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Olfactory deficits decrease the time resolution for trigeminal lateralization☆

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ABSTRACT

Objectives: To date the temporal resolution of the detection of almost simultaneously applied intranasal trigeminal stimuli is unknown. The aim of our study was to examine this temporal resolution in an/hyposmic subjects, who are known to have reduced trigeminal sensitivity and compare it with healthy controls.
Methods: Participants were 20 posttraumatic an/hyposmic patients, and 23 healthy controls (matched with regard to sex and age). Olfactory function was tested psychophysically using the Sniffin´ Sticks test battery. Bilateral trigeminal stimulation was carried out using a birhinal high-precision olfactometer. The trigeminal stimulus used was CO_2 60% v/v, the interstimulus interval ranged from 28 to 32 s, stimulus duration was 200 ms. Time-lags tested between right and left side of stimulation were at 40, 80, 120, 160 and 200 ms. Subjects raised their left or right hand to indicate the side on which the stimulus had been perceived first.
Results: In both groups the accuracy in the trigeminal lateralization task increased with the time-lag but normosmic subjects significantly outperformed an/hyposmics in the 200 ms time-lag condition. Normosmics significantly exceeded 50% chance level at the time-lag of 80 ms, whereas an/hyposmics were only able to score above chance starting from 120 ms time-lag. Lateralization scores significantly decreased with age.
Conclusions: At a time lag of 200 ms intranasal trigeminal stimuli can be lateralized. The reduced trigeminal sensitivity in patients with anosmia or hyposmia leads to an increased time lag required for correct perception of intranasal, almost simultaneously, applied stimuli.

1. Introduction

Most of the odors encountered in daily life activate both the olfactory and the trigeminal systems Which are known to interact (Cain and Murphy, 1980; Hummel and Livermore, 2002; Welge-Lüssen et al., 2004). Odorants bind to olfactory receptor neurons as well as free nerve endings of trigeminal fibers in the nasal mucosa. At lower concentrations the elicited sensation reflects the olfactory component, whereas in higher concentrations they also irritation, stinging or burning (Hummel and Kobal, 1992). Anosmic patients exhibit increased odor thresholds (Gudziol et al., 2001) and lower amplitudes of chemosensory event-related potentials in response to intranasal trigeminal stimuli (Hummel et al., 1996). Other studies have shown that trigeminal stimuli have an inhibitory effect on olfactory activation (Bouvet et al., 1987; Cain and Murphy, 1980; Kobal and Hummel, 1988) and that central-nervous activation following olfactory or trigeminal stimulation is found in overlapping areas including the amygdala and the piriform cortex (Albrecht et al., 2010; Hummel et al., 2009; Savic et al., 2002). The potential changes were observed in the same neurons as those observed during electric stimulation of the olfactory bulb (Schaefer et al., 2002).

Lateralization is a widely acknowledged method for the assessment of intranasal trigeminal sensitivity (Hummel, 2000), because in contrast to odorant stimulation, intranasal trigeminal stimuli can be localized (Kobal et al., 1989). As already mentioned above, intranasal trigeminal sensitivity is decreased in patients with partial or complete olfactory loss (Hummel et al., 1996). This is also apparent in a reduced ability to lateralize monorhinally applied irritants (Hummel et al., 2003a). Although studies in olfactory kinetics suggest, that the olfactory system is capable of resolving rapid events (Laing and MacLeod, 1992), temporal resolution in terms of the lateralization of intranasal trigeminal stimuli received little attention. Exploration of the temporal resolution of trigeminal stimuli would provide evidence for the relationship between

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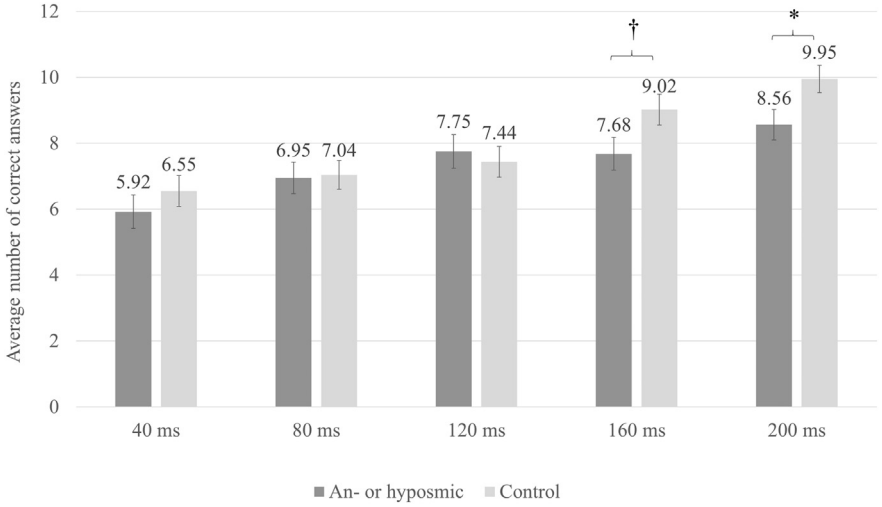

Fig. 1. Mean scores obtained in the trigeminal lateralization task across the five time-lag conditions by participants with olfactory deficits and healthy controls (± standard error); * - $p < 0.05$; † < 0.10.

olfactory and trigeminal systems and would further increase the knowledge about trigeminal sensitivity in the context of olfactory performance. To this end we investigated the temporal resolution of bilaterally applied intranasal trigeminal stimuli in controls; in addition, we studied whether this is modulated by differences in olfactory performance. Overall, we expected to observe lower time resolution in participants with reduced olfactory function compared to normosmics. We attempted to estimate the time lag between lateralized stimuli that separates normosmic from people with olfactory loss.

2. Materials and methods

A total of 43 subjects participated in the study, 20 of whom were an/hyposmic patients with olfactory loss due to head trauma (10 women; age [in years] $M = 47.3 \pm 11.4$; *Min* = 24; *Max* = 67), and 23 were healthy controls matched with regard to sex and age (16 women, age [in years] $M = 37.2 \pm 16.6$; *Min* = 23; *Max* = 79). To ascertain that olfactory and trigeminal testing was not influenced by intranasal pathologies all subjects underwent a clinical examination performed by an ENT-specialist. The diagnosis of an/hyposmia in patients was confirmed through psychophysical and electrophysiologic examination using an olfactometer. Subjects with other potential interfering factors like neurodegenerative disorders were excluded from the study. The study was conducted under consideration of the guidelines on biomedical research involving human subjects (Declaration of Helsinki) and it was approved by the local ethics committee.

2.1. Psychophysical olfactory testing

Olfactory function was assessed using the Sniffin' Sticks test battery (Hummel et al., 2007; Kobal et al., 1996). Threshold and discrimination subtests were conducted by blindfolding the subject to prevent visual detection. By adding the scores of the three subtests the TDI score can be determined allowing the classification into functional anosmia, hyposmia and normosmia (Hummel et al., 2007).

2.2. Psychophysical trigeminal testing

Bilateral intranasal trigeminal stimulation was carried out using a birhinal olfactometer (OM6b, Burghart Instrumants, Wedel, Germany). The trigeminal stimulus used was odourless carbon dioxide (CO_2, 60% vol/vol) which is known as a selective trigeminal stimulant (Cain, 1974; Carlson et al., 2013; Chevy and Klingler, 2014) with little or no activation of the olfactory system. The olfactometer allows the intranasal application of CO_2 under controlled conditions and without concomitant mechanical or thermal stimulation. The applied stimuli were embedded into a constant flow (8 l/min) of odourless, humidified air (80% relative humidity) at a temperature of 36 °C. The stimulus duration was 200 ms, the interstimulus interval (ISI) ranged from 28 to 32 s. Stimuli were applied in a total of 60 pairs, separated by different time lags, starting randomly from the left or right nostril. The time lags between right and left side of stimulation were at 40, 80, 120, 160 or 200 ms. The sequence of time lags was also randomised. To indicate the side on which the stimulus was perceived first participants were asked to raise their left or right hand. Correct answers were then summed up for each time-lag.

2.3. Statistical analyses

For analysing the results statistical analysis SPSS v. 22 (Statistical Package for the Social Sciences, SPSS Inc. Chicago, IL, USA) was used with an alpha-level set at 0.05. To examine the effects of olfactory deficits on scores obtained within the trigeminal lateralization task we performed repeated measures analysis of variance with time lags (40 vs 80 vs 120 vs 160 vs 200 ms) as within-subject factor and olfactory deficits (an/hyposmic group vs control group) as between-subject factors. Age and subjects' sex were added to the model as a covariate.

3. Results

The tested model revealed main effect of the time lag, $F(4156) = 4.1$, $p = 0.004$, $\eta^2 = 0.09$, suggesting that accuracy in trigeminal lateralization task increased with increasing time lag. We also found a significant interaction effect between the time lag and olfactory deficits, $F(4160) = 2.5$, $p = 0.048$, $\eta^2 = 0.06$. A closer look at the pairwise comparisons showed that the difference between controls and an/hyposmics was not significant in the time lags of 40 ms, 80 ms and 120 ms ($ps > 0.39$), but it became marginally significant in the 160 ms condition ($p = 0.07$) and it was significant in the 200 ms condition ($p = 0.03$; see: Fig. 1). Finally, we observed a main effect of age, $F(1, 39) = 7.2$, $p = 0.01$, $\eta^2 = 0.16$, suggesting that across most time lag conditions (except the 40 ms condition), performance in trigeminal lateralization task decreased with age (Fig. 2). There were no other significant main or interaction effects.

To test whether an/hyposmics and controls performed above the level of chance across time-lag conditions, we performed one sample *t*-tests comparing mean scores in both groups with expected value of 6 (50% of 12 trials). In case of an/hypsmic subjects, the level of chance was significantly exceeded in the 120 ($p = 0.02$), 160 ($p = 0.03$) and 200 ms ($p < 0.001$) conditions, whereas for shorter time-lags the difference was not significant ($p > 0.05$). Normosmic subjects exceeded the level of chance in the 80 ($p = 0.02$), 120 ($p = 0.002$), 160