AJNR

Functional MR imaging of regional brain responses to pleasant and unpleasant odors.

R K Fulbright, P Skudlarski, C M Lacadie, S Warrenburg, A A Bowers, J C Gore and B E Wexler

AJNR Am J Neuroradiol 1998, 19 (9) 1721-1726
http://www.ajnr.org/content/19/9/1721

AJNR Am J Neuroradiol 19:1721–1726, October 1998

Functional MR Imaging of Regional Brain Responses to Pleasant and Unpleasant Odors

Robert K. Fulbright, Pawel Skudlarski, Cheryl M. Lacadie, Stephen Warrenburg, Alexandra A. Bowers, John C. Gore, and Bruce E. Wexler

BACKGROUND AND PURPOSE: **Odors can elicit a range of behaviors and emotions. Our purpose was to identify regional activation of the human cerebral cortex in response to pleasant (positive hedonic value) and unpleasant (negative hedonic value) odors.**

METHODS: **Thirteen neurologically normal adults underwent functional MR imaging of frontal and anterior temporal brain regions with a gradient-echo echo-planar technique. Eleven candidate regions of interest (ROIs) were identified on the first half of the data set based on *t*-map comparisons of signal intensities during administration of clementine (pleasant odor), isovaleric acid (unpleasant odor), and clear air (control odor). These ROIs were applied to the second half of the data set, and the number of voxels activated with the odorants was compared with the number of voxels activated during clear air trials, using independent *t*-tests.**

RESULTS: **Clementine activated five cortical areas: Brodmann's area (BA) 8, BA 32 (lateralized to left), BA 46/9, BA 6 (lateralized to right), and the insula. Isovaleric acid activated four of the five regions without lateralization; no BA 8 activity was seen. Clementine produced more activity than isovaleric acid in the left insula, and isovaleric acid produced more activity than clementine in the left BA 6. No activation was detected in the orbitofrontal cortex or in the medial temporal lobes. Subjects rated clementine, isovaleric acid, and clear air as being pleasant, unpleasant, and neutral, respectively.**

CONCLUSION: **Activation in frontal regions may represent brain processes linked to olfactory networks. There may be regional specialization based on odorant hedonic values.**

The olfactory system involves phylogenetically old and new parts of the brain, including centers involved in appetitive, social, and symbolic behaviors (1). Neuroanatomic work in primates has established that odor processing proceeds by direct links from the olfactory bulb to the entorhinal and piriform cortices of the temporal lobes, and also to the thalamus, hypothalamus, and parts of the limbic system (2, 3). Secondary connections to the orbitofrontal cortex are made from the hypothalamus, thalamus, and entorhinal cortex.

Similar anatomic connections exist in humans. Subjects with focal brain damage of the orbitofrontal cortex may have limited ability to identify odors (4), and subjects with lesions of the medial temporal lobes may have impaired odor discrimination despite normal ability to detect odors (5–7). In unimpaired subjects, functional mapping with positron emission tomography (PET) can detect increased cerebral blood flow in response to pleasant and unpleasant odorants in the right orbitofrontal cortex and in both medial temporal lobes, suggesting a functional asymmetry (8).

Odors can affect a variety of perceptual, motor, and cognitive functions (9), but whether odors enhance or interfere with task performance depends on task parameters, odor delivery method, and specific odors tested (Lorig TS, Elmes DG, and Yoerg VL, unpublished data). Pulsed presentations of peppermint improved vigilance performance on a visual sustained-attention task, but the odor of lily of the valley had no effect (10). During a visual search task, pulses of a synthetic musk odor interfered with performance (11). The ambient room administration of several odors had either deleterious effects (12, 13) or no effect on various paper-and-pencil tasks (14). Ambient odors, however, do appear to influence behavior of consumers in a shopping environment (15–17) and can also affect evaluation of job applicants and other interpersonal behavior (18–21). EEG and event-re-

Received January 14, 1998; accepted after revision June 3.

From the Departments of Diagnostic Radiology (R.K.F., P.S., C.M.L., J.C.G.) and Psychiatry (A.A.B., B.E.W.), Yale University School of Medicine, New Haven, CT; the Department of Applied Physics, Yale University CT (J.C.G.); and International Flavors and Fragrances, Inc, Union Beach, NJ (S.W.).

Address reprint requests to Robert K. Fulbright, MD, Section of Neuroradiology, Department of Radiology, Yale University School of Medicine, Box 208042, New Haven, CT 06520.

lated potentials during auditory or visual-motor tasks are modified when odorants are presented during the task (9, 22, 23). Pleasant and unpleasant odors modulate the startle reflex in a manner indicative of their effects on positive and negative emotion, respectively (24–26). In general, pleasant odors tend to improve mood or induce approach behaviors, and unpleasant odors tend to disturb mood or induce avoidance behaviors (15–21, 27–31), although studies do not always obtain significant results (14). In some cases, these immediate effects of mood or behavior can become long-lasting (13, 19).

The wide range of behavioral and emotional changes following exposure to odors suggests that regions of the brain in addition to the primary (medial temporal lobe) and secondary (orbitofrontal) cortices respond to olfactory stimuli. The purpose of this study was to use functional MR imaging to investigate regional brain activation following exposure to odors that have either positive (pleasant odors) or negative (unpleasant odors) hedonic qualities.

Methods

Task

The study group consisted of 13 neurologically normal adult subjects (five men and eight women; mean age, 30 years). Two of the men and three of the women were studied twice (18 total studies). Subjects gave written consent, and studies were approved by the institutional review board at our institution. We compared clementine (a pleasant, sweet citrus odor), isovaleric acid (IVA, an unpleasant, sweaty odor), and clear air (control odor). Clementine and IVA have been shown to be consistently rated as pleasant (positive hedonic value) and unpleasant (negative hedonic value), respectively (personal communication, Stephen Warrenburg, proprietary information, International Flavors and Fragrances, Inc). Odors and clear air were presented just below the opening of both nares using a pump system and odorless tubing to selectively route air at a constant flow rate through sample vials. For each fragrance, three saturated beads were used in the sample vials. We intermixed the presentation order of clementine, IVA, and clear air, and waited a minimum of 90 seconds between presentations of successive odors. Residual odors were removed by routing air through an activated charcoal filter. For each subject, there were two to four clementine trials, two to four IVA trials, and one to two blank trials. Immediately after presentation of odor or clear air, subjects indicated whether they had smelled anything and verbally rated odor intensity on a scale of 1 (faint) to 10 (strong), and odor hedonic on a scale of negative 10 (strongly unpleasant) to positive 10 (strongly pleasant). Hedonic and intensity ratings (mean ± standard error) were 5.5 ± 0.39 and 4.9 ± 0.32, respectively, for clementine; −7.19 ± 0.33 and 7.1 ± 0.33, respectively, for isovaleric acid; and 0.00 and 0.00, respectively, for clear air.

Imaging

Functional MR imaging was performed on a 1.5-T system equipped with echo-planar imaging hardware from Advanced NMR (Wilmington, MA). Subjects lay supine in the magnet with their heads immobilized by a neck support, foam wedges, and a restraining band drawn tightly around the forehead. Scout images in the sagittal plane were acquired with parameters of 500/11 (TR/TE), a field of view of 24 cm, an imaging matrix of 256 × 192, and 5-mm contiguous sections. Eight anatomic images were acquired with parameters of 500/11, a field of view of 40 cm, an imaging matrix of 256 × 192, and 7-mm-thick sections with a 2-mm gap in an oblique coronal plane perpendicular to the intercommissural line, extending from the frontal pole anteriorly to the level of the mammillary bodies posteriorly (coronal plane posteriorly includes the posterior frontal lobe and anterior temporal lobe). Eighty activation images were collected at the same eight locations using an echo-planar gradient-echo sequence obtained with parameters of 1500/45/1, a flip angle of 60°, a field of view of 40 × 20 cm, an imaging matrix of 128 × 64, and 7-mm-thick sections with a 2-mm gap. An imaging trial consisted of two epochs: a baseline epoch, in which 40 baseline images were acquired for each section during a 40-second prestimulation period, during which clear air was administered; and an odor epoch, in which 40 more task images were acquired during 40 seconds of continuous odor presentation. In the clear air trials, clear air was the odorant, so that the subject received clear air in both epochs. For each study, there were two to four clementine trials, two to four IVA trials, and one to two clear air trials. Imaging trials for the 18 studies were combined into one data set that consisted of 50 trials of clementine, 47 trials of IVA, and 29 trials of clear air.

Data Analysis

First-order statistical parametric maps (SPMs) were created for each trial (Matlab, MathWorks, Natick, MA). For each trial, the first three images were discarded from the beginning of each series of baseline epochs and the first five images were discarded from the beginning of each series of odor epochs. For the baseline epochs, we routinely discard three images to provide sufficient time to account for variation in signal intensity owing to lack of a steady state in the echo-planar sequence. Five images were discarded from the beginning of the odorant epochs because of the delay in the onset of brain hemodynamic changes in response to a task (32). The remaining images from each epoch were median filtered (33). Trials were discarded if a change in position of the in-plane center of the mass exceeded 25% of the size of a voxel. In each trial, MR signal intensities when an odorant or clear air was presented were compared with MR signal intensities during baseline periods of clear air presentation, resulting in first-order SPMs for each trial.

The first-order SPMs and the anatomic images from individual subjects were transformed into a proportional three-dimensional grid defined by Talairach and Tournoux (34). This transformation was performed first by in-plane transformation and then by section interpolation. For in-plane transformation of each subject, the position of the anterior and posterior commissures, the edges of the cerebrum (right, left, superior, inferior), and the direction of the midline were found manually. These landmarks divided each section into six rectangles. Interpolation of these rectangles by linear (weighted) averaging created nine sections in Talairach space centered at $y = +57$, $+49$, $+40$, $+32$, $+23$, $+14$, $+5$, -4, and -12. Transformation into a uniform three-dimensional array allowed definition of regions of interest (ROIs) based on gyral and sulcal landmarks and Brodmann's areas (BAs) using rectangular volumes (polyhedra) of the atlas of Talairach and Tournoux (34). The rectangular volumes (approximately 8 × 8 × 8 mm, half-size of unit Talairach volume) were large enough to account for anatomic variability among subjects (35) and ensured reproducible coverage of areas of interest in a large number of subjects (smaller volumes would not represent the same anatomy in different brains).

In initial analyses, 23 ROIs in the frontal and temporal lobes in each hemisphere were defined by anatomy and Brodmann's areas. Voxels from the first-order SPMs were considered active if a Student's *t*-test was greater than or equal to 1.0 when signal intensities from images in the odor epochs were compared with signal intensities from images in the baseline epochs. An analysis of variance (ANOVA) of the mean number of active voxels was performed with odorant (clementine, IVA, or clear air)

Brain activation in response to the odorants clementine and isovaleric acid

Region	Odorant (Hemisphere)	Gyrus	Talairach Coordinates, *x/y/z* (mm)*
BA 8	Clementine (BH)	Superomedial aspect of superior frontal gyrus and middle third of middle frontal gyrus.	8.4/37/49
BA 32	Clementine (LH)†	Anterior paracingulate cortex, posteroinferior aspect of medial aspect of superior frontal gyrus.	17/35/18
	Isovaleric acid (LH)		
BA 46/9	Clementine (RH)	Lateral aspects of middle frontal gyrus and anterosuperior aspect of pars triangularis of inferior frontal gyrus along anterior half of inferior frontal sulcus.	33/35/23
	Isovaleric acid (RH)		
BA 6	Clementine (RH)†	Anterior aspect of precentral gyrus and posterior aspect of medial border of superior frontal gyrus.	19/2.6/52
	Isovaleric acid (BH)		
Insula	Clementine (BH) Isovaleric acid (RH)	Circular sulcus superior to long and short gyri of insula.	26/4.4/23

Note.—BA indicates Brodmann's area; LH, left hemisphere; RH, right hemisphere; BH, both hemispheres.

* Coordinates approximate center of region; *x* coordinates are positive (right hemisphere) and negative (left hemisphere).

† Lateralization reached statistical significance.

and brain ROIs as repeated measures. No main effects of odorant or interactions with a region were found. We investigated the possibility that the olfactory response occurs rapidly by examining only the first 16 images in an epoch, but again found no significant main effects or interactions (allowing for images discarded at the beginning of the epoch, 16 images represent approximately half the odorant epoch of 40 images). Reasons for the absence of significant effects include the number of ROIs explored and their arbitrary definition based on anatomy and Brodmann's areas, the relatively large size of some ROIs (ROIs ranged in size from 40 to 300 voxels) that might obscure small areas of activation, the off-on paradigm that is more sensitive to signal drift, and, in the case of the primary and secondary olfactory cortices, the signal degradation that can occur at the skull base due to magnetic susceptibility.

To further investigate brain regions for statistically significant activation in response to the odorants, we allowed the data to guide our selection of ROIs and applied a constraint of internal replication. We first divided the data set in half to simulate two experiments, providing a way to asses the reproducibility of our results. In the first half of the data set, candidate ROIs were identified on composite SPMs by comparing *t*-maps of clementine and IVA to *t*-maps of clear air trials. In the second half of the data set, odor-related activation in these ROIs was compared by using quantitative statistical comparisons. The data set was divided in half based on chronological order. The first data set came from the first studies of the five subjects studied twice and from four other subjects, and consisted of the first 25 clementine trials, the first 24 IVA trials, and the first 15 clear air trials. The second data set came from the second studies of the five subjects studied twice and from four different subjects, and consisted of 25 clementine trials, 23 IVA trials, and 14 clear air trials. For the five subjects studied twice, then, the first studies from each of the subjects were in the first half of the data set, and the second studies were in the second half of the data set, providing another level of internal replication. Both halves of the data set, including SPMs and anatomic images, were transformed into Talairach space as described above.

To identify candidate ROIs, second-order composite SPMs (*t*-tests using the *t* values obtained for each voxel from the first-order SPMs as the dependent variable) were created by using the first half of the data set only. One composite SPM was created by identifying voxels that had significantly more activation ($t > 1.7$) in clementine versus clear air epochs than in clear air versus clear air epochs, and another composite SPM was created by identifying voxels that were significantly more active in IVA versus clear air epochs than in clear air versus clear air epochs (the arbitrary *t* value of 1.7 provided *t*-maps with activation centered primarily in gray matter and not in ventricles or white matter). Activated voxels on these composite maps were used to identify 11 candidate ROIs: superior-lateral aspect of BA 9, 10; BA 8; BA 32; BA 46, lateral 9; BA 44, 45; BA 6; insula; BA 22; BA 4; BA 24; and medial-inferior aspect of BA 9, 10. Regions were evaluated bilaterally even if activation was present on one side only.

The 11 ROIs identified from the first half of the data set were applied to the first-order *t*-maps from the second half of the data. Voxels from these *t*-maps were considered active if a Student's *t*-test was greater than or equal to 1.0 in comparisons of signal intensities from images in the odor epochs with signal intensities from images in the baseline epochs. A *t* value of 1.0 is within the accepted range of *t*-value distributions to increase detection of true-positive activation and to decrease detection of false-positive activation (36). The number of active voxels within each ROI during clementine versus clear air epochs and during IVA versus clear air epochs, respectively, were then compared with the number of active voxels during clear air versus clear air epochs by independent *t*-tests, with a criterion *P* value of .05. For a region to be considered active, then, it must first have been identified on the composite activation maps as showing greater activation during odor trials than during clear air trials on the first half of the data set, and then must have included statistically significantly more activated voxels during odor trials than during clear air trials on the second half of the data set. After active regions were identified, subsequent secondary analyses included a region-by-region ANOVA to test for laterality effects; paired *t*-tests directly comparing IVA and clementine in active areas; and correlation analysis between hedonic ratings, intensity ratings, and the number of active voxels using the Pearson *r* statistic.

Results

Five regions (see Table) showed statistically significant activation. Cortical activation in response to clementine (Fig 1) was found in BA 8 bilaterally ($P = .02$ in the right hemisphere, $P = .01$ in the left hemi-

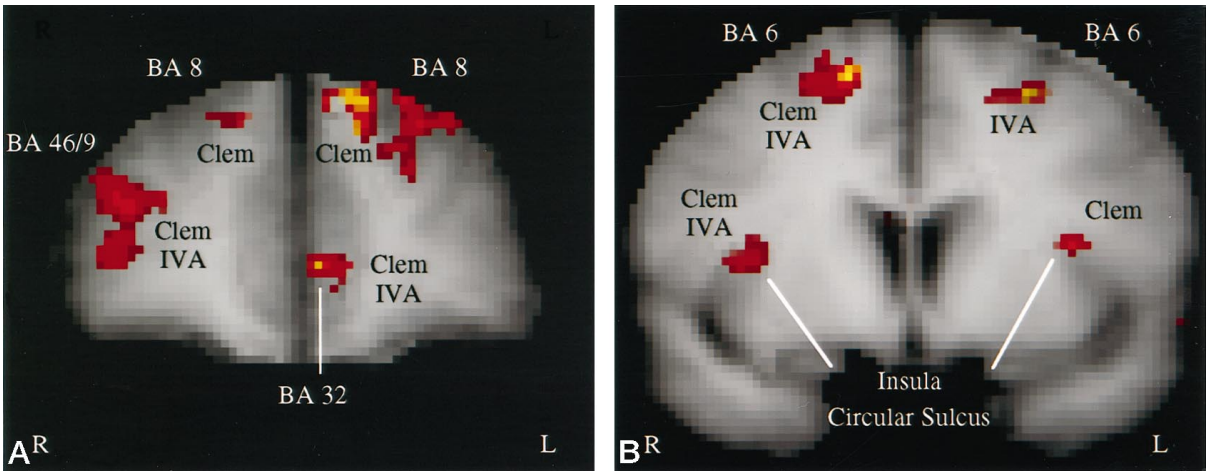

FIG 1. Regional brain activation in response to clementine (Clem) and isovaleric acid (IVA).

A and *B*, Voxels from composite statistical parametric maps were selected to illustrate activation patterns seen in the quantitative statistical comparisons (Table). The *t*-value threshold was 1.7; red voxels ranged from 1.7 to 2.5, orange voxels from 2.5 to 2.9, and yellow voxels from 2.9 to 3.7. Active voxels were overlaid on composite anatomic T1-weighted images (667/13/1). The center of the section along the *y*-axis is at 40 in *A* and at 5 in *B*. For clementine, activation is seen in right BA 46/9, in left BA 32, in BA 8 bilaterally, in right BA 6, and in the circular sulcus/insula bilaterally. IVA resulted in activation in right BA 46/9, in left BA 32, in right BA 6, and in the right circular sulcus/insula. Other areas with voxels having a *t*-value threshold above 1.7 on composite images but that did not meet statistical significance are not shown.

sphere); in BA 32 in the left hemisphere ($P = .001$); in BA 46/9 (lateral aspect of BA 9) in the right hemisphere ($P = .05$); in BA 6 in the right hemisphere ($P < .02$); and in the insula bilaterally ($P = .02$ in the right insula, $P = .05$ in the left insula). IVA (Fig 1) elicited significant activation in BA 32 in the left hemisphere ($P = .006$); in BA 46/9 in the right hemisphere ($P = .02$); in BA 6 bilaterally ($P = .001$ in the right hemisphere and $P = .018$ in the left hemisphere); and in the right insula ($P = .001$). Although the medial temporal lobes and orbitofrontal cortices did not meet the criteria required to be considered candidate ROIs, they were examined for quantitative activation in the second half of the data because they have been implicated as the primary and secondary olfactory cortices. No odor-related activation was detected in these areas ($P > .8$).

To evaluate the statistical significance of the laterality in each of the regions showing significant odor-related activation, we performed a region-by-region ANOVA with odorant (clementine versus clear air or IVA versus clear air) and hemisphere as factors. Significant interactions between odorant and hemisphere (Table) were found with clementine in BA 6, right hemisphere greater than left ($P = .05$), and with clementine in BA 32, left hemisphere greater than right ($P = .001$). Although significant activation was seen in the right insula and in the left BA 32 with IVA and in the right BA 46/9 for IVA and clementine, the contralateral regions (left insula, right BA 32, and left BA 46/9) approached significance closely enough to nullify a hemispheric interaction in the ANOVA analysis ($P = .126$ for the left insula with IVA; $P = .11$ for the right BA 32 with IVA; $P = .13$ for the left BA 46/9, $P = .09$ for the right BA 46/9).

To directly evaluate possible differences between IVA-related and clementine-related activations, we compared the number of active voxels under the two conditions in each of the areas that showed odor-related activity. Clementine trials showed significantly more activity than IVA trials in the left insula ($P = .01$) and there was a trend in the same direction in the left BA 32 ($P = .068$). IVA trials resulted in significantly more activation than clementine trials in the left BA 6 ($P = .045$).

Correlation analysis was performed on hedonic ratings, intensity ratings, and the mean number of active voxels in the five ROIs during clementine and IVA administration. Significance criterion was set at $P = .01$ to correct for multiple comparisons. Hedonic and intensity ratings during clementine and IVA administration were strongly correlated ($r = .67$, $P < .001$ for clementine; $r = -.871$, $P < .001$ for IVA). Mean voxel count in the left insula during IVA administration was correlated with hedonic ratings ($r = -.46$, $P = .002$); activation was greater when subjective ratings of unpleasantness were more intense. We found a correlation between IVA mean voxel count and intensity in the left insula ($r = .40$, $P = .005$). Clementine mean voxel count was correlated with intensity ratings in the left BA 46/9 ($r = -.38$, $P = .01$). The negative correlation indicates that activation was lower when subjects perceived the odor as more intense.

Discussion

Odor-related activation was found in frontal lobe sites (Table), confirming previous cerebral metabolic, EEG, and subdural EEG studies that found frontal activation after olfactory simulation (8, 22, 23, 37). Because odorants are known to effect changes in cognitive, perceptual, and motor function (10–12, 18, 27, 38), the five brain regions identified in this study

most likely represent additional secondary or higher-order olfactory sites that link olfactory networks with other brain processes. Activation in the motor association areas BA 6 and BA 8 implicates these as regions that modulate motor responses to odors, and also provides functional anatomic support to a study showing modification of EEG patterns during visual-motor tasks when odorants are presented (11). BA 46/9 (middle and inferior frontal gyri of the dorsolateral prefrontal cortex) was activated with both clementine and IVA, and the left BA 46/9 activity was correlated with intensity ratings to clementine. Since components of memory processing have been ascribed to the dorsolateral prefrontal cortex, activation in this region might represent processing of olfactory memories stimulated by the repeated presentation of odorants or by past personal experience with these or similar odors (39–41). Insula activation is consistent with rat and primate studies showing axonal projections from primary and secondary olfactory cortical areas to the insula (3, 42) and with PET data, indicating a probable insular response to odorants (8). Another chemical sense, gustation, has also been shown to activate insula regions (43).

Direct comparison of the two odorants suggests the possibility of regional brain specialization depending on hedonic quality. In the left insula, the pleasant odorant clementine produced more activity than the unpleasant odorant IVA, and in the left BA 6, IVA produced more activity than clementine. With clementine showing left hemisphere dominance in BA 32 and right hemisphere dominance in BA 6, our study indicates a hemispheric specialization in frontal lobe areas involved in higher-order olfactory processing, consonant with previous PET imaging findings (8). Emotions can also produce asymmetric hemispheric responses (44, 45) and may contribute to the asymmetric activation, especially in BA 32. Located in the paracingulate cortex and medial aspect of the superior frontal gyrus, BA 32 is a paralimbic region richly connected with the primary olfactory cortex in the medial temporal lobe and with the limbic system (3), and may link brain regions involved with emotion. Additional study with more than one exemplar of pleasant and unpleasant odors will help determine whether different brain activation patterns to clementine and IVA are class-specific (based on differences in hedonic value) or are exemplar-specific (based on differences between clementine and IVA that might not be related to hedonic value).

Activation of these frontal areas does not define completely the brain's response to olfactory stimuli. Anatomic and PET studies have shown that the medial temporal lobe and the orbitofrontal cortices are important in olfactory processing (2, 8). No activation was found in these areas, possibly because they are adjacent to bone and air-containing structures that result in marked magnetic susceptibility artifacts (46). We also cannot exclude potential olfactory processing sites in the parietal and occipital lobes, since these regions were not imaged.

We have used quantitative statistical methods to evaluate activation in brain ROIs after presentation of different odors. Such a methodological approach is relatively straightforward when previous studies provide a basis for the selection of appropriate ROIs. It is important, however, for imaging methods to identify task-related activity in regions not previously known to be associated with a task. Difficult methodological questions arise when much or all of the brain is imaged, as can now be accomplished routinely. If all possible regions are considered, the data analysis is subject either to type I statistical errors or to overly conservative correction to protect against such errors. In the present study, we adopted an established approach to data analysis. We divided the data set in half to simulate two experiments, providing a way to assess internal replication of our results. Another level of internal replication was built into the experiment by studying five subjects twice. We applied conventional SPM methods to the first half of our data set to identify candidate ROIs. Task-related activity was then evaluated in the ROIs by applying them to the second half of the data set and using quantitative statistical procedures. This approach provides a conservative way to search systematically for brain regions not previously known to be involved in a particular task. A potential weakness is the loss of statistical power that can occur when the sample is divided in half.

Conclusion

Frontal activation of the human cerebral cortex occurs in response to odors. Odors with a positive hedonic value (pleasant odor, clementine) and a negative hedonic value (unpleasant odor, isovaleric acid) activated four frontal sites: BA 32, BA 46/9, BA 6, and the insula. Only clementine resulted in activation in BA 8 and in lateralized activation in BA 6 (right) and BA 32 (left). These results suggest that frontal activation may represent brain processes linked to olfactory networks, and that there may be regional specialization based on odorant hedonic value.

References

1. Kier EL. **The cerebral ventricles: a phylogenetic and ontogenetic study.** In: Newton TH, Potts DG, eds. *Radiology of the Skull and Brain.* St Louis: Mosby; 1977:2787–2914
2. Takagi SF. **Olfactory frontal cortex and multiple olfactory processing in primates.** In: Peters A, Jones EG, eds. *Cerebral Cortex.* New York: Plenum; 1991:133–152
3. Price JL, Carmichael ST, Carnes KM, Clugnet M-C, Kuroda M, Ray JP. **Olfactory input to the prefrontal cortex.** In: Davis JL, Eichenbaum H, eds. *Olfaction: A Model System for Computational Neuroscience.* Cambridge, MA: MIT Press; 1991:101–120
4. Jones-Gotman M, Zatorre RJ. **Olfactory identification deficits in patients with focal cerebral excision.** *Neuropsychologia* 1988;26: 387–400
5. Jones-Gotman M, Zatorre RJ. **Odor recognition memory in humans: role of right temporal and orbitofrontal regions.** *Brain Cogn* 1993;22:182–198
6. Eskenazi B, Cain WS, Novelly RA, Friend KB. **Olfactory functioning in temporal lobectomy patients.** *Neuropsychologia* 1983;21:365–374

7. Eskenazi B, Cain WS, Novelly RA, Friend KB. **Odor perception in temporal lobe epilepsy patients with and without temporal lobectomy.** *Neuropsychologia* 1986;24:553–562
8. Zatorre RJ, Jones-Gotman M, Evans AC, Meyer E. **Functional localization and lateralization of human olfactory cortex.** *Nature* 1992;360:339–340
9. Lorig T. **Cognitive and non-cognitive effects of odour exposure: electrophysiological and behavioral evidence.** In: Van Toller S, Dodd GH, eds. *Fragrance: The Psychology and Biology of Perfume.* New York: Elsevier; 1992:161–173
10. Warm JS, Dember WN, Parasuranam R. **Effects of olfactory stimulation on performance and stress in a visual sustained attention task.** *J Soc Cosmet Chem* 1991;42:199–210
11. Lorig TS, Huffman E, DeMartino A, Demarco J. **The effects of low concentration odors on EEG activity and behavior.** *J Psychophysiol* 1991;5:69–77
12. Ludvigson HW, Rottman TR. **Effects of ambient odors of lavender and cloves on cognition memory, affect and mood.** *Chem Senses* 1989;14:525–536
13. Rotton J. **Affective and cognitive consequences of malodorous pollution.** *Basic Appl Soc Psychol* 1983;4:171–191
14. Knasko SC. **Ambient odor's effect on creativity, mood and perceived health.** *Chem Senses* 1992;17:27–35
15. Gulas CS, Bloch PH. **Right under our noses: ambient scent and consumer responses.** *J Bus Psychol* 1995;10:87–98
16. Mitchell DJ, Kahn BE, Knasko SC. **There's something in the air: effects of congruent or incongruent ambient odor on consumer decision making.** *J Consum Res* 1995;22:229–238
17. Spangenberg ER, Crowley AE, Henderson PW. **Improving the store environment: do olfactory cues affect evaluations and behaviors?** *J Market* 1996;60:67–80
18. Baron RA. **"Sweet smell of success"? The impact of pleasant artificial scents on evaluation of job applicants.** *J Appl Psychol* 1983;68:709–713
19. Baron RA. **Environmentally induced positive affect: its impact on self-efficacy, task performance, negotiation, and conflict.** *J Appl Soc Psychol* 1990;20:368–384
20. Baron RA, Thomley J. **A whiff of reality: positive affect as a potential mediator of the effects of pleasant fragrances on task performance and helping.** *Environ Behav* 1994;26:766–784
21. Baron RA, Bronfen MI. **A whiff of reality: empirical evidence concerning the effects of pleasant fragrances on work-related behavior.** *J Appl Soc Psychol* 1994;24:1179–1203
22. Klemm WR, Lutes SD, Hendrix DV, Warrenburg S. **Topographical EEG maps of human responses to odors.** *Chem Senses* 1992;17:347–361
23. Lorig TS, Mayer TS, Moore FH, Warrenbure S. **Visual event-related potentials during odor labeling.** *Chem Senses* 1993;118:379–387
24. Miltner W, Matjak M, Braun C, Diekmann H, Brody S. **Emotional qualities of odors and their influence on the startle reflex in humans.** *Psychophysiology* 1994;31:107–110
25. Ehrlichman H, Brown S, Zhu J, Warrenburg S. **Startle reflex modulation during exposure to pleasant and unpleasant odors.** *Psychophysiology* 1995;32:150–154
26. Ehrlichman H, Kuhl SB, Zhu J, Warrenburg S. **Startle reflex modulation by pleasant and unpleasant odors in a between-subjects design.** *Psychophysiology* 1997:34:716–729
27. Ehrlichman H, Bastone L. **The use of odour in the study of emotion.** In: Toller SV, Dodd GH, eds. *Fragrance: The Psychology and Biology of Perfume.* New York, Elsevier; 1992:410–438
28. Ehrlichman H, Bastone L. **Olfaction and emotion.** In: Serby MJ, Chobor KL, eds. *Science of Olfaction.* New York: Springer; 1992:410–438
29. Warren CB, Warrenburg S. **Mood benefits of fragrance.** *Perfumer Flavorist* 1993;18:9–16
30 Todrank J, Byrnes D, Wrzesniewski A, Rozin P. **Odors can change preferences for people in photographs: a cross-modal evaluative conditioning study with olfactory USs and visual CSs.** *Learning Motivation* 1995;26:116–140
31. Knasko SC. **Pleasant odors and congruency: effects on approach behavior.** *Chem Senses* 1995;20:479–487
32. Kwong KK, Belliveau JW, Chesler DA, et al. **Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation.** *Proc Natl Acad Sci USA* 1992;89:5675–5679
33. Pugh KR, Shaywitz BA, Shaywitz SE, et al. **Cerebral organization of component processes in reading.** *Brain* 1996;119:1221–1238
34. Talairach J, Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain.* New York: Thieme; 1988
35. Andreasen NC, Flashman L, Flaum M, et al. **Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging.** *JAMA* 1994;272:1763–1769
36. Constable RT, Skudlarski P, Mencl E, et al. **Quantifying and comparing region-of-interest activation patterns in functional brain MR imaging: methodology considerations.** *Magn Reson Imaging* 1998;16:289–300
37. Davidson RJ, Fox NA. **Asymmetrical brain activity discriminates between positive and negative affective stimuli in human infants.** *Science* 1982;218:1235–1237
38. Yoshida M. **Studies of psychometric classification of odors.** *Psychol Res* 1964;6:145–154
39. Grasby PM, Frith CD, Friston KJ, Bench C, Frackowiak RSJ, Dolan RJ. **Functional mapping of brain areas implicated in auditory-verbal memory function.** *Brain* 1993;116:1–20
40. Jonides J, Smith EE, Koeppe RA, Awh E, Nimoshima S, Mintun MA. **Spatial working memory in humans as revealed by PET.** *Nature* 1993;363:623–625
41. Alkire MT, Haier RJ, Fallon JH, Barker SJ. **PET imaging of conscious and unconscious verbal memory.** *J Consciousness Stud* 1996;3:448–462
42. Mesulam MM, Mufson EJ. **The insula of reil in man and monkey.** In: Peters A, Jones EG, eds. *Cerebral Cortex.* New York: Plenum Press; 1990:179–226
43. Kinomura S, Kawashima R, Yamada K, et al. **Functional anatomy of taste perception in the human brain studied with positron emission tomography.** *Brain Res* 1994;659:263–266
44. Hughes JR, Hendrix DE, Wetzel N, Johnston JW. **Correlations between electrophysiological activity from the human olfactory bulb and subjective responses to odoriferous stimuli.** In: Pfaffman C, ed. *Olfaction and Taste: III.* New York: Rockefeller University Press; 1969
45. Morris JS, Frith CD, Perrett DI, et al. **A differential neural response in the human amygdala to fearful and happy facial expressions.** *Nature* 1996;383:812–815
46. Yang QX, Dardzinski BJ, Shizhe L, Eslinger PJ, Smith MB. **Multi-gradient echo with susceptibility inhomogeneity compensation (MGESIC): demonstration of fMRI in the olfactory cortex at 3.0 T.** *Magn Reson Med* 1997;37:331–335