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Left temporo-limbic and orbital dysfunction in schizophrenia during odor familiarity and hedonicity judgments

Jane Plailly,^{a,*} Thierry d'Amato,^b Mohamed Saoud,^b and Jean-P. Royet^{a,c}

^aLaboratoire Neurosciences & Systèmes Sensoriels, Université Claude Bernard Lyon1, UMR CNRS 5020, IFR 19, Institut Fédératif des Neurosciences de Lyon, 50 avenue Tony Garnier, 69366 Lyon cedex 07, France

^bVulnérabilité à la schizophrénie: de la prédiction à la prévention, Université Claude Bernard Lyon1 (EA3092), Centre hospitalier 'Le Vinatier', 69677 Bron, France

^cCERMEP, 69003 Lyon, France

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Impairments of olfactory processing in patients with schizophrenia (SZ) have been reported in various olfactory tasks such as detection, discrimination, recognition memory, identification, and naming. The purpose of our study was to determine whether impairments in odor familiarity and hedonicity judgments observed in SZ patients during a previous behavioral study are associated with modifications of the activation patterns in olfactory areas. Twelve SZ patients, and 12 healthy comparison (HC) subjects, were tested using the H₂¹⁵O-PET technique and 48 different odorants delivered during 8 scans. In addition to an odorless baseline condition, they had either to detect odor, or to judge odor familiarity or hedonicity, giving their responses by pressing a button. Regional cerebral blood flows during olfactory conditions were compared with those for baseline condition. Between-group analyses were then performed, and completed by regions of interest analyses. Both groups had equivalent ability for the detection of suprathreshold odorants, but patients found odors less familiar, and pleasant odors less pleasant than HC subjects. These behavioral results were related to functional abnormalities in temporo-limbic and orbital olfactory regions lateralized in the left hemisphere: the posterior part of the piriform cortex and orbital regions for familiarity judgments, the insular gyrus for hedonicity judgments, and the left inferior frontal gyrus and anterior piriform cortex/putamen region for the three olfactory tasks. They mainly resulted from a lack of activation during task conditions in the SZ patients. These data could explain olfactory disturbances and other clinical features of schizophrenia such as anhedonia.

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Keywords: Schizophrenia; activation deficit; odor familiarity judgment; odor hedonicity judgment; PET

Introduction

Schizophrenia is a chronic, severe, and disabling brain disease that presents impairments of cognitive and emotional functions, such as perception, inferential thinking, motivation, thought, and speech (Schultz and Andreasen, 1999). The processing of olfactory information is a cognitive function which is disturbed in patients with schizophrenia (SZ), and behavioral evidence of this dysfunction is found with odor discrimination, recognition memory, identification, and naming tasks (Kohler et al., 2001; Kopala et al., 1993, 1994; Moberg et al., 1999; Saoud et al., 1998; Stedman and Clair, 1998; Wu et al., 1993). Although abnormalities were found at the level of the peripheral olfactory pathways (Arnold et al., 2001; Turetsky et al., 2000), several studies reported no decrease in the olfactory sensitivity of patients (Geddes et al., 1991; Good et al., 1998; Kohler et al., 2001; Kopala et al., 1989, 1993), suggesting that deficits in suprathreshold olfactory tasks partly arise from dysfunction of the central olfactory areas.

Over the last 10 years, our knowledge of olfactory neural networks in healthy subjects has been increasing through the use of cerebral imaging. It has been shown that the temporo-limbic (piriform cortex, amygdala, insular gyrus) and inferior frontal (orbitofrontal and inferior frontal gyri) regions are strongly involved in odor discrimination, recognition memory, and identification tasks (for review, Kober and Kettenmann, 2000; Royet and Plailly, 2004; Savic, 2001, 2002, 2005; Zald and Pardo, 2000; Zatorre and Jones-Gotman, 2000). It has also been shown that the anatomy and metabolism of these neural networks are disturbed in SZ patients, particularly with a reduction in grey matter volume (Turetsky et al., 2003b) and a lower rate of cerebral glucose metabolism (Bertollo et al., 1996; Clark et al., 1991).

Despite the behavioral, structural, and metabolic clues associated with olfactory deficits in schizophrenia, only three previous studies have focused on the functional bases of such olfactory impairments. Turetsky et al. (2003a) showed abnormalities in the amplitude and latency of the evoked potentials obtained from

* Corresponding author. Fax: +33 4 37 28 76 01.

E-mail address: plailly@olfac.univ-lyon1.fr (J. Plailly).

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passive odor presentation, and explained them by impaired odor sensitivity and identification. Evoked potentials were nevertheless obtained from the scalp and these data only indirectly allowed them to infer which neural networks were presenting a disturbance. Using single photon emission computed tomography, Malaspina et al. (1998) demonstrated that schizophrenia patients did not increase activation of their hippocampus and visual association areas for the odor identification test compared to a picture matching task, as did the control group, and showed hypometabolism in right-sided cortical areas for odor identification. Thus, the only regions disclosed were those where activation differed between both tasks but did not evidence any specific dysfunction of the olfactory networks. Finally, Crespo-Facorro et al. (2001) studied the loss of the capacity to experience pleasure in SZ patients and investigated the specific neural systems underlying olfactory emotional disturbances. Participants experienced a pleasant odor and an unpleasant odor, and the authors then found that patients failed to activate several limbic and paralimbic regions during the experience of an unpleasant odor.

An olfactory experience involves not only an emotional response but also perceptual processes associated with recognition memory and related to identification. In our work, we currently use several olfactory tasks such as the detection task and intensity, hedonicity, familiarity, and edibility judgments, and have shown through cerebral imaging in healthy subjects that several areas of the limbic and paralimbic regions participate in these processes (Plailly et al., 2005; Royet et al., 1999, 2000, 2001, 2003). The purpose of examining functional abnormalities in these various structures as a function of the different olfactory tasks performed by patients therefore appears crucial if we are to better understand the psychopathology of schizophrenia. Recent behavioral studies have proved that, in addition to the hedonicity judgment, that of familiarity but not intensity is impaired in SZ patients (Hudry et al., 2002; Moberg et al., 2003).

The current study was undertaken to investigate whether activation patterns specifically associated with the odor suprathreshold detection task and the odor familiarity and hedonicity judgment tasks in healthy subjects are modified in SZ patients. Twelve SZ patients and 12 healthy comparison (HC) subjects were tested, using positron emission tomography (PET) to compare regional cerebral blood flow (rCBF) patterns between both groups. Four different conditions were tested twice: an odorless baseline (B) condition, a detection (D) task, and familiarity (F) and hedonicity (H) judgment tasks.

Material and methods

Subjects

Twelve SZ patients and 12 HC subjects, all male and right-handed, participated in this study (Table 1). HC subjects were recruited by local newspaper advertisement. Patients were recruited from the Vinatier Hospital (Lyon, France) and met the DSM-IV criteria for schizophrenia (American Psychiatric Association, 1994). Psychiatric diagnoses were established, by consensus of the two psychiatrists involved in the current study, in accordance with the Schedule for Affective Disorders and Schizophrenia (SADS) (Fyer et al., 1985) and included an in depth review of the patients' medical records. The Positive And Negative Syndrome Scale (PANSS; Kay et al., 1987) was then used to assess the

Table 1

Demographic and clinical data for HC subjects and SZ patients

	HC subjects	SZ Patients
<i>Demographic variables</i>		
Age	32.83 ± 5.78	29.67 ± 7.06
Education (years)	10.63 ± 1.76	10.50 ± 1.86
Smoking history (cigarettes/day)	4.71 ± 6.95	11.67 ± 10.52
<i>Personal psychiatric history</i>		
Length of psychiatric history (months)	–	66.33 ± 46.13
<i>Medication</i>		
Antipsychotic (mg/day CPZ Eq.)	–	429.17 ± 216.83
<i>PANSS scores</i>		
Negative symptoms score	–	22.83 ± 4.91
Positive symptoms score	–	16.00 ± 4.33

Mean ± standard deviations.

patients' psychopathology (Table 1). Patients were clinically stable with no change in medication for at least 1 month before the study. Through SADS evaluations, selected HC subjects had neither current DSM-IV Axis I psychiatric diseases nor schizophrenia spectrum personality disorders, i.e. schizotypal, schizoid and paranoid personality disorders. Furthermore, none of them had any family history of psychopathology. Both groups were paired in age ($F_{(1,22)} = 1.445$, $P = 0.2422$), educational level ($F_{(1,22)} = 0.029$, $P = 0.8672$), and smoking history ($F_{(1,22)} = 3.657$, $P = 0.0690$). Subjects were all selected on the basis of their olfactory ability with a forced-choice suprathreshold detection test (at least 75% correct) and on the mean duration of their breathing cycle (from 2.5 to 6 s/cycle). The exclusion criteria for all subjects included possible brain damage, major medical problems, current substance abuse, lithium medication, known anosmia, rhinal disorders (colds, active allergies, history of nasal–sinus surgery, or asthma), and anxiety. Participation required medical screening and written informed consent. The study was approved by the local Institutional Review Board and conducted according to French regulations on biomedical experiments on healthy volunteers and out-patients.

Odorous stimuli

Seventy odorants and 14 odorless stimuli were used during the scans: 28 odorants for each of the F and H conditions, and 14 odorants and 14 odorless stimuli for the D condition (Table 2). For the F condition, each of the 2 sets was composed of 7 familiar and 7 unfamiliar odorants to respectively provide the highest or lowest familiarity scores (rated from 0 to 10 with a rating scale) from data previously obtained by Royet et al.'s (1999) study (set 1: 5.99 ± 0.79 and 3.48 ± 0.49 , respectively; set 2: 5.56 ± 1.21 and 3.59 ± 0.90 , respectively). For the H condition, 2 sets were each composed of 7 pleasant and 7 unpleasant odorants, to provide the highest or lowest hedonicity scores (set 1: 6.48 ± 0.45 and 1.77 ± 0.72 , respectively; set 2: 6.25 ± 0.56 and 2.00 ± 0.55 , respectively). For the D condition, 2 sets were composed of 7 neutral odorants and 7 bottles with odorless air. For training, 14 odorants and 14 odorless stimuli were used, split into 2 sets of 7 neutral odorants and 7 bottles with odorless air. In each set, the presentation order of the stimuli was pseudorandomized but identical for all subjects. Odorants were diluted to a concentration

Table 2

Lists of odorants used for the three olfactory conditions (D, F, and H) during the two scans (Scan1 and Scan2)

	Olfactory conditions		
	D	F	H
Scan1	Cypress	Pine needle	Honeysuckle
	3-Methyl anisol	<i>Isopropylacetate</i>	Lemon
	NO	Liquorice	<i>Tetralin</i>
	NO	<i>Violet</i>	<i>Tetrahydrofurane*</i>
	Geranium	<i>Citronella</i>	Passion fruit
	NO	White spirit	Lavender
	Basil	<i>Diethyl ether</i>	<i>Butyric acid</i>
	NO	Parsley	<i>2-Heptanol</i>
	Eucalyptus	<i>Vervain</i>	<i>Tetrahydrothiophene*</i>
	Chamomile	Guaiacol	Apricot
	NO	Hexyl cinnamaldehyde	Pear
	Tarragon	<i>Anise</i>	<i>Garlic</i>
	NO	<i>trans-2-Hexenal</i>	Gardenia
	NO	<i>Hexanal</i>	<i>Ethyl diglycol</i>
Scan2	Toluene	Ethyl benzoyl acetate	<i>1,4-Dichlorobutane</i>
	NO	2-Octanol	Lilac
	Green lily	<i>Ethyl acetate</i>	<i>Heptanal</i>
	NO	<i>Banana</i>	<i>Isovaleric acid*</i>
	Coffee	<i>Tar</i>	Caramel
	Patchouli	Blackcurrant	Rose
	NO	β -Caryophyllene	<i>Furfuryl mercaptan*</i>
	NO	<i>Bitter almond</i>	Coconut
	Carrot	Diethyl maleate	Wild Strawberry
	NO	<i>Thyme</i>	<i>2-Bromophenol</i>
	Smoked salmon	<i>Acetophenone</i>	Mint
	NO	Cedar	<i>Ethylmercaptan*</i>
	NO	<i>Garrigue</i>	<i>2,5-Dimethyl pyrrole</i>
	Turpentine	Hazelnut	Jasmine

D, detection; F, familiarity; H, hedonicity; NO, no odor; italics, odorants selected as familiar for the F condition, and unpleasant for the H condition

* 1% diluted odorant.

of 10% using mineral oil (Sigma Aldrich, France). The concentration of the products with very high potency was limited to 1%. Five milliliters of this solution was absorbed into compressed polypropylene filaments inside 100-ml white polyethylene squeeze bottles with a dropper (Osi, France).

Stimulating material

The stimulating material used allowing synchronization of the stimulation with breathing has been described in a previous paper (Vigouroux et al., 2005). Briefly, vector air is pumped with a compressor, treated with a charcoal filter, and flows into an air-dilution olfactometer. At the end of expiration, the stimulus is injected into the olfactometer by squeezing the bottle and delivered into a commercially available anesthesia mask (Respiron, Europe Medical, France). Breathing is recorded with a thermal probe close to the right nostril, and controlled by stereo headphones. Our subjects were stimulated during every other breathing cycle. For a mean respiratory cycle of about 3–4 s, about 13 (13.3 ± 1.8) stimulations were performed per scan.

Experimental procedure

During scanning, each subject underwent a total of 8 PET scans, with two scans (Scan1 and Scan2) for each of the following 4

conditions: B, D, F, and H. To control the cognitive processing performed by the subjects, tasks were conducted in an invariant order. The odorless B condition was the first one to avoid the influence of the olfactory conditions. The D condition preceded the F and H conditions to prevent subjects from performing high-level processing. The H condition, that included highly aversive odors, was performed last to avoid inducing a strong emotional reaction in SZ patients who may then have refused to continue the experiment. A scan was performed approximately every 10 min. To avoid surprising the subjects and to optimize data acquisition, the stimulations started 30 s before the beginning of the scan.

General instructions were provided at the beginning of the experiment, and specific task instructions were given before each scan to limit contamination between the different cognitive tasks. During olfactory conditions, the subjects were asked to rate whether they smelled an odor or not (D condition) or whether the odor was familiar or not (F condition), or unpleasant or not (H condition). They had to answer by pressing a one-key press button with the index finger of their right hand only when the response was 'yes', but not to press it at all if the response was 'no'. The use of the one key instead of the usual two-key press button box was in response to experimental observation during the preliminary study; patients mixed up the two buttons and had much better abilities using only a one-button response-box. During the B condition, the subjects were requested to press the button at random. The 'yes' judgments and the reaction times were recorded with a Macintosh PowerBook G3 computer (Apple Computers, Cupertino, CA). The experimental design was programmed using 'PsyScope' software (Cohen et al., 1993). Scans were performed while the subjects kept their eyes closed and the room lighting was dimmed. Prior to scanning, subjects performed a training session in which they were trained to breath regularly without sniffing, to detect (odor vs. no odor) stimulations during inspiration and to give a manual response as quickly as possible with the one-key press button before the following breath.

PET imaging

Subjects were imaged with a whole-body tomograph (Siemens EXACT HR+) in 3-D mode, with a transaxial resolution of 4.5 mm (FWHM). Sixty-three slices of 2.43 mm with an axial field of view of 15.2 mm were acquired during each scan. Subjects were positioned using a thermoplastic facemask (Tru-Scan Imaging Inc., Annapolis, MD, USA) that reduced head movement and allowed reproducible positioning. The effects of radiation self-attenuation were corrected by an initial 10-min transmission scan of each subject using an external positron-emitting isotope (^{68}Ge). An i.v. bolus injection of 333 MBq H_2^{15}O was given for each run in the brachial vein of the left forearm through an indwelling catheter. The scan to record rCBF began when the radioactive counts exceeded the background activity by 200% and lasted 60 s. The images were attenuation-corrected and reconstructed with filtered back projection using a Hanning filter.

Image analysis

Statistical Parametric Mapping (SPM) 99 (Wellcome Department of Cognitive Neurology, London, UK) was used for image preprocessing and analysis. The steps included interscan realignment, spatial normalization (default $7 \times 8 \times 7$ basis function, 12 nonlinear iterations) to stereotactic space defined by the Montreal

Neurological Institute's (MNI) reference brain, and smoothing of the images using a 12-mm isotropic 3-D Gaussian kernel. The localization of activation clusters was given with reference to the MNI MRI template and the atlas produced by Mai et al. (1997).

Random effects analyses were performed on the whole brain using the 'single-subject: conditions and covariates' PET model to average task conditions into a single contrast image. Three contrasts were performed by comparing brain responses obtained in olfactory conditions to those obtained in the B condition: D–B, F–B, H–B. Activations related to the use of the one-key press button could be suppressed in the olfactory conditions since participants also used it in the B condition. In a second step, contrast images were then analyzed in separate 'basic model' two-sample *t* tests to highlight between-group differences (SZ vs. HC), using an uncorrected height threshold ($P < 0.001$), a cluster of more than 15 adjacent voxels, and a $Z \geq 3.40$ at voxel level. Since the aim of the study was to investigate differences between the two groups, only results from the between-group analyses were examined. We limited our statistical inferences to principal olfactory regions (temporo-limbic and inferior frontal areas), and will report here only those activation foci that fell within these areas.

Firstly, to evidence the brain areas significantly activated in the three contrasts (D–B, F–B, and H–B), an analysis of conjunction was performed. Contrast images were transformed into true-false maps of significant and nonsignificant voxels (using the threshold of $P < 0.001$ uncorrected and an extent threshold of $k > 5$), and voxels with 'true' values in the three contrasts were considered as being part of the overlap.

Secondly, to determine activation levels as a function of the different conditions (groups $\times$ tasks), we extracted, from the random effects analyses, the activation levels found for each of the 12 HC subjects and the 12 SZ patients and for both conditions of a given contrast at the level of the peak voxel coordinates. The presence of significant activation in the regions contralateral to those observed in the piriform and insular areas of the left hemisphere was tested by measuring the activation levels in the right hemisphere at the level of contralateral coordinates of the maximum peak voxel of these activation clusters.

Lastly, to test the task-specificity of the between-group differences in the piriform region and the left inferior frontal gyrus, we performed functional ROI analyses in contrasts comparing the olfactory conditions with themselves (D, F, and H). Anatomical ROIs of the amygdalae were finally defined and the mean activation levels within these ROIs were extracted for each of the 24 participants and for the different conditions. Analyses of variance (ANOVA) and mean comparisons were then performed to compare the activation levels as a function of the groups and tasks. The MarsBar SPM toolbox (<http://marsbar.sourceforge.net/>) was used to define ROIs and to perform all analyses, except for the anatomical ROIs of the amygdala which were defined using MARINA software (<http://www.bion.de/Marina.htm>).

Results

Behavioral results

For the detection task, the mean scores for the accuracy of the responses in both repetitions (Scan1 and Scan2) were 0.863 ± 0.158 and 0.871 ± 0.108 in HC subjects, and 0.858 ± 0.149 and 0.878 ± 0.076 in SZ patients. A two-way ANOVA with repeated

measurements did not show any significant difference between groups ($F_{(1,22)} = 0.003$, $P = 0.954$) and repetitions ($F_{(1,22)} = 0.291$, $P = 0.595$), and no significant interaction ($F_{(1,22)} = 0.029$, $P = 0.8663$) between these two factors, indicating that both groups detected suprathreshold odors with the same accuracy.

To analyze the accuracy of behavioral responses, and since familiarity and hedonicity judgments depend on personal experience, familiar/unfamiliar, and pleasant/unpleasant odors were selected as a function of the HC subjects' responses rather than simply using the initial selection chosen by the experimenters. The percentage of odors judged familiar and unpleasant in both groups of subjects is illustrated in Fig. 1. For the familiarity judgment task, a two-way ANOVA indicated a significant effect for group ($F_{(1,22)} = 5.961$, $P = 0.0231$), and familiarity judgment ($F_{(1,22)} = 125.34$, $P < 0.0001$) factors, but no significant task $\times$ group interaction ($F_{(1,22)} = 1.112$, $P = 0.3031$).

For the hedonicity judgment task, a two-way ANOVA indicated a significant effect for the hedonicity task factor ($F_{(1,22)} = 193.26$, $P < 0.0001$), but not for the group factor ($F_{(1,22)} = 2.734$, $P = 0.1124$). A significant hedonicity judgment $\times$ group interaction was also noted ($F_{(1,22)} = 20.106$, $P = 0.0002$), further showing that the patients judged pleasant odors less pleasant than the HC subjects ($P = 0.0050$). No difference between either group was observed for unpleasant odors ($P = 0.4430$).

Reaction times were analyzed for detection, familiarity, and hedonicity judgment tasks as a function of group (HC and SZ) and repetition (Scan1 and Scan2) factors. A three-way ANOVA showed a significant effect for group ($F_{(1,22)} = 12.624$, $P = 0.0018$), task ($F_{(2,44)} = 44.632$, $P < 0.0001$), and repetition ($F_{(1,22)} = 9.017$, $P = 0.0066$) factors, and a significant task $\times$ repetition interaction ($F_{(2,44)} = 6.402$, $P = 0.0036$). No other interaction was significant. The group effect was due to longer reaction times in SZ patients than HC subjects (Fig. 2). Multiple mean comparisons indicated that reaction times, all the subjects considered together, were longer for the hedonicity judgment task than for detection ($P < 0.0001$) and longer for the familiarity than the hedonicity judgment task ($P < 0.0001$).

PET results

Significant rCBF differences between HC subjects and SZ patients groups (HC minus SZ, and SZ minus HC) for olfactory minus B contrasts were extracted and are listed in Table 3.

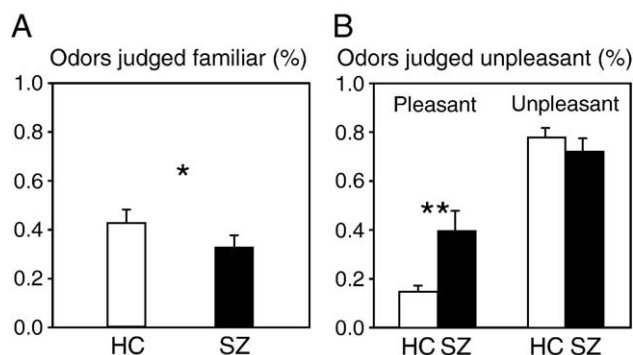


Fig. 1. Percentages in HC subjects and SZ patients of odors judged (A) familiar among all odors, and (B) unpleasant among odors considered pleasant (left) and unpleasant (right) by most of the HC subjects. Vertical bars, standard errors of the mean; * $P < 0.05$; ** $P < 0.01$.

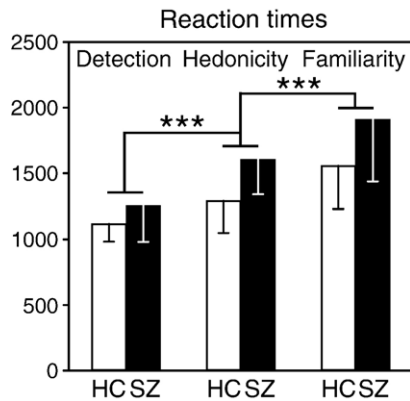


Fig. 2. Mean reaction times in ms to detect odors, and judge them unpleasant and familiar in HC subjects and SZ patients. Vertical bars, standard errors; *** $P < 0.001$.

HC minus SZ contrast

For the D–B contrast, significant rCBF variations were detected in the left anterior part of the frontal piriform cortex ($-24, 10, -14$), and the left inferior frontal gyrus in its orbital part ($-46, 40, -8$) (Fig. 3). Detailed examination of data for the piriform cortex showed that the significant group $\times$ task interaction ($F_{(1,22)} = 21.266$, $P < 0.0001$) resulted from a higher activation level in the HC subjects ($P < 0.0001$) in the D than B condition. For the inferior frontal gyrus, the significant group $\times$ task interaction ($F_{(1,22)} = 17.340$, $P = 0.0004$) resulted from a lower activation level in the SZ patients ($P < 0.0001$) in the D than B condition. No activation levels difference was noted in the B condition between groups (piriform cortex: $P = 0.1999$; inferior frontal gyrus: $P = 0.9002$).

For the F–B contrast, differences in rCBF were observed in the left inferior part of the putamen extending ventrally to the posterior part of the frontal piriform cortex ($-20, 2, -6$), left superior temporal gyrus ($-48, 8, -16$), right gyrus rectus ($10, 36, -24$), left medial orbital gyrus ($-18, 30, -18$), and left orbital part of the inferior frontal gyrus ($-42, 32, -4$). For the putamen/piriform cortex region, the between-group difference [group $\times$ task interaction: $F_{(1,22)} = 32.959$, $P < 0.0001$] was due to an rCBF

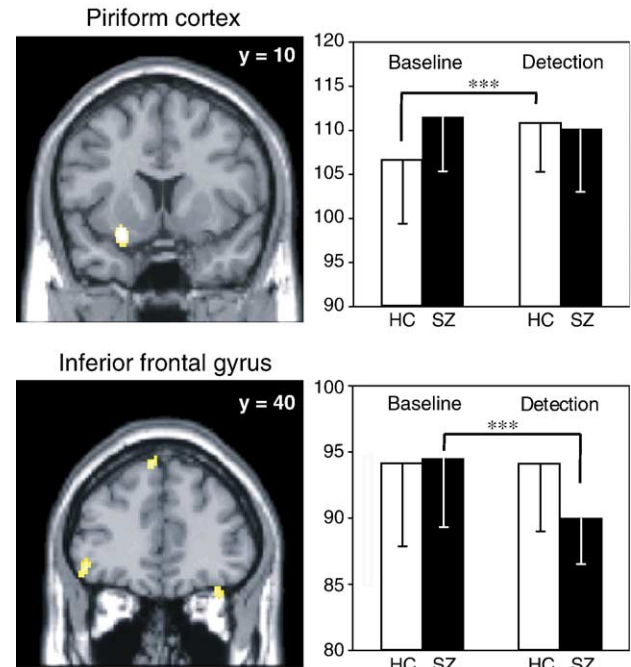


Fig. 3. rCBF differences found in the D–B contrast between HC subjects and SZ patients in the piriform cortex and inferior frontal gyrus. The SPMs are superimposed on coronal sections of a T1-weighted scan (thresholded at $P = 0.0001$). Graphs: levels of activation in the B and D conditions in these two areas in HC subjects and SZ patients inferred from functional ROIs. Vertical bars, standard errors; *** $P < 0.001$.

increase in HC subjects ($P < 0.0001$) and an rCBF decrease in SZ patients ($P = 0.0080$) in the F condition when compared with the B condition (Fig. 4). The rCBF was also significantly higher in SZ patients than HC subjects ($P = 0.0090$) in the B condition. Significant group $\times$ task interactions noted for the four other areas [superior temporal gyrus: $F_{(1,22)} = 21.010$, $P = 0.0001$; gyrus rectus: $F_{(1,22)} = 19.551$, $P = 0.0002$; medial orbital gyrus: $F_{(1,22)} = 17.542$, $P = 0.0004$; inferior frontal gyrus: $F_{(1,22)} = 15.781$, $P = 0.0006$] resulted from a higher activation level in the HC subjects ($P = 0.0047$, $P < 0.0001$, $P < 0.0001$, and $P < 0.0001$, respectively) in the F than B condition. No activation level

Table 3

Brain regions with significant rCBF differences when comparing the contrast images of both groups ('HC–SZ' and 'SZ–HC' contrasts)

Contrasts	Anatomic regions	L/R	k	Z	MNI		
					x	y	z
<i>HC-SZ</i>							
D–B	Frontal piriform cortex, anterior part	L	101	4.13	–24	10	–14
	Inferior frontal gyrus, orbital part	L	64	3.54	–46	40	–8
F–B	Putamen/frontal piriform cortex, posterior part	L	95	4.44	–20	2	–6
	Superior temporal gyrus	L	25	3.80	–48	8	–16
	Gyrus rectus	R	57	3.70	10	36	–24
	Medial orbital gyrus	L	41	3.55	–18	30	–18
H–B	Inferior frontal gyrus, orbital part	L	19	3.41	–42	32	–4
	Insular gyrus, anterior and ventral part	L	218	4.13	–26	20	–6
	Inferior frontal gyrus, orbital part	L	43	3.58	–46	34	–8
<i>SZ-HC</i>							
D–B	Insular gyrus	R	44	4.65	40	2	12

Note. D, detection; F, familiarity; H, hedonicity; B, baseline; HC, healthy comparison subjects; SZ, patients with schizophrenia; L/R, left or right hemisphere; *k*, cluster of voxels size; *Z*, *Z* value; *x*, *y*, *z*, MNI co-ordinates in left–right (*x*), posterior–anterior (*y*), and inferior–superior (*z*) planes.

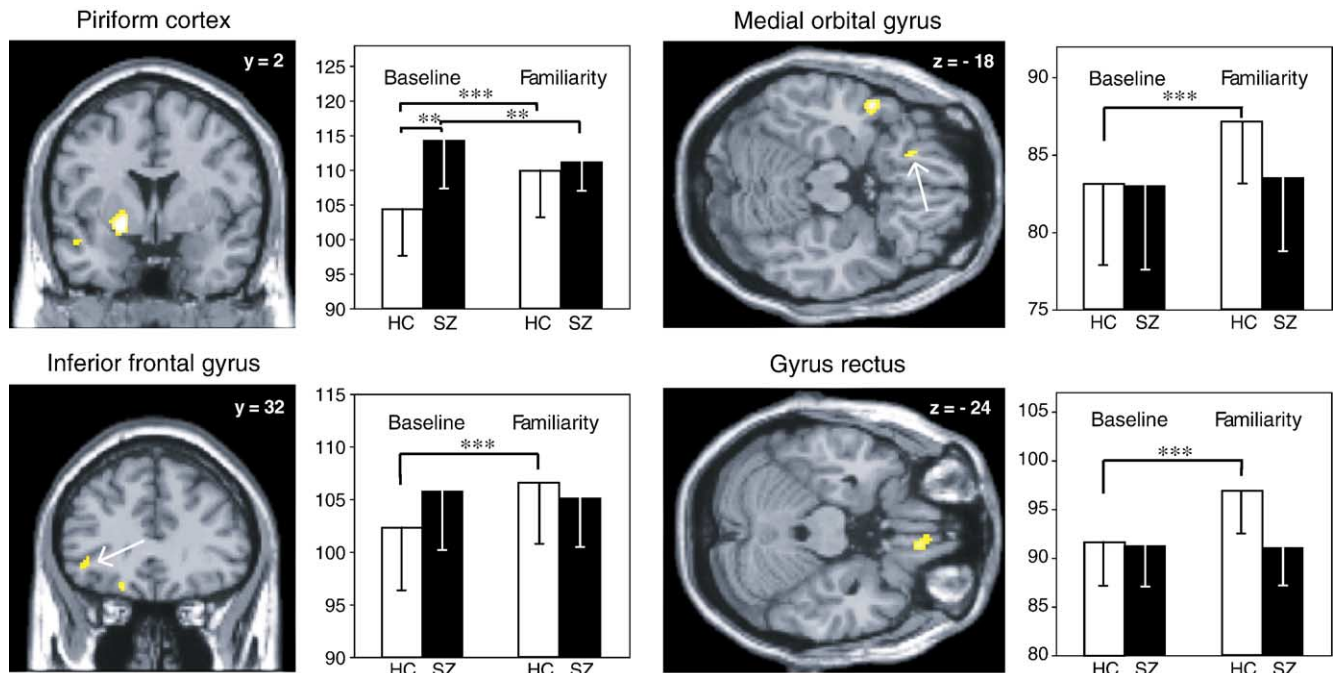


Fig. 4. rCBF differences found in the F–B contrast between HC subjects and SZ patients in the piriform cortex, inferior frontal gyrus, medial orbital gyrus, and gyrus rectus. The SPMs are superimposed on coronal and horizontal sections of a T1-weighted scan (thresholded at $P = 0.0001$). Graphs: levels of activation in the B and F conditions in these four areas in HC subjects and SZ patients inferred from functional ROIs. White arrow, activation for which a ROI was performed; vertical bars, standard errors; $**P < 0.01$; $***P < 0.001$.

difference in the B condition was found between groups ($P = 0.2458$; $P = 0.8271$; $P = 0.9580$; and $P = 0.2748$, respectively).

For the H–B contrast, significant variations in rCBF were detected in the left anterior ventral insular gyrus ($-26, 20, -6$) extending laterally and posteriorly to the anterior part of the frontal piriform cortex, and in the left inferior frontal gyrus, in its orbital part ($-46, 34, -8$) (Fig. 5). Significant group $\times$ task interactions found for the insular gyrus ($F_{(1,22)} = 26.490$, $P < 0.0001$) and the inferior frontal gyrus ($F_{(1,22)} = 17.833$, $P = 0.0004$) were due to a higher activation level in the H than B condition in the HC subjects ($P < 0.0001$ and $P = 0.0010$, respectively). The second interaction was also explained by a lower activation level in the H than B condition in the SZ patients ($P = 0.0394$). No activation difference was found in the B condition between groups for both areas ($P = 0.5113$, and $P = 0.4346$, respectively).

The conjunction analysis showed an overlap between the three olfactory conditions when compared to the B condition in a region

between the left anterior part of the temporal piriform cortex and the lower part of the putamen ($-25, 11, -12$), and in the left inferior frontal gyrus ($-45, 32, -5$) (Fig. 6).

Comparing olfactory conditions among themselves, ROI analyses on the functional clusters overlapping at the level of the left piriform/putamen region (clusters centered on $-20, 2, -6$ coordinates in the F–B contrast, and on $-26, 20, -6$ coordinates in the H–B contrast) showed significant activation differences in the piriform/putamen region in the F–D and F–H contrasts ($t = 2.56$, uncorrected $P = 0.0089$; and $t = 2.14$, uncorrected $P = 0.0216$, respectively), and an activation difference which tended to be significant in the insular/piriform region in the H–D ($t = 1.44$, uncorrected $P = 0.0816$), but not in the H–F ($t = 1.15$, uncorrected $P = 0.1315$) contrast. ROI analyses on the functional clusters overlapping at the level of the left inferior frontal gyrus (clusters centered on $-42, 32, -4$ coordinates in the F–B contrast, and on $-46, 34, -8$ coordinates in the H–B contrast) showed significant

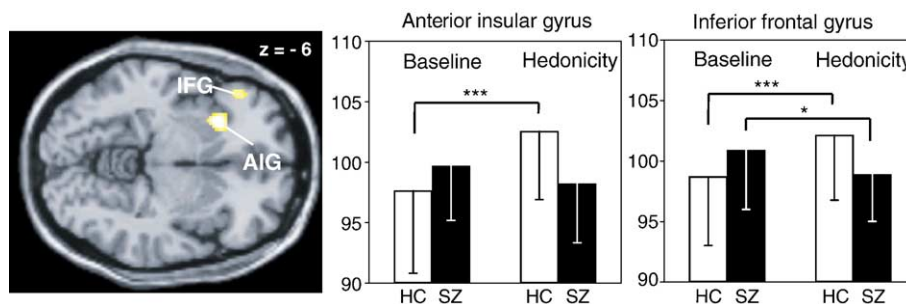


Fig. 5. rCBF differences found in the H–B contrast between HC subjects and SZ patients in the anterior insular gyrus (AIG) and inferior frontal gyrus (IFG). The SPMs are superimposed on a horizontal section of a T1-weighted scan (thresholded at $P = 0.0001$). Graphs: levels of activation in the B and H conditions in these two areas in HC subjects and SZ patients inferred from functional ROIs. Vertical bars, standard errors; $*P < 0.05$; $***P < 0.001$.

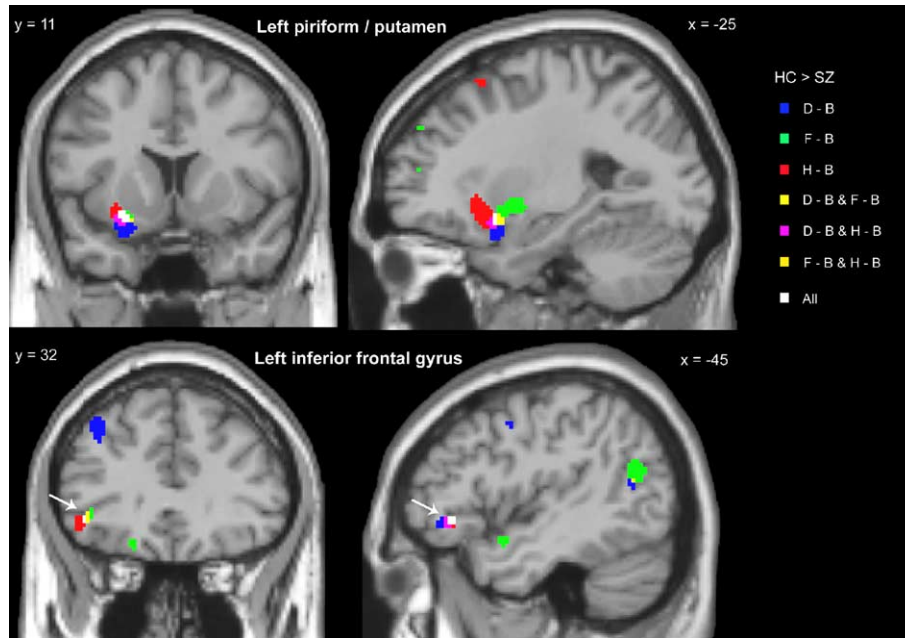


Fig. 6. Overlap of the rCBF differences found in the D–B (blue color), F–B (green color), and H–B (red color) contrasts between HC subjects and SZ patients in the left piriform cortex/putamen region (top) and left inferior frontal gyrus (bottom). The overlap between D–B and F–B contrasts is represented in yellow; the overlap between D–B and H–B contrasts is represented in pink; the overlap between F–B and H–B are represented in orange; and the overlap between the three contrasts is represented in white. The contrast images are superimposed on coronal (left) and sagittal (right) sections of a T1-weighted scan (thresholded at $P = 0.001$).

activation differences for the first cluster, in the F–D and F–H contrasts ($t = 3.91$, uncorrected $P = 0.0003$; and $t = 2.91$, uncorrected $P = 0.004$, respectively), and for the second cluster, in the H–D and H–F contrasts ($t = 2.73$, uncorrected $P = 0.006$; and $t = 1.98$, uncorrected $P = 0.0300$, respectively).

SZ minus HC contrasts

Only comparisons between D and B conditions showed a significant rCBF difference (Table 3). This was detected in the right medial part of the insular gyrus (40, 2, 12) and resulted from a higher activation level in the D than B condition in the SZ patients ($P < 0.0001$), but not in the HC subjects ($P = 0.0793$). No difference in between-group activation was found in the B condition ($P = 0.2003$).

Activations in other olfactory areas

To test lateralization of cerebral dysfunction in SZ patients in the temporo-limbic olfactory areas, we performed analyses in areas contralateral to those found to be activated in our study. Comparing HC subjects minus SZ patients, we thus measured activation in the piriform cortex in the D–B contrast (24, 10, –14), the putamen/piriform cortex region in the F–B contrast (20, 2, –6), and the anterior insula in the H–B contrast (26, 20, –6). A four-way ANOVA with repeated measurements on hemisphere, region, and task factors showed a significant effect of group ($F_{(1,22)} = 23.894$, $P < 0.0001$), but not hemisphere ($F_{(1,22)} = 0.037$, $P < 0.8501$) or region ($F_{(2,44)} = 0.050$, $P = 0.9516$), and task ($F_{(2,44)} = 0.531$, $P = 0.5918$) factors. Only the group $\times$ hemisphere interaction (Fig. 7) was found to be significant ($F_{(1,22)} = 11.477$, $P = 0.0026$) and was explained by higher activation in HC subjects than SZ patients in the left ($P < 0.0001$), but not right ($P = 0.4744$) hemisphere, and higher

activation in the left than right hemisphere in HC subjects ($P = 0.0190$).

Since differences of activation levels between the olfactory and B conditions could be similar for the HC subjects and SZ patients, between-group comparisons could consequently equal zero. To test this, and since the amygdala has been shown to be involved in emotional intensity processing (Zald and Pardo, 1997; Royet et al., 2003), we examined the H–B contrast in the two groups combined (HC + SZ) and observed bilateral activation clusters centered in the temporal claustrum, just beside the amygdala, but spreading over its lateral part (–28, 2, –18; $k = 317$; $Z = 4.93$; and 24, 4, –24; $k = 64$; $Z = 3.59$). These results were reinforced by ROI analyses of

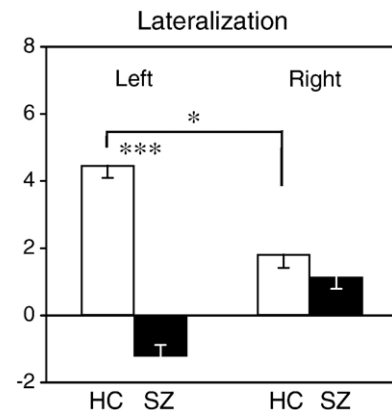


Fig. 7. Interaction between groups (HC vs. SZ) and hemispheres (right vs. left) of rCBF differences found in the piriform cortex in the D–B and F–B contrasts (peak coordinates: 24, 10, –14 and 20, 2, –6, respectively), and in the anterior ventral insula in the H–B contrast (26, 20, –6). Vertical bars, standard errors; * $P < 0.05$; *** $P < 0.001$.

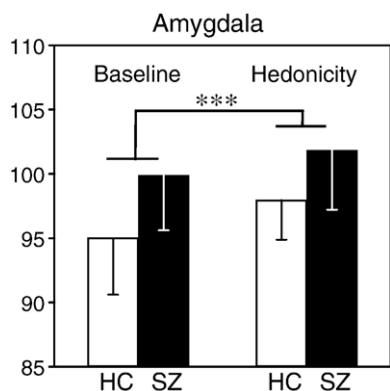


Fig. 8. Levels of activation evoked in the HC subject and SZ patient groups and in the B and H conditions in the left and right amygdalae inferred from ROIs. Vertical bars, standard errors; *** $P < 0.001$.

the amygdalae performed with the H–B contrast in the two groups. A three-way ANOVA applied to these data showed significant differences in the H–B contrast as a function of groups ($F_{(1,22)} = 8.917$, $P = 0.0068$) and tasks ($F_{(1,22)} = 22.664$, $P < 0.0001$), but not of brain side ($F_{(1,22)} = 0.088$, $P = 0.7696$). Activation was thus higher in SZ patients than HC subjects and higher in the H than B condition (Fig. 8). No significant interaction between the three factors was noted.

Discussion

The current study was undertaken to determine whether impairments in odor familiarity and hedonicity judgments in SZ patients are associated with modification of activation patterns in their olfactory areas. Our results are consistent with other findings suggesting that schizophrenia is a neurobehavioral disorder resulting partly from a dysfunction in the temporo-limbic brain areas. In contrast to HC subjects, patients evidenced functional abnormalities in the olfactory areas during detection of odors as well as during familiarity and hedonicity judgment tasks. Major functional disturbances were observed in the left frontal piriform cortex, the left inferior frontal, anterior ventral insular, medial orbital, superior temporal gyri, and the right gyrus rectus. They resulted from a lack of activation in brain areas during olfactory tasks in all cases but one.

Central olfactory impairments in SZ patients

In the current study, patients had the same acuity for detecting suprathreshold odors as healthy subjects. This leads us to speculate that the olfactory deficits observed in the SZ patients during more complex tasks such as familiarity or hedonicity judgments (both in terms of correct responses and reaction times) could be associated with central impairments. However, despite the same detection accuracy observed in both groups during the suprathreshold detection task, patients exhibited activation patterns different from those in healthy subjects. They had a relative lack of activation in the left piriform cortex and inferior frontal gyrus, and showed hyperactivation in the right insular gyrus, compared to the HC group. It could be hypothesized that, when subjects and patients detected an odor, they performed minimal cognitive judgments that differed between populations.

Since no breathing data were recorded in this study, a source of potential confound may lie in the different breathing patterns across

conditions and groups, as it has previously been shown that sniffing alone can induce piriform activation (Sobel et al., 1998). However, subjects in the present study were trained to breathe regularly and not to sniff. In previous studies, when breathing data were recorded and analyzed (Plailly et al., 2005; Royet et al., 2003), we did not evidence respiratory flow differences between experimental conditions when subjects were asked to breathe in the same way. Furthermore, Kareken et al. (2004) recently compared piriform activation induced by either the sniffing or the velopharyngeal closure method, which prevents subject-induced airflow through the nasal passage. They did not show any difference in piriform activation between the two conditions, a result leading to the view that sniffing, in the absence of odorants, does not activate the piriform cortex.

Since SZ patients performed less well on the familiarity and hedonicity judgment tasks, it may be suggested that the lack of brain area activation in the present study was not the direct result of temporo-limbic dysfunction, but the consequence of the patients' inability to perform the tasks. In other words, temporo-limbic structures could be functionally intact in SZ patients, but may not be activated due to the behavioral impairment. This hypothesis is nevertheless unlikely because most studies indicate sizeable cytoarchitectural abnormalities in these regions with grey matter volume reductions or a deficit of the cortical surface size in the orbitofrontal, insular, entorhinal, perirhinal and temporopolar cortices, the amygdala, the hippocampus, and the gyrus rectus (Ananth et al., 2002; Arnold et al., 1991; Crespo-Facorro et al., 2000a,b; Goldstein et al., 1999; Gur et al., 2000; Shenton et al., 2001; Turetsky et al., 2003b; Wright et al., 1999). Furthermore, we and others have shown (Hudry et al., 2002; Moberg et al., 2003) that SZ patients can give appropriate intensity judgments and correct hedonic responses for unpleasant odors, demonstrating their fundamental ability to perform tasks. Consequently, behavioral impairments observed in the current study were probably caused by structural and functional abnormalities, and the lack of activation observed during the olfactory judgment tasks probably reflected this dysfunction.

Disturbance of familiarity judgments

Patients judged odors less familiar than HC subjects, replicating the results of our previous behavioral study (Hudry et al., 2002). Recognition memory implies two different processes known as familiarity, which is perceptual in nature, and recollection, which includes the retrieval of contextual information (Mandler, 1980). It has been shown that SZ patients have reduced recollection abilities, yet intact familiarity judgments (Achim and Lepage, 2003; Huron and Danion, 2002; Tendolkar et al., 2002), but also that the recollection deficits could be compensated by an increased proportion of familiarity judgments (Edelstyn et al., 2003). The dissociation between both kinds of processing was not specifically addressed in the current study and participants could have performed recollection processing while they were requested only to perform familiarity judgments. Although related to familiarity deficits, our results could therefore partly reflect a weak ability to recollect memories associated with previously encountered odors. However, it could also be suggested that the familiarity judgments of odors have distinct neural bases from those observed for the familiarity judgments of other sensory modalities, and that previously observed results from visual and verbal items cannot be compared with our

results. The impairment found in the temporo-limbic and orbital regions of our patients could thus reflect a deficit in the familiarity judgment specific to the olfactory modality.

The piriform cortex has been implicated in odor recognition memory in healthy subjects (Dade et al., 2002; Gottfried et al., 2004) and more specifically in familiarity judgments (Plailly et al., 2005). The decreased activation observed in the piriform cortex when patients judged odor familiarity could therefore mirror their low familiarity judgment scores. We must nevertheless note that the decrease in this activation in patients is combined with an abnormally high activation in the baseline condition in patients, an unusual finding suggesting that schizophrenia could show itself in hypermetabolism in the resting state. Along the same lines, Friston et al. (1992) showed that deterioration in the psychopathology was associated with an increased rCBF in the left medio-temporal regions. It could thus be hypothesized that patients in the baseline condition were not in the same cognitive state as the HC subjects. This hyperactivation, however, concerned only a small part of the brain (a subregion of the piriform cortex) and was observed only for this comparison (out of 11 comparisons). It is therefore not possible to generalize the result and interpretation of hypermetabolism indicated above. The fact remains that activation differences found between the baseline and odor familiarity judgment conditions in HC subjects were not observed in SZ patients. In addition, we demonstrated that this difference was task-specific, since activation differences were also found in the familiarity judgment task when compared with the detection task or with the hedonicity judgments condition.

During odor familiarity ratings, SZ patients did not exhibit activation in the left medial orbital gyrus. Although slightly more lateral and dorsal, this region was previously observed in the familiarity judgment of odors (Royet et al., 2001). This impairment in patients, related to behavioral response deficits, could reinforce the role of this region in odor familiarity judgments. Nevertheless, this region was also observed in hedonicity judgments of various emotional odors (Royet et al., 2000, 2001), suggesting that it could be involved in the common cognitive demands of the two olfactory judgment tasks.

Finally, we noted an rCBF decrease in the opercular part of the left inferior frontal gyrus, and right gyrus rectus in patients. The conjunction analysis also demonstrated differences in the activation of the inferior frontal gyrus for patients and healthy subjects in the two other olfactory tasks when compared with the baseline condition. This difference was more marked in the familiarity and hedonicity judgment tasks than the detection task, since differences between the two groups persisted with the F–D or H–D contrasts. This region was found to be activated during odor identification (Kareken et al., 2003; Royet et al., 1999; Savic and Berglund, 2004), and involved in the selection and integration of semantic information in a modality-independent manner (Homae et al., 2002). The lack of activation in this area in patients could therefore indicate their widely reported inability to gather evidence to identify odors (Hudry et al., 2002; Kopala et al., 1989; Serby et al., 1990; Stedman and Clair, 1998). Regarding the gyrus rectus, corresponding regions in the macaque receive projections from lower olfactory areas such as the agranular orbital cortex and anterior olfactory nucleus (Carmichael and Price, 1996). No activation associated with olfactory stimulation has been reported in these low orbitofrontal regions in previous fMRI studies, but they are particularly sensitive to susceptibility artifacts, and only Kareken et al. (2003), using PET, found them to be activated

during odor discrimination and identification. Although the role of this region in odor processing is unclear, white matter abnormalities have been shown both in it, in the inferior frontal gyrus and in the medial orbital gyrus (Spalletta et al., 2003), leading to the hypothesis that the lack of activation found in the present study could be partly inferred from connection defaults.

Disturbance of hedonicity judgments

Although patients had appropriate hedonicity judgments with unpleasant odorants, they estimated pleasant odorants less pleasant than HC subjects, as has already been observed (Crespo-Facorro et al., 2001; Moberg et al., 2003). In Hudry et al.'s (2002) study, patients found odors more neutral than HC subjects, but scores were not compared as a function of hedonic valence. Reanalyzing these data, we found a reduction in the scores for pleasant odors only, patients then finding pleasant odors more neutral than healthy comparison subjects ($P = 0.0021$). This inability to judge pleasant stimuli in an appropriate manner has also been observed with visual stimuli (Quirk et al., 1998; Paradiso et al., 2003). Cacioppo and Gardner (1999) argued that, from an evolutionary standpoint, it is much more important to quickly detect facial expressions that signal unpleasant or threatening events than expressions that signal positive events, but they also emphasized that a patients' inability to recognize a positive valence for pleasant pictures is reflective of the suffering they experienced during survival. The loss of the capacity to subjectively experience pleasure is a typical clinical feature of SZ patients and has been referred to as the anhedonia state (Becker et al., 1993).

The amygdala is well known to play a central role in the emotional processing of stimuli, but we did not observe any difference in activation of the amygdala using a between-group analysis. Focusing on this region, we demonstrated that hedonicity judgments induced activation in both groups thereby explaining the fact that no differential amygdalar activation was observed. This finding is surprising since patients had inappropriate judgments of pleasant odors during the experiment, and that abnormalities have been found in this structure in previous studies (Shenton et al., 2001). Two explanations can account for these data. Firstly, amygdala activation in patients may explain either their appropriate judgments of unpleasant odors or the higher proportion of odors perceived as unpleasant relative to the HC subjects. These data are consistent with previous results indicating that there is more activation of the amygdala during exposure to aversive than positively valenced stimuli and that the responses of the amygdala are modulated by the hedonic strength of the stimuli (Royet et al., 2003; Zald, 2003; Zald and Pardo, 1997; Zald et al., 1998). They further corroborate Cacioppo and Gardner's (1999) hypothesis described above and the assertion that describes the amygdala as "a router that permits a rapid and adaptive response to dangerous stimuli" (Paradiso et al., 2003). Secondly, it has been suggested that an unmodified response of the amygdala to affective stimuli could be due to active neuroleptic medication in patients during task performance (Paradiso et al., 2003). Since our patients were not drug naïve, this hypothesis could also explain our activation results in the amygdala.

The question is why pleasant odors are perceived as more neutral or less pleasant by patients, and which cerebral structures code pleasant experiences. Whereas aversive stimuli need not reach conscious awareness to engage the amygdala in processing (Zald, 2003), pleasant stimuli can induce conscious processing

that must then engage neural substrates other than the amygdala. The orbitofrontal cortex has for instance been shown to be involved in affective processing. In olfaction, Zald and Pardo (1997) observed that exposure to mildly aversive, so rather neutral odorants, only activated the left orbitofrontal cortex (−42, 35, −14), and not the amygdala, and we have already shown that the left orbitofrontal (−44, 32, −6) could mediate conscious assessment of emotional odorants (Royet et al., 2003). This region, described in both the above studies, was also found to be activated during the present study in healthy subjects (−46, 34, −8), and was called the left inferior frontal gyrus. The decrease in the activation of this area in SZ patients during the hedonicity judgments could thus be related to their poor performance for pleasant odors.

The weakened pleasantness judgments of the patients in our study could also be associated with the lack of activation observed in the anterior part of the left frontal piriform cortex. This assumption would corroborate Gottfried et al.'s (2002) assertions that this subdivision is receptive to hedonic quality, and findings in animals showing a functional dissociation in the piriform cortex (Litaudon et al., 1997; Mouly et al., 1998). Crespo-Facorro et al. (2001) studying the emotional response to odor in SZ patients did not demonstrate any functional disturbance of this structure. However, they directly compared unpleasant and pleasant odors, which is a more restrictive contrast than our analysis which compared olfactory conditions with an odorless condition. In addition, by using a single odor repetitively in each condition, they might have limited the signal strength by increasing habituation (Poellinger et al., 2001). Further experiments are needed to determine whether this part of the piriform cortex participates in the coding of hedonicity judgments with pleasant odors.

A lack of activation was also noted in the anterior ventral insula during hedonicity judgments. This result can be associated with previously observed reductions of cortical surface size and grey matter volume in SZ patients (Crespo-Facorro et al., 2000a). The insular cortex is known to be a multimodal integration region linking sensory experiences with their appropriate emotional response (Paradiso et al., 2003; Peyron et al., 2000; Royet et al., 2003), but no clear data have been reported regarding its involvement as a function of hedonic valence. Considering the design of our experiment, brain activation depending on hedonic valence could not be distinguished in the present study, but Crespo-Facorro et al. (2001) found that SZ patients failed to activate the insula only when experiencing an unpleasant, but not a pleasant odor. This result agrees with hypotheses suggesting that it may serve as an internal alarm center that alerts individuals to potentially distressing interoceptive sensory stimuli, and may be involved in both the perception and the feelings of disgust produced by very unpleasant odors (Wicker et al., 2003). However, it is inconsistent with both their and our behavioral results which showed that subjective hedonicity judgments in SZ patients were altered only for pleasant odors.

A functional disturbance lateralized in the patients' left hemisphere

In our study, medio-temporal dysfunction in patients was lateralized in the left hemisphere while normal cerebral activation was found in the right side. This could be related to structural abnormalities found on the left side in most studies performed with SZ patients and schizotypal subjects. Volume reductions of

grey matter and white matter abnormalities have mainly been observed in the left temporal lobe and prefrontal cortices (Dickey et al., 1999; Shenton et al., 2001; Spalletta et al., 2003; Woodruff et al., 1997). Since we previously demonstrated the strong involvement of the left hemisphere in emotional odor processing (Royet et al., 2000; Royet and Plailly, 2004), we suggest that this dysfunction could explain the frequent anhedonia associated with this illness.

Conclusion

SZ patients had inappropriate familiarity and hedonicity judgments of odors. They judged odors less familiar and pleasant than HC subjects. These results were related to functional abnormalities in temporo-limbic and orbital olfactory areas. These dysfunctions were mainly lateralized in the left hemisphere and concerned the left piriform cortex, inferior frontal, and medial orbital gyri, but also the right gyrus rectus, for the familiarity judgments and the left piriform cortex/insular gyrus and inferior frontal gyrus for the hedonicity judgments. They resulted almost exclusively from a lack of activation during task conditions. Our results clearly show that schizophrenia is a neurobehavioral disorder resulting partly from a dysfunction in the temporo-limbic and orbital regions of the brain and including those core areas involved in olfactory processing.

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