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Time-course of trigeminal versus olfactory stimulation: Evidence from chemosensory evoked potentials

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ABSTRACT

Habituation of responses to chemosensory signals has been explored in many ways. Strong habituation and adaptation processes can be observed at the various levels of processing. For example, with repeated exposure, amplitudes of chemosensory event-related potentials (ERP) decrease over time. However, long-term habituation has not been investigated so far and investigations of differences in habituation between trigeminal and olfactory ERPs are very rare. The present study investigated habituation over a period of approximately 80 min for two olfactory and one trigeminal stimulus, respectively. Habituation was examined analyzing the N1 and P2 amplitudes and latencies of chemosensory ERPs and intensity ratings. It was shown that amplitudes of both components – and intensity ratings – decreased from the first to the last block. Concerning ERP latencies no effects of habituation were seen. Amplitudes of trigeminal ERPs diminished faster than amplitudes of olfactory ERPs, indicating that the habituation of trigeminal ERPs is stronger than habituation of olfactory ERPs. Amplitudes of trigeminal ERPs were generally higher than amplitudes of olfactory ERPs, as it has been shown in various studies before. The results reflect relatively selective central changes in response to chemosensory stimuli over time.

1. Introduction

Adaptation and habituation after perception of olfactory stimuli are mechanisms often encountered in daily life. A smell that is very peculiar at first perception becomes less intense after repeated stimulation or is even not perceived anymore. This is a useful mechanism as it enables animate beings to perceive novel odors or changes in odor concentration separately from the overall present odor mixture in the air (Dalton, 2000; Gottfried, 2010). It can thus be described as a simple form of non-associative learning during which the response to non-relevant stimuli declines (Freedman et al., 2013).

In the past, peripheral and central effects of repetitive stimulation have been treated separately in chemosensory research. Although this separation is probably too strict to explain the whole body of research, it is useful to explain the research approach of the current experiment: Habituation (i.e., changes that are due to the central nervous system — CNS) and adaptation (i.e., changes that happen in the periphery (Thompson and Spencer, 1966)) to chemosensory stimulants were in the past investigated thoroughly by the use of many different methods: In animal research, one has to rely either on behavioral variables to estimate the consequences of repeated olfactory stimulation (Cleland et al., 2002); for a review see (Wilson and Linster, 2008) or to single-cell recordings from the brain of rodents (Potter and Chorover, 1976; Wilson, 1998; Deshmukh and Bhalla, 2003; Kadohisa and Wilson, 2006). It was found in rats that examination time for smelling objects decreased with habituation to the smell (Cleland et al., 2002) and that central nervous response in the anterior piriform cortex (but not in the mitral cells of the olfactory bulb) decreased with longer/more exposure to certain odors in hamsters (Potter and Chorover, 1976), rats and mice (Wilson, 1998; Kadohisa and Wilson, 2006).

In humans, it could be shown that habituation to smells manifested in decreased intensity ratings after a prolonged time of odor stimulation (Ekman et al., 1967; Kobayashi et al., 2007). Also, when applying psychophysical measures, it was found that repeated stimulation with the same odorant lead to higher perception thresholds and therefore to a decrease in olfactory sensitivity (Pryor et al., 1970) and that this change in sensitivity might take up to two weeks to recover (Dalton and Wysocki, 1996). Poellinger et al. (2001) were able to demonstrate that the BOLD-signal in primary and secondary olfactory areas, such as

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the piriform cortex, the amygdala and the hippocampus, decreased over a time-course of 60 s, but not over shorter time-periods, indicating that the olfactory system habituates to constant stimulation after a certain time.

Until today, the question whether changes in the response to olfactory stimuli are due to adaptation (i.e., peripheral) or habituation (i.e., central nervous) processes remains under debate. It could be shown, that relatively small changes over time in potentials recorded directly from the olfactory mucosa (electro-olfactogram — EOG) do not explain massive changes in intensity ratings collected within the same trials (Hummel et al., 1994, 1996). Additionally, that EOG response in the hamster quickly returned to normal after brief stimulation breaks (Potter and Chorover, 1976). It seems that peripheral adaptation mechanisms are not strong enough to explain habituation processes and therefore central nervous mechanisms play a pivotal role.

One possibility to investigate changes in the CNS after repetitive stimulation of the nose is chemosensory event-related potentials (ERP; (Kobal, 1981; Hummel and Kobal, 2002). Changes in chemosensory ERPs have been investigated in single-trial approaches (Wetter and Murphy, 2003; Wetter et al., 2004), where, under very specific conditions, no habituation has been found. A study by Croy et al. (2013) did not find habituation of chemosensory ERPs in a blocked design, when comparing the first three stimuli of a block respectively. Considering the small sample size ($n = 8$) in the studies by Wetter and colleagues and the low number of trials, it is difficult to draw general conclusions about olfactory habituation to longer or more stimuli.

Another approach to investigate habituation of chemosensory ERPs used different lengths of inter-stimulus intervals (ISI) to estimate time-dependent changes in the olfactory system. It could be shown that the longer the time between stimuli the stronger the reaction to discrete stimuli (Hummel et al., 1994; Scheibe et al., 2009). It was argued that the response to the first stimulus overlapped with the response to the second one when applying a short ISI and therefore the olfactory system habituated to the stimulus. However, this approach does not answer the question of whether there are changes in response to the same olfactory stimulus over a longer time period and whether these changes differ between different olfactory and trigeminal stimulants.

1.1. Aims of study

It was hypothesized that over a long time course of olfactory and trigeminal stimulation, amplitudes of chemosensory ERPs would decrease. The same should be true for intensity ratings of the same stimuli. It was examined whether habituation curves of olfactory and trigeminal stimulants showed a different time course. To our knowledge, the present study is the first one to provide sufficient resolution to disentangle the processing of prolonged olfactory and trigeminal stimulus series.

2. Methods

2.1. Subjects

Twenty-two subjects participated in the study. Two participants had to be excluded due to technical problems during data recording. A total of 20 participants were included into the analysis, 9 females and 11 males (mean age: 23.9 years, ranging from 15 to 35 years). Subjects were recruited among visitors at the Smell and Taste Clinic of the Department of Otorhinolaryngology of the Technical University of Dresden. To ascertain normal olfactory function, participants underwent testing with the Sniffin' Sticks odor identification test (Hummel et al., 1997b). Only normosmic persons were included in the study (Kobal et al., 2000). Other exclusion criteria were health problems like Parkinson's disease, renal insufficiency, hypothyreodism, and diabetes. Prior to the study, potential participants were therefore thoroughly interviewed concerning their health. Participants received monetary reimbursement for their participation.

2.2. Stimuli and apparatus

2.2.1. Odors

Two olfactory stimuli (phenylethylalcohol [PEA] and hydrogen sulfide [H_2S]) and one trigeminal stimulus (carbon dioxide [CO_2]) were used in the study, PEA and H2S being considered as relatively selective olfactory stimuli and CO_2 considered to be processed almost exclusively trigeminally. The following concentrations were used: H_2S: 6.8 ppm; PEA: 20% v/v; CO_2: 44% v/v. All stimulants were applied to the right nostril. Stimuli were presented for 200 ms with a randomized intertrial interval between 25 and 35 s, around 30 s.

2.2.2. Olfactometer

A computer-controlled olfactometer (Om6b; Burghart, Wedel, Germany), based on the principles of air-dilution olfactometry, was used for stimulus presentation. It allows odor presentation without producing concomitant sensations of changes in pressure or temperature because stimulants are embedded in a constant air flow (36 °C; 80% relative humidity). Air flow within the olfactometer was kept at 8 l/min. Velopharyngeal closure was performed during application of the odors directly into the nose (Kobal, 1981). This procedure allows rapid presentation of odors in order to elicit chemosensory event-related potentials. Velopharyngeal closure had been trained before the start of the experiment. During stimulus presentation, participants heard white noise over a headset to prevent distraction by solenoid closure and opening. The experiment took place in a room with adequate air-conditioning. In addition, nasal cavities were “rinsed” with clean, humidified, warm air during inter-stimulus intervals.

2.2.3. Measurement

EEG data were recorded from six electrode sites using the international 10–20-system (Jasper, 1957). Gold EEG electrodes (Grass Technologies, Warwick, R.I., USA) were applied to the scalp using self-adhesive EEG-cream. Reference electrodes were attached to both earlobes and ground electrodes to the mastoid bones. EEG electrodes were placed on the positions Cz, Fz, Pz, C3, and C4. An additional electrode above the right eyebrow (FP2) was used to check for vertical eye movements. An online bandpass filter (0.2–30 Hz) was applied to the data. Segments of 2048 ms were recorded, starting 500 ms before stimulus presentation. Sampling rate was set at 250 Hz. An eight-channel pre-amplifier (S.I.R., Rötenbach, Germany) was used to record EEG-data.

2.3. Procedure

When participants arrived in the lab, they provided their written informed consent for the study. The study was approved by the Ethics Committee of the Technical University of Dresden. Afterwards, they were tested using Sniffin' Sticks and interviewed concerning their health status. EEG-measurements were performed on three consecutive days. On every day, one of the three odors was applied in a randomized order. In total, three EEG sessions were performed, each for one of the three odors. In order to minimalize eye movements and to stabilize vigilance throughout the experiment, participants had to perform a tracking task: they had to keep a white dot inside a gray square that moved slowly across the screen, using the joystick. This task has been used before in several experiments (e. g., Hummel et al., 1997a; Frasnelli et al., 2003; Iannilli et al., 2013) and performance has been shown not to change throughout the experiment (Hummel et al., 1997a).

For each EEG session, the same procedure was applied: 160 trials were performed. After every trial, participants had to indicate the perceived intensity of the odors on a visual analog scale (approximately 25 cm long) using the joystick. For ratings and export of the rating data,