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Chemosensory event-related potentials to trigeminal stimuli change in relation to the interval between repetitive stimulation of the nasal mucosa

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Abstract Event-related potentials (ERPs) to olfactory and trigeminal stimuli have been used commonly to evaluate chemosensory dysfunction. The aim of the present study was to investigate how ERPs could be modified by repetitive stimulations of the intranasal trigeminal nerve using 52% v/v CO_2 stimuli for 200 ms periods. Nine subjects were exposed to 6 sessions each during which trains of 16 stimuli were applied. The interval between stimuli was constant for each experiment, but varied between experiments (10, 20, 30, 40, 60, and 90 s). Trigeminal ERPs were obtained from three positions on the skull. Both intensity ratings and ERP amplitudes decreased as the interstimulus interval (ISI) shortened. Specifically, ratings and response amplitudes were most strongly reduced by approximately 30–50% at the shortest ISI used (10 s) and were largest at an ISI of 90 s. The decrease of amplitudes was strongest for the P_{46} amplitude. Our findings suggest that this may be the result of both habituation and stimulus predictability. We hypothesize that the ISI dependence of chemosensory ERPs may also be a function of an interaction between A_{delta} and C fibers.

Key words Olfaction · Nasal irritation · Adaptation · Habituation · Trigeminal stimuli

Introduction

During the past 30 years event-related potentials (ERPs) to olfactory and trigeminal stimuli have used in increasing frequency for the evaluation of chemosensory dysfunction, as for example for the evaluation of medicolegal cases. Although the recording of these responses is based on the averaging of reactions to repeated stimuli [8], surprisingly few data are available on the behavior of responses when different interstimulus intervals (ISIs) are used. Kobal [24] addressed this question in a study of 16 subjects, investigating ISIs of 12, 22, 32, 42, and 52 s. Eucalyptol was used as a stimulant that produces both olfactory and trigeminally mediated sensations. In essence, Kobal found no major differences between ERP amplitudes for ISIs longer than 32 s. In contrast, amplitudes decreased at shorter ISIs. This was most pronounced for an ISI of 12 s. Peak latencies did not exhibit major changes in relation to the ISI. However, the results of this study were compromised by the fact that the different ISIs were not investigated in separate sessions. All of them were tried in two experiments that probably led to carry-over of desensitizing effects [27] and a consequent decrease in vigilance and attention, which are determining factors of ERPs [12, 35]. Based on these observations, most subsequent investigations of chemosensory ERPs used ISIs longer than 30 s [16, 17, 19, 28, 33]. Considering that 20–30 averages are necessary for one chemosensory ERP, this approach requires a significant amount of time to obtain an evoked response. In turn, decreased vigilance can occur that may (1) significantly alter EEG background activity and (2) exhibit an influence on various components of the ERP [10, 34]. The impact of these factors could be reduced by the shortening of the ISI between stimuli.

The aim of the present study was to test how ERP and intensity ratings in response to trigeminal stimulation could be modified when stimuli are presented at different ISIs. Carbon dioxide (CO_2) was used since it is commonly recognized to be a natural stimulant of trigeminal chemoreceptors in the nasal mucosa. Its nociceptive specificity has been shown in a number of studies [43, 44, 47, 48]. In addition, sources of ERPs elicited by CO_2 have been localized in the secondary somatosensory cortex [20, 23], which can be assumed to be a primary cortical projection area for nociceptive afferents [5].

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Materials and methods

Nine healthy volunteers (4 female, 5 male, mean age 28.2 years) participated in the study after giving written informed consent. The study was conducted according to the declaration of Helsinki on biomedical research involving human subjects (Hong Kong amendment 1989).

After participation in a training session, each subject underwent six test sessions at the same time of day. During each experiment, 16 stimuli of the same intensity were applied intranasally via 8-cm-long Teflon tubing, using 52% v/v CO_2. The total air flow was 145 ml/s at 80% relative humidity and 36 °C. The inner diameter of the tubing at outlet was 2.4 mm. The interstimulus intervals were 10, 20, 30, 40, 60, or 90 s; these conditions were randomized across subjects. CO_2 stimuli of 200 ms duration were delivered to the left nostril as previously described [25]. Subjects were seated comfortably in an electrically shielded chamber with good air circulation. White noise at approximately 70 dB HL using an evoked auditory response stimulator (Tönnies, Germany) prevented subjects from hearing the switching process. To avoid respiratory flow of air into the nose, subjects were trained to practice velopharyngeal closure [26, 36].

EEG was recorded from three positions of the 10/20 system (Fz, Cz, and Pz) referenced to A1+A2, using a Mingograf EEG 10 (Siemens, Germany). The bandpass was 0.2–70 Hz, and the sampling frequency 250 Hz. EEG segments of 2048 ms included a 50 ms pre-stimulus period. Possible blink artifacts were registered from the Fp2 site. After A/D conversion, EEG segments were evaluated offline. Single responses contaminated by eye blinks larger than 50 μV were discarded. Averaging of the responses yielded late near-field event-related potentials. Peaks occurring at mean latencies of 235, 302, 363 and 460 ms were termed P_{24}, N_{30}, P_{36}, and P_{46}, respectively. The peak-to-peak amplitudes $P_{24}N_{30}$, $N_{30}P_{36}$, and $N_{30}P_{46}$, the base-to-peak amplitudes P_{24}, N_{30}, P_{36}, and P_{46}, and the peak latencies P_{24}, N_{30}, P_{36}, and P_{46} were measured [3], as illustrated in Fig. 1.

After presentation of each stimulus, subjects rated perceived intensity in relation to a standard stimulus (52% v/v CO_2 at 200 ms duration) presented at the beginning of each experiment. The intensity of this standard was defined as 100 estimation units (EU). Intensity ratings were made by means of a visual analogue scale displayed on a computer monitor that could be manipulated by a joystick.

For statistical analyses, SPSS (Statistical Product & Software Solutions) 6.1.3 for Windows was used. ERP data were submitted to a two-way analysis of variance (MANOVA) in a repeated measurements design; for "interval" [*df* 5/30] and "position" [*df* 2/12] as within subject factors, as well as interaction between factors "interval" and "position" [*df* 10/60]. An additional one-way MANOVA was performed for results of intensity ratings for "interval" [*df* 5/40] as within subject factor. The alpha-level was generally set at 0.01 to avoid error accumulation.

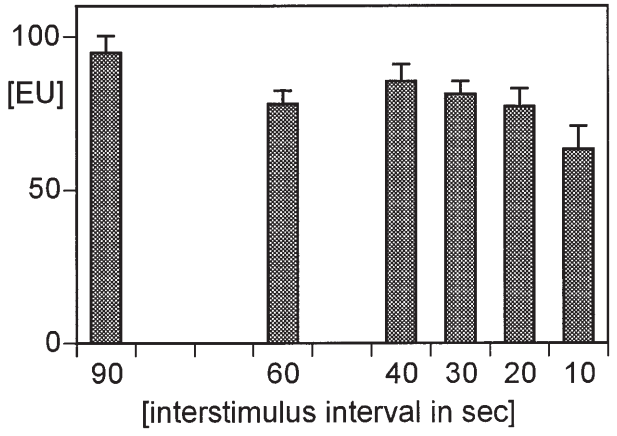


Fig. 1 Grand means averaged across chemosomatosensory event-related potentials (CSSERPs) of all participating subjects (n = 7, recording position Cz) for interstimulus intervals (ISIs) 10, 20, 30, 40, 60, and 90 s. The inset (*top right*) shows schematic drawings of both the evoked potential peaks and the location of the Cz recording site

Results

Descriptive statistics of intensity ratings and evoked potential data at position Cz are presented in Table 1.

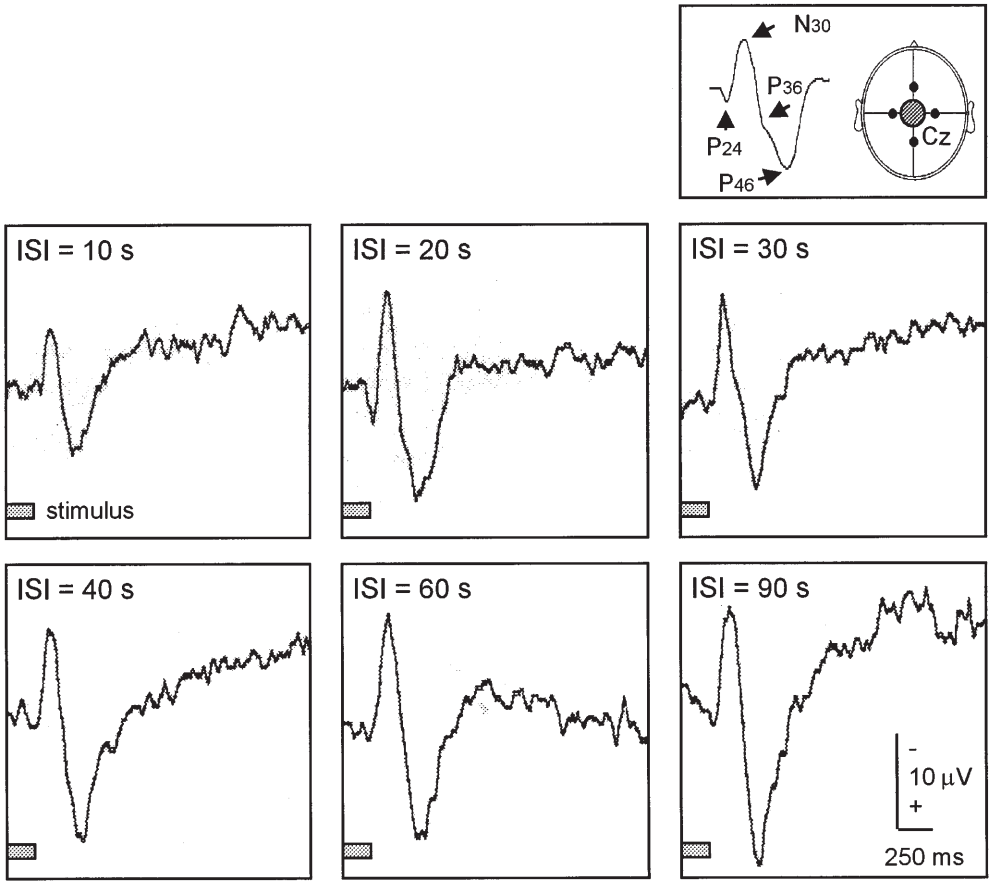
Intensity ratings

Perceived intensities decreased throughout sessions, especially during the second half. The decrease was most pronounced when the shortest ISI of 10 s was used: i.e., the perceived intensity of the stimuli decreased by approximately 50% at this interval. Only when stimuli were presented at an ISI of 90 s did perceived intensities remain relatively constant throughout the session. These changes were also reflected in the averaged intensity ratings and

Table 1 Means (M) and standard deviations (SD) of psychophysical and ERP data (n = 7) for the six interstimulus intervals at recording position Cz

		Interstimulus interval					
		10 s	20 s	30 s	40 s	60 s	90 s
Ratings (estimation units)	M	63.4	77.2	81.3	85.4	78.1	94.8
	SD	22.1	17.8	12.5	16.5	13.3	16.7
Amplitude $P_{24}N_{30}$ (μV)	M	13.4	19.8	17.8	25.4	21.7	23.1
	SD	6.2	12.6	8.9	20.5	11.6	11.6
Amplitude $N_{30}P_{36}$ (μV)	M	13.8	18.7	16.1	22.4	18.8	19.6
	SD	4.0	7.8	8.0	12.6	6.4	7.9
Amplitude $N_{30}P_{46}$ (μV)	M	23.7	34.2	28.8	41.6	42.1	42.2
	SD	9.9	11.3	13.6	27.6	19.9	13.2
Latency P_{24} (ms)	M	248	237	257	217	245	235
	SD	43	40	66	53	25	35
Latency N_{30} (ms)	M	307	305	307	288	315	302
	SD	37	34	55	49	24	44
Latency P_{36} (ms)	M	375	379	389	369	383	363
	SD	35	45	60	51	28	40
Latency P_{46} (ms)	M	463	491	484	479	467	460
	SD	32	74	68	57	41	47
Amplitude P_{24} (μV)	M	–0.3	2.9	0.7	2.7	–1.9	4.5
	SD	4.4	4.8	2.5	5.8	4.7	5.4
Amplitude N_{30} (μV)	M	–13.6	–16.9	–17.1	–22.8	–23.6	–18.6
	SD	4.6	9.3	8.6	20.7	14.9	8.5
Amplitude P_{36} (μV)	M	0.1	1.8	–1.0	–0.3	–4.9	1.0
	SD	4.9	3.1	7.9	10.3	12.6	7.3
Amplitude P_{46} (μV)	M	10.1	17.3	11.7	18.8	18.5	23.6
	SD	8.5	3.5	7.3	9.6	8.2	7.3

Fig. 2 Means and standard errors (n = 9) of intensity ratings in estimation units (EU) for interstimulus intervals (ISIs) 10, 20, 30, 40, 60, and 90 s. The shorter the ISI, the smaller the perceived mean intensity



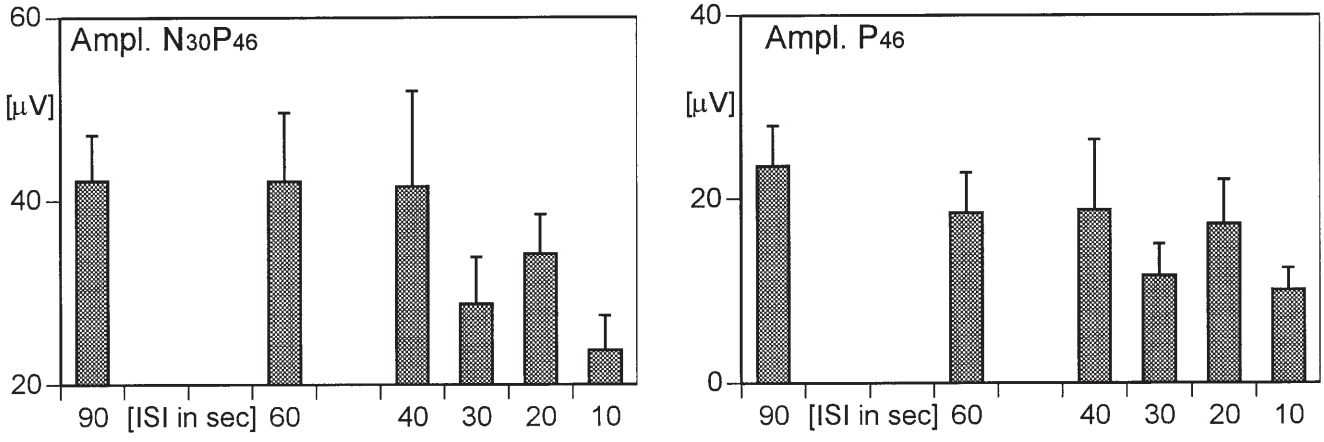


Fig. 3 Means and standard errors (n = 9) of ERP amplitudes at recording position Cz (in µV) for interstimulus intervals (ISIs) 10, 20, 30, 40, 60, and 90 s. The shorter the ISI, the smaller the CSERP amplitude

were smallest for an ISI of 10 s (Fig. 2). Statistical analysis revealed a significant effect of the factor "interval" (F = 4.28, P = 0.003). This was likely to be the result of the amount of CO_2 per time applied to the subject being tested and was greatest at an ISI of 10 s after 16 stimuli in approximately 3 min and smallest at an ISI of 90 s using 16 stimuli in approximately 23 min.

Chemosomatosensory ERPs

Results of two of the nine subjects could not be analyzed due to an excessive number of eyeblinks. Averages across the responses of all other subjects are presented in Fig. 1. The insert is a schematic drawing of the ERP peaks and the location of the Cz recording site.

Amplitudes were largest at an ISI of 90 s and became progressively smaller with a shortening of the ISI. A significant effect of the factor "interval" was seen for the base-to-peak amplitude P_{46}, as illustrated in Fig. 3 (F = 6.20, P < 0.001). Short ISIs generally produced smaller amplitudes. The smallest amplitudes were found for an

ISI of 10 s, with amplitudes P_{46} here diminished by 57% compared to amplitudes obtained at an ISI of 90 s.

Amplitudes and latencies exhibited differences in their topographical distribution along midline recording sites. Effects of the factor "position" became significant for amplitudes of $N_{30}P_{36}$ (F = 10.37, P = 0.002), $N_{30}P_{46}$ (F = 8.46, P = 0.005), and N_{30} (F = 11.17, P = 0.002). The maximum of these amplitudes was found at position Cz. Differences between recording sites were also observed for the P_{24} latency (F = 10.31, P = 0.002) and were shortest at Cz.

No changes of the ERP peak latencies were observed in relation to changes of the ISI. In addition, there were no significant interactions between "position" and "interval" factors, indicating that the ISI influenced ERPs at midline recording sites to a comparable degree.

Discussion

The results of our present study established a decrease in both intensity ratings and ERP amplitudes in relation to the ISI. The topographical distribution of amplitudes and latencies represented a pattern described previously [13, 14, 31]. The decrease of both ratings and response amplitudes was most pronounced at the shortest ISI of 10 s, whereas largest responses were obtained at the longest ISI (90 s). In general, our data indicated that an ISI of less than 20 s may not be useful for clinical investigations, as the response amplitude becomes relatively small.

Our results are comparable to the findings of Kobal [24] which were obtained for eucalyptol as a mixed trigeminal/olfactory stimulant. This latter study showed that the decrease of response amplitudes was most pronounced at an ISI of 10 s, with the late positivity reduced to a stronger degree than earlier peaks. Other research in the area of ERPs to nociceptive stimuli also indicates that long ISIs should be used. For electrical stimulation of the tooth pulp it was shown that amplitudes were ISI-dependent at intervals of up to 10 s [6, 21], with ERPs to noxious thermal stimuli amplitudes increased until an ISI of 20 s [4].

This behavior of chemosensory ERPs differs from ERPs evoked by auditory or visual stimuli where a "saturation" of the ISI dependence of ERP amplitudes has been observed at ISIs between 5 and 10 s [11, 30, 37, 40]. This difference between sensory systems does not seem to be a result of receptor-related events. As indicated by responses obtained at the periphery of the nociceptive system [18, 25], adaptation at the level of A_{delta} nociceptors seems to be involved to a lesser degree in this desensitization process than central nervous processes (compare [1, 45]). That no changes occurred in relation to changes of the ISI is consistent with findings in the auditory, visual and somatosensory systems [2, 40, 41].

It is not clear why the ISI dependence of nociceptive responses differs from those in other sensory systems. A possible explanation, however, might be found in the "pain inhibits pain" phenomenon [9], which may occur at spinal or supraspinal sites [29, 49]. Specifically, CO_2-induced activation of nociceptive C-fibers [44] may lead to a decrease of the ERP amplitude, which appears to be predominantly related to excitation of A_{delta} nociceptors [15]. In this sense, the ISI dependence of chemosensory ERPs could be used to estimate the interaction between C fibers and A_{delta} fibers.

The ISI-related decrease in amplitudes was most pronounced for the P_{46} amplitude. In the auditory and visual systems it has been demonstrated that the late positive components change as a function of the expectedness of the stimulus: i.e., the more predictable the stimulus, the smaller the positivity [7]. In analogy the presently observed decrease of the P_{46} amplitude may also have been the result of an increased predictability of the stimulus occurrence, with a shortening of the interval between stimuli [22].

Observations by Lorig et al. [32] are comparable to our data. They collected ERPs in response to butanol under an "active" and a "passive" paradigm. In the "active" condition stimulus administration was synchronized to inspiration (ISI > 8 s, mean ISI 16 s). In the "passive" condition stimulation was applied independently of the respiratory cycle (8 s ≤ ISI ≤ 24 s). One of the major results was that the late ERP positivity decreased when stimulus occurrence was more predictable ("active" condition). The authors concluded that the late ERP positivity was similar to the P300 component, which is highly sensitive to manipulations of stimulus probability.

On the other hand, based on previous research it can also be assumed that habituation [46] contributed to the presently observed decrease in ERP amplitudes [15, 24, 39]. This is supported by the fact that both ERP amplitudes and intensity ratings decreased as a function of the ISI. On the basis of this observation it can be hypothesized that the P_{46} peak is related to the P3a component, as described for other sensory systems. P3a occurs in response to target stimuli that do not demand immediate action of subjects [42]. Other than the P3b component, the P3a clearly exhibits habituation during repeated stimulation [38].

Taken together, our present data demonstrate that both ratings and chemosensory ERP amplitudes decrease as a function of the ISI. This decrease was most pronounced for the late P_{46} amplitude at an ISI of 10 s. Since the response amplitude become relatively small, interpretation of the responses may become difficult when the ISI is less than 20 s. On the basis of previous research it is hypothesized that this is the result of both habituation and stimulus predictability. The ISI dependence of ERPs to nociceptive trigeminal stimuli may also be a function of an interaction between A_{delta} and C fibers.

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ANNOUNCEMENTS

First European Symposium on Computer Aided Surgery in Otorhinolaryngology 10–11 April 1999, Mainz, Germany

For further information, please contact: Dr. Klimek c/o Mrs. Finkenauer, Universitäts-HNO-Klinik Mainz, Langenbeckstrasse 1, D-55101 Mainz; Tel.: 06131-177361, Fax: 06131-176637, e-mail: klimek@hno.klinik.uni-mainz.de

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