor neurons are likely to be restricted to the olfactory neuroepithelium, trigeminal chemoreceptors innervate the entire nasal mucosa, probably with a relatively higher density at the anterior portion of the nasal cavity. Some evidence exists that olfactory and trigeminal activation exhibits similarities [(2)]. Mutual interactions between both systems have been shown to exist in healthy subjects and in patients with olfactory disorders [(3)].

The electrophysiological exploration of the olfactory and trigeminal systems using chemosensory event related brain potentials (CSERPs) has been proposed as a diagnostic tool for evaluating chemosensory functions [(4)]. This has also been considered as a complementary method to traditional chemosensory testing based on psychophysical techniques [(5)]. Chemosensory ERPs may be elicited by selective olfactory stimuli (then referred to as olfactory ERPs) or by relatively selective trigeminal stimuli (referred to as trigeminal ERPs). Subjects with normal olfactory acuity usually elicit consistent and reproducible CSERP to both olfactory and trigeminal stimuli [(4-6)].

Several studies have demonstrated that patients with olfactory deficits, congenital or acquired, have a reduced trigeminal sensitivity compared to controls [(3,7,8)] with the putative mechanism probably based on the lack of central-nervous amplification of trigeminal input through olfactory activation in those patients. Thus, while the relations between the two major intranasal chemosensory systems are manifold, the effect of olfactory dysfunction on trigeminal sensitivity has rarely been evaluated

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using psychophysical or electrophysiological techniques. Specifically, it is unclear how trigeminal testing could contribute to the diagnostics of olfactory dysfunction. As a step towards an answer to this question, the purpose of this study was to examine trigeminal ERPs recorded in patients with olfactory dysfunction related to (i) the results from olfactory psychophysical testing and (ii) presence or absence of olfactory ERPs. In others words, aim of the study was to examine whether central responses to trigeminal stimulation are different in patients with a severe or a moderate olfactory loss.

MATERIALS AND METHODS

This prospective study was conducted at the Department of Otorhinolaryngology of the Cliniques Universitaires Saint-Luc (Brussels, Belgium). Data were collected between January and December 2006. Informed consent was obtained after outlining the experimental protocol. Rules of the Ethics Committee of the Université catholique de Louvain were followed which are in accordance with the principles of the revised Declaration of Helsinki.

All participants complained of olfactory dysfunction, and presented at the outpatient clinic. Etiologies of the olfactory disorder encompassed postinfectious olfactory loss (n = 19), posttraumatic olfactory loss (n = 28), toxic, drug-induced and idiopathic olfactory loss (n = 2+2+9 = 13). Mean duration of the olfactory complaint was 21 months (range 2-34 months).

Sixty-three patients were initially included in the study. Results from three patients (two with posttraumatic and one with idiopathic olfactory loss) had to be rejected due to high muscular activity and / or eye blink reflexes that do not allow to analyse CSERPs. The cohort study group was thus composed by sixty patients, with 29 female. They had an average age of 50.2 years (standard deviation = 12.4). The youngest patient was 20 years old, while the oldest patient was 73 years old.

Experimental procedure

Psychophysical testing and CSERPs were obtained for all 60 patients. Psychophysical and electrophysiological data were collected on the same day (with a resting period of one hour separating the psychophysical testing session from the electrophysiological recording session). Recording of CSERPs always followed psychophysical testing. Duration of the entire experiment was approximately 2.5 hours.

Psychophysical olfactory testing

Each patient underwent orthonasal psychophysical assessment of olfactory function using the standardized “Sniffin’ Sticks” test [9]. Olfactory stimuli were presented birhinally. At first, odour perception threshold was assessed for n-butanol using stepwise dilutions in a series of 16 felt-tip pens; odour threshold. Following that procedure, patients were asked to attempt discriminating one odour within a triplet of three different odorants in a series of 16 trials; odour discrimination. Finally, a series of 16 odours were presented to the patient along with a multiple-choice list of four responses each; odour identification. For each patient, results of the testing of odour threshold, odour discrimination, and odour identification were used to compute the ‘threshold-discrimination-identification’ (TDI) score, ranging from 1 to 48 [9]. In healthy subjects, the TDI score at the 10^{th} percentile is 24.9 in subjects younger than 15 years, 30.3 for ages 16–35 years, 27.3 for ages 36–55 years and 19.6 for subjects over 55 years [9].

Chemosensory event-related potential

A selective and brief monorhinal olfactory stimulus and trigeminal stimulus were used to record olfactory and trigeminal CSERPs. The stimulus was produced by a computer-controlled olfactory stimulator based on air-dilution olfactometry (olfactometer OM2S; Burghart instruments, Wedel, Germany) [4]. The stimulator allowed delivering chemical stimuli without concomitantly altering the mechanical or thermal conditions of the nasal cavity. Stimuli reached the nasal cavity through a Teflon™ tube placed in one nostril (preferentially the right nostril), ending beyond the nasal valve, and pointing towards the olfactory cleft. The total flow rate was 8 l/min. Temperature (36°C) and relative humidity (80%) were kept constant across trials. Stimulus rise-time was shorter than 20 ms. Stimulus duration was 200 ms; 2-Phenyl Ethyl Alcohol (50% v/v) was used for olfactory stimulation, and CO_2 (50% v/v) for trigeminal stimulation.

Patients were sitting in a well-ventilated room, were asked to reduce their eye movements and eye blinks, and to breathe through their mouth. Furthermore, to avoid possible contamination of the ERP recordings by sound associated with the valve switching which occurs during presentation of the odorant stimulus, patients wore headphones playing a constant, binaural white noise of 60-70 dB SPL. Forty stimuli (20 olfactory and 20 trigeminal) were presented with an interstimulus interval of 30 s. EEG was recorded at 250 Hz from the vertex (position C_Z), using a SAM 32EP EEG amplifier and digitizer (Micromed, Mogliano Veneto, Italy). Linked earlobes (A_1A_2) were used as reference. Impedance was kept below 20 kOhm. Epochs extended from 500 ms before to 1500 ms after stimulus onset. After baseline correction (reference interval: -500 to 0 ms), epochs were band-pass filtered (0.3 – 12 Hz FFT filter). Trials containing eye-blinks and/or showing an activity higher than 50 μV were rejected before averaging. A minimum of 60% of artefact free recording was considered as the limit allowing any further interpretation of the CSERP (12/20 trials). Average waveforms were computed for each subject. All offline signal processing procedures was performed using the LETSWAVE EEG toolbox (Université catholique de Louvain, Brussels, Belgium) [10].

ERPs (both olfactory and trigeminal ERPs) were considered as present if the averaged waveforms demonstrated a negative-positive complex consisting of an initial negative peak (N1: latency: 290 – 490 ms, amplitude $<$ -2 μV) followed by a positive peak (P2: latency: 460 – 820 ms, amplitude $>$ +2 μV).

Table 1. Descriptive statistics of trigeminal ERPs parameters separately for subjects with and without olfactory ERPs. KS Test: Kolmogoroff-Smirnow Test.

		N1 latency [ms]	N1 amplitude [μV]	P2 latency [ms]	P2 amplitude [μV]	N1P2 amplitude [μV]
olfactory ERP not present	N	35	35	35	35	35
	Mean	393.1	3.31	695.9	5.82	9.19
	Std. Deviation	45.5	1.01	60.36	2.11	2.85
	Minimum	307	2.1	578	2.9	5.2
	Maximum	478	6.3	863	12.2	18.5
	KS Test (p-value)	.72	.48	.76	.77	.27
olfactory ERP present	N	25	25	25	25	25
	Mean	404.0	4.236	614.1	7.528	11.76
	Std. Deviation	47.6	1.58	43.6	2.28	2.96
	Minimum	316	2.1	514	3.9	6.6
	Maximum	496	8.1	696	13.4	18.7
	KS Test (p-value)	.92	.60	.80	.98	.98
All subjects	N	60	60	60	60	60
	Mean	397.7	3.70	661.8	6.53	10.26
	Std. Deviation	46.27	1.35	67.3	2.32	3.14
	Minimum	307	2.1	514	2.9	5.2
	Maximum	496	8.1	863	13.4	18.7

Responses were independently analysed by two different observers (PR and AM). Patients were classified as responders to an olfactory stimulus if they showed olfactory ERPs, and as non-responders if they failed to demonstrate such responses.

Statistical analysis

Statistical analyses were performed using SPSS 15.0 [(11)]. Parameters related to trigeminal responses were tested for deviation from normal distribution using a Kolmogoroff-Smirnow test. Parametric two sided t-tests were used to compare means of parameters related to trigeminal responses. Coefficients of correlations were calculated according to Pearson between TDI scores and results from electrophysiological recordings. To account for the multitude of tests, correlations with $p < 0.003$ were considered to be significant (Bonferroni correction of 0.05 level with factor 15 because of 15 parameters).

RESULTS

In this cohort of patients with an olfactory disorder, olfactory ERPs were recorded in 25 patients (responders) and not recorded in 35 patients (non-responders). In the distinctive groups, olfactory ERPs were recorded in 9/19 with postinfectious, 12/28 posttraumatic, 1/2 toxic, 1/2 drug-induced and 2/9 idiopathic olfactory loss. In contrast, trigeminal ERPs were obtained for every patient.

Demographic parameters were not different among patients with or without reproducible olfactory ERPs (age: t-Test – $p = 0.76$; sex distribution: $\chi^2 = 0.23$, $p = 0.83$). Descriptive statistics are given in Table1 for N1 and P2 latencies and amplitudes

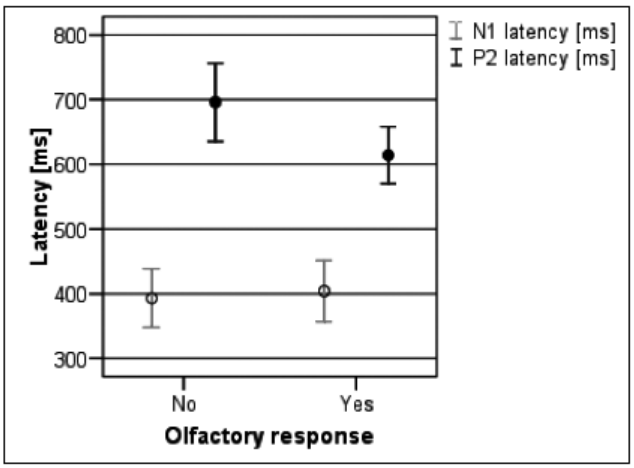

Figure 1. Mean-SD-Plot for N1 and P2 latencies in trigeminal ERPs between patients with no olfactory ERPs (No) vs patients with olfactory ERPs (Yes).

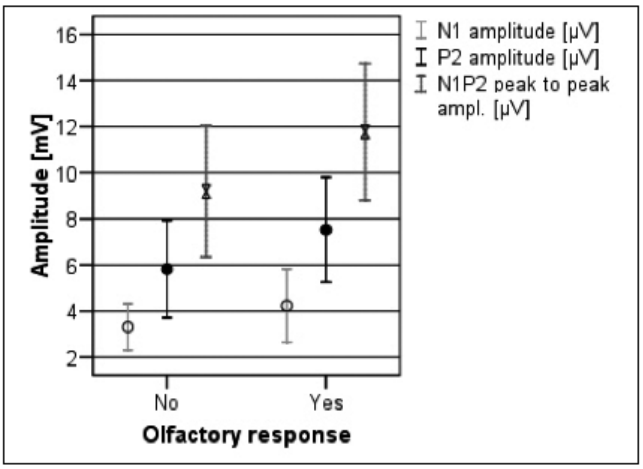

Figure 2. Mean-SD-Plot for N1 and P2 amplitudes, and N1P2 peak-to-peak amplitudes in trigeminal ERPs between patients with no olfactory ERPs (No) vs patients with olfactory ERPs (Yes).

and for N1-P2 peak-to-peak amplitudes obtained after a trigeminal stimulus. No deviation from normal distribution was found with the Kolmogoroff-Smirnow test.

Trigeminal response amplitudes were generally larger, and latencies were shorter in responders compared to non-responders (Figures 1 and 2; Table 1; N1 latency: 404 vs. 393 ms, P2 latency: 614 vs. 696 ms, N1 amplitude: 4.24 vs. 3.31 μV, P2 amplitude: 7.53 vs. 5.82 μV and N1P2 peak to peak amplitude: 11.76 vs. 9.19 μV). Responders had significantly shorter P2 latencies ($p < 0.001$), larger P2 amplitudes ($p = 0.004$), and higher N1P2 amplitudes ($p = 0.001$) in the trigeminal response. Relatively largest differences were found for P2 amplitudes (relative difference = -26.2%) and peak-to-peak N1P2 (relative difference = -25.1%) (Table 2).

Results from correlations between psychophysical and electrophysiological measurements are shown in Table 3. TDI scores correlated negatively with P2 latencies ($r = -0.46$, $p < 0.0003$) and positively with N1P2 peak to peak amplitudes ($r = 0.39$, $p < 0.003$) in the trigeminal response. This indicated that increasing TDI scores (meaning better olfactory function) were associated with increasing amplitudes and decreasing latencies in the trigeminal ERPs (Figure 3).

DISCUSSION

This study provides further evidence for a relationship between trigeminal and olfactory sensitivities in patients with acquired olfactory dysfunction. Patients in whom olfactory loss is so pronounced that they do not exhibit olfactory ERP have an altered trigeminal responsiveness. Increased latencies and decreased peak-to-peak amplitudes of the trigeminal ERPs were found in those patients compared to patients with less pronounced olfactory loss. It can therefore be concluded that patients with severe olfactory loss have a decreased trigeminal sensitivity at least when explored at the central level with CSERPs.

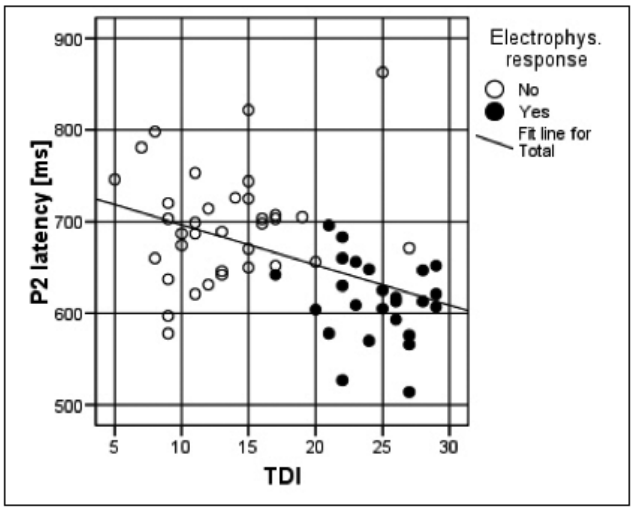

Figure 3. Scatterplot P2 latency of the trigeminal ERPs and TDI score. White circle: No: absence of olfactory ERPs. Black circle: Yes: presence of olfactory ERPs.

Table 2. Absolute and relative differences between the two groups of subjects with and without olfactory ERPs, and results from the statistical comparison of the parameters of trigeminal ERPs between the two groups (t-Test). Relative differences are calculated as the ratio of mean differences and mean across all subjects (see Table 1).

	t	df	p	mean difference	relative difference
N1 latency [ms]	0.90	58	0.37	-10.9	-2.7%
N1 amplitude [μV]	2.58	37.8	0.014	-0.93	0.0%
P2 latency [ms]	5.79	58	0.0000003	81.9	12.4%
P2 amplitude [μV]	3.00	58	0.004	-1.71	-26.2%
N1P2 amplitude [μV]	3.40	58	0.001	-2.58	-25.1%

Interactions between olfactory and trigeminal chemoreception have been studied in congenital or acquired olfactory disturbances and at peripheral and central-nervous levels [3,12-15].

In congenital olfactory disturbances, Frasnelli et al. demonstrated that patients have an increased peripheral responsiveness to trigeminal stimuli (CO_2) whereas central responses were equivalent in patients and healthy controls [12]. In patients with acquired olfactory loss the same results were shown for the periphery but central responses after a trigeminal stimulus were lower in patients with olfactory disorders compared to controls [13,14].

In these cases, interactions between the olfactory and trigeminal systems may lead to compensatory changes at the peripheral level with an increased responsiveness to trigeminal stimuli. Thus, when olfactory function is decreased, trigeminal responsiveness – specifically to intranasal chemical stimuli, but not to cutaneous electrical stimuli – is also reduced when explored at a central level of processing [14]. This decreased trigeminal responsiveness, however, seems to be reversible and should increase with time due to adaptive mechanisms [13]. Although we expected that trigeminal sensitivity would increase with the duration of the disease, this was not observed in this study. The possible reason for this failure to observe such a positive correlation is the relatively low variation of the mean duration of olfactory complaints in our study, so that the present results do not constitute the best database for such investigations.

The interaction between the two chemosensory systems may be explained by some close relationship at the peripheral or central levels of processing. The fact that patients with olfactory dysfunction demonstrated higher trigeminal sensitivity at the peripheral level (negative mucosal potential amplitude) leads to suppose that a normal olfactory working system would inhibit the trigeminal system [13]. At a central level, when both the olfactory and the trigeminal systems act normally, CSERP would be recorded with a normal amplitude, which is not the case when olfactory input are missing leading to a decreased

Table 3. Correlations between TDI score and parameters of trigeminal ERPs. Significant results are printed in bold letters.

Pearson correlation coefficients r, and significance of correlation (p)		N1 latency [ms]	N1 amplitude [μV]	P2 latency [ms]	P2 amplitude [μV]	N1P2 amplitude [μV]
TDI	r	0.18	0.28	-0.46	0.37	0.39
	p	0.17	0.029	0.0003	0.004	0.002

response in trigeminal ERPs amplitude. The neuroanatomical overlapping in olfactory-trigeminal activation pattern may explain these psychophysical or electrophysiological findings . For example, trigeminal nerves ending reach the olfactory bulb [(2)] and some cortical area (rostral insula, middle frontal gyrus, orbitofrontal cortex) receive inputs from both chemosensory systems as demonstrated with functional MRI [(16)].

Unfortunately, treatment of olfactory dysfunction is limited, except for sinunasal related olfactory loss. Thus, for most patients prognostic information based on results from psychophysical and electrophysiological testing is of high significance. The presence of olfactory ERPs in patients with olfactory disorders indicating moderate olfactory loss [(5,6)] is likely to have such a positive prognostic value in terms of the spontaneous recovery of olfactory loss in that residual olfactory function is still present - although, to our knowledge, such a correlation has never been confirmed in clinical studies. Considering the close relations between the olfactory and the trigeminal systems, a response to trigeminal stimulation with large amplitudes and short latencies could also represent a sign of a good prognosis in terms of spontaneous recovery. This hypothesis is currently the subject of further investigations with EEG recordings from multiple sites.

Finally, a significant and negative correlation between the TDI score and all the components of the trigeminal ERPs has been demonstrated. Even after controlling for the TDI score, subjects without olfactory ERPs exhibited higher trigeminal P2 latencies. This indicates that patients with severe olfactory loss exhibit a reduced responsiveness per se to the trigeminal stimulus that is not only determined by the degree of olfactory function. It can be hypothesized that attentional or cognitive changes play a major role in this differential responsiveness of patients with olfactory loss; trigeminal stimulus being more boring and less attractive for patients with severe olfactory loss than for the patients with a moderate olfactory dysfunction.

CONCLUSION

This study emphasizes the relationship between the olfactory and the trigeminal systems in the chemoreception of odorous stimuli. It has been demonstrated that patients with severe olfactory loss who do not demonstrate any olfactory responses at the electrophysiological evaluation have a decreased trigeminal sensitivity as indicated by trigeminal ERPs. Thus, loss of olfactory function changes the processing of trigeminally mediated sensations. Cross-modal interactions between the olfactory and the trigeminal system may contribute to the spontaneous recovery of olfactory dysfunction.

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Ph. Rombaux, MD, PhD
Department of Otorhinolaryngology
Université catholique de Louvain
Cliniques Universitaires Saint Luc
Hippocrate Avenue 10
1200 Brussels, Belgium

Tel: +32-2-764 1930
Fax: +32-2-764-8935
E-mail: philippe.rombaux@uclouvain.be