Olfactory Stimulated Functional MRI: Effects of Age, Sex, and Handedness

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Purpose
The purpose of this study was to examine the effect of age, gender and handedness on olfactory using functional MRI.

Introduction
The olfactory system in humans demonstrates numerous intracerebral connections. From the olfactory bulbs and tracts there are connections to the temporal lobe (entorhinal cortex, piriform cortex, amygdala, and insular regions), the dorsomedial thalamus, the hippocampus, the cingulate gyrus, the orbitofrontal regions, and the limbic system. PET scanning has demonstrated increase in regional blood flow upon olfactory stimulation in the orbitofrontal regions (right greater than left), and in the piriform cortex (1). A preliminary functional MRI study using olfactory stimulation has also suggested a right sided orbito-frontal dominance (2). This preliminary study reported on just 4 right handed male subjects and recommended further evaluation. The effects of gender, handedness and age could not be assessed due to the small sample size.

Methods
Functional MRI using multislice gradient echo echoplanar imaging was performed in 19 subjects (3 left handed, ages 18-77, mean of 36, 12 male) with a normal smell of smell as determined by the University of Pennsylvania Smell Identification Test. Scan parameters included a 64x40 matrix, 24x20 cm FOV, TR of 3000, TE 30, 5 mm thickness and a 90 degree flip angle. A total of 120 images were acquired at each of 24 slice locations per run over the course of 6 minutes. Conventional T1-weighted axial images were acquired for performing talairach normalization.

The task paradigm consisted of alternating rest-stimulus cycles (30 seconds each) over the 6 minutes. Olfactory stimuli were presented using a Burghart OM4-B olfactometer (Wedel, Germany) with a continuous flow method (4 l/min). Stimuli were administered for 1 second every 3 seconds in a 30 seconds on, 30 seconds off room air protocol. The olfactometer is equipped with a nozzle which can present 4 different odors and room air.

Three sets of stimulants were utilized: (1) a combination of hydrogen sulfide and phenylethylalcohol (H2S-PEA), (2) benzaldehyde, and (3) carbon dioxide (CO2). The H2S-PEA combination was chosen to selectively stimulate the olfactory nerve, whereas the benzaldehyde stimulates both olfactory and trigeminal nerve, and CO2 is a selective trigeminal stimulant(3).

Each subject underwent 2 runs each of H2S-PEA and benzaldehyde, and a single run of CO2. A separate analysis of 21 individuals (4 left handed, ages 18-77, mean of 35) was performed utilizing varying olfactory stimulants (H2S, phenylethylalcohol, and eugenol).

The FMRI raw image data was transferred via DAT tape to a SUN Sparcstation for off-line reconstruction and motion correction using in-house software developed in IDL (Research Systems Inc., Boulder Colorado). Statistical parametric maps (SPMs) were computed using the square root of the F statistic with 1 degree of freedom for the numerator and 120 degrees of freedom for the denominator. The F distribution becomes insensitive to n for large n and the square root is approximately distributed with a normal distribution (z distribution) with a variance of 1. An affine transformation to talairach space was computed based on the T1-weighted scan using a manual normalization routine, and applied to the SPMs. SPMs for each group analysis were summed and averaged over the square root of the number of SPMs to maintain the z distribution. The group SPMs were thresholded for a bonferroni corrected p < 0.05. Group average SPMs of the left handed and right handed individuals, males and females, and older right handed males (55 - 77, n = 5) and younger right handed males (25-35, n = 5) were constructed. Volumes of activated voxels were calculated based on region-of-interests drawn on the group SPMs.

Results
Group average maps of the 19 subjects (38 runs) after H2S-PEA intranasal (olfactory) stimulation demonstrated right sided frontal activation and bilateral peri-insular activation (right greater than left). In addition left sided cerebellar activation was noted. With CO2 (trigeminal) stimulation entorhinal and piriform cortex appeared on the right side which was not demonstrated with the other stimulants. In addition right inferior parietal and brain stem activation was noted. No cerebellar activation was demonstrated with the trigeminal stimulant. With mixed olfactory and trigeminal stimulation (benzaldehyde), the activation was primarily right frontal, left dorsomedial thalamic, and cerebellar. A small amount of medial right entorhinal and bilateral peri-insular activation was demonstrated.

 Inferiorly the left handed individuals demonstrated greater left sided activation in the perisylvian regions. More inferiorly in the perisylvian region, more activation was seen on the right sided in the right handed individuals. No gross differences in frontal activation was identified.

The volume of activation in female subjects was greater than for males in the bilateral perisylvian regions and right frontal areas. The sites of activation demonstrated were similar.

In the older right handed males, there was less activation demonstrated in the right frontal and right entorhinal cortex than in the younger right handed males. Areas of activation demonstrated were similar between the 2 groups.

Discussion
Tests of odor identification and detection threshold have demonstrated that across all age groups women tend to perform better than men. In addition, after the age of 60, both women and men show a progressive decline in their ability to detect and identify odors (4). In our study, we noted a marked difference in the volume of activation between women and men, however, the differences between older male and younger male subjects were more subtle. Right handed individuals may be more sensitive on the left side of their nose for odor detection, whereas left handed subjects may have a right nostril preference (5). The relationship of these findings to hemispheric preference for olfaction is unclear with respect to handedness.

The most dramatic difference between group average maps were the differences between activation sites with pure olfactory nerve stimulants (where orbitofrontal and cerebellar activation predominated) versus trigeminal stimulation (where parietal and entorhinal cortex activation appeared, but cerebellar activation was absent). The difference between men and women (where activation was dramatically decreased in the former), paralleled the results on clinical psychophysical tests of odor identification.

Regional activation with intranasal trigeminal stimulants differs from that of olfactory nerve stimulants. Gender appears to play a dominant role with respect to volume of activation in normal subject.

References
2. Yousem et al., Radiology 204(3):833-8;1997

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