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BIMODAL ODOR PROCESSING WITH A TRIGEMINAL COMPONENT AT SUB- AND SUPRATHRESHOLD LEVELS

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Abstract—Odors are typically bimodal in nature, interacting with the olfactory and trigeminal systems. The trigeminal component may be noticed (e.g. menthol) or perceptually ignored, leading to different neural substrates being recruited during odor encoding. Therefore, the current study was designed to explore the perceptual and central-nervous activations in response to pleasant bimodal odors using functional magnetic resonance imaging (fMRI). In this study, healthy subjects were exposed to odorants alone (unimodal) or with a "cooling" trigeminal component (bimodal) at sub- and suprathreshold concentrations with a portable olfactometer in a 3 T fMRI scanner. Within the scanner, subjects reported all odorants as pleasant and intensity increasing with trigeminal concentration. Many of the regions of interest [orbital frontal cortex (OFC), insula, thalamus, cerebellum, postcentral gyrus and cingulate cortex] were activated during bimodal odor conditions when contrasted with unimodal, and interestingly, most of these activations were seen prior to trigeminal perception (e.g. at a subthreshold level). This includes large bilateral activations within the OFC, insula, cerebellum and parts of the cingulate cortex. Additionally, activation of the thalamus was seen early in the stages of bimodal odor encoding suggesting its role of mediating attention toward the presence of two stimuli. Lastly, intensity encoding during bimodal processing shows overlap of previously demonstrated simple trigeminal encoding areas (medial cingulate cortex) and the more complex olfactory encoding areas (bilateral insula, superior temporal gyrus, OFC, and cerebellum), but not the amygdala.

Key words: olfaction, trigeminal, bimodal odor, fMRI, thalamus, subliminal.

INTRODUCTION

The perception of objects may be represented by a single sense, but it typically incorporates other senses to provide more information. For instance, an object's shape can be determined through our senses of touch or vision; however, using both senses gives us more information about the object. Despite the multiple brain routes taken by these senses, we perceive a single representation of the object through the process of multisensory integration. Similarly, natural odors represented to the olfactory system typically interact with more than one sense to relay additional information about the encountered stimuli. Here, an odorant interacts with both the olfactory and the trigeminal systems (Doty et al., 1978).

Olfactory and trigeminal systems interact during chemosensory perception which can be shown on perceptual and neural levels. For instance, the intensity of trigeminal stimuli (CO_2) increases when perceived together with an olfactory stimulus (H_2S or vanillin) (Kobal and Hummel, 1988; Livermore et al., 1992), and individuals with an impaired or absent sense of smell perceive trigeminal stimuli to a lesser degree than those with a healthy olfactory system (Hummel et al., 1996).

A pure odorant (vanillin) elicits activity in typical primary and secondary olfactory cortex areas such as the insula, amygdala and piriform cortex, whereas bimodal odors (e.g., acetone which stimulates both olfactory and trigeminal systems) induce widespread activation of brain regions including the insula, claustrum, anterior cingulate cortex, somatosensory cortex, cerebellum, thalamus, hypothalamus and pons/medulla (Savic et al., 2002). Furthermore, weaker activations are found for trigeminal stimuli (e.g. CO_2) in anosmic people compared to healthy individuals in typical nociceptive areas (Albrecht et al., 2010) including the somatosensory cortex, prefrontal cortex and insula (Boyle et al., 2007a,b; Iannilli et al., 2007).

The influence of trigeminal stimuli on the perception of odors has been less studied. Here, olfactory thresholds (for the rose-like odor phenyl ethyl alcohol) decrease with prior exposure to trigeminal stimuli (allyl isothiocyanate) (Jacquot et al., 2004); conditioning with a trigeminal stimulus can increase olfactory event-related potentials (ERP) (Bensafi et al., 2007). Furthermore, neural activations in response to trigeminal or olfactory stimuli of different intensities have only been studied for unimodal stimuli (Bensafi et al., 2008). Therefore, the current study was designed to explore the perceptual and central-nervous activations in response to pleasant bimodal odors using functional magnetic resonance imaging (fMRI).

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Abbreviations: fMRI, functional magnetic resonance imaging; OFC, orbital frontal cortex.

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EXPERIMENTAL PROCEDURES

Participants and stimuli

Sixteen healthy individuals, ten females and six males (mean age 25.9 years, sd 4.5), volunteered to participate in the study. All participants were non-smokers and right-handed as established by means of the Edinburgh Inventory (Oldfield, 1971). None of the women were pregnant, and none of the participants had significant health problems (e.g. kidney failure) that may be associated with disorders of olfactory function, nor any acute or chronic inflammation of the nose and paranasal sinuses. Each individual was assessed for olfactory and trigeminal function with the ''Sniffin' Sticks" test battery and the menthol lateralization test, respectively (Frasnelli et al., 2011; Hummel et al., 1997). All participants scored in the healthy range for both olfactory and trigeminal tests. Additionally, subjects reported no claustrophobia and were able to undergo MRI examinations. The study design met the requirements of the Declaration of Helsinki and had been approved by the Ethics Committee of the Medical Faculty Carl Gustav Carus at the Technical University of Dresden (EK394102014).

Two bidmodal odors were chosen, strawberry and orange odor (at 10% concentration) with a ''cooling" trigeminal component (Coolact P, Takasago International Corp, Tokyo, Japan) at sub- and suprathreshold concentrations based on individual thresholds to coolact. Coolact was used since it produces a pleasant trigeminal sensation with minimal odor perception. Stimuli were presented to the right nostril using a computer-controlled air-dilution olfactometer with multiple channels for each odorant (Sommer et al., 2012). Right-nostril stimulation was chosen because of evidence indicating that the right hemisphere seems to be more strongly involved in aspects of the processing of olfactory and trigeminal chemosensory information than the left hemisphere (Zatorre et al., 1992; Iannilli et al., 2007; Lübke et al., 2012).

The experiment, which lasted approximately 60 min, comprised six conditions presenting each odor alone and with subliminal and supra-threshold concentrations of Coolact P (further termed coolact). For fMRI acquisition, a block design was applied, with six alternating periods of a condition and odorless air (stimulus duration 1 s, interstimulus interval 2 s; duration of each period of stimulation 20 s) within each session. One condition was set for each session, and the session odor was randomized per individual. After each of the six sessions, subjects verbally reported intensity and pleasantness of the stimuli. Intensity was rated along a scale between 0 (not perceived) and 10 (extremely strong), while the hedonics scale ran from −5 (very unpleasant) through 5 (very pleasant).

fMRI acquisition

A 3 T MRI scanner (Siemens Verio, Erlangen, Germany) and an eight-channel receiver head coil were used for image acquisition. A gradient echo T2*-sensitive echo planar imaging (GE-EPI) sequence was employed (TR 2500 ms, TE 40 ms, image matrix 64 × 64, in-plane resolution 3 mm, through-plane resolution 3.75 mm). Images were acquired in the axial plane oriented parallel to the planum sphenoidale to minimize artifacts. A total of 96 functional volumes per session in thirty-three slice locations (covering the entire head) were acquired per session. A full brain T1-weighted turbo FLASH 3D-sequence was acquired to overlay functional data (TR 2180 ms, TE 3.93 ms, slice thickness: 1 mm).

fMRI data processing

Pre- and post-processing of the data was performed using SPM8 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, University College London, London, UK). Functional images were motion corrected and coregistered with the respective anatomical images, normalized (to MNI template) and smoothed (7 * 7 * 7 mm^3 FWHM Gaussian kernel). Alternating periods of condition and odorless air were contrasted sessionwise for each subject, and the resulting data fed into group analyses.

A factorial design was created with *odor* (orange and strawberry) and *coolact level* (no coolact, subliminal, supra-threshold) as within-subject factors. Comparisons were calculated for orange and strawberry stimuli separately and pooled, contrasting zero (no coolact) vs. 1 (subliminal coolact), 1 vs 2 (supra-threshold coolact), and zero vs. 2, and vice versa. Areas of significant activation underwent ROI analysis for areas known to be relevant to olfactory and trigeminal processing [orbitofrontal cortex (OFC), thalamus, postcentral gyrus, insula, cerebellum, and amygdala] and multisensory processing [superior temporal gyrus and cingulate cortex]. The cingulate cortex was further partitioned to its anterior (ACC), medial (MCC) and posterior (PCC) parts and a mask for the mediodorsal part of the thalamus was also created. All masks were created using the ''automated anatomical labeling (aal)" atlas (Tzourio-Mazoyer et al., 2002), embedded in WFU PickAtlas 2.4 software (Maldjian et al., 2003), except for the OFC [defined according to the criteria described in (Kahnt et al., 2012)] and the mediodorsal thalamus [defined by (Mavridis, 2014)]. For ROI analysis, thresholds were set at $p < 0.005$.

Additionally, psychophysical data were analyzed with the SPSS software (vs. 23; SPSS Inc., Chicago, Ill., USA) using a mixed ANOVA with either hedonic or intensity ratings for each odor as the response to coolact level while the participant was set to a random predictor.

RESULTS

Psychophysics

According to the ANOVA (see Fig. 1), the intensity of the strawberry odor significantly increased linearly with more coolact ($F[2,28] = 4.52$, $p = 0.02$). A similar, but non-significant trend was seen with the orange odor ($F[2,28] = 2.79$, $p = 0.078$). No significant difference to hedonic ratings by coolact level was shown for either strawberry