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Functional MRI of Intranasal Chemosensory Trigeminal Activation

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Introduction

Numerous brain imaging studies using positron emission tomography or functional magnetic resonance imaging (fMRI) have provided considerable information regarding the processing of sensory information. While many studies have also been performed on olfactory mediated sensations, cerebral activation following intranasal trigeminal stimulation has not been systematically addressed. The aim of this pilot study was to look at cerebral activation following trigeminally induced activation using CO_2, a stimulant which almost exclusively activates the trigeminal system. This activation was compared to effects of stimulation with 'pure' olfactory stimuli [i.e. H_2S and phenyl ethyl alcohol (PEA)].

Based upon the intimate connections between the trigeminal and olfactory systems (Doty *et al.*, 1978; Hummel and Livermore, 2002), we hypothesized that there would be overlap between central activation induced by separate stimulation of the olfactory and trigeminal systems. We expected that olfactory stimulation would produce activation in, for example, the insular, piriform and orbitofrontal cortices, as well as in the cerebellum and gyrus rectus (Savic, 2002). We sought to determine which, if any, of these structures were activated by trigeminal stimulation. In terms of lateralization, stronger activation of the right hemisphere was expected (Hummel *et al.*, 1995; Hari *et al.*, 1997).

Materials and methods

Subjects were screened for smell dysfunction prior to entering the study using the University of Pennsylvania Smell Identification Test. The project was approved by the IRB of the University of Pennsylvania; patients completed informed consent forms. Nineteen healthy, right-handed subjects participated (seven women, 12 men; mean age 36 years).

Studies were performed on a 1.5 T GE Horizon echospeed scanner. fMRI studies consisted of a T_1-weighted (T_1W) sagittal scan with repetition time (T_R) of 500 ms, time to echo (T_E) 11 ms and 1 average (500/11/1). For anatomic overlays this scan was followed by an axial 500/11/1 scan with a 192×256 matrix and 5 mm thick interleaved sections through the entire brain. fMRI studies were performed in the axial plane using multislice gradient echo echoplanar imaging. Scans (64×40 matrix, 24×15 cm^2 FOV, T_R 3000 ms, T_E 30 ms, 5 mm thickness, 90° flip angle) delivered a voxel resolution of ~$4 \times 4 \times 5$ mm^3. A total of 120 images were acquired at each of 24 slice locations per paradigm over the course of a 6 min fMRIscan. Each task paradigm consisted of six alternating rest–stimulus cycles (30 s each). More details of the paradigm are described elsewhere (Yousem *et al.*, 1998).

Stimulants were presented birhinally using a Burghart OM4b olfactometer. Chemical stimuli were embedded in a constant flow of odorless air (2 l/min) that was delivered through tubing inserted into the subjects' nostrils. Stimulants were applied for 1 s every 4 s during the 30 s 'on-period'. During the 30 s 'off-period', subjects received odorless air. For olfactory stimulation we used PEA and H_2S; CO_2 was chosen for trigeminal stimulation.

Following correction for image distortion and alternate *k*-space line errors statistical parametric maps (SPMs) were generated using SPM96. Functional data sets were motion corrected and normalized to Talairach space. A 60 s time-shifted box-car waveform was used as the reference paradigm and the ANCOVA model with global activity as a confound was employed for statistical analysis. The resulting sets of images represent SPMs of the *t*-statistic SPM$\{t\}$. For details of the analysis, see Yousem *et al.* (1998).

Results

Group analyses indicated that both olfactory and trigeminal stimulation produced activation in the ventral insula, the middle frontal gyrus and supplemental motor area (Figure 1). In addition, both types of stimulation produced a stronger right-sided activation. Unlike trigeminal stimulation, olfactory stimulation activated the cerebellum (left anterior lobe, right posterior lobe) and the parahippocampal gyrus. Trigeminal stimulation activated structures not activated by olfactory stimulation, namely the midbrain, dorsolateral orbito-frontal cortex, frontal operculum, superior temporal gyrus, medial frontal gyrus and anterior caudate nucleus. Overall, trigeminal activation was more pronounced compared to olfactory activation.

Discussion

Trigeminal stimulation specifically activated the midbrain, corresponding to the nucleus tractus solitarii. Trigeminal stimulation also produced activation in areas involved in the processing of olfactory information, including (i) the superior temporal gyrus, reported to be involved in the early cognitive processing of olfactory information (Kettenmann *et al.*, 1996); (ii) the dorsolateral orbito-frontal cortex, which is typically activated through odors and has been mentioned in the context of odor identification (Jones-Gotman and Zatorre, 1988); and (iii) the caudate nucleus found to be involved in odor quality discrimination (Savic *et al.*, 2000).

In addition, results from the present pilot study indicated overlap between activations through olfactory or trigeminal stimulation which was seen in the ventral insula and the middle frontal gyrus. In addition, both types of stimuli produced larger right-sided activation, indicating that the right hemisphere is important to the processing of chemosensory information (Hummel *et al.*, 1995; Hari *et al.*, 1997).

Trigeminal stimulation produced much weaker cerebellar activation than olfactory stimulation (Sobel *et al.*, 1998), despite the strong overall activation from trigeminal stimulation. The cerebellum has been frequently reported to be activated during sniffing and it has been speculated that it is directly involved in the processing of odorous information. Based upon the present data, it may be

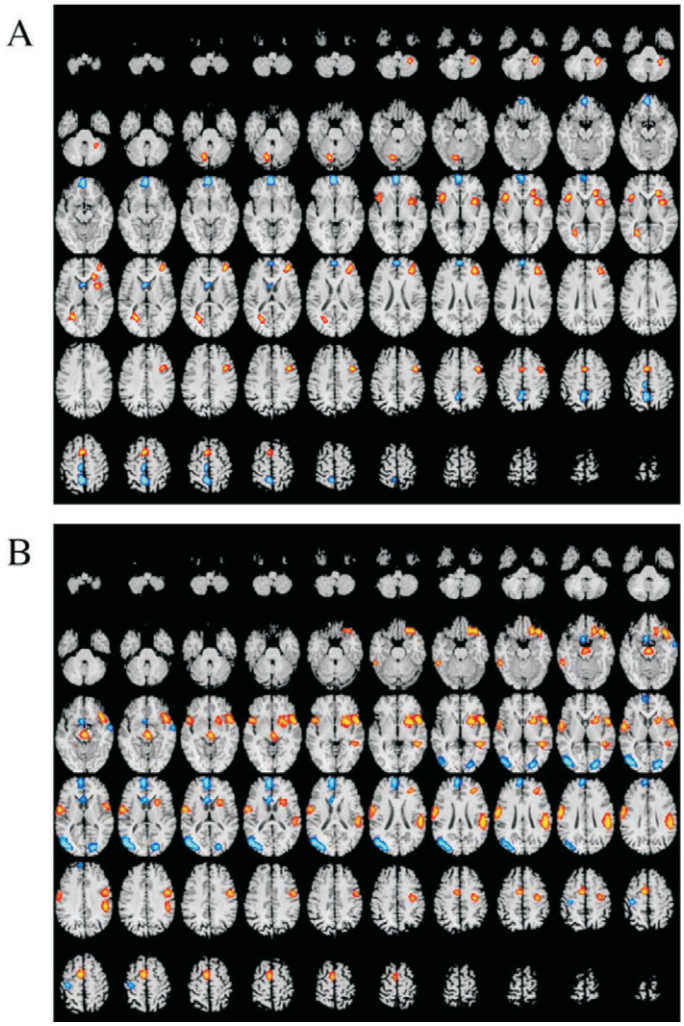

Figure 1 Group-averaged map of 19 individuals following **(A)** olfactory stimulation with H**2**S and PEA, or **(B)** trigeminal stimulation with CO_2. Areas of activation are indicated by red/yellow colors (inactivation is indicated by blue colors, but is not discussed here).

hypothesized that cerebellar activation may be less important to trigeminal than to olfactory stimulus processing.

Mixed olfactory–trigeminal (OT) stimuli appear to produce a different pattern of activation than 'pure' trigeminal stimulation. Yousem *et al.* (1997) observed that olfactory stimuli activated the right OFC and the cerebellum 'mildly'. Mixed stimuli produced additional cingulate, temporal and cerebellar activation. Savic *et al.* (2002) also reported differences between olfactory and mixed OT stimuli. For the mixed stimulus, strong activation has been found in the anterior/central insula and claustrum, anterior cingulate, somatosensory cortex, cerebellum, thalamus, lateral hypothalamus and brainstem.

It is of interest to note that intranasal trigeminal stimulation failed to produce the pattern seen after cutaneous stimulation of the trigeminal nerves, which typically activates the thalamus and the primary and secondary somatosensory cortices. It may be hypothesized that the intransal sensations mediated through the trigeminal nerve are specifically processed, which may argue for a specific role of the 'common chemical sense'. Overall, the present results highlight the fact that some common brain structures are activated by olfactory and trigeminal stimulation and that there are also marked differences between the two.

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