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A network of occipito-temporal face-sensitive areas besides the right middle fusiform gyrus is necessary for normal face processing

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Summary

Neuroimaging studies have identified at least two bilateral areas of the visual extrastriate cortex that respond more to pictures of faces than objects in normal human subjects in the middle fusiform gyrus [the 'fusiform face area' (FFA)] and, more posteriorly, in the inferior occipital cortex ['occipital face area' (OFA)], with a right hemisphere dominance. However, it is not yet clear how these regions interact which each other and whether they are all necessary for normal face perception. It has been proposed that the right hemisphere FFA acts as an isolated ('modular') processing system for faces or that this region receives its face-sensitive inputs from the OFA in a feedforward hierarchical model of face processing. To test these proposals, we report a detailed neuropsychological investigation combined with a neuroimaging study of a patient presenting a deficit restricted to face perception, consecutive to bilateral occipito-temporal lesions. Due to the asymmetry of the lesions, the left middle fusiform gyrus and the right inferior occipital cortex were damaged but the right middle fusiform gyrus was structurally intact. Using functional MRI, we disclosed a normal activation of the right FFA in response to faces in the patient despite the absence of any feedforward inputs from the right OFA, located in a damaged area of cortex. Together, these findings show that the integrity of the right OFA is necessary for normal face perception and suggest that the face-sensitive responses observed at this level in normal subjects may arise from feedback connections from the right FFA. In agreement with the current literature on the anatomical basis of prosopagnosia, it is suggested that the FFA and OFA in the right hemisphere and their re-entrant integration are necessary for normal face processing.

Keywords: prosopagnosia; face recognition; visual cortex; fusiform gyrus; FFA; feedback

Abbreviations: BORB = Birmingham Object Recognition Battery; FFA = fusiform face area; fMRI = functional MRI; OFA = occipital face area; rFFA = right fusiform face area; rOFA = right occipital face area

Introduction

Understanding how the human brain perceives and recognizes faces is one of the most exciting and debated areas of research in cognitive neuroscience (e.g. Haxby *et al*., 2000; Tarr and Gauthier, 2000). Pursuing this general goal, neuroimaging studies (mostly PET and functional MRI) have identified a number of relatively small functional areas lying outside the retinotopic cortex that respond more to pictures of faces than other objects in the normal human brain. The most robust difference in activity between faces and objects has been described in the lateral middle fusiform gyrus, bilaterally, but often stronger in the right hemisphere (e.g. Halgren *et al*., 1999; Haxby *et al*., 1999; Kanwisher *et al*., 1997; McCarthy *et al*., 1997; Rossion *et al*., 2000). This is the region that has been named the 'fusiform face area' (FFA) and defined as a module for face perception (Kanwisher *et al*., 1997). Posterior to the FFA, a region of the inferior occipital gyrus (termed OFA for occipital face area, Gauthier *et al*., 2000) also responds more to faces than

objects, with a larger differential response in the right hemisphere as well (Sergent *et al*., 1992; Halgren *et al*., 1999; Haxby *et al*., 1999; Gauthier *et al*., 2000; Rossion *et al*., 2000). A smaller number of studies have also disclosed larger activation for faces than objects in the posterior part of the superior temporal sulcus, but these observations are much less consistent (e.g. Puce *et al*., 1998; Haxby *et al*., 1999). Although their relative functions in face processing remain unclear, these regions are considered to form a common neural network for face perception, providing outputs to further areas and processes related for instance to facial expression processing, or retrieval of semantic knowledge about persons (see Haxby *et al*., 2000).

Besides the precise function of these regions, there are several important questions regarding the neuro-functional basis of face processing which cannot be addressed by neuroimaging alone. First, neuroimaging cannot indicate whether these functional brain regions are necessary for the successful perception and recognition of faces. It may well be that some of these regions are activated in response to the presentation of faces in normal humans and yet do not play a crucial role in any important aspects of face recognition. As a matter of fact, selective lesions of the regions where the largest proportion of face-selective cells (~20%, see Gross, 1992) are usually found in the monkey brain (namely in the superior temporal sulcus) do not appear to prevent monkeys from recognizing faces (Heywood and Cowey, 1992). A second, related, question that is difficult to resolve by neuroimaging experiments alone is the nature of the interactions between the different functional brain areas involved in face processing. For instance, in a recent neuro-functional model of face processing, Haxby and colleagues (see also Halgren *et al*., 1999) proposed that the most anterior face-sensitive regions of the visual cortex, such as the FFA, receive their input from the OFA, which would be involved in a basic analysis of facial features (Haxby *et al*., 2000). However, this hypothesis has not yet been verified by neuroimaging studies of normal subjects.

Neuroimaging studies of brain-damaged patients may help resolve these questions (Price and Friston, 2001). One of the most spectacular deficits observed following brain damage is prosopagnosia, a deficit classically defined as the inability to recognize faces of conspecifics, despite normal intellectual abilities and apparently normal recognition of other object categories. Although a few cases had been reported at the end of the 19th century, the term 'prosopagnosia' was coined by Bodamer in 1947 (Bodamer, 1947). Since then, despite its rarity, a certain number of cases with a major deficit of face recognition have been described (see Farah, 1990; for more recent cases, e.g. Sergent and Signoret, 1992; Clarke *et al*., 1997; Gauthier *et al*., 1999; Laeng and Caviness, 2001). Prosopagnosic patients are usually able to distinguish between a face and another object category ('face detection'), but are unable to identify familiar faces—including famous faces, friends and relatives or even their own face—and are also unable to learn new faces (Damasio, 1985). Different types of prosopagnosia have been described in the literature (e.g. Damasio *et al*., 1990), but it is generally acknowledged that every patient is unique and most studies focus on the detailed analysis of single cases in order to clarify current theoretical debates regarding normal face processing (see Farah, 1990).

The lesions that cause prosopagnosia are usually found in ventral occipito-temporal cortex, involving the lingual and fusiform gyri, and are bilateral in most of the cases (Damasio *et al*., 1982; Sergent and Signoret, 1992) although right unilateral lesions can be the cause of the syndrome (e.g. Landis *et al*., 1988; Wada and Yamamoto, 2001; Uttner *et al*., 2002). However, establishing relationships between structures and function based on clinical studies alone has always been problematic; the lesions of prosopagnosic patients are not always clearly identifiable, can be highly variable from case to case, and are usually very large and not limited to the structures subtending face processing. Relative to the study of patients with naturally occurring brain lesions, neuroimaging thus affords far greater anatomical precision and avoids the confounding factors associated with patient studies, such as any compensatory functional reorganization of the brain (Sergent *et al*., 1992).

In the present paper, we combine a detailed neuropsychological testing with a neuroimaging investigation of a prosopagnosic patient (P.S.) in order to: (i) test whether a structurally and functionally normal FFA is sufficient for normal face processing or if other high-level visual areas besides the right FFA are necessary for normal face perception; and (ii) test the hypothesis that the FFA activation is dependent on face-sensitive feedforward inputs from the OFA.

Methods

Subjects

Patient P.S.

P.S. is a 52-year-old woman (born in 1950; right-handed) who sustained a closed head injury (hit at the back of the head by a bus) in 1992. CT scans first indicated contusions in the occipital and parieto-occipital regions, and the left cerebellum. A recent MRI scan revealed lesions to the lateral part of the occipital and temporal lobes, bilaterally, as well as in the anterior part of the left cerebellum. The right hemisphere lesion extends from the posterior part of the inferior occipital gyrus to the posterior fusiform gyrus. The left hemisphere region is more anterior and covers a large part of the fusiform gyrus, extending into the lower part of the temporal lobe (Fig. 1).

Following months of neuropsychological rehabilitation and spontaneous recovery, P.S. was normal at all the non-visual functions that were slightly impaired following the injury (motor aspects of language, calculation, imagery and memory), yet she was slow at all visual tasks requiring a fine-grained discrimination (September 1993**:** overlapping figures,

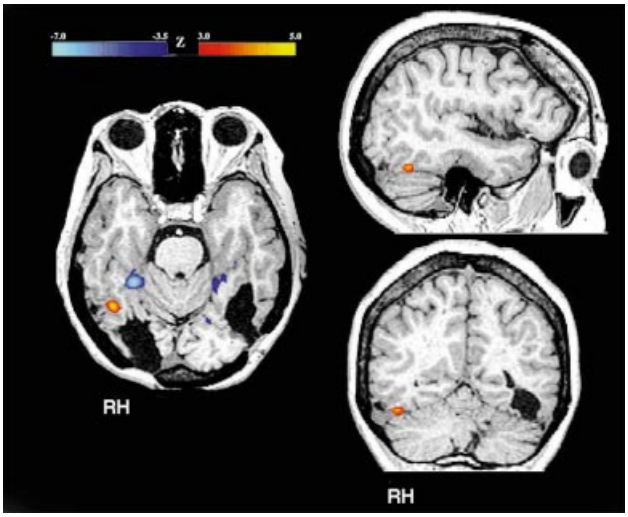

Fig. 1 P.S.'s lesions are bilateral but asymmetrical, covering the occipital inferior gyrus and posterior fusiform gyrus in the right hemisphere and the middle and anterior fusiform gyrus in the left hemisphere. As shown on the three slices, the most robust faces–objects activation (in red) is at the level of the right middle fusiform gyrus, anterior to the lesion. The homologous region in the left hemisphere has been damaged by the lesion, as illustrated on the transverse and coronal slices. The reverse comparison (objects–faces) led to a large significant difference in the parahippocampal gyrus (in blue, transversal slice), as shown previously (e.g. Epstein and Kanwisher, 1998).

dots counting tasks), presented a deficit in contrast sensitivity and a massive prosopagnosia. Helped by a neuropsychological rehabilitation programme, P.S. returned to her work as a kindergarten teacher, and she has to be trained regularly at a neuropsychological rehabilitation centre to use external cues to distinguish among children of her new class (see Mayer *et al*., 1999). P.S. complains of a profound difficulty in recognizing faces, including those of her own family, and her own face. To determine a person's identity, P.S. is reliant on cues such as haircut, hat, moustache or earrings, but also on the person's voice, his/her posture and clothes. We presented P.S. with 60 faces of famous people, whose faces were well-known by her before her accident (selected on the basis of a questionnaire that she had to fill up months before testing), and 60 unfamiliar faces. Each face was presented for 3000 ms and P.S. had 5000 ms to press one of two keys according to the familiarity/unfamiliarity of the face. Whereas she correctly classified all the unfamiliar faces, P.S. pressed the key 'familiar' for 14 out of the 60 famous faces only. After the experiment, she was shown the famous faces she classified correctly (14) and asked to name them or give some information about them; she was correct only for four faces. P.S. does not complain of any difficulty at object recognition, but she reads more slowly than she used to.

The performance of P.S. on standard clinical tests of visual perception and recognition is given in Table 1. P.S.'s visual acuity is good, but not perfect and she is slightly slower than normal controls at detecting letters and numbers in her right visual field. She is also slower than normal controls at a simple reaction time task, detecting a cross in the centre of the screen, as typically observed in brain damaged patients (e.g. Benton, 1986). Her contrast sensitivity is in the normal range except at higher frequencies (>22 c/degree). She is perfect at all tests of low level visual processing as tested by the Birmingham Object Recognition Battery (BORB) (Riddoch and Humphreys, 1993; tests 1 to 6), including matching objects under different viewpoints (tests 7 and 8), and she has no difficulty in perceiving and identifying objects, including semantic associations and naming (Table 1 Object recognition). She was also tested in an object decision task on a computer (line drawing objects taken from Snodgrass and Vanderwart, 1980; non-objects taken from Kroll and Potter, 1984), which she performed perfectly. Her short-term and long-term visual memory are in the normal range (Table 1), as well as reading (slower than normal controls but perfectly accurate) and visual imagery (BORB, test 9). She was presented with the full set of colorized Snodgrass and Vanderwart's objects (Rossion and Pourtois, 2001) to name, each object being presented for 3000 ms or until response on a computer screen. She was perfect at this task, always giving the most common object label or a close label also given by normal young subjects (see Rossion and Pourtois, 2001) without any hesitation.

These observations contrast with her face perception and recognition performance. She achieved a score of 27 out of 54 in the Benton face perception test, which rank her as highly impaired (<39). Her score at the Warrington face recognition test was 18 out of 25, being also significantly less accurate than controls.

Normal controls

In addition to P.S., six age- and sex-matched normal subjects performed all the behavioural tasks described in the sections below. Eleven normal controls (five females, mean age 29.8 years, all right-handed) were used in the neuroimaging study. Young normal controls of both genders were used in the neuroimaging study mainly for practical reasons, but there is no evidence of gender differences in face-sensitive responses, which also appear to remain stable until the ninth decade of age (Brodtmann *et al*., 2002). Both P.S. and the normal controls in the neuroimaging study gave informed consent to the experiments, which were approved by the Ethics Committee of the University of Geneva (Hopital Universitaire).

Materials and procedure

Behavioural tests

Computer tests of face processing. P.S.'s face processing abilities were tested extensively using a variety of computer tasks with well-face stimuli (see Fig. 2). Sex decision on faces was tested with 50 face stimuli (25 males) presented on the

Table 1 *Summary of visual functions of patient P.S.*

Basic perceptual processes	
Visual field	Slower than normals on left superior field
Acuity	0.7 bilaterally
Contrast	Nicolet contrast sensitivity test: OK
Colour perception (Ishihara)	12/17, lower range
Low-level visual processing	
Benton line orientation	Normal (57/60)
Birmingham Object Recognition Battery (BORB)	
Object copying test 1	OK
Line length (test 2)	OK
Size (test 3)	OK
Orientation (test 4)	OK
Gap position (test 5)	OK
Overlapping shapes (test 6)	OK, slowed down for three subtests
Minimal feature match (test 7)	OK
Foreshortened views (test 8)	OK
Object recognition	
BORB (test 10) Object decision task	OK
Object decision task on computer	OK (98%) Objects: 946 ms; non-objects: 1626 ms
BORB (test 11) Item match (class recognition)	OK
BORB (test 12) Semantic association	OK
Object naming (Colorized Snodgrass and Vanderwart)	OK
Short-term visual memory	
Test de la ruche (French)	OK
Long-term visual memory	
Doors test	OK
Rey complex drawing	OK
Face processing	
Benton face recognition test	27/54 (strongly impaired); 32 s
Warrington face recognition battery	18/25 (impaired, percentile 3)
Reading	Slow but accurate
Visual imagery	
Object Drawings (test 9: BORB)	OK
Reaction Time (phasic alert)	Slower than normals, percentile 5

centre of the screen for 10 s maximum (next trial as soon as key press). P.S. and control subjects had to indicate the sex of the person by pressing one of two keys as accurately and as quickly as possible. Facial expression analysis was tested in two blocks. In the first block, three kinds of facial expression were presented: joy; fear; and anger (each face for 10 s maximum; next trial on key press), and subjects had to press one of three keys according to the kind of expression presented (second block: choice among disgust; sadness; and surprise). Age judgement was also a three-forced choice task: subjects were presented with 40 successive faces (10 s maximum) of different age and had to categorize them in three age classes: child (10 trials); adult (17 trials); and old person (13). Face matching, as indicated in Table 2, was tested using a same/different task with two faces presented simultaneously (a full front face and a three-quarters face) for 10 s maximum (two blocks of 35 trials).

Discrimination of non-face objects from visually homogenous categories. P.S. was presented with a matching task with a set of homogeneous objects: cars (Fig. 2). Seventy-two pairs of three-quarter profile cars were presented successively in the centre of the screen for 7000 ms each maximum or until the subject's response (a blank screen of 1000 ms separated two trials). Subjects simply had to press a key if the two cars were the same (half of the trials) as accurately and quickly as possible. P.S. was also tested with a matching task using different sets of multi-parts novel objects (Fig. 2). In the first twoblocks, objects were presented simultaneously in the same viewpoint. For each block, there were 60 trials (7000 ms maximum, 1000 ms inter-stimulus interval).

Analysis. The *Z*-score is the ratio of the difference between P.S.'s score and the normal controls average score by the SD of the normals. A *Z*-score >2 means that P.S.'s performance is above or below 2SDs of the normals. A′ is a nonparametric measure of sensitivity used in previous investigations of prosopagnosic patients (Gauthier *et al*., 1999). Chance performance yields a score of 0.5 and positive values indicate better than chance sensitivity.

MRI acquisition

Stimuli. Twenty full front photographs of unknown faces (http://faces.kyb.tuebingen.mpg.de/) and 20 pictures of com-

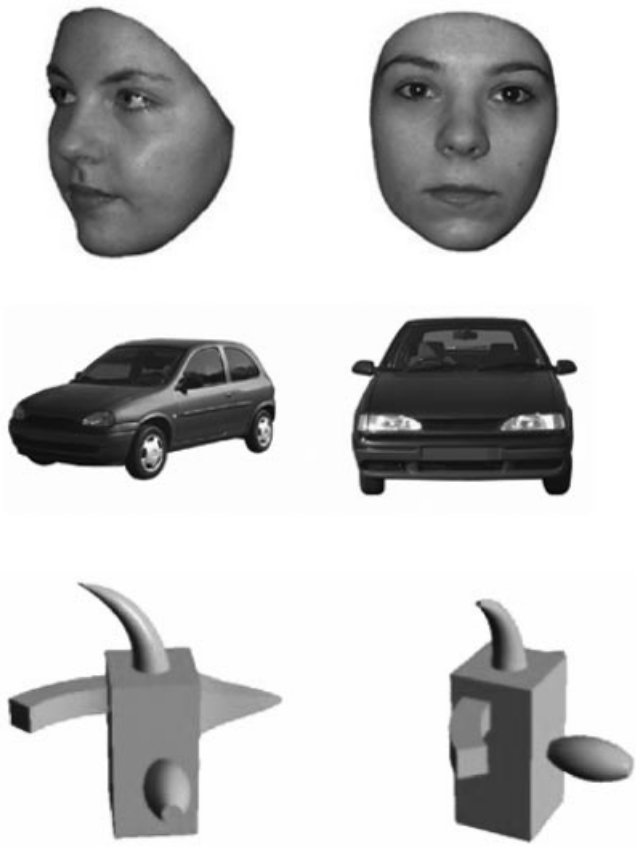

Fig. 2 Examples of stimuli used in testing P.S.'s face and object perception. (**A**) Two pictures of faces presented simultaneously under different viewpoint. (**B**) Two pictures of cars used in the study. (**C**) Two novel ('scott' objects, http://www.cog.brown.edu/~tarr/stimuli.html).

mon objects (object databank at http://www.cog.brown.edu/~tarr/stimuli.html) were used. Stimuli were presented to the subjects via a video projector, a front-projection screen and a system of mirrors fastened to the head coil. The visual field spanned by this set-up was approximately 15° × 11°.

Scanning procedures. For anatomical scans, experiments were performed on a 1.5 T whole-body ECLIPSE system (Marconi Medical Systems, Cleveland, OH, USA) using the standard head coil configuration (body coil for excitation, head coil for detection). Acquired multi-slice volume was positioned on sagittal scout images. A first GRE (gradient-recalled-echo) T_1-weighted sequence [TR (repetition time) = 162 ms; TE (echo time) = 4.47 ms; flip = 80°; FOV (field of view) = 250 mm; matrix = 256 × 256; slice thickness = 5 mm] was performed to acquire the same volume as in the functional session. Anatomical reference images consisted of a 3D GRE T_1-weighted sequence (TE = 15 ms; FOV = 250 mm; matrix = 256 × 256; slice thickness = 1.25 mm).

For the fMRI localizer experiment, functional imaging consisted of an echo planar imaging (EPI) GRE sequence (TR = 3000 ms; TE = 40 ms; flip = 80°; FOV = 250 mm; matrix = 128 × 128; 30 contiguous 5 mm axial slices). Epochs of face and object presentations (18 s, 6 × TR) were counterbalanced and separated by baseline epochs (fixation cross, 9 s; 3 TR). Two runs were performed, with six epochs of each experimental condition (faces or objects) in each run. In each face/object epoch, 24 stimuli were presented for 750 ms, without any offset, but a small shift of position (20 pixels) between consecutive images. Twenty different images were used in each epoch, with four images repeated twice consecutively, and subjects were required to detect the repetitions (one-back task) by pressing a response key. In addition, patient P.S. was scanned twice, with the same paradigms, in two different sessions at a 5 month interval in order to ensure reproducibility of our findings.

Data analysis. Collected data was processed with cross-correlation analysis (Bandettini *et al*., 1993) after motion correction (Woods *et al*., 1992) using MEDX software (Sensor Systems, Sterling, VA, USA) (Gold *et al*., 1998). Data were smoothed spatially by convolution with a Gaussian [full width half maximum (FWHM) = 6 × 6 × 6] kernel. The cross-correlation, expressed in terms of *Z*-values (Le Bihan *et al*., 1993) was calculated pixelwise between a delayed box-car function and the set of measurements, without temporal auto-correlation correction (Friston *et al.,* 1995).

Individual maps were then normalized to the Talairach space (Talairach and Tournoux, 1988). Afterwards, the statistical distribution of the *Z*-values for each subject was calculated and a probability value for each *Z*-value was attributed. Clusters size of >0.08 cm^3 (>10 voxels; voxel size after normalization was 2 × 2 × 2 mm^3) showing statistically significant *Z*-score (typically *Z*-threshold = 3.0, at $P < 0.002$, uncorrected) in the faces–objects comparison were considered (Forman *et al*., 1995). In addition, clusters with signal intensity <50% of the mean intensity of the functional images were ruled out, in particular in the vicinity of P.S. lesions.

Results

Neuropsychological investigations

Computer tests of face processing

The results of the face processing tests in P.S. and normal controls are given in Table 2. P.S. was impaired at a sex decision task, both in accuracy and sensitivity (percentage: $Z = 7.94$, $P < 0.001$; A′: $Z = 8.30$; $P < 0.001$) and response times ($Z = 7.77$, $P < 0.001$). Although she could discriminate faces of different expressions, P.S. was not as good as normal subjects at these tasks (first block: percentage: $Z = 21$, $P < 0.001$; reaction times: $Z = 9.66$, $P < 0.001$; second block: percentage: $Z = 0.79$, NS; reaction times: $Z = 3.96$, $P < 0.001$). As for judging the age of faces, P.S. had a normal performance at this task (accuracy: 90%; $Z = 1.282$, $P = 0.10$), but was significantly slower than control subjects ($Z = 8.84$, $P < 0.001$). Finally, P.S. was strongly impaired at a

Table 2 *Summary of P.S.'s performance during the computer tests on face processing*

	Control subjects (mean age: 51 years)		P.S. (age 50 years)	
	Accuracy (%)	Reaction times (ms)	Accuracy (%)	Reaction times (ms)
Gender decision	96	1162	79	3316
Facial expression				
Block 1 (joy, fear, anger)	98	1318	77	2265
Block 2 (disgust, sadness, surprise)	89	1468	88	2348
Age assessment	96	1218	92	2315
Face matching	90	2721	62	5105

Table 3 *Summary of P.S.'s performance during the computer tests on object processing*

	Control subjects		P.S.	
	Accuracy (%)	Reaction times (ms)	Accuracy (%)	Reaction times (ms)
Cars	90	2437	83	3218
Novel objects—same viewpoint (set A)	97	1798	95	3202
Novel objects—same viewpoint (set B)	79	4071	82	4412
Novel objects—different viewpoint	77	5158	72	6571

face matching task, both in accuracy and sensitivity (percentage: $Z = 7.74$, $P < 0.001$; A′: $Z = 11$; $P < 0.001$) and she was also much longer than control subjects (reaction times: $Z = 4.23$, $P < 0.001$).

Discrimination of non-face objects from visually homogenous categories

As indicated in Table 3, P.S.'s performance was good, although slightly lower than the age-matched controls (sensitivity: $Z = 2.23$; $P < 0.05$) due to her higher rate of false alarms, but she was not significantly slower then controls ($Z = 1.67$, not significant). In the first two blocks, objects were presented simultaneously in the same viewpoint. For set A, P.S.'s sensitivity was very good; she made only three mistakes but she was slower than the controls ($Z = 4.19$, $P < 0.001$). A similar pattern was found for set B, which was more difficult overall, objects being more similar to each other. P.S.'s sensitivity was in the normal range (see Table 3), but she was also slower than the controls ($Z = 4.48$, $P < 0.001$). Finally, we ran a block of trials with the different and same trials presenting objects under different viewpoints. Again, P.S.'s performance was within the normal range, but she was slightly slower than normal controls ($Z = 2.45$, $P < 0.01$) and hits ($Z = 2.19$, $P < 0.05$).

Neuroimaging study

A significant activation for the comparison between faces and objects was found in the right middle fusiform gyrus for all the normal subjects ($P < 0.002$ uncorrected, 10 voxels minimum, see Table 4 and Figs 3 and 5). This is the region that has been termed the FFA (Kanwisher *et al*., 1997) and will be referred to in this paper as the right fusiform face area (rFFA). The mean coordinates of activation for this region (Table 4) in the Talairach coordinates correspond to the coordinates found in previous neuroimaging studies (e.g. Kanwisher *et al*., 1997; Gauthier *et al*., 2000; Rossion *et al*., 2000). Compared with the Talairach-transformed individual brain of our prosopagnosic patient P.S., this average activation corresponds to an area of cortex completely spared by the lesions (Figs 1 and 6). Most importantly, when P.S. was tested in the same experiment, the rFFA presents a significant differential response between faces and objects just like normal subjects (Figs 1, 4 and 6; Table 5). Furthermore, the extent and height of the rFFA activation in P.S. do not differ from normal controls (see Figs 3–6; Table 5). Structurally and functionally, her rFFA thus appears to be perfectly normal, and these observations were replicated after an interval of several months (Tables 5 and 6, Fig. 4). These observations were made despite the fact that, as expected, P.S. performed quite well in the one-back object discrimination task (37 out of 48 correctly responded <750 ms; mean reaction times for correct trials: 499 ms), but her performance was very low for the face stimuli (12 out of 48; 526 ms).

In most normal subjects ($n = 9$ out of 11), there was also a significantly larger activation for faces compared with objects in the right inferior occipital cortex [Table 4; Fig. 5; 'right occipital face area' (rOFA)]. The coordinates of the maxima

Table 4 *Mean coordinates, level of activation and size of the functional regions observed in all the normal control subjects*

	Right FFA Talairach					Left FFA Talairach				
	x	*y*	*z*	*Z*-score	*n* voxels	*x*	*y*	*z*	*Z*-score	*n* voxels
S1	38	–62	–15	4.66	108	–33	–46	–19	4.62	16
S2	45	–62	–17	4.03	219	–28	–61	–13	3.24	14
S3	38	–46	–16	3.74	69	*–37*	*–50*	*–12*	*3.63*	*5*
S4	46	–50	–15	3.9	314	–35	–49	–17	4.66	191
S5	42	–44	–9	5.23	90	–41	–44	–14	5.08	25
S6	41	–48	–14	3.46	45	–40	–48	–13	3.41	16
S7	32	–53	–21	3.38	27					
S8	*31*	*–54*	*–25*	*2.92*	*5*	–33	–67	–22	4.46	60
S9	*48*	*–41*	*–18*	*2.80*	*5*					
S10	47	–40	–15	3.16	33					
S11	47	–54	–13	4.23	417	–38	–58	–11	4.49	161
Mean ± SE	41 ±2	–50 ±2	–16 ±1	11/11 subjects		–36 ±2	–53 ±3	–15 ±1	8/11 subjects	

	Right OFA Talairach					Left OFA Talairach				
	x	*y*	*z*	*Z*-score	*n* voxels	*x*	*y*	*z*	*Z*-score	*n* voxels
S1	37	–87	–3	4.74	55					
S2						–33	–80	–11	3.02	5
S3						–35	–83	–14	3.90	44
S4	27	–83	0	3.62	46	–29	–83	–11	3.99	50
S5	38	–69	–11	5.00	50					
S6	34	–80	–10	3.30	30					
S7	48	–76	3	3.40	25	–37	–78	–18	3.36	17
S8	*38*	*–73*	*–19*	*2.97*	*10*					
S9	44	–80	–11	3.4	49	–34	–81	–18	3.45	19
S10	31	–93	–12	3.26	11					
S11	42	–83	–3	4.41	97					
Mean ± SE	38 ± 2	–80 ± 2	–7 ± 2	9/11 subjects		–34 ± 1	–81 ± 1	–14 ± 2	5/11 subjects	

A significant faces–objects difference was clearly observed in 11 subjects in the right middle fusiform gyrus, albeit slightly lower for two subjects (5 voxels, in italics). Eight subjects presented significant differences in the left fusiform gyrus and in the right inferior occipital cortex (rOFA), and it was slightly below threshold for subject S8. In the left hemisphere, a small subset of subjects (five out of 11) but not P.S., presented a larger faces–objects difference in the inferior occipital cortex.

of activation in the group analysis correspond to a region that has been damaged by the lesion in P.S.'s brain (Figs 1 and 6). Furthermore, the individual Talairach coordinates for the maximum of activation in the rOFA of each subject also correspond spatially to a structurally damaged area of cortex in P.S.'s brain (Fig. 6).

In the left hemisphere, a number of subjects (n = 8 out of 11; see Table 4) showed a significant increase in the left middle fusiform gyrus for faces (–objects). Strikingly, these areas of activation were all localized in a region that is completely damaged in P.S.'s brain (Fig. 6). Few (five out of 11) subjects also showed a significant differential response to faces in an area of the left inferior occipital cortex (Fig. 6). For P.S., there was a small but significant extent of activation in the left inferior occipital cortex only in the first session, which was posterior to the damaged area. However, the mean signal intensity of this activation was reduced by 60% compared with the mean intensity of the functional images, such that this activation in the vicinity of the lesion may reflect an artefactual combination of partial volume and head motion effects.

Finally, as described previously (e.g. Epstein and Kanwisher, 1998), there was a significant increase of activation for the opposite contrast (objects–faces) in a more medial and anterior region of the temporal lobe, in the parahippocampal gyrus, for both P.S. ($P < 0.002$; size >10 voxels; see Table 6; Fig. 3) and the normal controls (11 out of 11 subjects at the same threshold).

Discussion

A selective deficit at recognizing faces

On the basis of the patient's complaints and her results at classical object recognition tests (Table 1), P.S.'s case can arguably be defined as one of the most selective deficits for face recognition that has been described in the neuropsychological literature. She is perfect at object recognition and naming. In this respect, she represents a clearer case of

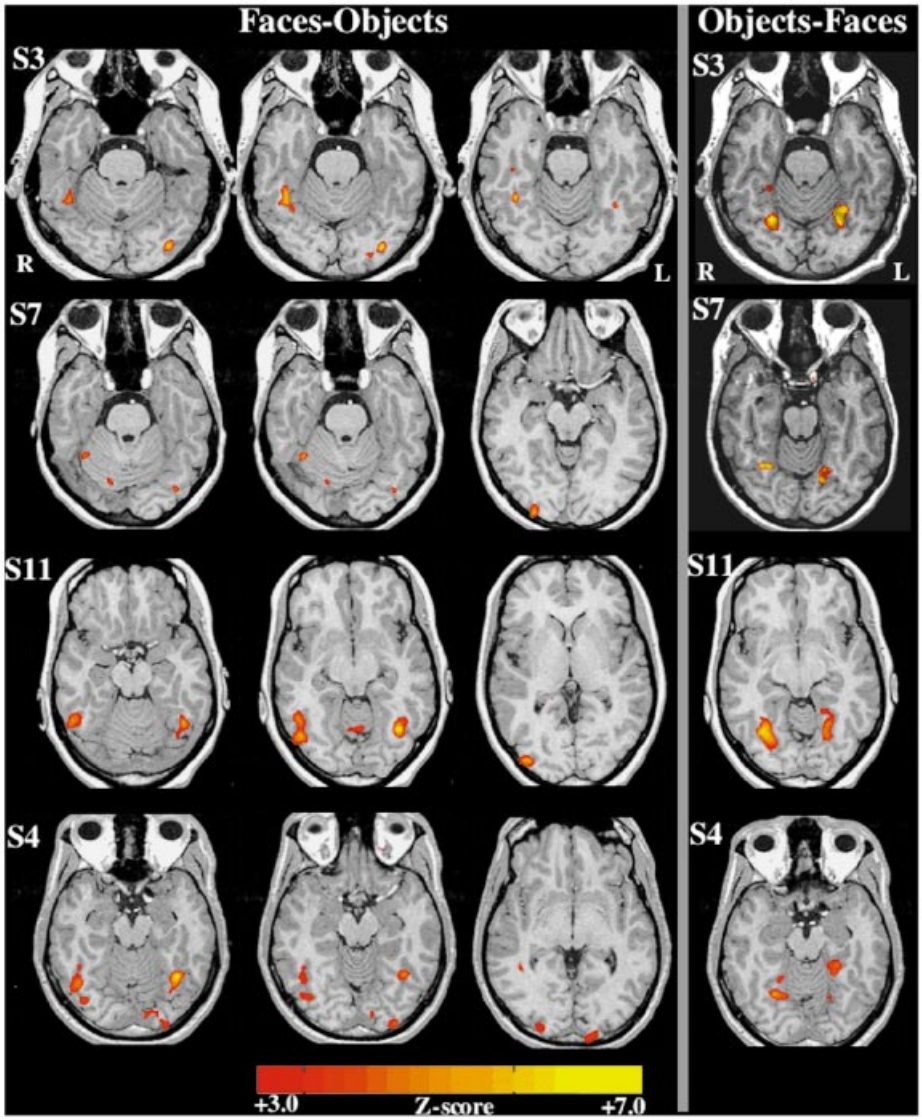

Fig. 3 Localization of the fusiform and occipital 'face areas' and the parahippocampal place area in a few normal subjects (with a similar level of activation as P.S.; see Table 5).

prosopagnosia than most previously well-described cases of acquired prosopagnosia, who presented evident deficits and complaints at object recognition, such as patients L.H. (e.g. Levine and Calvanio, 1989; Farah *et al*., 1995), S.M. and C.R. (Gauthier *et al*., 1999), or E.L.M. (Dixon *et al*., 1998) for instance. Although the distinction between apperceptive and associative (prosop)agnosia is certainly not clear-cut (see Farah, 1990), P.S. is definitely of the former type, as shown by her impairment at simultaneous face matching tasks.

P.S. is also slightly impaired at other face processing tasks such as sex categorization and facial expression analysis, whereas a number of previous cases of apperceptive prosospagnosia have been reported to be intact at these functions (e.g. Tranel *et al*., 1988). Evidence from functional imaging in humans (e.g. Sergent *et al*., 1992; Morris et al., 1998) and neurophysiological recordings in monkeys (e.g. Hasselmo *et al*., 1989) indicates that facial expression processing and face recognition depend on separate brain substrates, but that they probably share several primitive perceptual mechanisms that could be impaired in P.S.'s case due to the posterior localization of her lesions. The fact that there was no activation of her amygdala (faces compared with objects $P > 0.05$, uncorrected), a region that is involved in emotional aspects of face processing (Haxby *et al*., 2000) is inconclusive because there was not any activation in this region for any of the control subjects for the face–object comparison.

P.S. has no problem with object perception, matching, recognition and naming. She also performed at a normal level and she was not significantly slower than normal controls (one control was actually slower than P.S.) at a within category discrimination task of control objects, namely cars.

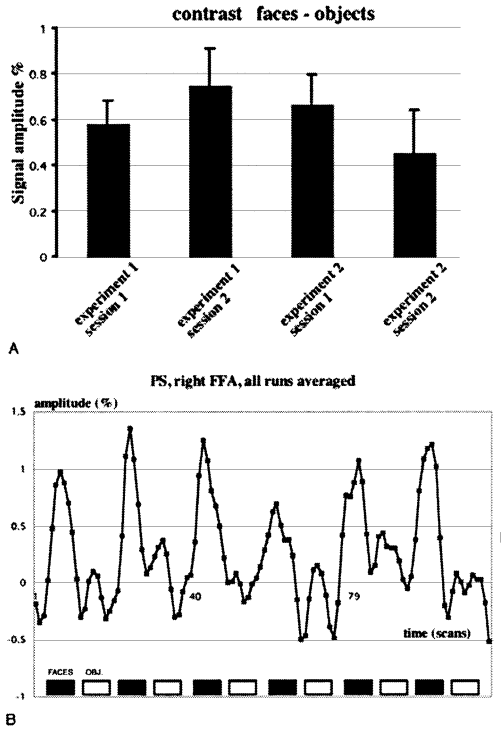

Fig. 4 (**A**) Percentage signal change (faces–objects) in the right FFA of P.S. across the two different sessions (two runs in each session). (**B**) Average time course of the magnetic signal in the FFA during all the runs for P.S.

When tested with novel objects sharing identical surface properties but differing slightly by their overall shape and the shape of their parts (not their organization), P.S.'s performance was again in the normal range. She was slightly slowed down overall, which should not be surprising given her general slowing down typical of brain-damaged subjects (e.g. Benton, 1986) and the fact that even normal control subjects were also particularly slow at this task (>2000 ms on average). Most importantly, however, increasing the visual homogeneity of the distractors or presenting the objects under different viewpoints caused a slight drop of performance and an increase of response times that was similar for P.S. and for normal subjects (Table 3). Other evidence reported elsewhere (Rossion *et al*., 2002) also indicates that she is not more sensitive than controls to manipulations of the level of categorization in object discrimination tasks as used previously in other patients (Gauthier *et al*., 1999).

How can P.S.'s object recognition performance be so remarkably preserved despite presenting such extensive lesions of the extrastriate visual cortex (Figs 1 and 6)? One possibility may be that non-face objects are recognized using a single well-localized system, different than that for faces and located in the medial ventral temporal cortex where the larger activation for objects was found to be normal for P.S. (see Figs 1 and 6). However, recent evidence suggests that the discrimination of object categories, including faces, can be carried out through a distinct pattern of response across a wide expanse of cortex in the occipital and ventral part of the temporal lobe (Ishai *et al*., 1999; Haxby *et al*., 2001). Because large but also small amplitude responses in the ventral temporal cortex carry information about the object appearance, only very large bilateral lesions of the ventral lateral and medial visual pathway would lead to impairments of basic level object recognition according to this view. The fact that P.S., despite extensive lesions of the ventral temporal cortex, is still able to easily perform such basic level discriminations, can be taken as supporting the view that object recognition (including faces) at the basic level is widely distributed (Ishai *et al*., 1999; Haxby *et al*., 2001): there is still enough information carried out in the visual cortex to perform basic level object recognition efficiently. Yet, contrary to most objects, faces pose a special challenge to the visual system because they belong to a highly visually homogeneous category (Damasio *et al*., 1982) and need to be recognized at the individual level for efficient social interactions (Tarr and Gauthier, 2000; Tanaka, 2001). The development of a visual expertize at recognizing faces at the individual level appears to require the fast extraction of configural relationships (Maurer *et al*., 2002), a mechanism that may extend to the discrimination of non-face categories from visually homogeneous categories following expertize training (Gauthier and Tarr, 1997) and seems to be impaired in P.S.'s case (Rossion *et al*., 2002).

The necessary integrity of the right hemisphere face-sensitive areas in face processing

The lesions of prosopagnosic patients usually concern the ventral part of the occipital and temporal cortex, bilaterally (e.g. Damasio *et al*., 1982; Sergent and Signoret, 1992; Clarke *et al*., 1997), with an area of maximum overlap between lesions including the right posterior and middle fusiform gyrus (Barton *et al*., 2002). Three recent case descriptions of prosopagnosia with unilateral damage have also identified the right middle fusiform gyrus as a critical area for normal face perception. In one case, the lesion concerned both the right fusiform gyrus and the lateral occipital cortex (Wada and Yamamoto, 2001), whereas in two other cases the lesion also extends posteriorly but possibly spares the right lateral occipital cortex, at least structurally (Uttner *et al*., 2002). These observations are in agreement with the proposal that the right middle fusiform gyrus or rFFA is a dedicated area that is critical for face perception, or a 'face module' (Kanwisher *et al*., 1997; McCarthy *et al*., 1997). However, in the present study, we observed a prosopagnosic patient presenting a structurally intact right middle fusiform gyrus or rFFA and, most importantly, a significantly larger response to faces–objects at this level (Figs 1 and 6). This result suggests that this region was also intact functionally, at least as far as basic level face categorization is concerned. These neuroimaging findings are in agreement with a recent fMRI study that disclosed a rFFA activation in a prosopagnosic patient (S.M.;

Table 5 *Comparison of the right FFA response observed in P.S. (scanned twice) and the normal subjects*

Subjects	Talairach coordinates			*Z*-mean	Size (cm^3)
	x	*y*	*z*		
S5	42	–44	–14	5.23	0.72
S1	38	–62	–15	4.66	0.86
S11	47	–54	–13	4.23	3.33
S2	45	–62	–17	4.03	1.75
S4	46	–50	–15	3.90	2.51
S3	38	–46	–16	3.74	0.55
S6	41	–48	–14	3.46	0.36
P.S.(1)	42	–59	–18	3.43	0.17
P.S.(2)	41	–59	–18	3.22	0.24
S7	32	–53	–21	3.38	0.22
S10	47	–40	–15	3.16	0.26
S8	31	–54	–25	2.92	0.04
S9	48	–41	–18	2.80	0.04

Subjects are ranked by order of magnitude in the height of activation for the difference between faces and objects.

Table 6 *Significant activations (Z > 3.0) observed for P.S. during the two scanning sessions*

Contrast	Region	Talairach coordinates			*Z*-mean	*n* voxels
		x	*y*	*z*		
Faces–objects 1	Fusiform gyrus RH	42	–59	–18	3.43	21
	Other regions:					
	Middle/inferior temporal gyrus RH					
	Inferior/middle frontal gyrus Bil					
	Cingular gyrus					
Objects–faces 1	Parahippocampal gyrus RH	30	–42	–15	4.43	106
	Parahippocampal gyrus LH	-23	–43	–12	3.73	36
	Other regions:					
	Middle temporal gyrus LH					
	Superior parietal lobule LH					
Faces–objects 2	Fusiform gyrus RH	41	–59	–18	3.22	30
	Other regions:					
	Inferior/middle frontal gyrus Bil					
	Inferior parietal lobule RH					
Objects–faces 2	Parahippocampal gyrus RH	31	–42	–16	4.44	136
	Parahippocampal gyrus LH	–24	–45	–11	4.12	55
	Other regions:					
	Middle temporal gyrus LH					
	Superior parietal lobule LH					
	Middle occiptal gyrus RH					

RH = right hemisphere; LH = left hemisphere. The bilateral activation of the parahippocampal gyrus for the comparison between objects and faces corresponds to the locus of activation defined as the 'parahippocampal place area', which usually responds less to faces than to other object categories.

Marotta *et al*., 2001), although this patient also presented large deficits at recognizing common objects (Gauthier *et al*., 1999) and his lesions were mostly anterior (temporal lobe), sparing the entire occipital lobe and the fusiform gyrus bilaterally. Together, these findings contradict the view that the rFFA represents a module for face perception and supports a critical role of other high-level visual regions for normal face processing (Tovée, 1998; Haxby *et al*., 2000, 2001).

What is the localization of these high-level visual regions that appear to be critical for normal face processing? Although the region of the left FFA is damaged in P.S., it is unlikely that the areas of the left occipital and temporal cortex that respond more to faces in normal subjects are also critical.

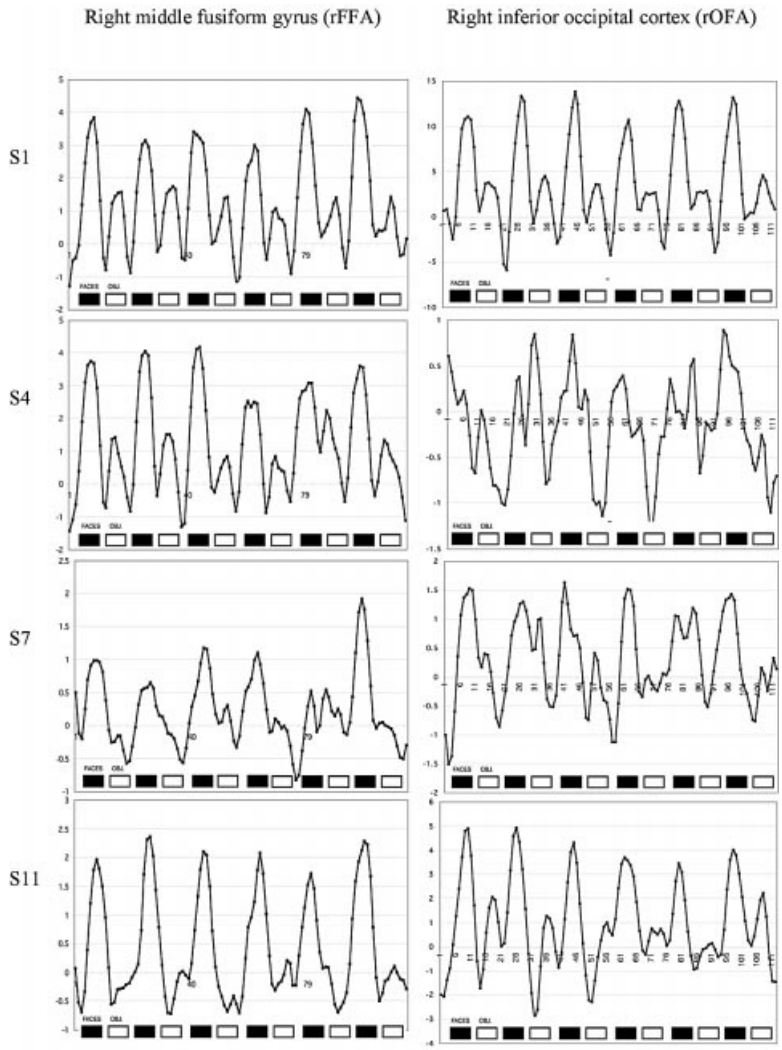

Fig. 5 Average time courses of activation in the right fusiform 'face area' and the occipital 'face area' for four control subjects illustrated in Fig. 3 (except for Subject 3, who was replaced here by Subject 1, who in turn showed significant activation in both regions).

Indeed, several cases of prosopagnosia have been observed previously with unilateral right hemisphere lesions (Landis *et al*., 1988; Wada and Yamamoto, 2001; Uttler *et al*., 2002). The functional integrity of the left face-sensitive areas was unknown in these cases, although there was no evidence for a decrease of blood flow in the left hemisphere in the case described by Wada and Yamamoto (2001). There are also a number of cases with extensive lesions of the ventral occipital and temporal left hemisphere without prosopagnosia that have been reported in the literature (see Farah, 1990). Yet, it has also been shown that a lesion to the left hemisphere, even in right-handed humans, may be necessary at least in some cases (Ettlin *et al*., 1992) to produce a prosopagnosic deficit, or even sufficient (Mattson *et al*., 2000), thus pointing to the individual-specific degrees of hemispheric dominance for face processing.

If the necessary role of the left hemispheric regions remains unclear, what our study indicates, however, is that the rOFA is not only involved during face processing in normals, but that it is a necessary component for such normally functioning face processes to take place.

The face-sensitive response in the inferior occipital cortex (rOFA), within the lateral occipital (LO) complex involved in shape perception (Malach *et al*., 1995), is observed in many neuroimaging studies (e.g. Halgren *et al*., 1999; Haxby *et al*., 1999; Gauthier *et al*., 2000; Ishai *et al*., 2000; Rossion *et al*., 2000). Yet, despite the robust co-occurrence of this region with the FFA, authors have been quick to reject the possibility that the OFA presents a particular sensitivity to faces (Kanwisher *et al*., 1997), probably because of its relatively early localization in the ventral pathway, and its somewhat weaker face-sensitive response compared with the FFA (Gauthier *et al*., 2000). On the other hand, Haxby *et al*. (2000) included this OFA in their neuro-functional architecture of face processing, suggesting that the rFFA receives most of its input information for face processing directly from

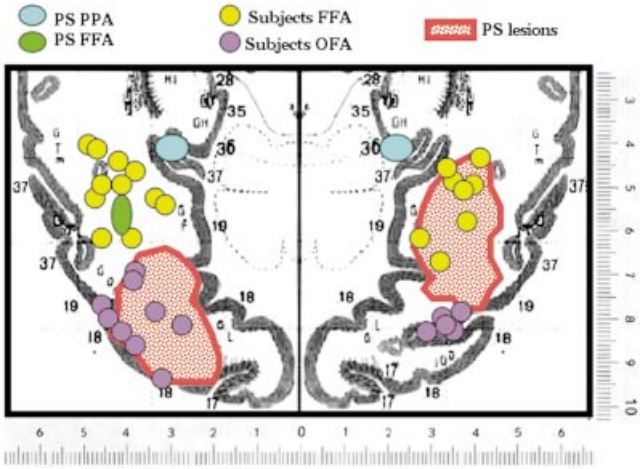

Fig. 6 Schematic representation on a Talairach slice ($z = -14$) of P.S.'s lesions and the areas of activation in the ventral extrastriate cortex for both P.S. and normal subjects. The lesions cover most of the functional network involved during the perception of faces, but spare completely the right middle fusiform gyrus, where the 'fusiform face area' is found in normal subjects.

this region (see also Halgren *et al*., 1999). Although our data suggest rather a role of feedback connections in leading to the face-sensitive response of the OFA (see below), they definitely support a critical role of the rOFA for normal face processing, and thus a distributed processing model in the ventral visual pathway for this function rather than a sparse coding (Young and Yamane, 1992).

What is the neuro-functional relationship between the OFA and FFA?

In their neuro-functional model of face processing, Haxby *et al*. (2000) proposed that the rFFA receives most of its input information for face processing directly from the posterior rOFA, albeit suggesting the presence of feedback mechanisms between the two areas (see also Ishai *et al*., 2000). According to this view, the rOFA is involved in the extraction of individual facial features and project in turn to the rFFA, which would respond more to the whole face configuration. This hypothesis is consistent with a classical hierarchical and feedforward view of the visual system (Hubel and Wiesel, 1977), according to which the flow of visual information goes from more posterior visual areas to more anterior areas, with an increase of the receptive field and the complexity of the visual information represented. At first glance, this proposal is also consistent with the observation that the rFFA, but not the rOFA, is more activated when the subject's attention is focused on the whole face versus single face features (Rossion *et al*., 2000). The less robust differential activation between faces and objects usually found at the level of the rOFA is also considered as supporting the view of a progressively increasing face-selectivity along the ventral visual pathway (Grill-Spector *et al*., 1999; Halgren *et al*., 1999).

However, the data reported here do not support this hypothesis of a main feedforward processing of information related to faces from the rOFA to the rFFA since there was a normal activation of the FFA in the right hemisphere of P.S., despite a structurally and functionally damaged rOFA. In addition, to our knowledge, there has not been any empirical evidence in normal subjects supporting such a feedforward and dependent processing of information from the OFA to the FFA, whose differential function in face processing remain largely unclear. Moreover, behavioural evidence clearly suggests that the processing of faces as integrated wholes has precedence over the processing of single face features (Tanaka and Farah, 1993)—an observation that does not fit with a feedforward hierarchical model of face processing that would go from processing features to whole faces. Electrophysiological recordings in humans also show that the peak latency of the N170 face-sensitive potential is delayed for isolated face features, compared with the response to whole face stimuli (e.g. Bentin *et al*., 1996). For these reasons and given the data reported here, we suggest that the larger response observed for faces compared with objects as early as in the inferior occipital cortex (OFA) rather arise from feedback connections from the rFFA—an hypothesis perfectly compatible with the concurrent and distributed processing of information (Felleman and Van Essen, 1991; De Yoe *et al*., 1994) as well as the presence of feedback (Lamme and Roelfsema, 2000; Bullier, 2001) and re-entrant phasic signalling (Edelman, 1993) in the visual cortex. Recent studies using cooling techniques in monkeys indicate that such feedback signals from higher order visual areas may contribute to the emergence of functional responses in early visual areas (Galuske *et al*., 2002; see also Bullier, 2001). If such mechanisms were in place within the ventral visual stream, the response to faces observed at the level of the inferior occipital cortex could arise as a consequence of higher-level face-sensitivity processes in the FFA, possibly to guide the fine-grained visual analysis of faces for individual discrimination (Gauthier *et al*., 2000) and old/new recognition (Rossion *et al*., 2003).

Although the findings reported here suggest strongly that the two right-sided face-sensitive regions and their possible re-entrant interactions are critical for normal within-category discrimination and recognition of human faces, the limited temporal resolution of fMRI does not allow us to clarify the nature of the dynamic interactions between these two functional areas at this stage. Future neuroimaging investigations of P.S. and other brain-damaged prosopagnosic patients may be directed towards this goal of understanding functional connectivity between visual areas (Friston, 2002). As far as this prosopagnosic patient is concerned, future neuroimaging studies will also have to clarify the exact localization of the lesions with respect to the retinotopic visual cortex and other extrastriate visual areas involved in object recognition in the ventral temporal and occipital

cortices (Ishai *et al*., 1999; Haxby *et al*., 2001), as well as to test the sensitivity of the rFFA to within category discrimination and recognition of faces.

Conclusions

Combining a neuropsychological and neuroimaging investigation on a case of prosopagnosia, we showed that besides the right middle fusiform gyrus (FFA), the right inferior occipital cortex (OFA) is critical for normal face perception and that the face-sensitive responses observed at the level of the occipital cortex in normal subjects may arise from feedback connections from the right FFA rather than from a feedforward mode of processing. We suggest that a re-entrant mechanism between these two regions in the right hemisphere subtends within category discrimination and recognition of faces.

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