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fMRI of emotional responses to odors: influence of hedonic valence and judgment, handedness, and gender

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Abstract

Previous positron emission tomography studies of right-handed individuals show that the left orbitofrontal cortex is dominant during emotional processing of odors. We collected functional magnetic resonance imaging data from 28 subjects to study this network as a function of odor hedonic valence (pleasant vs. unpleasant), active hedonic judgments versus passive sensation of hedonically charged odors, handedness, and gender. Two functional runs were performed, with pleasant and unpleasant odors presented in different epochs. In the first run, subjects passively smelled odorants, whereas in the second run they rated degree of odor pleasantness or unpleasantness by using a "finger-span" technique that simulated a visual rating scale. Electrodermal and plethysmography responses were simultaneously recorded to control for covert, physiological manifestations of the emotional response. The piriform-amygdala area and ventral insula were activated more for unpleasant than pleasant odors. More extreme ratings were also associated with higher electrodermal amplitude, suggesting that activation stemmed more from emotional or hedonic intensity than valence, and that unpleasant odors induced more arousal than pleasant odors. Unpleasant odors activated the left ventral insula in right-handers and the right ventral insula in left-handers, suggesting lateralized processing of emotional odors as a function of handedness. Active decisions about odor pleasantness induced specific left orbitofrontal cortex activation, implicating the role of this area in the conscious assessment of the emotional quality of odors. Finally, left orbitofrontal cortex was more active in women than men, potentially in relation to women's well-documented advantage in odor identification.
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Keywords: Olfactory emotion; Hedonic valence; Hedonic judgment; Handedness; Gender; fMRI

Introduction

Emotion and hedonic judgment are primary facets of olfaction (Herz and Engen, 1996). Odors are also known to influence mood, induce alertness or relaxation, and evoke long-forgotten emotional memories. The close relationship between olfaction and emotion is a logical consequence of how both processes share several limbic regions. Despite the view espoused by several authors that negative emotions are associated with the right hemisphere (Davidson, 1992; Canli et al., 1998), several recent positron emission tomography (PET) studies have instead reported strong activations of the left amygdala and orbitofrontal cortices (OFC) when subjects smell highly aversive odors (Zald and Pardo, 1997; Zald et al., 1998a), or perform a hedonic judgment task (Royet et al., 2001). We also demonstrated that emotional judgments share similar left hemispheric networks, independently of whether emotions are induced via olfactory, visual, or auditory sensory modalities (Royet et al., 2000). Other neuroimaging studies have similarly indicated strong involvement of the left hemisphere in emotional processing (Pardo et al., 1993; Morris et al., 1998).

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Nevertheless, there are limitations to this corpus of work. First, in studies on hedonic judgment, the activity specific to a given hedonic valence could not be determined since pleasant (P) and unpleasant (U) odors were intermingled during the same scan. Thus, it remains an open question as to whether P and U odors activate the same neural network. Second, our previous PET studies were conducted in right-handers (RH) only, begging the question as to whether the results generalize to left-handers (LH). In some behavioral studies on olfaction, lateralized differences as a function of handedness have been reported, but the data conflict and other studies reveal no differences (Koelega, 1979; Youngentob et al., 1982; Zatorre and Jones-Gotman, 1990; Frye et al., 1992; Hummel et al., 1998). Third, our previous study of cross-modal emotional activation revealed a large neural network stretching from the amygdala to the superior frontal gyrus. However, these regions might participate in different levels of emotional processing. For example, Reiman et al. (1997) suggested that the superior frontal gyrus might play a role in the conscious experience of emotion. Finally, behavioral studies show that women clearly outperform men in odor identification (Cain, 1982; Doty et al., 1985; Engen, 1987). Nevertheless, neuroimaging studies of odor perception have not shown consistent gender differences in cerebral activation (Levy et al., 1997, 1999; Yousem et al., 1999; Bengtsson et al., 2001).

The purpose of this fMRI experiment was to study brain regions associated with odor hedonic valence, and the effect of handedness on the lateralization of emotionally induced activation. P and U odors were presented in different epochs while subjects rated their degree of pleasantness or unpleasantness. Electrodermal (ED) and plethysmography (PL) responses were also recorded to control for covert, physiological manifestations of the emotional response. The study further examined the extent to which different neural networks were engaged by explicit hedonic judgments, and included a sufficiently large sample of men and women to enable a robust comparison between activation patterns across genders.

Materials and methods

Subjects

Twenty-eight subjects (20–30 years of age) participated, comprising 4 groups of 7 subjects classified by handedness (as determined by the Edinburgh Handedness Inventory) and gender. Subjects were selected on the basis of their olfactory ability with a forced-choice suprathreshold detection test (at least 91% correct) and of the mean duration of their breathing cycle (4.08 $\pm$ 1.12 s). Subjects with rhinal disorders (colds, active allergies, history of nasal-sinus surgery, or asthma), neurologic disease, ferrous implants (e.g., pacemakers, cochlear implants, etc and so on), or claustrophobia were excluded. Subjects with anhedonia, as rated with the Physical Anhedonia Scale (score $>$ 29; Chapman et al., 1976), were also excluded. Participation required a medical screening and written informed consent. Seven female subjects were on contraceptive medication and 7 other females not on contraceptive medication tested negative for pregnancy. The study was approved by the local Institutional Review Board and conducted according to French regulations on biomedical experiments on healthy volunteers.

Odorous stimuli

One hundred twenty-six odorants were used. Ninety odorants were used for both functional runs. They were split into 6 sets of 15 odorants as a function of perceived hedonicity and intensity ratings (Table 1) from data obtained in previous work (Royet et al., 1999). For pleasant (P) conditions, 3 sets (Pa, Pb, and Pc) contained P odorants selected so as to provide the highest scores. Similarly, in the unpleasant (U) condition 3 sets (Ua, Ub, and Uc) contained U odorants selected for their lowest scores. Odorants were also selected such that mean intensity scores were identical between hedonic conditions and between sets. Accordingly, analyses of variance (ANOVA) showed that hedonicity, but not intensity scores, significantly differed between P and U conditions [$F(1,84) = 503.433$, $P < 0.0001$ and $F(1,84) = 2.016$, $P = 0.1593$, respectively], and that neither hedonicity nor intensity scores differed between sets within the same hedonic condition [$F(2,84) = 0.103$, $P = 0.9026$ and $F(2,84) = 0.660$, $P = 0.5164$, respectively]. No hedonic valence $\times$ set interaction was present for hedonicity and intensity scores [$F(2,84) = 0.001$, $P = 0.9991$ and $F(2,84) = 0.595$, $P = 0.5540$]. In each set the order of presentation of P or U odors was pseudorandomized but identical for all subjects. For training, 36 neutral odorants (score range of 4–5) and 9 bottles with odorless air were used. Odorants were diluted to a concentration of 10% using mineral oil. For presentation, 5 ml of this solution was absorbed into compressed polypropylene filaments inside of 100-ml white polyethylene squeeze bottles with a dropper (Osi, France).

Stimulating and recording materials

Odors were presented with an airflow olfactometer, which allowed synchronization of stimulation with breathing. The stimulation equipment was essentially the one used in a previous PET study (Royet et al., 1999), but adapted so as to avoid interference with the static magnetic field of the scanner. Specifically, the apparatus was split into two parts: the electronic part of the olfactometer positioned outside the magnet room (shielded with a Faraday cage), and the nonferrous (aluminum) air-dilution injection head installed near the magnet. Compressed air (10 l/min) was pumped into the olfactometer, and delivered continuously through a commercially available anesthesia mask. At the beginning of each inspiration, odor was injected into the olfactometer,

Table 1
List of odors selected for epoch of Pa, Pb, Pc, Ua, Ub, and Uc conditions

	Pa	Pb	Pc	Ua	Ub	Uc
1	Apricot	Pear	Citronella	Garlic	Onion	Santalol
2	Lemon	Raspberry	Apple	Tar	*Mustard*[a]	4-pentanoic acid
3	Lavender	Violet	Rose	Ethyl phenyl acetate	Furfuryl mercaptan	Pine needle
4	Sage	Honeysuckle	Lime	Butyl bromide	Beer	Butyl sulfide
5	Coconut	Jonquil	Mint	IAPA[b]	Butyric acid	2-Bromophenol
6	Wild rose	Orange	Strawberry	Hexane	Nonyl acetate	Guaiacol
7	Caramel	Chewing-gum	Biscuit	Pyrrole	*Isovaleric acid*[a]	*Ethylmercaptan*[a]
8	Lis	Chocolate	Bread	Mushroom	Caproic acid	Valeraldehyde
9	Melon	Tobacco	Grapefruit	2-Heptanol	Acetone	Tetrahydrofurane
10	Anise	Banana	Carnation	2,5-Dimethyl pyrrole	Methyl isonicotinate	Butanol
11	Ethyl nitrite	Hazel	Bitter almond	*Tetrahydrothiophene*[a]	Heptanal	Wine
12	Nutmeg	Jasmine	Gardenia	Tetralin	2-Octanol	Ethyl acetate
13	Passion fruit	Fennel	Bergamote	Ethyl propionate	Amyl valerate	Methyl-2-furoate
14	Lilac	Vervain	Cinnamon	Hexanal	Pizza	1,4-Dichlorobutane
15	Vanilla	Iris	Garrigue	Ethyl pyrazine	Ethyl diglycol	Valerolactone
Hedonicity						
Mean score (SD)	5.85 (0.86)	5.75 (0.68)	5.82 (0.85)	2.13 (0.71)	2.05 (0.76)	2.10 (0.84)
Score range	4.55–7.24	4.51–6.65	4.59–7.04	0.79–3.01	0.80–2.85	0.45–3.04
Intensity						
Mean score (SD)	5.46 (0.67)	5.47 (0.80)	5.80 (0.51)	6.07 (0.88)	5.70 (1.48)	5.91 (1.28)
Score range	4.30–6.62	4.14–6.65	4.70–6.48	1.55–7.92	3.35–7.73	1.20–8.25

[a] Underlined name, odorant with high potency and of which the concentration was limited to 1%.
[b] *iso*-Amylphenyl acetate.

which carried it to the subject's anesthesia mask. Breathing (B) was recorded with the aid of a PVC foot bellows (Herga Electric Ltd, Suffolk, UK) held on the stomach with a judo belt. An operator monitored breathing and squeezed the odor bottle so as to flush the odor into the injection head during inspiration. The ED signal was recorded from two stainless steel electrodes placed on the tips of the index and middle fingers of the nondominant hand. PL responses were recorded from a sensor fixed to the tip of the thumb of the nondominant hand.

Subjects rated hedonic intensity in Run2 (and responded randomly in Run1) by using the "finger-span" (FS) technique (Berglund et al., 1978; Larson-Powers and Pangborn, 1978; Yamamoto et al., 1985; Cerf-Ducastel and Murphy, 2001), which simulated a visual rating scale by having subjects vary the distance between the thumb and forefinger to approximate a linear scale. Two long rectilinear potentiometers (4.5 and 6.3 cm of sliding travel) were used depending on a given subject's actual finger span. The thumb of the dominant hand was fixed to one end of the potentiometer while the forefinger moved a slide. The potentiometer was connected to a 1-Hz low-pass filter and then to an analog-to-digital converter.

ED, PL, FS, B, and odor stimulation signals were transmitted by means of optical fibers to AD converters powered by nickel-cadmium batteries. Behavioral and physiological data were recorded online (100 Hz sampling rate) using an NEC PC computer equipped with a digital acquisition board DAQCard-500 (National Instruments, USA). LabView 5.0 software (National Instruments) was used to acquire, store, and read data. Data analysis was performed with the WinDaq Waveform Browser 1.91 software (DataQ Instruments, USA).

Experimental procedure

Two functional runs (Run1 and Run2) were performed (Fig. 1) in a single fMRI session. A block paradigm was applied and consisted of hedonic odor conditions (P and U epochs) alternating with odorless rest (R) epochs. Each epoch lasted 60 s. This relatively large epoch was employed to compensate for slight asynchronies in the beginning and end of each epoch and the subject's inspiratory phase, which is concomitant with odorant stimulation. For each run, both P and U conditions were presented three times each, so as to permit a balanced experimental design (Latin square). The order of conditions/odor sets for a given subject in Run1 was repeated in Run2. For olfactory stimulation in Run1, subjects passively smelled the odorants and responded randomly with the FS apparatus. For olfactory stimulation in Run2, subjects made a hedonic judgment by moving the FS slide according to their perceived level of pleasantness or unpleasantness. For P, ratings ranged from neutral, which required very little movement, to very pleasant at the extreme of FS. For U, ratings similarly ranged from neutral to very unpleasant Subjects were asked not to move the slide in the absence of perceived odors in either of the hedonic conditions. For R, subjects were requested not to respond at all. The "passive smelling" condition (Run1) always preceded the "hedonic judgment" condition (Run2) to not bias the subject during the passive condition with the explicit knowledge of the hedonic judgment task.

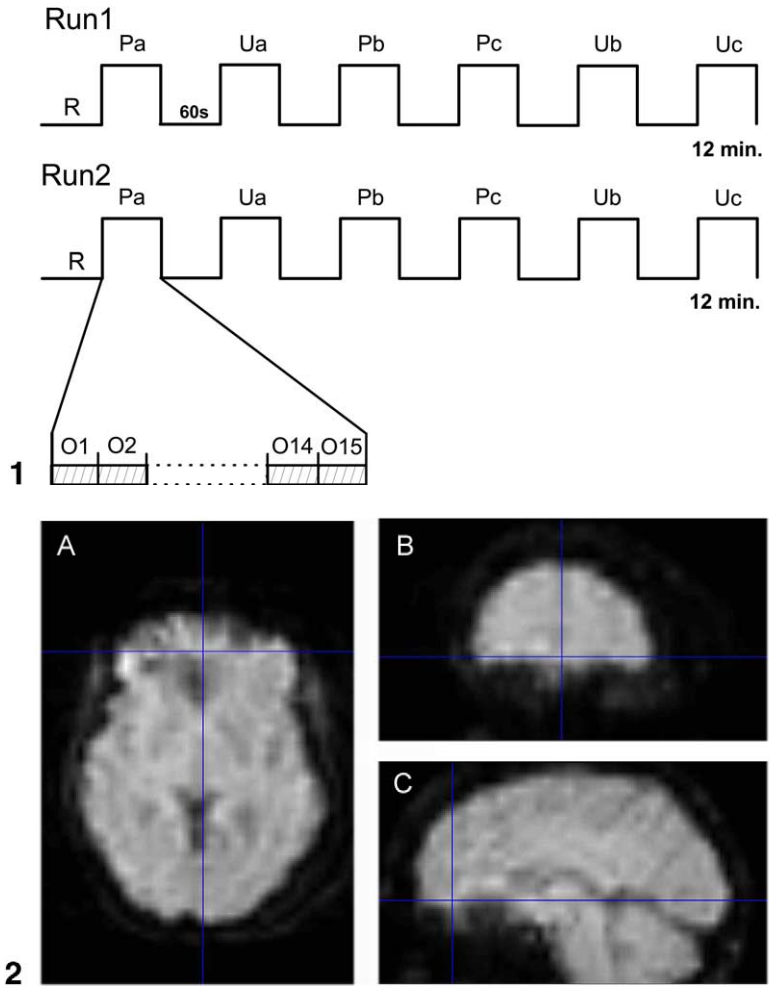

Fig. 1. Experimental procedure including two runs (Run1 and Run2) with 12 epochs of 60 s each. Two hedonic conditions were performed with P odorants presented for 3 epochs (Pa, Pb, Pc), and U odorants presented for 3 epochs (Ua, Ub, Uc). Each run provided 144 temporal volumes of 12 slices each. R, rest.
Fig. 2. Three orthogonal slices from an averaged 3D functional three-shot PRESTO image from one of the subjects. The signal-to-noise ratio in the OFC were computed using the approach of Parrish et al. (2000), and ranged from approximately 80 to 200. The minimum value of 80 allowed detection of a 1% BOLD signal change with a detection rate (beta) of 95% in case of a *t* test with an alpha of 1%. Axial (A), coronal (B), and sagittal (C) orientations.

General instructions were provided to subjects before each run. During each run, and 3 s before each experimental condition (P, U, or R), the subjects were instructed orally by means of specific key words ("pleasant," "unpleasant," and "rest") which task was to be performed next. Subjects wore earplugs as protection from the scanner noise and kept their eyes closed during scanning. The day before fMRI, subjects were trained outside the MR facility to breathe regularly, to detect odorants without sniffing during normal inspiration, and to rate odor intensity using the FS technique during expiration.

Imaging parameters

Functional MR imaging was performed on a 1.5-T MR imager (Philips NT). Twenty-five adjacent, 5-mm-thick axial slices were imaged. The imaging volume covered the subjects' whole brain and was oriented parallel to the bicommissural plane (Fig. 2). The image planes were positioned on scout images acquired in the sagittal plane. A 3D PRESTO three-shot MR imaging sequence (Liu et al., 1993) was used with the following parameters: TR = 26 ms, TE = 38 ms, flip angle = 14°, field-of-view = 256 × 205 mm^2, imaging matrix = 64 × 51 (pixel size of 4 × 4 × 5 mm^3). The PRESTO sequence is less prone to the artifacts induced by susceptibility differences between brain tissue and the underlying bone and air than is the echoplanar imaging (EPI) sequence usually applied in fMRI (Frahm et al., 1988). These susceptibility artifacts induce MR signal loss, particularly in the OFC and mesial temporal region (Zaldo and Pardo, 2000). To illustrate the typical image quality from the PRESTO sequence, three orthogonal slices from an averaged 3D functional image from one subject are depicted in Fig. 2. During each functional scan, the volume of interest was scanned 144 times successively. The signal was averaged three times, leading to an acquisition time per

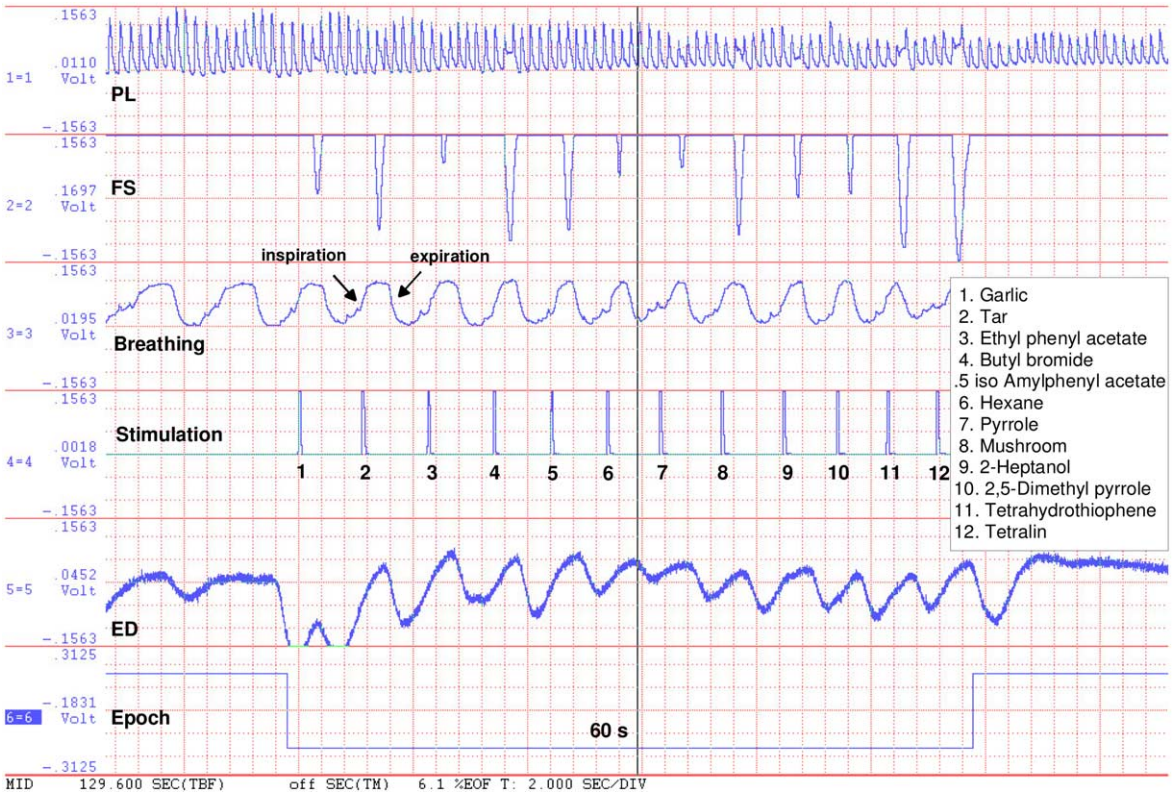

Fig. 3. Recording of behavioral and physiologic measures. Example of an epoch of 60 s for which 12 U odorous stimulations were synchronously delivered at the beginning of inspiration. Finger-span (FS), plethysmography (PL), and electrodermal (ED) responses were recorded for each odorant.

volume of 5 s. A high-resolution anatomic 3D T1-weighted MR scan was acquired between both functional runs. In LH, an additional gradient-recalled echo EPI MR pulse sequence (GRE-EPI) functional scan was run during a verbal fluency task (Pujol et al., 1999) to assess hemispheric dominance for language. Our results indicated that 10 subjects (71.4%) were left lateralized, 2 (14.3%) had right hemispheric language dominance, and 2 had bilateral involvement.

Data processing and statistical analyses

fMRI runs were analyzed using Statistical Parametric Mapping (SMP99, The Wellcome Department of Cognitive Neurology, London, UK; Friston et al., 1995a, 1995b). Image processing included interscan realignment, spatial normalization to stereotactic space as defined by the ICBM template provided by the Montreal National Institute (MNI), and image smoothing with a three-dimensional Gaussian kernel (FWMH: 8 × 8 × 10 mm) to overcome residual anatomical variability and increase signal-to-noise. A boxcar reference function was convolved with SPM99's "canonical" hemodynamic response function. Global differences in BOLD signal were covaried out of all voxels, and comparisons across conditions were effected with *t* tests. The significance of signal differences was assessed through *Z* scores in an omnibus sense (Friston et al., 1995b), using an uncorrected probability with a threshold of $P < 0.001$. An MRI template and Duvernoy's (1991) anatomic nomenclature were used to localize and describe anatomic regions of activation.

Olfactory main effects were calculated by contrasting the olfactory and rest conditions (e.g., U1-R). Specific effects were calculated by comparing unpleasant (U1 and U2) with pleasant (P1 and P2) conditions for both functional runs (U1 vs. P1, U2 vs. P2, and U1U2 vs. P1P2), and by comparing passive smelling (Run1) and hedonic judgment (Run2) with U2 vs. U1, P2 vs. P1, and U2P2 vs. U1P1 contrasts. Random effects analyses (SPM99, Wellcome Foundation, London) were applied to extrapolate statistical inferences into the healthy population. This two-stage analysis accounted first for intrasubject (scan-to-scan) variance, and second for between-subject variance. During the first step, scan-to-scan variance was modeled for each subject individually by creating a summary contrast image from weighted parameter estimates that reflected each scan condition. These contrast images were then used in a second, between-subjects level of analysis that employed basic model *t* tests to assess the condition effects. Four kinds of groups were considered according to handedness and gender. Since random effects analyses require large subject samples, analyses could not be performed on 4 groups of 7 subjects each. Therefore, males and females with the same handedness were re-

grouped either into the RH or LH groups. Similarly, RH and LH of the same sex were regrouped into the male or female groups. Separate analyses by subject group were then performed using basic model, one-sample *t* tests. Between-groups analyses were also performed using two-sample *t* tests to compare patterns of activation as a function of handedness and gender. However, these direct comparisons were hampered by the fact that we were forced to analyze only relative olfactory differences, as our rest condition did not involve motor activity. The signal strength of the relative differences between groups is thus a more difficult phenomenon to test in a between-groups model. For this reason, we compared groups on the basis of their thresholded activation.

Results

Behavioral and physiological data

A typical example of the physiological and behavioral data recorded during a 60-s epoch of olfactory stimulation is depicted in Fig. 3. From 12 to 20 odor stimulations were delivered per epoch, depending on the subject's respiratory rate.

Mean FS, ED, and PL measurements per epoch were analyzed as a function of Handedness (RH vs. LH), Run (Run1 vs. Run2, i.e., random response vs. explicit hedonic judgment), and Hedonic (Pa, Pb, Pc, Ua, Ub, Uc) conditions (Fig. 4). FS data were normalized with respect to both potentiometer sizes. Multivariate ANOVA of these sets of dependent measures showed significant main effects for Handedness [Wilks' $\lambda(3,310) = 10.45$; $P < 0.001$], Run [Wilks' $\lambda(3,310) = 13.96$; $P < 0.001$], and Hedonicity [Wilks' $\lambda(15,856) = 2.69$; $P < 0.001$], but no significant interactions between these factors. We then performed three-way ANOVAs separately on FS, ED, and PL, with Handedness as a between-groups factor, and Run and Hedonicity conditions as repeated measures. For FS, there were significant main effects for Run and Hedonicity [$F(1,26) = 17.87$, $P < 0.0003$, and $F(5,130) = 5.62$, $P = 0.001$, respectively], and a significant Run × Hedonicity interaction [$F(5,130) = 3.70$, $P < 0.0035$]. The main effect of Run reflects higher FS ratings during Run1 than during Run2, likely secondary to the subjects' random responses during Run1. The main effect for Hedonicity reflects significantly more extreme FS ratings for U odors (Fig. 4), and suggests that these odors were hedonically more intense. For ED, there was a significant main effect of Hedonicity [$F(5,130) = 6.08$, $P < 0.001$] and a significant interaction-between Handedness and Hedonicity [$F(5,130) = 3.57$, $P < 0.005$]. This interaction was due to the LH's higher ED responses in U than P conditions for both runs, irrespective of explicit hedonic analysis. For PL, there was a significant main effect of Run [$F(1,26) = 22.67$, $P < 0.001$] and Hedonicity [$F(5,130) = 14.78$, $P < 0.001$], as well as a significant Run × Hedonicity interaction [$F(5,130) = 3.15$, $P = 0.010$]. Thus, while cardiac rhythm was clearly related to hedonic intensity, it declined generally over the course of the imaging period, suggesting progressive habituation during the experiment.

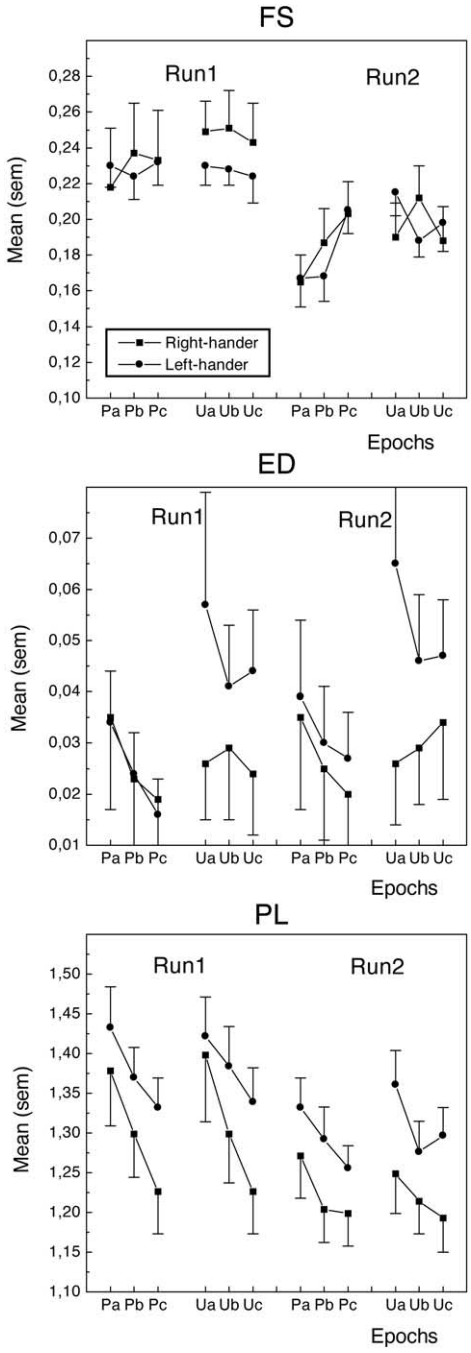

Fig. 4. Behavioral and physiological scores as a function of Handedness (Right-hander vs. Left-hander), Run (Run1 vs. Run2), and Hedonic valence (Pa, Pb, Pc vs. Ua, Ub, Uc) for finger-span (FS, top), electrodermal (ED, middle), and plethysmography (PL, bottom). The vertical bars (plus or minus directions) show the SEM. The *y*-axis for FS represents both P and U odors, spanning the range from "neutral" to the extreme of P or U.

Table 2
Correlations (Fischer's *r* test) between FS and ED values in different conditions

Subject	Run1				Run2			
	P		U		P		U	
	r	p	r	p	r	p	r	p
1	0.102	0.6375	0.368	0.0765	0.378	**0.0225**	0.636	**0.0001**
2	0.151	0.3828	0.396	**0.0162**	0.069	0.6904	0.430	**0.0083**
3	0.168	0.3303	0.3327	0.0511	0.009	0.9590	0.431	**0.0080**
4	−0.082	0.7068	0.247	0.4486	0.579	**0.0001**	0.635	**<0.0001**
5	0.481	0.0035	0.387	**0.0229**	0.169	0.3348	0.472	**0.0032**
6	0.385	**0.0195**	0.337	**0.0440**	0.081	0.6409	0.209	0.226
7	0.034	0.8462	0.379	**0.0219**	0.640	**<0.0001**	0.378	**0.0223**
8	−0.065	0.7102	−0.125	0.4689	0.043	0.8068	0.471	**0.0033**
9	0.364	**0.0284**	0.344	**0.0392**	0.097	0.5769	0.395	**0.0164**

Note. Bold, significant probability wtih $p < 0.05$.

Table 3
Areas activated in P and U conditions of both runs relative to the R condition in RH and LH

Handedness	Contrast	Brain region	Size voxels	*T* values	MNI coordinates		
					x	*y*	*z*
RH	P1-R	Insula	212	6.39	46	18	−10
	U1-R	Hypothalamus	35	5.27	10	−6	−10
	P2-R	Insula	1317	10.28	−40	14	0
		Insula		9.61	−36	18	−6
		OFC		7.16	−42	42	−12
		OFC	763	9.30	40	28	−8
		Hypothalamus	24	5.90	−10	−2	−10
	U2-R	Insula	852	7.58	−38	16	−6
		Insula		7.14	−46	20	−6
		OFC		6.31	−30	28	−16
		Insula	399	6.68	38	16	−10
		OFC		6.36	38	28	−8
		Limen insulae		4.78	30	10	−12
		Amygdala	67	5.19	−22	−2	−12
	P1U1P2U2-4R	Insula	1233	9.91	−42	24	−4
		Insula		7.77	−44	10	−2
		Precentral gyrus		6.36	−54	14	8
		OFC	933	7.31	58	18	12
		OFC		7.30	40	28	−8
		OFC		6.73	48	22	−6
		OFC	149	7.18	−42	46	−12
LH	P1-R	OFC	369	8.16	44	18	−2
		Precentral gyrus		6.43	58	10	10
		Precentral gyrus		4.77	46	8	2
	U1-R	Insula	53	6.61	−42	8	−12
		OFC	281	6.06	−26	38	−18
		Insula		5.59	−34	20	0
	P2-R	OFC	77	5.02	−40	50	6
		OFC		4.46	−36	42	14
		OFC		4.04	−34	44	22
		Lateral sulcus	44	4.40	44	14	−10
	U2-R	Insula	146	5.10	−42	6	−8
		Insula		4.77	−48	14	−8
		Insula	96	4.82	40	8	−12
		Insula		3.97	40	16	−4
	P1U1P2U2-4R	Insula	309	7.09	−34	18	0
		Insula		6.82	−40	4	−8
		Insula	215	6.05	42	18	−4
		Insula		4.66	38	8	−12
		OFC	78	5.69	−40	50	6
		Hypothalamus	40	5.05	−10	−6	−14

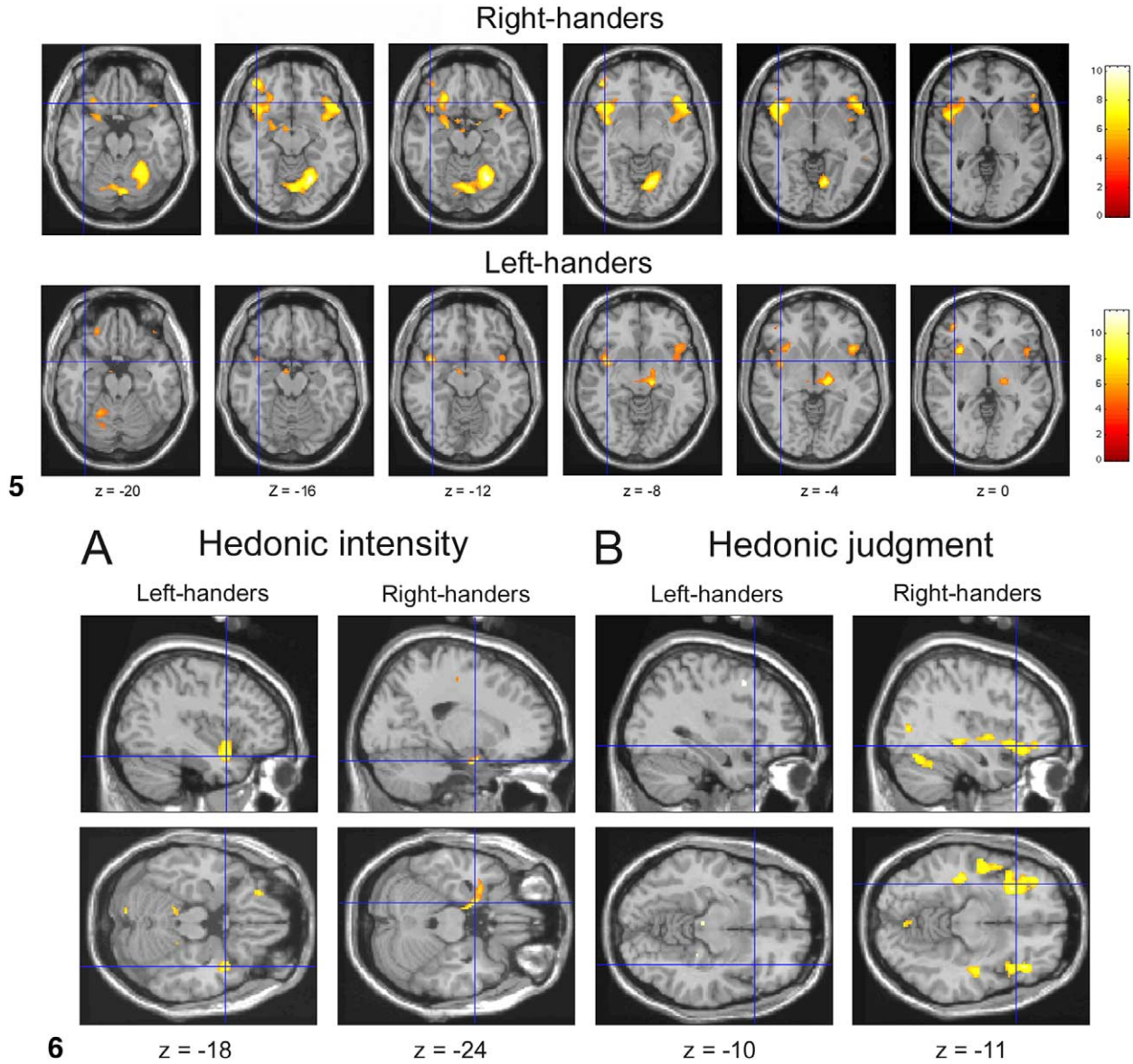

Fig. 5. Localization of task-specific activations (P1U1P2U2-4R) as a function of handedness. Activations were superimposed on horizontal sections (2 mm apart) from an anatomically normalized standard brain. Sections extended from −20 to 0 mm (MNI *Z* coordinates provided below the image), the zero value defining the horizontal plane passing through the anterior and posterior commissures. Clusters were thresholded at $T = 3.1$. Color scales indicate *T* values. Fig. 6. Localization of activations as a function of hedonic valence and hedonic judgment task in RH and LH. Sagittal and horizontal sections showing olfactory activations in hedonic valence (U1U2-P1P2) and hedonic judgment task (P2U2-P1U1) conditions. *Z* indicates the coordinate along the vertical line passing through the intercommisural plane. See Fig. 4 for details.

ED amplitude showed high intersubject variability: whereas a few subjects did not show any response, 9 subjects exhibited clear changes with olfactory stimulation. Correlation coefficients between ED and FS values were calculated for these 9 subjects as a function of both Run and Hedonic valence (Table 2). ED and FS were correlated mainly in the U condition of both runs. Significant correlations in the U condition for Run1 show that behavioral responses from these 9 subjects were not completely random, but influenced by the odorants' hedonic intensity.

fMRI activations

Olfactory conditions vs. rest

When the images from the P and U conditions were contrasted with those from the rest (R) condition (U1-R, P1-R, U2-R, P2-R, U1U2P1P2-4R), significant activations were found in a neural network encompassing the insula, OFC, cingulate gyrus, piriform cortex, amygdala, hypothalamus, and superior temporal gyrus (Table 3 and Fig. 5). In both RH and LH, there were significant activations bilaterally, but predominantly in the left insular and inferior frontal

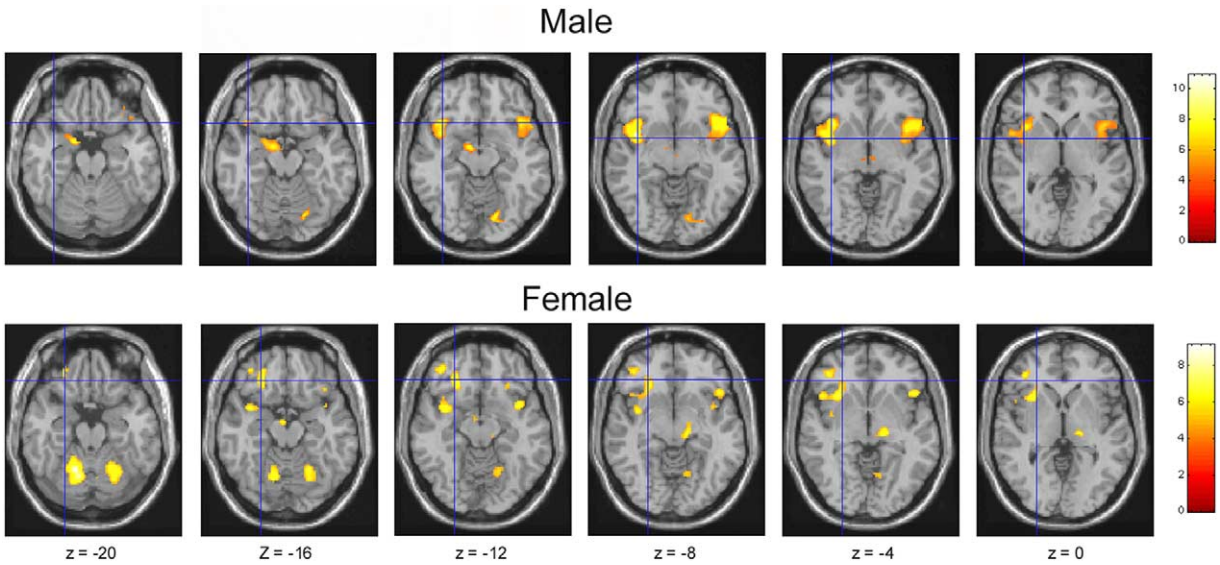

Fig. 7. Localization of olfactory activations as a function of gender. Horizontal sections depicting olfactory activations (P1U1P2U2-4R) in males and females for every 2 mm in *z* coordinates from −20 to 0 mm. The clusters were thresholded at $T = 3.1$. See Fig. 4 for details.

cortices. In addition, more areas were activated in Run2 (U2-R, P2-R) than in Run1 (U1-R, P1-R), with particularly strong OFC activation during hedonic judgments (Run2). Since FS was not used during the rest period, motor area activation was evident when contrasting the olfactory and resting conditions.

Hedonic valence and handedness effects

To reveal activations specific to hedonic valence, we compared images acquired in the P condition with those acquired in the U condition (Table 4 and Fig. 6A). We found many more activations for the U-P contrasts (U1-P1, U2-P2, U1U2-P1P2) than for the P-U (inverse) contrasts. The former contrasts led to activations in the piriform cortex, the amygdala, and the ventral insula in the left hemisphere in RH, and only in the right ventral insula in LH. We also observed cingulate activation in RH and left superior temporal gyrus activation in LH.

Hedonic judgment task

Activations due to explicit hedonic judgments were obtained by subtracting images acquired in Run1 from those acquired in Run2 (P2-P1, U2-U1, P2U2-P1U1). Significant activations were found mainly in the insula and the OFC in RH (Table 4, Fig. 6B). No significant activation was observed in LH.

Gender effects

The 28 subjects were divided into 2 groups according to gender (14 males and 14 females). In men, contrasting the olfactory conditions with the resting conditions led to activation principally in the bilateral insula and in the left piriform-amygdala region. In women, activations were located in these same areas, as well as in the left OFC (Table 5 and Fig. 7).

Discussion

This study of the neural correlates of emotionally valenced olfactory stimuli shows that the same left hemisphere neural network was engaged, regardless of the odors' hedonic valence. Nevertheless, parts of this network, including the ventral insula and piriform-amygdala region, were more active in RH with U odors, which according to FS and ED data, were hedonically more intense. The hemispheric predominance of this response appears to depend on handedness, with the left ventral insula responding most in RH and the right ventral insula responding most in LH. Further, active hedonic judgments recruited additional areas in the insula and caudal OFC—areas that did not activate when subjects only passively smelled the hedonically charged odors. Finally, the OFC was more strongly activated in women than men.

Olfactory network as a function of hedonic valence

A similar neural network was activated by P and U odorants when contrasting olfactory against rest conditions. This included the piriform-amygdala region, the hypothalamus, the superior temporal gyrus, the insula, the OFC, and the anterior cingulate gyrus. This network includes areas described in our previous studies (Royet et al., 2000, 2001), and appears to be similar in RH and LH, albeit with weaker activations in the latter. It is well known, however, that cognitive function is less lateralized in LH (Laeng and

Table 4
Areas activated in hedonic valence and hedonic judgment task conditions in RH and LH from contrasts applied between olfactory conditions

Condition	Handedness	Contrast	Brain region	Size voxel	*T* values	MNI coordinates		
						x	*y*	*z*
Hedonic Valence	RH	U1-P1	Piriform/amygdala	46	5.53	−30	4	−24
			Piriform/amygdala		5.21	−22	2	−24
		P1-U1	Cingulate gyrus	116	4.76	−12	−30	32
		P2-U2	Middle temporal gyrus	60	7.18	−44	−38	−2
			Insula	79	5.64	36	12	14
		U1U2-P1P2	Piriform/amygdala	19	5.03	−20	0	−24
			Amygdala		5.03	−14	−8	−22
			Insula		4.12	−44	−2	−8
	LH	U1U2-P1P2	Ventral insula	56	4.99	38	6	−16
Hedonic Judgment Task	RH	P2-P1	Insula	93	5.85	−36	20	−10
			OFC	72	4.89	−42	40	−6
			OFC		4.59	−36	40	−14
		U2-U1	Insula	145	6.59	38	16	−6
			OFC		5.68	36	22	−16
			OFC		5.59	40	28	−4
			OFC	37	5.27	−34	28	−14
			OFC	59	4.51	54	30	8
			OFC		3.89	54	28	18
		P2U2-P1U1	OFC	66	6.24	40	30	−6
			Middle temporal gyrus	35	6.07	−44	−28	−8
			Insula	32	5.71	34	−14	0
			Middle temporal gyrus	63	5.21	−52	−4	−6
			Insula		4.32	−44	−6	−4
			Insula	86	5.19	−34	20	−10
			OFC		4.73	−34	30	−14
			OFC	34	4.75	−42	40	−8
			OFC		4.24	−44	32	−6
			Insula	21	4.30	36	6	−2
			Insula		4.06	36	16	−6
	LH		No significant results					

Peters, 1995), consistent with our language data showing only 70% of the LH to be left-dominant for language. A possible confound also exists in that parts of this putative network might have been obscured by FS-related activation. For example, we cannot rule out the possibility that some prefrontal areas might mediate both the planning of an FS response and explicit hedonic analysis. By contrasting the P and U conditions directly, such confounds may be avoided, but those contrasts provide only relative differences between U and P odors and not the overall network involved in more general decisions about hedonic perception. For U-P contrasts, we mainly observed amygdala-piriform and ventral insula activations, while no activation was observed with the P-U contrasts.

Zald and Pardo (1997) previously found substantial activation in both amygdalae and the left OFC during exposure to highly aversive odors, but only in left OFC during exposure to less aversive odorants. Gottfried et al. (2002) found that unpleasant odors also activated the left OFC, but only the right amygdala. By contrast, no activation in both amygdalae was found with pleasant odors. Zald and Pardo (1997) suggest that the more aversive an odor, the more it evokes activity in the amygdala. In the current study, more activation in the amygdala for U compared to P odorants cannot be related to perceived intensities since the odors were selected to be of identical intensity on the basis of psychophysical ratings (Royet et al., 1999). The behavioral and physiological data acquired during active hedonic judgments further revealed that hedonic reaction was stronger with U than with P odors, and that individual subject variations in ED amplitude were significantly correlated with FS ratings in a few subjects, especially in U conditions. The remaining subjects who did not show this correlation may not typically express autonomic activity via ED responses. For example, Vernet-Maury and colleagues (1991, 1999) studied 6 different autonomic nervous system parameters and found that subjects typically reacted through a specific, preferential channel.

From these findings, we speculate that activation in the amygdala-piriform area is mostly from the strength of the perceived emotion (emotional or hedonic intensity), rather than from the type of emotion per se (hedonic valence). That is, our U stimuli induced a stronger emotional response than our P stimuli, independently of perceived intensity. This formulation is consistent with Rolls' (1999) hypothesis that the amygdala mediates both negative and positive emotions,

Table 5
Areas activated in P and U conditions relative to the R condition in male and female subjects

Gender	Contrast	Brain region	Size voxels	*T* values	MNI coordinates		
					x	*y*	*z*
Male	P1-R	Insula	748	6.93	44	16	−2
		Insula		6.41	42	4	0
		OFC		6.10	56	12	16
		Superior temporal gyrus	214	5.95	−52	10	0
		Insula		5.51	−40	16	−4
	U1-R	OFC	63	8.32	54	14	14
		Insula	302	6.40	−38	12	−12
		Insula		6.14	−40	4	−8
		OFC		5.61	−40	20	−14
		Precentral gyrus	65	6.33	−56	10	26
		OFC		4.50	−60	6	16
		Insula	104	5.87	40	6	−12
	P2-R	Insula	361	7.28	−44	8	−4
		OFC		6.75	−44	20	−12
		OFC		4.66	−32	20	0
		Lateral sulcus	311	6.53	48	20	−8
		OFC		6.41	38	24	−8
		OFC		4.50	32	28	−14
		Hypothalamus	89	5.54	−12	−6	−12
	U2-R	Insula	270	9.15	−50	12	−8
		Insula		4.86	−42	20	−6
		Superior temporal gyrus	731	7.77	46	4	−10
		OFC		7.28	38	22	−12
		Lateral sulcus		7.06	50	14	−10
		Piriform/amygdala	141	5.86	−22	0	−18
	P1U1P2U2-4R	Insula	766	10.85	−40	4	−6
		Insula		8.51	−40	20	−4
		OFC		6.41	−44	20	−12
		OFC	999	6.79	38	24	−10
		Insula		6.59	38	16	−6
		Lateral sulcus		6.55	48	20	−8
		Piriform/amygdala	203	6.27	−20	0	−18
		Amygdala/hypothalamus		6.24	−12	−6	−12
Female	P1-R	Precentral gyrus	45	7.53	−54	4	34
		OFC	180	6.09	50	22	0
		Precentral gyrus		5.02	58	12	10
	U1-R	OFC	122	7.12	24	34	4
		OFC	373	6.58	−20	28	8
	P2-R	OFC	394	8.56	−50	26	2
		Precentral gyrus		6.94	−46	20	6
		OFC		5.83	−44	40	−2
		Insula	109	6.34	−32	18	−4
		Insula	801	9.97	−36	14	−6
	U2-R	OFC		6.67	−28	30	−16
		OFC		6.18	−44	44	−10
	P1U1P2U2-4R	OFC	538	9.05	−28	34	−14
		Insula		7.07	−32	20	−4
		Insula		5.32	−50	18	−4
		OFC	68	6.70	44	22	−6
		Insula	146	6.45	−38	4	−12
		Insula		3.99	−40	16	−12
		Insula	71	5.87	36	8	−12
		OFC	283	5.64	−42	40	−2
		OFC		5.59	−40	46	−14
		OFC		4.77	−38	38	10
		Hypothalamus	28	5.21	−6	−8	−16
		Hypothalamus		3.87	−10	−2	−10

and that differences in activity of this area stem from the intensity of the induced emotion. Whereas amygdala activation has been observed principally for negative stimuli (e.g., the current study, Zald and Pardo, 1997; Gottfried et al., 2002), this can be explained by the level of arousal that these stimuli induce (Zald, 2003). For example, it has been demonstrated that arousal correlates with valence intensity: in stimuli ranging from neutral to highly unpleasant, there is almost always a strong correlation between arousal ratings and ratings of unpleasantness (Lang et al., 1993). By contrast, the relationship between valence intensity for pleasantness and arousal appears more complex, since highly pleasant stimuli can be experienced as arousing, but also as extremely relaxing and calming (Zald, 2003).

Recently, Anderson et al. (2003) found that amygdala activation was associated with odor intensity, rather than odor valence. In manipulating two odorants, they observed a greater response in the amygdala from high-intensity valeric acid than low-intensity valeric acid when these odors were equated for valence (i.e., both odors about equally unpleasant). By contrast, they did not observe a greater response to the unpleasant (low-intensity) valeric acid when compared to the pleasant (low-intensity) citral odor when they were equated for subjective intensity. They therefore concluded that the amygdala's response was associated with stimulus intensity, but not valence. However, it so happens that these authors selected odors in a narrow intensity range (from 4 to 6 for a 9-point visual rating scale) to manipulate odor valence, and also a narrow valence range (from 4 to 5) to manipulate intensity. The authors thus used odors that were close to the neutral range, or in other words, odors with a limited range of emotional intensity. In our study, odors that were clearly at more extremes of unpleasantness (maximum hedonicity of 0.7 for maximum intensity of 8.0) were perceived as more intense and more likely to have evoked a much stronger emotional reaction than the pleasant odors (maximum hedonicity of 7.0 and maximum intensity of 6.6). This is probably because very unpleasant odors are well known to induce more violent reactions of disgust, whereas rarely do pleasant odors induce an analogous reaction (i.e., intense euphoria). It is for this reason that we believe that the greater response of the left piriform-amygdala to unpleasant odors most reflected the strength of the emotional response. Thus, whereas we agree with Anderson et al. (2003) that the amygdala does not respond to valence per se, we strongly suspect that emotional intensity, and not simply perceived psychophysical intensity, is the decisive factor in activating the amygdala.

Odorous stimulation produced a number of activations in ventral insula, a structure into which piriform cortex extends a limb at the insula's most anterior and ventral extent (Mesulam and Mufson, 1985). Insular activation has been reported in response to a large variety of innocuous tactile, electrical, vibratory, and thermal stimulations, as well as to swallowing, urinary retention/micturation, and visceral stimulation (see Peyron et al., 2000, for review). Olfactory and gustatory stimulations similarly evoke activation within the insular cortex (Zatorre et al., 1992; Fulbright et al., 1998; Small et al., 1997, 1999; Sobel et al., 1998; Faurion et al., 1999; Savic et al., 2000; Cerf-Ducastel and Murphy, 2001; Kareken et al., 2003), especially when stimuli are unpleasant (Kinomura et al., 1994; Kettenmann et al., 1997; Zald et al., 1998b). Insular activity is also found during biological urges, such as dyspnea, hunger, thirst, and nausea (Tataranni et al., 1999; Banzett et al., 2000; Peiffer et al., 2001), as well as during emotional conditions such as hypnosis (Rainville et al., 1999), exposure to frightening faces (Phillips et al., 1997; Morris et al., 1998), sadness, anguish, fear, happiness (Damasio et al., 2000), sexual excitation (Stoleru et al., 1999), phobia, obsessive-compulsive urges (Rauch et al., 1995, 1996), and anticipation of anxiety and pain (Chua et al., 1999; Ploghaus et al., 1999), and aversive conditioning (Büchel et al., 1999). The anterior insula may, in fact, serve as an internal alarm center that alerts individuals to potentially distressing interoceptive sensory stimuli, and imbues them with negative emotional significance (Reiman, 1997).

Lateralization of emotional processing as a function of handedness

We found evidence of lateralized emotional processing, as the OFC and insula showed stronger activation in the left hemisphere. The right OFC was also activated, but more weakly in intensity and spatial extent. We previously reported that the right OFC is mainly related to odor familiarity judgments (Royet et al., 2001). Interestingly, odors presented to the right nostril are perceived as more familiar than when presented to the left (Broman et al., 2001).

Although the data conflict, lateralized differences in olfactory performances (sensitivity and discrimination) as a function of handedness have also been reported (e.g., Toulouse and Vashide, 1899; Youngentob et al., 1982; Cain and Gent, 1991; Frye et al., 1992; Hummel et al., 1998). Recently, hedonic judgments have further been associated with handedness (Dijskerhuis et al., 2002), although the effects were complex due to the interaction between handedness and gender. In the present study, the U-P contrasts showed activation of the left piriform-amygdala region and the most ventral part of the left insula in RH, and of the right insula ventral part in LH. These results constitute the first neuroimaging observation of an interaction between lateralization of olfactory emotional processing and handedness, although Hirsch et al. (1994) and Faurion et al. (1999) also found unilateral activation mainly in the ventral insula of the hemisphere contralateral to the dominant hand in subjects whose tongue was stimulated with various tastes. We did not find lateralized olfactory emotional processing in the right piriform-amygdala region of LH, perhaps because their cognitive functions are less lateralized in general (Laeng and Peters, 1995), or alternatively, because this area does not lateralize strongly in general. Anatomic differences

as a function of handedness have nevertheless been described. Szabo et al. (2001) for instance noted that the right amygdala is larger than the left amygdala in right-handers, but also showed that such an asymmetry is lacking in left-handers. An olfactory stimulus can include a trigeminal component when the intensity of the stimulus is high. Since trigeminal projections are known to be controlateral, activation observed in the present study could be associated with the trigeminal (somatosensory) dimension of our stimuli. It appears, however, that pure somatosensory stimuli activate the second somatic cortex (SII), and that temperature, pain, and numerous interoceptive modalities stemming from the body instead activate dorsal insular cortex (Craig, 2002). The anterior ventral part of insula (closely associated with piriform cortex region) activated in the current study, and this finding is more consistent with the emotional consequences of stimulation, as reported in other data of this literature (e.g., Rauch et al., 1995; Büchel et al., 1999; Morris et al., 1999; Eliott et al., 2000).

Influence of hedonic judgment task

This study is the first to experimentally dissociate cerebral areas involved in either primary hedonic perception or a conscious hedonic judgment task of P and U odors. Since the passive smelling condition systematically preceded the hedonic judgment task condition, comparisons of activation patterns between these two conditions were confounded by an order effect, but also contaminated by possible central habituation from stimulus repetition. Specific activation was nevertheless observed in the hedonic judgment task despite of these different effects. Actively performing the hedonic judgment task specifically induced bilateral activation in the insula and the OFC, but more so in the left hemisphere in RH. This result is consistent with our previous findings with PET (Royet et al., 2000, 2001). Thus, while the piriform-amygdala region is directly involved in the perception of an odor's hedonic intensity, the lateral OFC appears to mediate conscious assessment of P and U odorants. We therefore suspect that the OFC activation in Zald and Pardo's (1997) subjects, who passively detected mildly aversive or P odorants, was evoked by spontaneous hedonic judgments. These observations are consistent with hypotheses that OFC plays a role in evaluating the appetitive or aversive reinforcement value of a stimulus (Zald and Kim, 1996; Rolls, 1999), while prefrontal cortex participates in generating behavior that is flexible and adaptive, rather than deterministically driven by the current sensory input (Elliott et al., 2000). Only a few studies have investigated the effect of task demands in other modalities. For instance, Gorno-Tempini et al. (2001) examined the correlates of incidental and explicit processing of the emotional content of faces expressing either disgust or happiness. Different structures including the left amygdala and OFC were activated depending on whether subjects made explicit judgments either of disgust or happiness, or of either of these emotions compared to a condition devoid of affect. These data indicate that hedonic decisions themselves can be a decisive component in activation, which given the nature of our design, we cannot address with these data.

Influence of gender

We demonstrated clear differences in brain activation patterns between males and females when passively smelling emotional odors or performing odor hedonic judgments. While males mainly showed bilateral activation of the insula, females also activated the left OFC. Cerebral processing of odor perception has been compared between the sexes (Levy et al., 1997, 1999; Yousem et al., 1999), although these studies compared either percentages of activated pixel area to total brain area (Levy et al., 1997, 1999), or percentages of activated voxels in right and left frontal or temporal lobe volumes (Yousem et al., 1999). In addition, the findings were inconsistent, since the size of women's activated fields was smaller in Levy's studies, but considerably larger in Yousem's study. In a more recent PET work, Bengtsson et al. (2001) specifically studied spatial patterns of cerebral activation with statistical parametric mapping and found no gender differences. One possible explanation for the discrepancy between these results is that subjects in the Bengtsson et al. (2001) study did not perform explicit olfactory tasks during scanning, and in particular a hedonic judgment task. Further, these authors used only 5 stimuli that were either pleasant (vanillin, lavender, cedar oil) or somewhat unpleasant (butanol, eugenol). Repeated use of this small number of stimuli might have also led to central habituation (Démonet et al., 1993). Gender-related differences in the patterns of hypothalamic activation were observed by Savic et al. (2001), but they used two odorous pheromone-like steroids as stimuli. Thus, while gender-related differences have been reported in the activation patterns of word processing, visual stimulation, spatial navigation, and working memory (Shaywitz et al., 1995; Levin et al., 1998; Grön et al., 2000; Speck et al., 2000), the present study is the first report demonstrating specific, localized gender differences in the processing of common odors.

Well-known gender differences in olfaction include a female advantage in odor identification (Cain, 1982; Doty et al., 1985; Engen, 1987). This difference holds for familiar, nonbody odors, and all age categories. Anatomical/physiological differences in the structure of the nasal airways, olfactory neural pathways, and endocrine system may account for some of these differences (Doty et al., 1985), but differences in socialization, discriminative ability, and more intentional learning, memory, and verbal facility (Coltheart et al., 1975; Engen, 1987; Schab, 1991) might also contribute. Olfactory hedonic judgments are likely closely related to odor identification (Royet et al., 1999, 2001) and require the left OFC, close to language areas. Split-brain patients who have undergone resection of the corpus callosum (but

not of the anterior commissure) identify odors better when they are presented to the left nostril (Risse et al., 1978; Eskenazi et al., 1988). Women may also process lexical-emotional stimuli more accurately than men (Grunwald et al., 1999), and this advantage might generalize to olfactory perception. Women's greater left OFC activation during olfactory hedonic judgments could thus correspond with better verbal skills and olfactory identification.

Conclusion

To our knowledge, this is the first functional imaging study to examine explicit hedonic processing of olfactory stimuli, and to compare the neural correlates of olfactory hedonic perception across handedness. The results show that, compared to passive perception, overt judgments of the odors' hedonic valence involved a left-dominant network including the insula and orbitofrontal areas. Our results also suggest that the left piriform/amygdala/ventral insula region activates more strongly with U than P odorants, that is, is strongly related to the strength of an emotion, but is independent of perceived subjective intensity and of the emotion's valence. Further studies in which emotional valence and intensity are systematically varied are however needed to confirm these hypotheses. Women also appear to activate left OFC more strongly than did the men. Finally, this same region also appears to be involved most significantly in RH, while LH activate the contralateral (right) piriform/amygdala in response to U odors, suggesting a relationship between olfactory emotional processing and manual dominance.

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