Passive Perception of Odors and Semantic Circuits

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Abstract: The sense of smell has been traditionally assumed to be different from other sensory modalities in that odors are encoded perceptually, without a semantic component. Recent findings of improved odor memory upon encoding with verbal cues question this view. Furthermore, familiar odors are easier to remember and discriminate than are unfamiliar ones, and odor familiarity is reported to predict odor naming. To investigate whether familiar odors are processed by different cerebral structures than those that process unfamiliar odors, ¹⁵O H₂O-positron emission tomography (PET) measurements of cerebral blood flow were carried out in 14 healthy men. The task was passive, birhinal, smelling of familiar odors (FAM), unfamiliar odors (uFAM), and odorless air (AIR). Significant activations ($P < 0.05$) were calculated using the contrasts FAM–AIR, uFAM–AIR, and FAM–uFAM, and deactivations running these contrasts in the opposite direction. In relation to AIR, both FAM and uFAM activated amygdala, piriform cortex, and parts of anterior cingulate cortex. FAM activated, in addition, left frontal cortex (Brodmann's areas 44,45,47), left parietal cortex incorporating precuneus, and right parahippocampus. Clusters covering parahippocampus and precuneus were observed also in FAM–uFAM. The activation of left frontal cortex and right parahippocampus was positively correlated with familiarity ratings. Smelling of familiar but not unfamiliar odorants seems to engage cerebral circuits mediating memory and language functions, in addition to the engagement of olfactory cortex. Already the most elemental form of odor processing, passive perception thus seems to engage semantic circuits. This is achieved by the ability of odorants to immediately elicit associations and judgments of odor characteristics. *Hum. Brain Mapp.* 21:271–278, 2004. © 2004 Wiley-Liss, Inc.

Key words: PET; olfaction; odor familiarity; semantic association; odor memory

INTRODUCTION

One of the most striking features of the sense of smell is the poor ability of odors to cue correct retrieval of odor names. Subjects frequently judge an odor as familiar but are unable to provide its label correctly (the “tip-of-the-nose” phenomenon). Furthermore, an individual can encode the same odor differently on successive presentations, and different subjects frequently generate different labels for the same odors [Engen, 1982]. Engen and Ross [1973] therefore suggested that unlike visual and auditory stimuli, odors are encoded “in a holistic, perceptual manner,” without involving circuits traditionally attributed to semantic processing (i.e., Brodmann's area [BA] 44, 45, and 47 in the frontal cortex, and BA 37 in the inferior temporal cortex) [see Bookheimer et al., 1995; Buchel et al., 1998; Petersen et al., 1988; Vanderberghe et al., 1996]. This view, however, has

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been challenged in more recent works. It has been shown that familiar odors are easier to remember and discriminate than are unfamiliar [Savic and Berglund, 2000; Schab and Crowder, 1995]. Royet et al. [1999] demonstrated recently that judgment of odor familiarity involves left inferior frontal gyrus, an area that is usually associated with semantic association [Bookheimer et al., 1995; Petersen et al., 1988; Ricci et al., 1999; Vandenberghe et al., 1996]. They also found that odor familiarity is a strong predictor of odor naming [Royet et al., 1999], which raises the question of whether familiar odors could be mediated by different neuronal circuits than those mediating unfamiliar odors. Possibly, familiar odors are capable of generating a verbal code already at the most elemental level of olfactory processing, i.e., passive perception. To investigate these issues, a series of positron emission tomography (PET) experiments was carried out measuring regional cerebral blood flow (rCBF) during passive, birhinal smelling of four familiar and four unfamiliar odors. Smelling of odorless air was the baseline condition. The study served as a further extension of previous efforts [Bengtsson et al., 2001; Savic et al., 2000, 2001; Savic, 2002] to evaluate the contribution of various cerebral structures on given aspects of olfactory perception, in this case odor familiarity.

MATERIALS AND METHODS

Subjects

Fourteen right-handed, nonsmoking, male subjects (age 23–32 years, education 13–17 years) participated in the study. All were healthy, had a normal otorhinological status (assessed before inclusion in the study) and were free of nasal congestion at the time of the study. They had normal olfactory thresholds [Eichenbaum et al., 1983]. The study was approved by the local ethics and safety radiation committees.

Odorous Compounds

From a kit of 50 odorous compounds, we selected four familiar and four unfamiliar odors, matched for odor intensity, pleasantness, and irritability. These odors were rated with a 100-mm bipolar visual analogue scale (VAS) [Jones-Gottman and Zatorre, 1988; Savic and Berglund, 2000; Savic et al., 2000] by 20 other subjects before the PET experiments. To guide the familiarity ratings, subjects were told that 0–33 mm signified a low familiarity score, 33–66 mm a medium score, and 67–100 mm a high score. An odor was defined as highly familiar if the subject could categorize it verbally or associate a verbal label with its perception. A medium score was given if the odor elicited associations or knowledge about it, whereas the score was defined as low if the subject had no or vague perception of familiarity. This three stage grading (0–33 mm, 33–66 mm, and 66–100 mm) was also used for intensity, irritability and pleasantness [Savic and Berglund, 2000].

Because of the coupling and positive correlation between odor familiarity and pleasantness [Distel et al., 1999], no

extremely unfamiliar odors could be selected for the PET study. The odors were therefore categorized as familiar if the average rating score on the 100-mm VAS scale was 70 mm or above, and unfamiliar if it was below 70 mm. The four familiar odorants selected for the PET experiments were grapefruit, camphor, coffee, and linseed oil. The four unfamiliar odorants were butanol, eugenol, lavender oil, and cedar oil. To minimize trigeminal stimulation, the concentration of butanol was 1%, and camphor 10%. Both compounds were diluted with distilled water. The other odorants were used without dilution.

Each odorant used was evaluated for possible stimulation of the trigeminal nerve by testing four anosmic patients according to the method of Wysocki et al. [1997]. Butanol elicited trigeminal sensations in one patient. The remaining three reported no sensations in association with any of the odorants.

Experimental Procedure

PET scans were conducted as described previously but using [^{15}O]H₂O as tracer [Savic et al., 2000]. Three different conditions were applied: (1) passive smelling of four familiar odors (FAM); (2) passive smelling of four unfamiliar odors (uFAM); and (3) passive smelling of odorless air (AIR).

During FAM and uFAM, each of the four odorants was presented in a glass bottle for 15 sec about 10 mm away from the nostrils, with an inter-presentation interval of 5 sec, during which the subject breathed the air in the scanner room. We used several odorants during the same scan to provide a better representation of the respective odor type, which otherwise would be confined to the specific characteristics of one item. Each presentation started 5 sec after the bolus injection, and was indicated by touching the subject's right index finger. One PET session lasted 80 sec [Savic et al., 2000, 2001; Savic, 2002]. During AIR the identical on-off mode was applied, but the stimulus was odorless air. To match the number of presentations, the AIR scans were repeated three times. Scans with FAM and uFAM were carried out only once, to avoid influence of recognition memory.

The experiments were part of a larger study including other olfactory tasks, which will be presented elsewhere. Subjects received therefore in total 12 bolus injections containing about 12 mCi of ^{15}O -water, of which five were included in the present study. Conditions were randomly ordered across subjects and scans.

The general instruction to subjects was that they would smell an odor or odorless air. They were told to breathe passively (i.e., not sniff). This procedure was trained at several occasions before the PET experiments. The subjects were also prompted to concentrate on the perception of the presented item, without trying to categorize or label it. They were uninformed about the identity/category of the item(s), or the order of conditions. After each scan, however, they were asked whether or not they smelled any odor.

Figure 1.

Respiratory parameters. Vertical axes indicate % change of amplitude and frequency during the scanning sessions, in relation to the 2-min baseline period before the scans of the respective condition. Bars express mean and standard error of the mean (SEM). No significant difference was found between familiar and unfamiliar odorants.

During the scans, we recorded respiratory frequency (breaths/min) and amplitude using a strain gauge around the lower thorax (Comair AB, Stockholm, Sweden). Relative change in frequency and amplitude, as well as their product (which was used as an index of change in respiratory volume), was calculated during each scan in relation to the corresponding base line data collected during the 2 min of resting condition preceding the same scan (Fig. 1). The formula applied was:

$$\frac{(\text{respiratory parameter during a scan} - \text{mean corresponding prescan value})}{(\text{mean corresponding prescan value})}$$

where the respiratory parameter was the mean frequency, the mean amplitude, or the mean respiratory index. The possible differences in these values during FAM, uFAM, and AIR were then tested in separate repeated-measures ANOVA, ($P < 0.05$).

After PET measurements, the subjects scored each odor for familiarity, pleasantness, intensity, and irritability using the visual analogue scale as described above (Fig. 2). The ratings of the two categories of odorants were compared using repeated measurements ANOVA ($P < 0.05$).

Image Analysis

The relative rCBF was calculated according to Fox et al. [1984], including PET data during 60 sec after onset of acquisition. PET images were reconstructed in a 3D mode, with a 10-mm Gaussian filter, corrected for possible shift

[Woods et al., 1992], and anatomically standardized to the normal brain of the Computerized Brain Atlas [Roland et al., 1994], using the individual magnetic resonance images. The mean rCBF value was arbitrarily set to a flow value of 50 ml/100mL/min.

Significant increases in rCBF during odor stimuli in relation to AIR were defined as activations, (contrast FAM–AIR, uFAM–AIR), and the odor-stimulus associated decreases as deactivations (AIR–FAM and AIR–uFAM).

The contrasts were tested with the general linear statistics, and employed in the cluster model of Ledberg et al. [1998]. The degrees of freedom were 55, because scans not related to the present study were excluded from statistical analysis. The z -threshold was 3.1 and the minimum cluster size was 0.8 cm^3 ($P < 0.05$). Location of significant clusters were determined according to Talairach's coordinates in relation to the computerized brain atlas, and the cytoarchitectonic areas [Schleicher et al., 1999].

RESULTS

Psychophysics

Odors assigned as FAM were judged to be significantly more familiar ($P = 0.0002$) than the odors assigned as uFAM (Fig. 2). During 33 of the 56 rating occasions of familiar odors, subjects automatically labeled the odor. The corresponding number for unfamiliar odors was two. No significant difference was observed in the ratings of odor pleasantness ($P = 0.201$), intensity ($P = 0.051$), or irritability ($P = 0.213$). Changes in respiratory frequency and amplitude were similar during smelling of familiar and unfamiliar odors (Fig. 1), as was the calculated changes in respiratory index (frequency $\times$ amplitude).

Figure 2.

Odor ratings. Vertical axes indicate visual analogue scale (VAS) in mm. Bars express mean and standard deviation (SD). NS, nonsignificant; *** $P < 0.001$

Figure 3.

Activations and deactivations with respective type of odorants. Similarities and dissimilarities between FAM and uFAM. **A:** Top: activations with familiar odorants (FAM vs. AIR) and unfamiliar odorants (uFAM vs. AIR). Bottom: deactivations with familiar (AIR vs. FAM) and unfamiliar (AIR vs. uFAM) odorants. **B:** Top: clusters activated during smelling of familiar odorants (FAM vs. AIR) in addition to those shown in A. Right, standard MR brain with cytoarchitectonic BA 44 (red) and 45 (blue), retrieved by the human brain atlas program; illustrates engagement of areas mediating semantic functions. Bottom: clusters activated during smelling of familiar odorants but not unfamiliar odorants (FAM vs. uFAM). Activated clusters are superimposed on a standard brain. The Sokoloff's color scale illustrates z-values. The clusters were thresholded at $z = 3.1$, cluster size $< 0.8 \text{ cm}^3$ ($P < 0.05$). Subject's right side is to the left in the image. Talairach's coordinates are given.

Activations

Both FAM and uFAM activated the amygdala and piriform cortex and parts of the anterior cingulate cortex (Fig. 3A). The FAM odors activated, in addition, left frontal lobe, left parietal cortex including precuneus, and right parahippocampal gyrus, (Fig.3B, Table I). The left frontal activation encompassed a major portion of area 47 and portions of area 44 and 45, according to the corresponding cytoarchitectonic regions of the computerized brain atlas [Amunts et al., 1999; Schleicher et al., 1999].

Deactivations

Deactivation of parietal cortex was found with FAM, as well as uFAM. There was an additional deactivation of right frontal cortex and left lingual gyrus with uFAM and left cerebellum with FAM (Fig. 3A, Table II).

Comparison between FAM and uFAM

Contrasting familiar and unfamiliar odorants with each other (FAM–uFAM) showed clusters in the right parahippocampal gyrus, right middle and inferior temporal gyrus, and in the left parietal cortex covering precuneus (Fig. 3B,

Table III). Running the contrast in the opposite direction (uFAM–FAM) revealed only a cluster in the right parietal lobe, which overlapped with the cluster generated by AIR vs. FAM (Table II), and was thus due to a deactivation by FAM rather than to a more pronounced activation with uFAM.

Post-Hoc Analyses

We hypothesized that the confrontation of a recognizable odorant could lead to immediate match of the odor percept with the previously stored information, eliciting recognition and a covert association to a semantic evocation with that odor. To test this hypothesis, the degree of perceived odor familiarity was correlated with the degree of activation of the parahippocampal gyrus and inferior frontal gyrus (BA 47) using the clusters generated by FAM–AIR and Pearson's regression statistics ($P < 0.05$). The input data consisted of the change in normalized rCBF in the respective VOI during FAM and uFAM in relation to AIR, (FAM–AIR, uFAM–AIR), and the familiarity score (mean of four odorants) for the respective odor type (FAM, uFAM) in each subject. The regression analysis showed that familiarity ratings were positively correlated to both the parahippocampal ($r = 0.59$,

TABLE I. Activation with familiar and unfamiliar odors

Region	Z score (mean)	Size (cm ³)	Coordinates		
			<i>x</i>	<i>y</i>	<i>z</i>
FAM vs. AIR					
L amygdala + piriform cortex	4.1	5.5	−22	0	−10
R amygdala + piriform + anterior cingulate cortex	3.9	4.8	19	4	−10
L frontal lobe ^a					
Inferior frontal gyrus	3.3	1.1	−37	28	1
BA 44,45	3.1	0.8	−40	2	18
R parahippocampal gyrus	3.4	1.6	16	−33	2
L parietal cortex covering precuneus	3.6	1.6	−24	−82	39
uFAM vs. AIR					
R amygdala + piriform cortex	3.6	2.5	20	2	−11
L amygdala + piriform cortex	3.9	4.5	−24	2	−9
Anterior cingulate cortex	4.6	1.0	−5	40	−7

^a Two separate clusters.

FAM, familiar odors; L, left; R, right; uFAM, unfamiliar odors.

$P = 0.001$; Fig. 4A), and the left frontal lobe activation ($r = 0.56$, $P = 0.001$; Fig. 4B). We also tested for possible correlation between the intensity ratings and the activations in the left frontal lobe cluster. The rationale was the observed tendency for different intensity ratings between FAM and uFAM odorants, and our previous finding that tasks involving odor intensity engage insular cortex adjacent to the inferior frontal lobe. No significant correlation, however, was observed.

DISCUSSION

The present experiments were designed to investigate whether the cerebral circuits processing passive perception of odors differ when the stimulus is familiar compared to unfamiliar. Of particular interest was to analyze whether cerebral circuits that are engaged in semantic associations to visual, auditory, or somatosensory stimuli [Bookheimer et al., 1995; Ricci et al., 1999; Petersen et al., 1988, Vandenberghe et al., 1996] may become recruited also when we passively smell odors.

At variance to the previous reports, our subjects were not prompted to judge odors during the scan, and all the judgments of odor characteristics were conducted after the PET measurements. We went down in the hierarchical complexity of the olfactory tasks, investigating the possibility of an automatic, sensation-driven engagement of semantic and recognition memory networks, rather than evaluating the effects of specific cognitive tasks.

In accordance with several previous reports, [Savic et al., 2000; Sobel et al., 1998; Zald et al., 1997; Zatorre et al., 1992], smelling of odors activated the amygdala + piriform, and cingulate cortices. We found, however, that when the stimulus consisted of only familiar odors, there was an additional activation of left frontal cortex (BA 44,45,47), left parietal cortex covering precuneus, and right parahippocampus, (Fig. 3B). The two latter clusters appeared also when FAM was contrasted with uFAM (Table III). Furthermore, the familiarity rating was correlated with left inferior frontal as well as the parahippocampal activation.

TABLE II. Deactivation with familiar and unfamiliar odors

Region	Z score (mean)	Size (cm ³)	Coordinates		
			<i>x</i>	<i>y</i>	<i>z</i>
AIR vs. FAM					
R parietal cortex	3.5	1.7	30	−40	42
L cerebellum	3.6	0.9	−19	−39	−26
AIR vs. uFAM					
R parietal cortex	3.1	0.9	49	−51	36
L lingular gyrus	3.2	1.4	−18	−83	−6
R frontal cortex	3.2	1.4	40	17	6

FAM, familiar odors; R, right; L, left; uFAM, unfamiliar odors.

TABLE III. Difference between activation with familiar and unfamiliar odors

Region	Z score (mean)	Size (cm ³)	Coordinates		
			<i>x</i>	<i>y</i>	<i>z</i>
FAM vs. uFAM					
R parahippocampal gyrus	3.3	0.9	15	−37	−3
R middle, inferior temporal gyrus	3.2	0.9	61	−45	2
L parietal cortex covering precuneus	3.4	2.0	−27	−79	40
uFAM vs. FAM					
R parietal cortex	3.6	1.6	34	−31	40

FAM, familiar odors; R, right; L, left; uFAM, unfamiliar odors.

Figure 4.

Correlation between familiarity ratings and activation in the respective VOI. **A:** Right parahippocampus VOI. **B:** Left inferior frontal VOI. The y-axis denotes difference in normalized rCBF between the respective activation (FAM, uFAM) and baseline condition (AIR). Numerical values indicate mean difference in normalized rCBF from the entire VOI. The x-axis shows familiarity ratings according to the visual analogue scale (in mm). Numerical values represent means of four familiar and four unfamiliar odorants for each subject. The respective VOI was determined from the respective cluster obtained in FAM vs. AIR. There are two values for each subject (one for uFAM and one for FAM), thus 28 elements. Omitting outliers does not change the results, although correlations become reduced slightly ($r = 0.42$ and $P = 0.03$ for regression in right parahippocampus VOI, and $r = 0.47$, $P = 0.02$ for the regression in left frontal VOI).

Methodological Aspects

The experimental procedure was identical with several of our previously published studies, in which the methods applied have been described more in detail [Savic et al., 2000, 2001; Savic, 2002]. The subjects rated the two categories of odors as different only with respect to the degree of familiarity, but not the intensity, irritability or pleasantness.

The observation that subjects had a veridical recognition of familiar odors during 33 of 56 rating occasions, makes it probable that semantic cues were involved during the history of familiarization. How the familiarization was acquired is not known, and the two groups of odorants were classified based on our previous experiments [Savic et al., 2000]. There were thus no specific learning sessions to achieve a controlled familiarization. Familiarization sessions were not employed because we wanted to mimic the natural situation in which the subjects were naive to the purpose of the experiment and simply confronted either with familiar or unfamiliar odors. A deliberate familiarization could trigger episodic memory processing during the scan, which was specifically related to the training situation. For the same reason, the scans with FAM and uFAM were not repeated. Influence of odor recognition memory could especially bias the activation pattern reflecting passive perception of unfamiliar odorants. Indeed, during the preparatory psychophysical experiments preceding the present PET study and carried out in other volunteers, there were several reports of conscious odor recognition in relation to the experimental situation when the same odorants were presented several times.

Only male subjects were investigated. The reason was to optimize the detection of possible activations of semantic circuits. Because of gender differences in semantic processing [Rossel et al., 2002; Shaywitz et al., 1995], there could be an increased risk for noise if the population consisted of both males and females.

The judgment of intensity tended to differ between familiar and unfamiliar odorants, albeit without reaching the level of significance. It is, however, improbable that the observed differences in the pattern of activation with FAM versus uFAM can be attributed to odor intensity. Judgment of odor intensity is reported to activate amygdala [Anderson et al., 2003], a region engaged by both FAM and uFAM. In our study of odor intensity discrimination, a cluster was detected primarily in left insula with a center of gravity more than 10 mm away from that of the present inferior frontal cluster. Importantly, the activity in this latter cluster was positively correlated with familiarity ratings, whereas no such correlation was found with the intensity ratings. The present results, therefore, address to two issues: (1) whether observed differences in cerebral activation imply that passive smelling of familiar but not unfamiliar odors engages semantic circuits; and (2) if smelling familiar odors automatically involves a recognition process.

Perception of Familiar Odors and Semantic Associations

The cytoarchitectonic map of the human brain atlas, as well as Talairach's atlas coordinates showed that the frontal lobe cluster covered portions of Brodmann's area 44/45 and 47, regions usually assigned to language functions [Petersen et al., 1988]. In contrast to the frontal lobe activations in tasks of episodic memory retrieval [Savic et al., 2000], the present frontal lobe clusters were strictly left sided. The coordinates for the inferior frontal lobe cluster corresponded well with those published from tasks of familiarity judgments [Royet et al., 1999]. This is of interest, because the same region has been attributed to the process of semantic association in visual and auditory perception [Buchel et al., 1998; Petersen et al., 1988] and in categorization [Kapur et al., 1994; Vandenberghe et al., 1996]. This region thus seems to be included in a distributed semantic network, which is shared by several input modalities [Vandenberghe et al., 1996]. In this respect, the sense of smell seems similar to other sensory modalities, contrary to what has generally been stated.

Our subjects could have been covertly associating names or evocations to the familiar odors, thereby recruiting the sensory-semantic areas and the language output regions. The observation that the left frontal cluster did not appear in the FAM-uFAM contrast may be an effect of the relatively high familiarity level (62 ± 24 mm on the VAS) of the uFAM odors (Fig. 2). Consequently, some subjects may have activated regions covering the left frontal cortex also when smelling the unfamiliar odors. Hence, the level of significance was not reached when applying the conservative explorative statistics.

Perception of Familiar Odors and Evocation of Long-Term Memory

Our second finding was that FAM but not uFAM activated right parahippocampus and left parietal cortex with precuneus. This raises the question of whether memory processing could have been triggered by FAM. Our previous study of episodic odor recognition memory [Savic et al., 2000] show cerebellar and precuneal activation, but no specific engagements of parahippocampal or fusiform gyri. Qureshy et al. [2000] observed an activation of left cuneus-precuneus during olfactory matching and olfactory naming. On the other hand, the parahippocampal gyrus has been associated with long-term memory [Dade et al., 1999; Engelien et al., 1995; Levy et al., 1999], whereas the fusiform and inferior temporal gyri are involved in encoding of the structural properties of objects [Kosslyn, 1988]. As shown earlier for the recognition of faces [Haxby et al., 1996], and for the listening to meaningful sounds [Engelien et al., 1995], odors here assigned as familiar (and thus meaningful) could have been encoded into the long-term memory. When the subjects were presented with these odors during the PET scans, the odor percept was matched to the automatically retrieved preexisting stored information, engaging the right parahippocampus. Furthermore, this process possibly also involved

an effort to visually imagine and automatically identify the origin of odors recognized, explaining the observed clusters in parietal cortex covering precuneus, and in inferior temporal lobe gyrus for the FAM-uFAM contrast.

CONCLUSIONS

Familiar and unfamiliar odorants are processed partly by different cerebral circuits. We suggest that the circuits involved depend both on primary perception and the association-driven processes. During confrontation with a recognizable odorant, there is an immediate match of the odor percept with the information stored previously, and a covert association to the name or evocation with this odor. Odors may thus be encoded based on both their verbal features and their perceptual attributes. In this respect, the sense of smell seems to be similar to other sensory modalities.

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