

# Face-selective Activation in a Congenital Prosopagnosic Subject

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## Abstract

■ Congenital prosopagnosia is a severe impairment in face identification manifested from early childhood in the absence of any evident brain lesion. In this study, we used fMRI to compare the brain activity elicited by faces in a congenital prosopagnosic subject (YT) relative to a control group of 12 subjects in an attempt to shed more light on the nature of the brain mechanisms subserving face identification. The face-related activation pattern of YT in the ventral occipito-temporal cortex was similar to that observed in the control group on

several parameters: anatomical location, activation profiles, and hemispheric laterality. In addition, using a modified vase-face illusion, we found that YT's brain activity in the face-related regions manifested global grouping processes. However, subtle differences in the degree of selectivity between objects and faces were observed in the lateral occipital cortex. These data suggest that face-related activation in the ventral occipito-temporal cortex, although necessary, might not be sufficient by itself for normal face identification. ■

## INTRODUCTION

Recent neuroimaging studies have identified a region within the human posterior fusiform gyrus (pFs), which appears to be preferentially activated by images of faces compared to many other object categories (Haxby, Hoffman, & Gobbini, 2000; Halgren et al., 1999; Ishai, Ungerleider, Martin, Schouten, & Haxby, 1999; Kanwisher, McDermott, & Chun, 1997). The fusiform face-related preference is in agreement with previous evidence based on electrophysiological recordings (event-related potentials [ERPs]) from both the surface of the occipito-temporal cortex (N200; for a comprehensive review, see Allison, Puce, Spencer, & McCarthy, 1999) and from the posterior-inferior temporal scalp (N170, Bentin, Allison, Puce, Perez, & McCarthy, 1996; George, Evans, Fiori, Davidoff, & Renault, 1996).

The selectivity for faces, as reflected in the fMRI signal, is preserved under various experimental manipulations of both the task and the configuration of the face stimuli. For example, similar levels of activation were found in the posterior fusiform face-related area (FFA) for either grayscale photographs or line drawings of human faces, cartoon faces, cat faces, and different viewpoints of the same face (Tong, Nakayama, Moscovitch, Weinrib, & Kanwisher, 2000). In addition, similar levels of activation were observed when subjects attended faces in a demanding "one-back" memory task and during passive

viewing (Tong et al., 2000). Similarly, the N170 is distinctive of schematically drawn faces as it is of photographs of natural faces (Sagiv & Bentin, 2001), and insensitive to task manipulations and/or attention factors (Carmel & Bentin, 2002). Thus, these brain activations are sensitive to faces, rather than to low-level visual features of the stimuli.

However, the functional role of the FFA in face processing is still a matter of ongoing debate. One possibility is that activity in the FFA is associated with within-category face identification (but see Gauthier, Skudlarski, Gore, & Anderson, 2000). Support for this view comes from studies that have shown differential pattern of activation for familiar and unfamiliar faces (Henson, Shallice, Gorno-Tempini, & Dolan, 2002; Henson, Shallice, & Dolan, 2000; Katanoda, Yoshikawa, & Sugishita, 2000; George et al., 1999). However, other studies did not show such an effect (Leveroni et al., 2000; Nakamura et al., 2000; Dubois et al., 1999). These latter studies argue against the involvement of the FFA in face identification, stressing its role in face detection (i.e., distinction of face from non-face stimuli), and in the structural encoding of face parts into a coherent whole.

An additional approach for examining the functional role of the FFA and other face-related areas in the brain is to study individuals who suffer from prosopagnosia, a specific impairment in face identification (Bodamer, 1947; for a recent review, see De Renzi, 1997). This syndrome is usually acquired after a bilateral lesion in the vicinity of the pFs (Farah, 1995). Indeed, Marotta,

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Genovese and Behrmann (2001) found alterations in the face related activity in the pFs region of two patients whose prosopagnosic deficit was acquired during adolescence. Specifically, although faces activated regions in the posterior fusiform gyri of these two patients, the activity was posterior relative to that found in normal subjects.

Whereas studies of acquired prosopagnosia reveal important information about face processing, their ability to unveil the function of essential regions in the normal brain is limited by several factors. First, natural lesions are rarely circumscribed to a particular region of interest (ROI). The lesions found in patients suffering from acquired prosopagnosia vary substantially in etiology, size, and location and are not strictly confined to the FFA (Schweich & Bruyer, 1993). In fact, there is considerable debate regarding the necessary and sufficient lesion that would result in prosopagnosia (see Farah, 1995, for a review). Second, brain lesions might have a distant effect that, through connective disruptions, goes beyond the specific locus of a lesion (diaschisis). Lastly, when functional imaging is performed in brain-damaged patients, particular caveats arise, depending on the method of measurement. For example, in measuring ERP, the conductivity of the brain is altered in the region of encephalomalacia, affecting the scalp distribution of potentials (e.g., Aboud, Bar, Rosenfeld, Ring, & Glass, 1996; see Deouell, Hämäläinen, & Bentin, 2000, for further discussion). In fMRI, either the underlying disease (e.g., atherosclerosis) or the mechanism of brain injury (e.g., closed head injury or infection) may alter blood flow or disrupt the normal neurovascular coupling (e.g., Pineiro, Pendlebury, Johansen-Berg, & Matthews, 2002). Thus, interpretation of hemodynamic alterations as reflecting neural changes is risky.

An approach that might bypass these limitations is to study individuals who suffer from congenital prosopagnosia without evident structural brain lesion. Bentin, Deouell, and Soroker (1999) recently reported such an individual—YT, a healthy 39-year-old businessman with no history of neurological disease, and no evidence of anatomical lesion, but who complained of having severe problems in recognizing faces since early childhood.

When formally tested, YT was able to identify only 24 of 670 famous faces (mixed with 580 faces of unknown individuals), whereas a control group of 24 subjects, matched with YT for age and education, identified an average of 391 faces from this set. In contrast to his face identification deficit, YT was able to easily determine the gender, age, and the emotional state on the basis of a person's face, had no difficulty in recognizing objects other than faces, and exhibited normal or above-normal performance in holistic and analytic visual, memory, and cognitive tests (for details, see Bentin et al., 1999). Bentin et al. further found that the N170, which is normally larger in response to faces than to other objects, is similarly large for face and non-face stimuli in YT.

Using fMRI, in the current study we tested the functional brain activity profile for face and non-face stimuli both in YT and in a control group of 12 subjects. In particular, we aimed at comparing the patterns of activity elicited by faces in the ventral occipito-temporal areas of YT and the control subjects. The contrast of face stimuli with building stimuli was initially used to localize the face-related regions in all participants including YT. Because YT's N170 response was not selective to faces (i.e., strong N170 response elicited by objects as well as by faces), we also looked at the response profile induced by objects in YT's face-related areas relative to the control group. Because face-related regions are part of a complex network of occipito-temporal object-related areas, we also looked at areas that are preferentially activated by non-face stimuli. In addition we tested for holistic integration processes in YT using a modified Rubin face–vase illusion (Hasson, Hendler, Ben Bashat, & Malach, 2001).

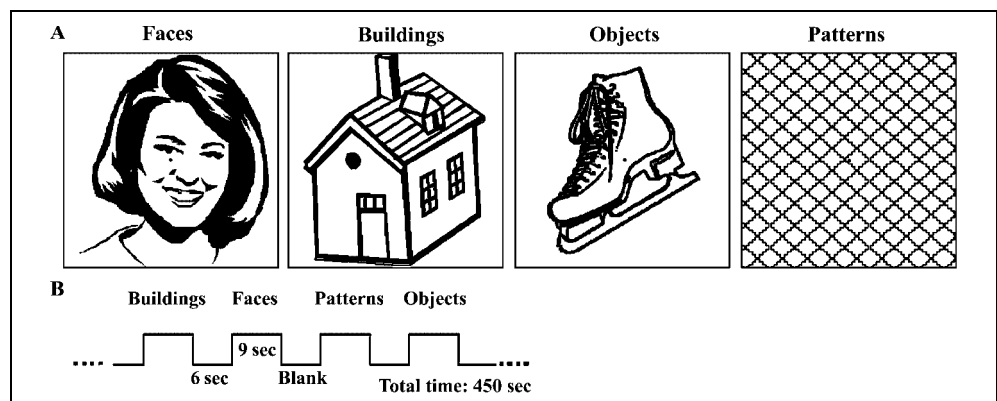
## RESULTS

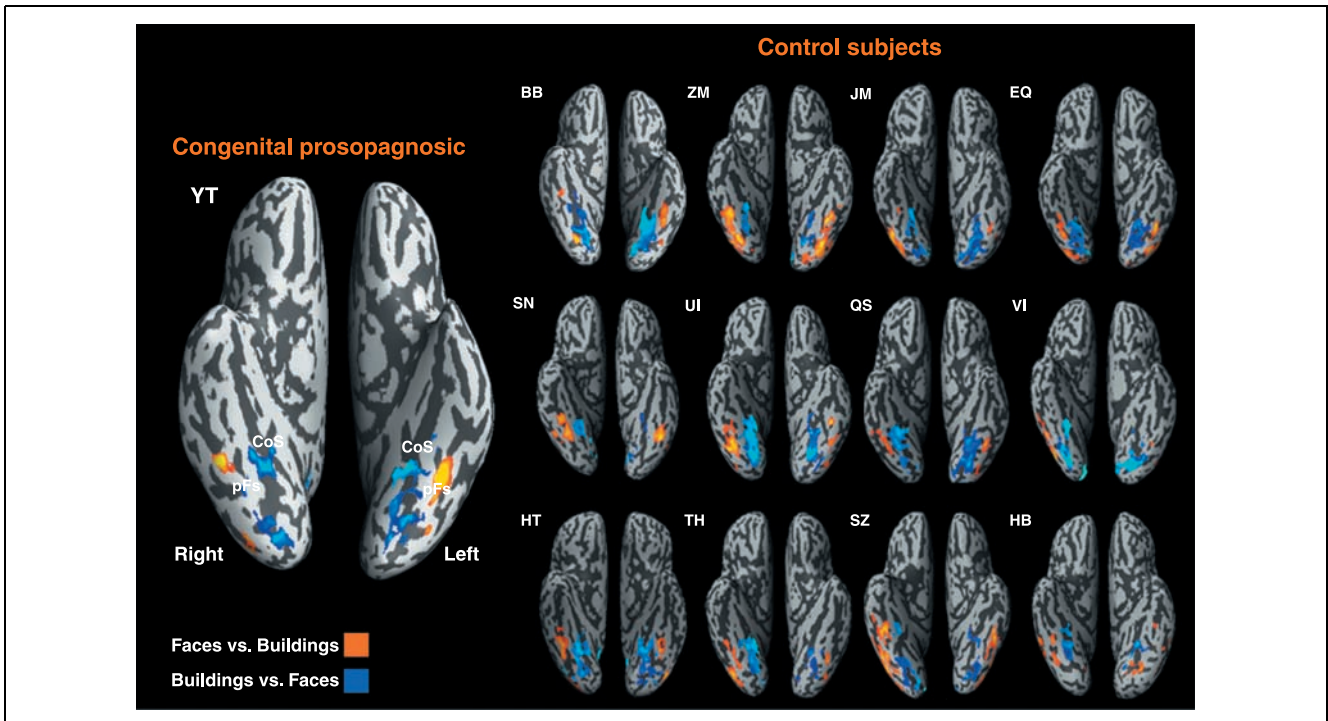
### Experiment 1: Localization of Face-Related Regions

First, we compared YT's blood oxygenation level dependent (BOLD) signal to face and non-face stimuli to that of a control group of 12 healthy subjects. The stimuli were line drawings of faces, buildings, man-made objects, and geometric patterns (Figure 1). These stimuli were presented in a short-block design fashion, while subjects

**Figure 1.** Experiment 1 design.

(A) Examples of the four stimulus categories used in the experiment: faces, buildings, common objects, and patterns. (B) An interleaved short-block presentation design was used in the experiment. Each epoch lasted 9 sec, followed by a 6-sec blank. Nine images of the same type were presented in each epoch.



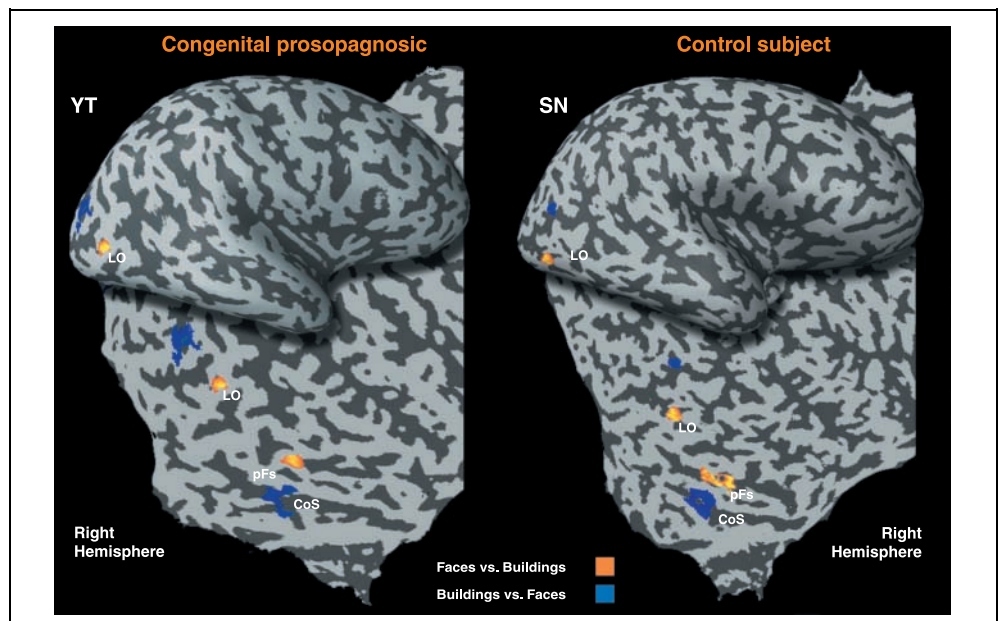


**Figure 2.** Ventral view of category-related activation in YT and 12 control subjects. Enlarged on the left is the activation obtained in YT's brain for faces (faces > buildings; orange) and buildings (buildings > faces; blue). The data is presented on an inflated brain shown from a ventral view. On the right is the same activation obtained for the 12 control subjects. Despite substantial intersubject variability, the preferential activation for faces was consistently located laterally to the building-related activation in all subjects including YT. Specifically note the clear face-related activation in the vicinity of the posterior fusiform gyrus (pFs).

performed a one-back memory task (see Methods for details). To localize preferential activation to faces and buildings, we conducted a statistical test searching for voxels that were preferentially activated by faces compared to buildings and vice versa. The results for each

subject in the control group and for YT are presented on inflated brains from a ventral view in the right and left panels of Figure 2, respectively. A lateral view and an unfolded view of the same data are shown for YT and a representative subject (SN) in Figure 3.

**Figure 3.** Category-related activation in YT and one representative control subject. The activation obtained in YT (left) and one representative control subject (SN, right), for faces (faces > buildings; orange) and buildings (buildings > faces; blue). The data are presented on a lateral view of an inflated brain and unfolded view of the same hemisphere.



**Table 1.** Talairach Coordinates of Face-Related Regions

		Left Hemisphere			Right Hemisphere		
		X	Y	Z	X	Y	Z
Lateral occipital	YT	-43	-66	-1	43	-69	3
	Controls	-42 ± 5	-73 ± 4	-12 ± 8	39 ± 4	-69 ± 7	-9 ± 6
Fusiform gyrus	YT	-31	-53	-19	35	-52	-15
	Controls	-38 ± 4	-50 ± 7	-19 ± 4	36 ± 5	-48 ± 8	-16 ± 4

Talairach coordinates for the lateral occipital and pFs face-related regions derived from YT and 12 control subjects in Experiment 1. Each ROI was defined by contrasting the face stimuli with the building stimuli; see also Figures 2 and 3. Values represent the mean ± SD in mm. Note that YT's coordinates are within the normal range of the Talairach coordinates of the control group.

In agreement with previous reports (Haxby et al., 2000; Halgren et al., 1999; Ishai et al., 1999; Kanwisher et al., 1997; McCarthy, Puce, Gore, & Allison, 1997; Puce, Allison, Gore, & McCarthy, 1995), in all control subjects faces consistently activated two regions: one in the pFs (Figure 2) and one in the lateral occipital cortex (LO; Figure 3). The face-related activity in the pFs corresponds to the FFA (Kanwisher et al., 1997). In 5 of 12 subjects, we also found a third focus anteriorly and dorsally to MT/V5, and in 7 of 12 subjects an additional face-related focus in the STS. These regions are known to be sensitive to eye movements and direction of gaze (e.g., Hoffman & Haxby, 2000; Puce, Allison, Bentin, Gore, & McCarthy, 1998), but were only weakly activated in the present study, probably due to the use of line drawings of faces, presented for a brief duration, which might reduce the subjects' ability to trace the direction of gaze. In agreement with previous reports (Aguirre, Zarahn, & D'Esposito, 1998; Epstein & Kanwisher, 1998) building-related activity was found in the vicinity of the collateral sulcus (blue foci in Figure 2).

YT exhibited a pattern of activation (left panel of Figures 2 and 3) similar to that observed in the control group. That is, there was a clear focus of face-related activity in the vicinity of the pFs. Note that despite substantial intersubject variability, we found preferential activation for faces in all subjects including YT, which was invariably located laterally to the activation for building images in the collateral sulcus (see also, Malach, Levy, & Hasson, 2002). A similar face-related activation map was found while contrasting the face stimuli with the object stimuli (not shown; for a similar contrast see also Experiment 2). Moreover, YT's face-related regions were located within the range of face-related Talairach coordinates of the control group, both in the pFs and in the lateral occipital cortex (Table 1).

### Activation Profile of Face-Related Regions

In order to assess the degree of selectivity of the face-related regions we measured the level of activation elicited in these areas by faces, buildings, objects, and patterns

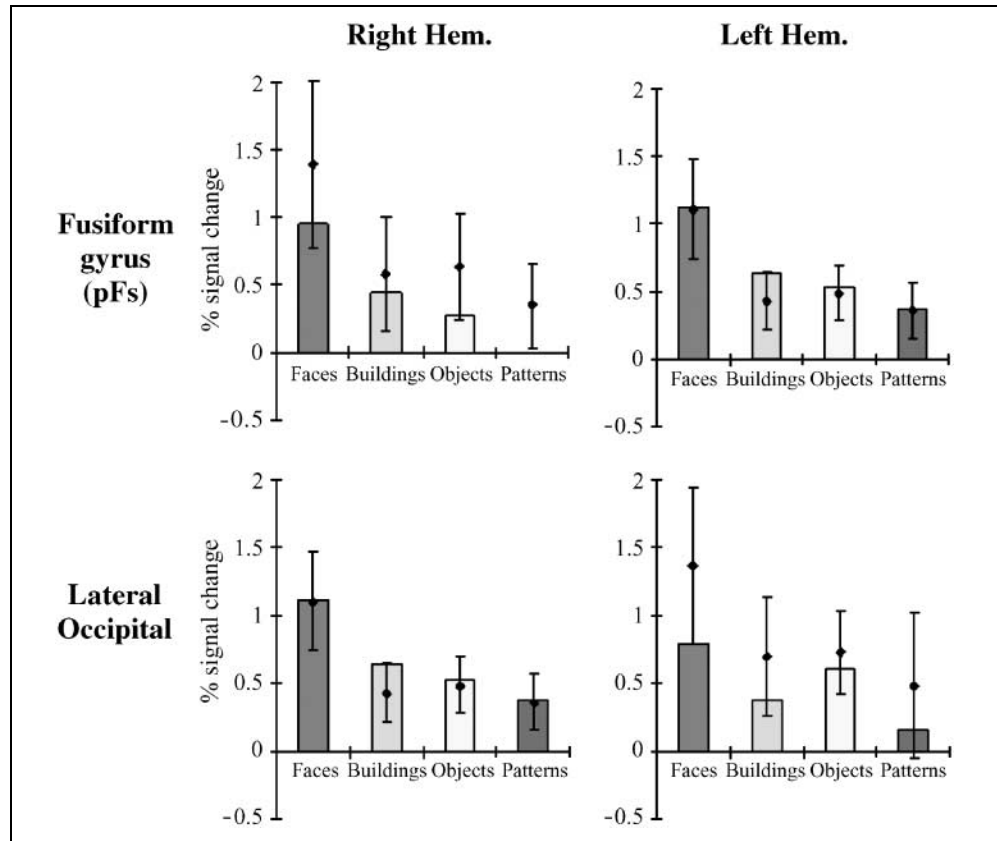
in YT and in the control subjects. Each face-related region was defined using the "internal localizer" approach (see Methods for details). The results are shown in Figure 4. In agreement with previous findings, in both the posterior fusiform and the lateral occipital face-related foci, the activation to faces in the control group (black diamonds) was significantly greater than the activation to buildings (paired *t* test,  $p < 10^{-6}$ ). YT's activation was similar to that of the control group. The level of activation for each category, within each ROI, was within the range of one standard deviation of the mean from the control group, hence, not statistically different (except for the activation elicited by patterns in the right FFA).

To further estimate the similarity between YT and the control group we also calculated a selectivity measure for faces compared to objects in each of these areas (see Methods). This measure calculated for YT was within the range of one standard deviation of the mean of the control group in the right and left FFA and in the right LO but not in the left LO. In order to estimate the statistical significance of these findings, we used the bootstrap method, which assessed the probability of observing the difference found between YT and the control group by chance (see Methods). In accordance with the pattern described above, the probability was high (indicating insignificant difference) for the right FFA (0.4), left FFA (0.44), and right LO (0.4), but low (approaching significance) in the left LO ( $p < .053$ ).

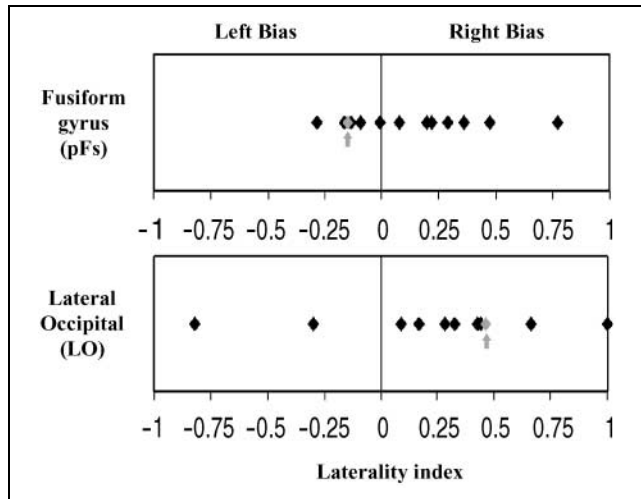
### Laterality Index

Many studies have shown that face-related activity in normal subjects shows a right-hemisphere bias (e.g., Hasson, Levy, Behrmann, Hendler, & Malach, 2002; Kanwisher et al., 1997). We therefore calculated a laterality index for each subject, which compared the number of right- versus left-hemisphere face-related voxels. The index ranges between 1 and -1, where positive values indicate a bias to the right hemisphere, and negative values indicate a bias to the left (see Methods for details). This laterality index was calculated for both

**Figure 4.** Activation profiles of face-related regions. Activation profiles of face-related voxels (faces vs. buildings) in the lateral occipital cortex and the pFs. The data were sampled using the “internal localizer” approach (see Methods for details). Each graph shows the activation profile obtained for YT and 12 control subjects for each stimulus category presented in the object mapping experiment (faces, buildings, objects, and pattern stimuli). Bars indicate the percent signal change for YT, black diamonds indicate the mean percent signal change across the control group, and error bars indicate  $\pm 1$  standard deviation. Note that the activation obtained for YT for each category in each face-related region is within the range of one standard deviation of the mean of the control group.



the posterior fusiform and the lateral occipital face-related regions (Figure 5). YT's laterality index in the



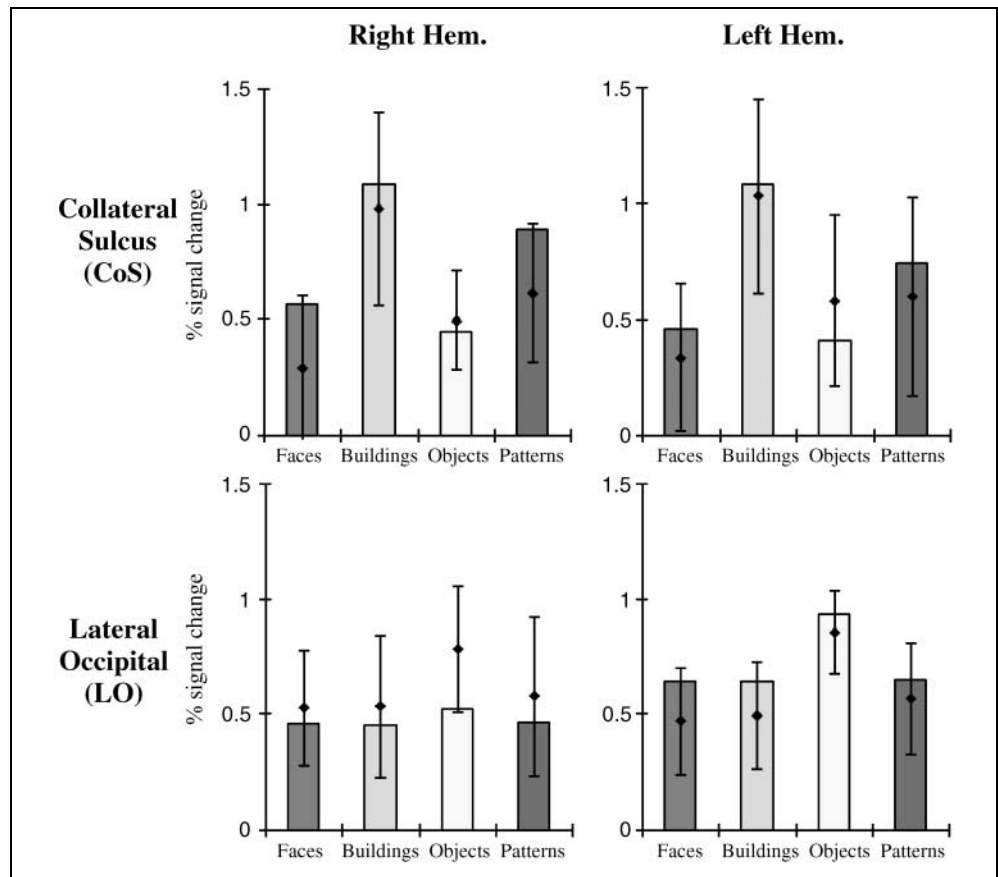
**Figure 5.** Laterality index. The laterality index, which compares the number of face-related voxels in the right versus left hemisphere, was calculated for each subject (see Methods for details). Top: laterality index in the pFs; bottom: laterality index in the lateral occipital cortex. Each black diamond represents the laterality index of a single control subject; the gray diamonds (marked also by gray arrows) represent YT. The laterality index ranges between 1 and  $-1$ ; positive values indicate a bias to the right hemisphere, and negative values indicate a bias to the left. Note that YT's laterality index is within the distribution of the control subjects.

pFs was biased toward the left. However, such a left bias was also found in four additional control subjects, with no apparent deficit in face identification. Moreover, the left bias of two control subjects (BB and HB) exceeds that of YT. Using the bootstrap method, the probability of finding YT's index compared to the group's by chance was 0.17 (i.e., not significant). Thus, YT's left lateralization within the pFs cannot be reliably taken as a functional marker for his behavioral deficit. In contrast to the pFs, YT's laterality index in the lateral occipital cortex is biased toward the right hemisphere, and is within the range of the control group.

### Activity Elicited by Non-Face Stimuli

The FFA is part of a complex network of areas specifically responsive to objects within the human occipito-temporal cortex (Ishai et al., 1999; Grill-Spector et al., 1998; Malach et al., 1995). Thus, it could be that YT's behavioral deficit would be manifested in the activity of other object-related regions within the occipito-temporal cortex. We therefore measured the level of activation in the collateral sulcus (buildings vs. faces) and lateral occipital cortex (objects vs. faces) in YT and in the control group (Figure 6). In agreement with previous reports (Levy, Hasson, Avidan, Hendler, & Malach, 2001; Kourtzi & Kanwisher, 2000; Epstein, Harris, Stanley, & Kanwisher, 1999; Malach et al., 1995), in the control group the activity in the collateral sulcus was stronger

**Figure 6.** Activation profiles of object-related regions. Activation profiles for building-related voxels (buildings vs. faces) in the collateral sulcus (top) and for object-related voxels (objects vs. faces) in the lateral occipital cortex (bottom). Notations as in Figure 4.



for buildings compared to faces (paired  $t$  test,  $p < 10^{-5}$ ), while the activity in the object-related region in the lateral occipital cortex was stronger for objects compared to faces (paired  $t$  test,  $p < 10^{-4}$ ).

YT's activation profile within the collateral sulcus was again similar to that of the control group, with levels of activity within the range of one standard deviation of the mean of the control group (Figure 6, Top). The stimulus selectivity measure for buildings compared to faces in this region was not significantly different than that of the control group ( $p < .41$ , for both the right and left collateral sulcus). The selectivity measure for objects compared to faces in the lateral occipital cortex revealed a more complex pattern (Figure 6, Bottom). Whereas YT's left object-related region was not significantly different from that of the control group ( $p < .22$ ), the right object-related region in YT, as opposed to the control group, showed only weak preference for objects, a trend that almost reached statistical significance ( $p < .056$ ).

To summarize the results so far, although YT is severely impaired in face identification, the activity elicited by faces in the pFs and lateral occipital regions was within the normal range of the control group in terms of the anatomical location (Figures 2 and 3), Talairach coordinates (Table 1), gross selectivity (Figure 4), and laterality index (Figure 5). Whereas no differences were found between YT and the control group in the FFA

region, subtle differences may still exist in the lateral occipital cortex, as a tendency was found towards reduced selectivity for objects versus faces in the right object-related LO, and for faces versus objects in the left face-related LO. Of course, activity per se does not imply that the perceptual process in the activated areas was normal. Experiment 2 was designed to partially address this issue.

### Experiment 2: Holistic versus Local Processing in Face-Related Regions

One of the hallmarks of face identification is its reliance on holistic processing; that is, grouping the face components into a global facial configuration. It is possible that YT's apparently normal face-related activity was induced by processing face parts (e.g., eyes, nose, and lips), while his performance impairment results from a failure to integrate those parts into a whole.

To explore this possibility, we used a modified version of the Rubin face-vase illusion, which was previously used by Hasson et al. (2001). In the Rubin face-vase illusion, the same local contours create two different visual percepts, depending on the figure-ground segmentation. Thus, if local features mediate face-selective activation, we would expect that activation in face-related regions would be similar in the Rubin-vase and



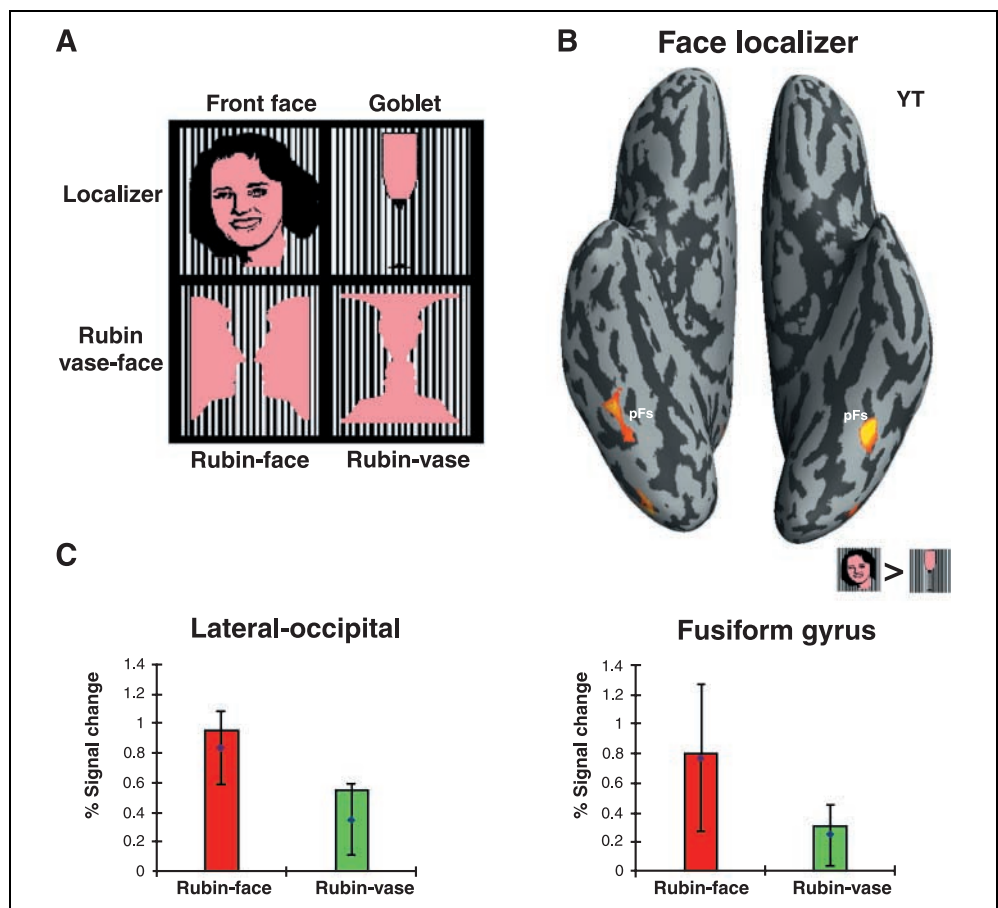
Rubin-face perceptual states inasmuch as the local feature structure is similar in the two images. In contrast, if global processes, which go beyond the local contours, drive the face-related activation, we would expect higher activation in these regions to the Rubin-face perceptual state compared to the Rubin-vase perceptual state. Our previous study showed that face-related activation in normal subjects is modulated by global grouping processes, and is not induced solely by representation of local stimulus features. In the current study, we used the same paradigm to test whether YT's face-related activation would also reveal such holistic processes.

Face-related regions were independently localized by contrasting line drawings of faces with goblet images (Figure 7A). As in the previous experiment, face-related regions in YT were found in two locations: the lateral occipital cortex and the pFs (Figure 7B). These regions overlapped the regions identified in Experiment 1 (lateral occipital cortex: right, 42, -74, -0; left, -47, -73, -1; fusiform gyrus: right, 33, -54,

-14; left, -31, -56, -19). This overlap, which was found despite the use of an entirely new set of object stimuli, provides an independent replication of the normal localization of face regions in YT, as observed in the previous experiment.

The holistic versus local processing was assessed by comparing the MR signal during the Rubin-face and Rubin-vase perceptual states. The mean MR signal in the control group for the Rubin-face and the Rubin-vase stimuli in the lateral occipital and posterior fusiform regions are presented in Figure 7C (data from Hasson et al., 2001). Despite the similarity between these stimuli, the face-selective regions were activated more by the Rubin faces compared to the Rubin vases. This effect occurred both in the pFs (paired *t* test,  $p < .01$ ), and in the lateral occipital region (paired *t* test,  $p < .01$ ). YT's activation for each category was again within the range of one standard deviation of the mean of the control group in both regions, as was the difference between the two categories ( $p < .45$  for the pFs,  $p < .26$  for LO).

**Figure 7.** Rubin face–vase experiment. (A) Examples of the stimuli used in the experiment: Localizer stimuli (top row)—to independently localize face-related regions we included line drawings of front faces, which were contrasted with goblet images (bottom row). Rubin vase–face stimuli—to reveal holistic aspects of face activation we employed a modified version of the Rubin vase–face illusion, presenting a Rubin face (left) and a Rubin vase (right). (B) Localization of face-related activation for YT: face-related activation obtained by contrasting the front-face stimuli with the goblet stimuli. (C) Activation profiles in the lateral occipital face related region (left), and the posterior fusiform face-related region (right). Each graph shows the percent signal change obtained for YT and the control group for the uniform vase and the uniform-profile stimuli. Bars indicate data from YT, black diamonds indicate the mean percent signal change across the control group, and error bars indicate  $\pm 1$  standard deviation. Note that in YT, as in the control group, face-related regions showed significantly higher activation to the Rubin face compared to the Rubin-vase condition, despite the presence of similar local features in the two conditions.



Thus, similar to the control group, activation in YT's face-related regions were affected by the holistic configuration of faces and not only by their local features.

## DISCUSSION

In the present study, we report the case of a congenital prosopagnosic individual, YT, who is markedly impaired in face identification, despite having a fairly normal pattern of face-related activation in the ventral occipito-temporal cortex as measured by fMRI. Moreover, preferential activation during the Rubin-face compared to the Rubin-vase perceptual states suggests that global grouping processes contribute to his face-related activation. These findings suggest that YT's profound prosopagnosia is not a result of decreased activation or lack of selectivity in ventral occipito-temporal face-related regions, nor can it be easily accounted for by holistic processing impairment. Therefore, we suggest that ventral occipito-temporal face-related activity, at least as measured with fMRI, is not sufficient for normal face identification.

YT reveals an intriguing discrepancy between behavioral impairment in face identification on the one hand, and an apparently normal face-related activity on the other hand, especially in the FFA. How could this discrepancy be interpreted?

Several alternatives can be considered. First, within the framework of a visual perception model that distinguishes between the detection and structural encoding of the visual percept, on the one hand, and its within-category identification, on the other hand (e.g., Marr, 1982), the present results support the hypothesis that the FFA and perhaps the lateral occipital cortex are more involved in the former than in the latter process. This conclusion is congruent with previous fMRI and electrophysiological findings.

In normal subjects, FFA activity was hardly affected by face inversion, despite a drastic reduction in face-identification performance (Kanwisher, Tong, & Nakayama, 1998). In contrast, in the same study, the activation in the FFA was drastically reduced when two-tone "Mooney faces" were inverted. The inversion of Mooney faces causes a substantial reduction in the ability to recognize these images as faces, probably because of disruption in the integration of the inverted Mooney face features into a coherent percept of a face. Thus, these data support the view that the FFA is involved in structural encoding of face stimuli as such, rather than with within-category identification. Similarly, ERP studies identified the scalp N170 as a component with prominent selectivity for faces, and have shown that while being preferentially elicited by face parts, this component is not sensitive either to the familiarity of the face (Bentin & Deouell, 2000), or to its internal configuration (Bentin et al., 1996).

The hypothesis that the FFA is involved in detection and structural encoding of faces is fully compatible with

YT's behavioral profile, because he can easily distinguish between face and non-face stimuli despite his impairment in face identification. Our finding of holistic figure-ground segregation in YT's face-related regions is also consistent with his performance, which exhibited normal holistic processing in a series of visual tasks (Bentin et al., 1999). Moreover, a recent behavioral study of another congenital prosopagnosic person, BC (Duchaine, 2000), showed that similar to YT, although BC was severely impaired in face identification, he performed normally in tasks requiring the reconstruction of visual configurations. Although there are reports of congenital prosopagnosics that did not develop configurative processing (e.g., case AV reported by de Gelder & Rouw, 2000, and case EP reported by Nunn, Postma, & Pearson, 2001), the case of BC demonstrates that prosopagnosia associated with apparently normal configurative processing is not peculiar to YT.

More generally, it should be noted that faces engage a wide range of recognition tasks among which face detection and face recognition are only two examples. The fact that YT showed normal performance on detecting facial expressions and gender might hint for a role of the FFA in such functions as well.

In a recent imaging study with two prosopagnosic patients whose deficit was acquired during adolescence, Marotta et al. (2001) also found face-related activation in the vicinity of the fusiform gyrus, but as opposed to control subjects the face-related activation in the two acquired patients was found in posterior parts of the fusiform gyrus and not in its more anterior parts, which correspond to the FFA (pFs). In another fMRI study, Hadjikhani & de Gelder (2002) did not find any face-selective activation within the occipito-temporal cortex, and particularly in the FFA, in two acquired prosopagnosic patients. The lack of FFA activation in acquired prosopagnosic patients might imply that the FFA is "necessary" for face identification. Our finding of a normal FFA activation in YT is a complementary finding suggesting that the activation in the FFA is not "sufficient" for face identification. Moreover, it may point to different mechanisms of impairments in the acquired and in the congenital cases. Hadjikhani and de Gelder also tested the activation pattern in a congenital prosopagnosic patient (AV). Whereas YT showed clear face-selective and object-selective activations with normal spatial distribution in ventral occipito-temporal region, in AV faces and objects produced similar level of activation in the regions corresponding to the FFA and LO. This discrepancy might point to variable mechanisms of prosopagnosia even in congenital cases. As mentioned above, AV, unlike YT, had impaired configurative processing (de Gelder & Rouw, 2000). YT therefore presents a minimal case in displaying pure deficit in face identification, with preserved selective activation in the FFA, providing critical information regarding the sufficiency of these brain activations for face identification.



In agreement with our current finding of normal face-related MR activation in YT, Bentin et al. (1999) found a distinct N170 for faces in YT, which was roughly similar in strength and distribution to that of the control group. However, they also found that whereas for control subjects the N170 was significantly larger for faces than for objects, for YT it was elicited to the same extent by both categories. This finding was recently replicated in two other congenital prosopagnosia cases (Sagiv, Barnes, & Robertson, 2000). In the current study, we found a strong trend toward reduced selectivity for objects in the right object-related LO, and for faces in the left face-related LO. The spatial relationship between LO face-related BOLD activation and the N170 face-related response observed in ERP studies is still unclear. Because electrical potentials, by means of volume conduction may be picked up by remote electrodes, the scalp N170 response may reflect selective neuronal processes in the dorsal lateral temporal cortex (Puce, Allison, & McCarthy, 1999) as well as those located more ventrally in the occipito-temporal cortex (Bentin et al., 1996) or in the inferior temporal cortex (Sagiv & Bentin, 2001; George et al., 1996). Assuming that the N170 is indeed sensitive (even if not solely) to face-related activation in LO, the reduced BOLD selectivity in LO may reflect the same abnormality that yielded YT's nonselective N170 results. Thus, taken together, the ERP and the fMRI findings suggest that the selectivity for faces in YT's lateral occipital regions is less prominent than in normal people. Accordingly, a possible source of congenital prosopagnosia is an inefficient distinction between the encoding of faces and other categories. This might lead to failure in the development of dedicated face-specific processing or storage strategies, which are necessary for face identification (Bentin et al., 1999).

Although our current finding suggests that the FFA is involved in face detection and configuration rather than in identification per se, we do not rule out the possibility that the FFA also contributes to face identification. Indeed, it is quite possible that the activation of the FFA (as a face "detector") is a necessary step in normal face identification, which is then followed by the operation of higher cortical regions (e.g., Bar et al., 2001). That is, the FFA activity might be necessary but is not sufficient nor a final stage of face identification. In agreement with this possibility, a recent study by Tippett, Miller, & Farah (2000) reported patients with preserved face perception, but with impairment in learning to recognize new (previously unfamiliar) faces. The authors termed this selective deficit prosopamnesia, and argued for a division of labor between neural systems for learning and neural systems for representation of familiar faces. The latter may be related to the intracranially recorded P350 (Allison et al., 1999; McCarthy, Puce, Belger, & Allison, 1999; Puce et al., 1999), observed anteriorly to the pFs along the ventral

temporal cortex. As opposed to the N200, this potential exhibits priming effects and habituation and may therefore reflect higher stages of face recognition. Thus, YT might have all the information needed to recognize faces (reflected in the normal pattern of fMRI activation in the FFA), but lacks the ability to adequately stream face information to higher order, face-specific knowledge-based representation (cf. Bentin et al., 1999). When this deficiency is congenital, the result is prosopagnosia rather than prosopamnesia.

Finally, it should be noted that the current fMRI spatial resolution is in the order of millimeters, whereas the functional units involved in face processing (as observed by optical imaging) might be in the range of hundreds of microns (Wang, Tanifuji, & Tanaka, 1998; Wang, Tanaka, & Tanifuji, 1996). Therefore, it remains a possibility that despite the preserved overall activation by faces, the representation of faces in the FFA itself is disrupted in a way that renders face identification inefficient, and this distortion is not captured in the overall fMRI signal (for a discussion of this issue, see Avidan, Hasson, Hendler, Zohary, & Malach, 2002).

## Conclusion

Studying individuals who lack specific cognitive abilities is a powerful approach for establishing the relation between brain activity and cognitive roles. The fact that YT's brain has not suffered trauma or neurological disease that may complicate the analysis of hemodynamic or electrical measurements makes this case particularly informative. The finding of selective activation in the ventral occipito-temporal cortex for face versus non-face stimuli in a subject who lacks the ability to recognize familiar faces suggests that this preferential activation is not sufficient on its own for normal face identification. In addition, the conjunction of fMRI and ERP data from the same subject suggest that adequate selectivity in the lateral parts of the occipito-temporal cortex, manifested as early as 170 msec, may be essential for face identification.

## METHODS

### Control Subjects

Thirteen control subjects (ages 26–49) participated in either one or two experiments: 12 (7 women) participated in Experiment 1 and 10 (5 women) in Experiment 2. All subjects, including YT, provided written informed consent. The Tel Aviv Sourasky Medical Center Ethic Committee approved the experimental procedure.

### MRI Setup

Subjects were scanned in a 1.5-T Signa Horizon LX 8.25 GE scanner equipped with a standard birdcage head coil. BOLD contrast was obtained with gradient-echo

echo-planar imaging (EPI) sequence (TR = 3000, TE = 55, flip angle = 90°, field of view 24 × 24 cm<sup>2</sup>, matrix size 80 × 80). The scanned volume included 17 nearly axial slices of 4-mm thickness and 1-mm gap. T1-weighted high-resolution anatomical images and 3-D spoiled gradient-echo sequence (TE = 9, flip angle = 40°, 124 slices, slice thickness = 1.2 mm, horizontal plane, field of view 24 × 24 cm<sup>2</sup>, matrix size 250 × 250) were acquired on each subject to allow accurate cortical segmentation, reconstruction, and volume-based statistical analysis.

### Visual Stimuli and Experimental Design

An interleaved short-block design was used in both experiments. Each epoch lasted 9 sec, followed by a 6-sec blank screen. A central, red fixation point was present throughout the experiments. The stimuli were generated on a PC and projected via LCD projector onto a tangent screen located in the scanner. During both experiments, subjects were instructed to identify whether two consecutive images were identical or not (one-back memory task). One or two consecutive repetitions of the same image occurred in each epoch.

#### Experiment 1

The visual stimuli used in the first experiment (Figure 1) included line drawings of faces, buildings, common man-made objects, and geometric patterns. Nine images of the same type were presented in each epoch; each image was presented for 800 msec and was followed by a 200-msec blank screen. Each experimental condition was repeated seven times in pseudorandom order. The experiment started with 27 sec and ended with 9 sec of a blank (fixation only) screen. The experiment lasted 450 sec.

#### Experiment 2

The second experiment (Figure 7) included a modified version of the Rubin-face and Rubin-vase stimuli, as well as line drawings of front faces and goblets, which served as an independent localizer of the face-related regions. Contours of the Rubin face were produced by tracing edges of face photographs. By duplicating each profile outline, a vase that shared the exact outline with the profiles was constructed. The illusion was modified by biasing the perception to one perceptual state or the other (vase or profiles). The biasing was accomplished by coloring one object in a uniform color and placing it over a striped background (see Figure 7A). In order to prevent subjects from seeing the complementary perceptual interpretation, each figure was presented for 200 msec only, and was followed by a masking grid that remained on the screen for 800 msec. The crucial point to note is that the Rubin vase and Rubin face have

similar local features but give rise to different global perceptual states. The experiment started with 21 sec and ended with 12 sec of a blank (fixation only) screen. The experiment lasted 507 sec (for more details, see Hasson et al., 2001).

### Data Analysis

fMRI data were analyzed using the BrainVoyager software package (Brain Innovation, Maastricht, Netherlands) and with complementary in-house software. For each subject the cortical surface was reconstructed from the 3-D-spoiled gradient-echo scan, and was transferred to Talairach coordinates system. Talairach transformation consisted of two consecutive transformation steps: first, rotation of a 3-D brain into the AC–PC plane (AC = anterior commissure, PC = posterior commissure); second, scaling the brain into Talairach space using the external specified borders of the brain. The surface of each Talairach normalized brain was then reconstructed. The procedure included segmentation of the white matter using a grow-region function, the smooth covering of a sphere around the segmented region, and the expansion of the reconstructed white matter into the gray matter. The sulci were smoothed using a cortical “inflation” procedure. The surface was cut along the calcarine sulcus and unfolded into the flattened format. The obtained activation maps were superimposed on the unfolded cortex, and the Talairach coordinates (Talairach & Tournoux, 1988) were determined for the center of each ROI.

Data of each subject from each scan were analyzed separately. Preprocessing of functional scans included 3-D-motion correction and filtering out of low frequencies up to ten cycles per experiment (slow drift). The first three images of each functional scan were discarded. Statistical analysis was based on the general linear model (Friston et al., 1995). Our analysis consisted of a multiple regression with a regressor for each condition in the experiment, using a boxcar shape and assuming a hemodynamic lag of 3 sec. The analysis was performed independently for the time course of each individual voxel. After computing the coefficients for all regressors, we performed a *t* test between coefficients of different conditions (e.g., faces vs. buildings). The degrees of freedom were the number of data points minus the number of predictors in the model (i.e., 142 in the first experiment and 161 in the second experiment). Only voxels whose *p* value was no more than 0.05 (not corrected) and which were part of a cluster of at least six contiguous voxels were considered significant. Percent signal change for each subject in each experiment was calculated as the percent activation from a blank baseline.

“Internal localizer” test: To obtain an unbiased statistical test within a scan, we took advantage of the short-block presentation and adopted a procedure, which we

termed the internal localizer approach (Lerner, Hendler, & Malach, 2002). In this procedure a subset of the epochs served to localize regions of interest, while another subset, not used in the statistical localization tests, was used to evaluate the activation level. More specifically, for each localizer test (e.g., “ faces” vs. “ buildings”) two statistical tests were conducted. In each test, four different epochs served as anatomical localizers, whereas the rest of the epochs were not included in the test and the level of activation during these epochs was measured separately. The data obtained from all epochs, which were ignored in the statistical test (but consisted of the same type of stimuli), were averaged within each subject. These data were averaged across subjects and are presented by the diamonds in Figures 4 and 6. Note that this approach has the advantage that the localizer test is performed on epochs that were included in the same scan in which the activation level was measured (rather than the more common separate localizer scan), thus minimizing inaccuracies due to head motion. Moreover, the time course analysis measured in the pertinent epochs is unbiased by the statistical test used to define each ROI, because these epochs were not included in the time course analysis.

**Selectivity measure and bootstrap analysis:** To assess the degree of selectivity in various activated areas, we calculated the difference between two categories of stimuli (e.g., faces vs. house). The null hypothesis in our analysis is that YT is not different from the group of controls in this measure of selectivity. However, whereas there are established methods for comparing two groups, there is no clear method of rejecting the null hypothesis comparing a single subject to a small group, which is not necessarily normally distributed. We therefore used a nonparametric bootstrap analysis, which examined the probability of finding the observed difference between YT and the group’s mean. The analysis consisted of the following procedure, repeated  $10^4$  times: (1) A group of 12 was selected randomly, with replacement, from among the 13 participants (including the controls and YT) and the mean was calculated; (2) a single “target” subject was randomly selected from among the 13 subjects; and (3) the difference between the random “target” (Stage 2) and the mean of the random group (Stage 1) was noted. The cumulative frequency distribution of these differences was plotted, and the place of the real observed difference between YT and the actual control group was found in this distribution. This place represents the probability of finding the observed difference by randomly selecting a subject and a group from the population.

### Laterality Index

A laterality index was calculated for all subjects. For each subject we defined face-related regions by contrasting

face stimuli with building stimuli. A weighted-average of number of face-related voxels in the left versus right hemisphere was calculated for each subject:

$$(RH - LH)/(RH + LH)$$

where RH and LH stand for the number of face-related voxels in the right and left hemispheres, respectively. The laterality index ranges between 1 and  $-1$ , with positive values indicating a bias to the right hemisphere, and negative values indicating bias to the left.

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The data reported in this experiment have been deposited in The fMRI Data Center (<http://www.fmridc.org>). The accession number is 2-2002-113AH.

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