Research report

When the brain remembers, but the patient doesn’t: Converging fMRI and EEG evidence for covert recognition in a case of prosopagnosia

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\textbf{A R T I C L E  I N F O}

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\textbf{A B S T R A C T}

The role of the occipito-temporal cortex in visual awareness remains an open question and with respect to faces in particular, it is unclear to what extent the fusiform face area (FFA) may be involved in conscious identification. An answer may be gleaned from prosopagnosia, a disorder in which familiar faces are no longer recognized. This impairment has sometimes been reported to be associated with implicit processing of facial identity, although the neural substrates responsible for unconscious processing remain unknown. In this study, we addressed these issues by investigating the functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) responses to familiar and unfamiliar faces in a well-known prosopagnosic patient (P.S.). Our fMRI results show that faces known prior to the onset of prosopagnosia produce an increase in activation in the lateral fusiform gyrus encompassing the FFA, as well as the right middle frontal gyrus, when compared to unknown faces. This effect is not observed with photographs of celebrities dating after the onset of prosopagnosia. Furthermore, electrophysiological responses show that previously familiar faces differ from unfamiliar ones at around 550 msec.

Since covert processing of familiarity is associated with activation in FFA, this structure does not appear to be sufficient to produce awareness of identity. Furthermore, the results support the view that FFA participates in face individuation.

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1. Introduction

Prosopagnosia – or face agnosia – is an impairment in the recognition of faces that can occur following bilateral, and occasionally unilateral lesions in the right occipito-temporal territories (acquired prosopagnosia, see Damasio et al., 1982; Farah, 1990). Due to the variability in the location and extent of the lesions, the neuropsychological deficits often extend to other functions, including colour vision or object recognition, whilst sensory, cognitive and intellectual abilities are largely spared. Prosopagnosic patients fail to identify faces of persons they know (including relatives) and do not experience any sense of familiarity when seeing them, although they maintain the capacity to identify the individuals through alternate means or modalities, using for example voice or gait (Sergent and Signoret, 1992). In these patients, the impairment affects overt behavioural tests of face recognition. However, growing evidence suggests that some degree of covert, non-conscious processing may occur.

Covert recognition of familiar individuals has been demonstrated using a broad set of methods, particularly in patients who present no configurational deficits for faces (Schweinberger and Burton, 2003). Evidence for this has been obtained using behavioural measures based upon perceptual and/or learning approaches (Cole and Perez-Cruet, 1964; Bruyer et al., 1983; Sergent and Poncet, 1990), as well as through electrodermal measures (Bauer, 1984; Tranel and Damasio, 1985), eye movement monitoring (Rizzo et al., 1987) and event-related potential recordings (Renaud et al., 1989). These studies demonstrated that, even though overt knowledge about the stimuli was absent, familiar and unfamiliar faces gave rise to different response times, somatic reactions, patterns of visual exploration and electrical brain responses, thus indicating differential processing for familiarity and/or identity without awareness. However, despite these reports evidencing covert processing of familiarity in prosopagnosics, the neuroanatomical underpinnings underlying this ability remain unclear. In particular, the role of the occipito-temporal face pathway in awareness is still debated.

In healthy controls, several functional magnetic resonance imaging (fMRI) studies, in which visual awareness of faces (Tong et al., 1998; Kleinschmidt et al., 1998) or facial identities (Grill-Spector et al., 2004; Rothsstein et al., 2005) were manipulated, showed that conscious perception of either faces or specific identities was linked to the activation of face-selective regions. It therefore appears that for conscious identification of a face to occur, activation of some areas included in the core system for face processing (Haxby et al., 2000) might be necessary. These are generally agreed to include the fusiform face area (FFA) medially (Kanwisher et al., 1997), and the occipital face area (OFA e.g., Gauthier et al., 2000) lying laterally in the inferior occipital gyrus.

However, this view has been called into question by several recent investigations. For example, Morris et al. (2007) observed that a briefly masked face could also produce BOLD activation in the FFA even without the participants’ awareness. Using a masked face priming paradigm, another fMRI study demonstrated an adaptation effect in the FFA following the repetition of a face, effect that was present even when the subjects were unaware of the initial face prime (Kouider et al., 2009). Another event-related fMRI design using a different masking procedure showed that the OFA was involved in the detection of changes in identity when faces were concerned. Of particular interest is the fact that a similar level of activation was present whether or not the change in facial identity was subjectively reported (Large et al., 2008). Hence, despite the fact that the facial identities were not consciously perceived, parts of the core face processing system were found to be differentially activated when previously encountered faces were displayed.

The putative role of the extrastriate visual areas in awareness of identity may be substantiated by investigating covert processing of familiarity in prosopagnosics. Since these patients lack awareness of familiarity, activation of extrastriate face areas in response to the presentation of familiar faces should constitute evidence that these areas are not sufficient for conscious identification. However, the number of neuroimaging studies of patients with acquired prosopagnosia patients remains low to date [i.e., to our knowledge, only three have been studied: Rossion et al. (2003) — on the current patient P.S. — Marotta et al. (2001) and Steeves et al. (2006)]. In these prosopagnosics, fMRI suggested a normal activation of FFA in response to faces, thus leading to the hypothesis that functional integrity of both the FFA but also the OFA in the same hemisphere (the right) is the necessary condition to achieve overt familiarity detection (Rossion et al., 2003; Rossion, 2008).

Although the contributions of these first studies on prosopagnosic patients were essential in delineating the cortical areas involved in face processing, none of them addressed the question of possible covert face recognition. Nevertheless, attempts have been made to determine whether faces, when presented repeatedly, produce the decrease in the fMR response that occurs in healthy participants, as demonstrated by the well-known paradigm called the suppression or fMR-adaptation effect (Grill-Spector and Malach, 2001). Both Schiltz et al. (2006) and Dricot et al. (2008) with patient P.S. and Steeves et al. (2006) with another patient investigated the response in functionally defined face preferential areas and demonstrated a lack of adaptation of the right FFA during multiple exposures to the same face. This was interpreted as the manifestation of the face-recognition deficit in patients. Unfortunately, no attempt has been made to search for residual correlates of face identification in prosopagnosic patients by means of tasks that are less biased towards short-term memory representations, but rely on longer-term exposure to the faces and therefore on previously well-established familiarity.

In this study, we investigated the processing of facial identity in an acquired prosopagnosic patient, P.S. in order to assess whether or not the brain responses for familiar, famous...
faces differed from those for unknown faces using a combination of fMRI and ERP techniques. Our aim was to determine the cortical regions involved in covert recognition processes as well as their temporal unfolding.

2. Methods

2.1. Patient P.S.

Patient P.S. is a densely prosopagnosic 58 year-old woman who was first reported by [Mayer et al., 1999], and was subsequently investigated in great detail (Rossion et al., 2003; Schiltz et al., 2006; Caldara et al., 2005; Sorger et al., 2007). Briefly, the patient suffered brain injury at the age of 42, following a violent occipital impact that produced two large lesions, laterally in the right inferior occipital cortex (extending rostrally into the posterior fusiform gyrus) and the left mid-ventral territory (including the posterior and middle parts of the fusiform gyrus and a part of the lingual gyrus), as well as two other smaller lesions in the right posterior middle and inferior temporal cortex and in the left posterior cerebellum (see Fig. 1. Panel A). Most importantly, P.S. seems to have an intact right FFA (Rossion et al., 2003; Sorger et al., 2007) and left OFA (Sorger et al., 2007), as evidenced by the normal response in a classical functional face localizer. Clinically, she presents a severe visual processing deficit that is restricted to face recognition, while colour vision and visual object recognition are preserved (Rossion et al., 2003; Schiltz et al., 2006). Her visual field is intact, except for a remaining small left paracentral scotoma. Subjectively, P.S. still experiences a severe impairment in the recognition of familiar faces, including faces of celebrities, her own face, and those of family members. She is also significantly impaired (Rossion et al., 2003) in recognizing newly-learned faces (18/25 in the Warrington Recognition Memory Test – Warrington, 1984; Warrington, 1996) and in face matching tasks (27/54 in Benton Face Matching test – Benton and Van Allen, 1972). It has been suggested that in order to determine a person’s identity, P.S. focuses on the mouth or external contours of the face and relies on non-visual cues (Caldara et al., 2005). In spite of these disorders, a number of residual “high-level” face processing abilities including recognition of gender, age and emotional expression, as well as subcategorical discrimination of objects are globally preserved (Rossion et al., 2003).

P.S. gave her informed written consent to participate in this experiment, which was approved by the Ethic Committee of Geneva University Hospitals. She underwent two separate procedures, first the electroencephalography (EEG) recording session, then 2 weeks later the fMRI session.

2.2. Selection of faces

Two categories of faces were selected for the whole study, one set of famous faces and one set of unfamiliar faces. The set of famous faces was established on the basis of an interview, which was carried out a year before testing. This had been performed using two methods. First, a name fluency task was performed in order to establish which famous personalities P.S. was familiar with on the basis of their names. On a subsequent session, names of celebrities were given to her (including, but not restricted to, those she had given in the fluency task) and P.S. was asked whether the individual was familiar and if she remembered having been exposed to the person’s face through the media. She was also asked to state whether she thought she had been familiar with the person’s face before her prosopagnosia, and if she thought she would have identified the person’s face prior to her accident. The list included local and international politicians, actors, musicians and TV stars who became celebrities before, as well as after, the patient’s injury. Not surprisingly, only 16 recent celebrities (from the 1990s and 2000s) were judged by the patient to be sufficiently well-known and were subsequently retained (referred to below as recently known faces or RF, 56% females). By contrast, 44 celebrities anterior to her prosopagnosia (dating from before the 1960s to the 1980s) were selected (referred to as previously known faces or PF, 48% females). The large PF subset was used for both EEG and fMRI experiments, while the smaller RF subset was not retained for the ERP procedure (due to the weak signal-to-noise ratio of the EEG measurements). Next, a series of 60 unfamiliar faces (UF) were selected from sources similar to those of the PF and RF stimuli i.e., magazines and internet sites (50% females).

All faces were scaled to a 6 × 7 cm area and converted in black and white photographs (photographs were front view portraits that included hair, but no other paraphernalia such as eyeglasses, hat, etc...). Faces appeared on a grey frame located inside a black background.

In order to establish whether P.S.’s detection was better than chance, i.e., if any awareness was present regarding the identities of the faces presented to her, a 2 alternative forced choice task was carried out approximately 1 year after the fMRI and EEG experiments. In this task, the 44 PF, along with 44 UF were presented on a computer screen in a random order for 2000 msec durations. The remaining parameters were otherwise identical to the ERP procedure (see below). P.S. was informed that the photographs were composed of known and unknown individuals and was asked to guess which category each face belonged to. Since there were an equal number of known and unknown faces, a random response rate would yield a 50% hit rate. Her performance in this task was at 39%, a rate which does not differ significantly from chance (p = .91). Thus, the faces used in the procedures were deemed not to produce any sense of familiarity.

2.3. fMRI experiment

All functional and structural data were collected in a single MRI session. Functional MRI consisted of several block-design runs: the main experiment, designed to address the question of covert familiarity recognition, and two functional
Fig. 1 – fMRI results. Localization of fMRI activations obtained during the object localizer (A), face localizer (B) and familiarity experiments (C). Activations (local maxima) are superimposed on axial, sagittal and coronal slices of P.S.’s normalized brain (neurological convention – see Table 1 for corresponding Talairach coordinates and for details on the performed contrasts). Panel A also shows P.S.’s brain lesions (3D images of right lateral and ventral surface reconstruction showing the main cortical lesions inside a red circle). vLOC and dLOC: respectively ventral and dorsal lateral occipital complex (Malach et al., 1995; Grill-Spector et al. 2001); rFFA and cFFA: respectively rostral and caudal parts of the functionally defined fusiform face area; STS: superior temporal sulcus; dLPFC: dorso-lateral prefrontal cortex. (D) Contrast of the parameter estimates for the familiarity experiment (Effect size in Arbitrary Units) averaged across up to 20 voxels defining the specific regions of interest (ROIs). The ROIs were clusters of activation determined in the Localizer experiment (vLOC) or in the Familiarity experiment (rFFA, cFFA and dLPFC). Histograms plotting rFFA activity were averaged from voxels activated in the PF–UF contrast, those from cFFA were computed from voxels activated in both the PF–UF and the PF–RF contrasts, those from dLPFC were averaged from
2.3.1. Localizers of low-level visual cortex
The patient was presented with a black and white flickering (3.3 Hz) checkeredboard (a 12-square by 12-square frame subtending a visual angle of 10.5 × 10.5°) presented at the centre of the visual field. P.S. was requested simply to maintain her gaze on the fixation cross (situated on the checkeredboard) during the session. A total of 4 epochs (duration 24 sec) were used during which the checkeredboard was displayed, and an alternating series of 4 epochs were presented during which only a central fixation cross appeared.

2.3.2. Localizers of face preferential and object selective areas
Three classes of stimuli were used, each of them presented in a separate block: black and white photographs of faces that were not used in the familiarity experiment, various Lepidoptera species (courtesy of Michael Tarr Lab, Department of Cognitive and Linguistic Sciences, Brown University, RI) and scrambled pictures of intermixed faces and butterflies (visual angle of 6.5 × 6.5°). Stimuli were presented for 750 msec with an inter-trial interval of 500 msec. During this time, P.S. was requested to perform a go/no-go 1-back matching task with all the stimuli, including faces (despite her obvious impairment). Responses were made by pressing a response box with the right index. Two short runs were applied, each consisted of 3 repetitions of a fixed ABAC design, where A was the face viewing condition, B the presentation of scrambled stimuli and C was the butterfly viewing condition (duration of an epoch: 24 sec). Many of the localizer procedures reported in the literature involve only one perceptual control, or one object category condition. We adopted a slightly more restrictive approach by localizing the face areas using a double comparison, instead of the single face versus object comparison. We therefore used a conjunction analysis involving the two non-face conditions versus the face condition (see 2Localizers), a method that yields a more specific estimate of face-preferential regions.

2.3.3. Familiarity experiment
The experiment comprised 5 runs each of 4 blocks, which alternated in a fixed pseudo-random order (4 repetitions of 24 sec). The blocks consisted of presentations of 8 stimuli from conditions PF, RF, UF, or an empty grey frame (resting condition) which subtended a visual angle of 6.5 × 7°. Each stimulus was displayed for 2 sec, with a 1 sec blank-interval during which P.S. was instructed to respond. The patient was requested to perform a gender discrimination task, an exercise that she was able to perform correctly. She was asked to press a key with her index finger for males and another key with her middle finger for females. In the resting condition, she was asked to maintain her gaze in the frame. PF were not presented more than once, but, due to their small number, each face of the RF series had to be shown twice or occasionally three times. Two repeated runs were applied and averaged to achieve an acceptable sensitivity in the contrasts.

2.3.4. Data acquisition
Experiments were conducted on a Siemens 3T Trio MRI scanner (Siemens Medical Solutions, Erlangen, Germany). An anatomical reference image for subsequent normalization of the patient’s brain was acquired using a 3-D MPRAGE T1-weighted sequence (TR/TE/TI = 2.5 sec/2.9 msec/1.1 sec, FOV = 230 mm, matrix 256 × 256, slice thickness = .9 mm). A 20 field inhomogeneity mapping sequence was applied to correct for geometrical distortion that occurred along the phase encoding direction (Jezzard and Clare, 1999). It consisted of two GRE sequences acquired at different echo times with the same acquisition plane and resolution as for the BOLD sensitive sequence (TR/TE/T2*flip = 400 msec/5.19 msec/7.65 msec/ 60°). A T2*-weighted GRE EPI sequence was applied for whole brain BOLD sensitive MRI (TR/TE/Flip = 2 sec/30 msec/85°, FOV 220 mm, matrix 108 × 128, in plane resolution 2 × 1.7, 30 contiguous 4 mm axial slices). Each fMRI run was preceded by three dummy scans to allow steady-state magnetization. Thus during the localizers, a total of 144 volumes were acquired for faces and 72 for each of the other classes of stimuli, whereas during the familiarity experiment, 120 volumes were acquired for each condition.

2.3.5. Data processing
Image processing was carried out with Statistical Parametric Mapping SPM5 package (Wellcome Trust Centre for Neuroimaging, London, http://www.fil.ion.ucl.ac.uk/spm) and statistical analyses of fMRI time series were carried out in SPM2. All functional volumes were subjected to classical preprocessing steps (see Friston et al., 2007): realignment of the time series, unwarping to correct for geometrical distortions along the phase encoding direction (antero-posterior), using the Field-Mapping Sequence was applied to correct for geometrically mapping sequence was applied to correct for geometrical distortion that occurred along the phase encoding direction (antero-posterior), using the Field-Map2 toolbox (Andersson et al., 2001), coregistration to the anatomical volume, smoothing with a Gaussian kernel (FWHM corresponding to two voxels), low- and high-pass filtered, and modelling using an auto-regressive [AR(1)] function to account for temporal correlations between voxels across the whole brain. A statistical analysis based on the general linear model (Friston et al., 1995; Worsley and Friston, 1995) was performed on each voxel within the native (non-normalized) brain of the patient. Each condition was modelled as a box-car function convolved with the canonical hemodynamic response function. Additional regressors for motion correction were included in voxels activated in both PF–UF and PF–RF contrasts, finally those from vLOC were computed from voxels activated in the object localization procedure (See Materials and methods). Error bars represent the 90% confidence interval of the estimation error of the SPM model. Significant differences (t-tests) between conditions are indicated by asterisks (*p < .05 corrected for multiple comparisons across voxels defined by the localizers; ns non-significant). UF: unknown faces; PF: previously recognized faces; RF: recently famous faces.
the model to minimize motion-related artefacts. Student t-test contrasts were performed between different blocks/conditions. Statistical significance threshold for individual voxels was set at \( p < .01 \), corrected for multiple comparisons using the false detection rate (Genovese et al., 2002) for the localizers, and at \( p < .001 \) uncorrected for the familiarity experiment (but see below). Only activation clusters containing a minimum of 8 voxels are reported and discussed further. For comparative purposes and visualization in the standard space (Talairach and Tournoux, 1988), the SPM-t (activation) maps were then subjected to a normalization procedure, using parameters which were initially estimated from a segmentation procedure of P.S.’s brain (Ashburner and Friston, 2005; Crinion et al., 2007). Finally, a suitable fit towards Talairach coordinates was computed for the statistical local maxima using the ICBM to Talairach transformation matrix (Lancaster et al., 2007).

2.3.6. Localizers

The comparison of the BOLD response for the checkerboard with that for the fixation cross display (baseline), allowed us to localize a part of the retinotopic areas and other low-level cortical regions. Face preferential areas recruited either during structural encoding (the FFA and OFA) or during the analysis of dynamic or emotional characteristics (the posterior superior temporal area STS – Hoffman and Haxby, 2000) were isolated using a conjunction analysis between (faces–scrambled pictures) and (faces–butterflies) (Price and Friston, 1997; Nichols et al., 2005). The rationale for this procedure was the following: on one hand, faces were contrasted with scrambled stimuli in order to ensure an acceptable matching of low-level visual characteristics, on the other hand, faces were compared to butterflies to exclude areas that are engaged in general processing of objects (Grill-Spector et al., 2001) or/and living versus non-living stimuli processing (Farah et al., 1991). This approach represents a compromise (Large et al., 2008) between multiple controls and a more reductive approach consisting of a single face versus non-face presentation that has been used in prior studies on patient P.S. (e.g., Schiltz et al., 2006). Non-face-specific processing areas (responding not only to faces but also to other object or non-object categories) that belong to the lateral occipital complex (LOC – Malach et al., 1995; Grill-Spector et al., 2001) were identified using the single contrast performed between the presentation of butterflies and that of scrambled pictures.

2.3.7. Familiarity experiment

Since PF and RF were the categories that could evoke familiarity, PF and RF conditions were each contrasted with the UF condition. More importantly, PF was compared to UF and RF to investigate covert recognition of faces known prior to the onset of prosopagnosia. The resting (fixation) condition was used to obtain a baseline level for brain activity. Therefore, each contrast between conditions of interest (including faces) was performed after having been inclusively masked by the appropriate condition against baseline (\( p < .01 \) uncorrected). This was performed in order to retain the activations that were significant against the resting state, and that were meaningful compared to a specific condition of interest. Functionally defined areas obtained either from the face or the object localizers (extending outside the cortex mapped with the checkerboard stimulation) were considered as functional ROIs allowing us to reduce the volume explored with the statistical analysis in the familiarity experiment (small volume correction). Plots reporting activation levels were generated with MarsBar (www.sourceforge.net/projects/marsbar) from activation clusters identified using the Localizer or the Familiarity experiments.

2.4. EEG experiment

2.4.1. Procedure

Due to limitations in the number of stimuli, only two categories of faces were used in this procedure: PF and UF. They were presented on a computer monitor placed at a distance of 100 cm in front of the subject, subtending a visual angle of \( 3° \times 4° \). As in the corresponding fMRI paradigm, P.S. was asked to perform a gender discrimination task using the two response keys. Each trial started with a fixation cross that was presented for 600 msec, followed by a face (PF or UF) that appeared for 225 msec at the centre of the screen. This was followed by a response prompt (“Male or female?”) that remained present until the patient’s response (but not less than 2500 msec). The following trial then began with another fixation cross. The experiment was carried out in 3 blocks. Each block consisted of a randomized presentation of the whole set of stimuli.

2.4.2. Recordings and data analysis

Patient P.S. was seated in an electrically shielded room and a continuous EEG was acquired at 500 Hz using the Geodesics system (Electrical Geodesics, Inc., OR) with 109 equally-spaced scalp electrodes referenced to the vertex. Impedances were kept below 50 kΩ throughout the experiment. The EEG was filtered offline from 1 to 30 Hz and recalculated against the average reference. Epochs of 800 msec were computed separately for PF and UF. A 100 msec pre-stimulus epoch served to establish baseline. Trials containing blinks, eye movements, or other artefacts were excluded upon visual inspection during the averaging procedure.

3. Results

3.1. Behavioural data

During the fMRI face localizer, P.S. missed a substantial number of targets in all conditions: 31% omissions for the butterflies, 38% for the faces, and 56% for the scrambled drawings. A few false alarms were noted in all conditions (1.4% for butterflies, 1.5% for faces and 6.9% for scrambled pictures). Despite the omissions, it appeared that she maintained her attention equally across the different classes of stimuli. During the familiarity experiments (both EEG and fMRI data), P.S.’s responses were not recorded by the software, due to technical problems. However, an online monitoring (via the response box light indicators) confirmed that the task was performed at a high accuracy level throughout the sessions in the three face conditions.
3.2. fMRI analysis

3.2.1. Localizers
Visual cortex that was not face-specific (as evidenced in the comparison between butterflies and scrambled drawings — Fig. 1A and Table 1A) was composed of the two main ventral areas sensitive to objects (vLOC and dLOC — Grill-Spector et al., 2001) and overlapped in part with the face versus scrambled pictures contrast. No functional vLOC could be detected within the left hemisphere, as was the case in prior studies, due to the lateral extension of the left ventral lesion.

Face-preferential cortex (Fig. 1B and Table 1B) was located within the right lateral fusiform gyrus (close to the FFA as observed in previous studies with P.S.). No face-related activation could be detected within the right hemisphere, as was the case in prior studies, due to the vicinity of the left cortical lesion. The volume of the right FFA appeared to be comparable to that of prior work, considering the large inter-subject variability (e.g., Puce et al., 1996; Kanwisher et al., 1997). Other activations related to faces were found in the left OFA but not the right (damaged), as well as in the right STS, with a posterior extension within the adjacent middle temporal gyrus. Also noticeable, was an additional previously unreported face-related activation located laterally in the inferior occipital gyrus. Overall, the regions of activation of face and non-face specific cortex in this study were highly concordant with those obtained in a previous study of P.S. (see Table 1A and B for a comparison of Talairach coordinates with that found in Sorger et al., 2007).

In addition, activation during checkerboard flickering in the striate and extrastriate cortex engaged in low-level vision processing (results not illustrated) confirmed a previous, detailed retinotopic mapping study of P.S. demonstrating damage to the right cortical area representing the central part of the upper left visual hemifield (Sorger et al., 2007).

3.2.2. Familiarity experiment
Several activation foci were identified in the comparison between PF and UF (covert face recognition — Fig. 1C and Table 1C), and between PF and RF (Table 1D). Two small foci within the right FFA were revealed in the PF–UF contrast: one

<p>| Table 1 – fMRI results for the Localizer and the Familiarity experiments. (A) Non-face-specific activations identified in the (butterflies–scrambled pictures) contrast. (B) Face preferential activations identified in the conjunction contrast between (faces–scrambled pictures) and (faces–butterflies). (C) Activations reflecting covert face recognition, as identified in the (PF–RF) contrast. (D): Activations reflecting covert face recognition, as identified in the (PF–UF) contrast. p is the probability that a given area is activated after correction for multiple comparisons (FWE) across all voxels. |</p>
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<th>Activation focus</th>
<th>Size (mm³)</th>
<th>pcorr.</th>
<th>Coordinates</th>
<th>Prev. coord.</th>
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<th>Overlap with</th>
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<td>Butterflies–scrambled drawings</td>
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<td>Conjunction between (faces–butterflies) and (faces–scrambled drawings)</td>
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<td>+38 − 53 − 22</td>
<td>+36 − 54 − 20</td>
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<td>Covert recognition</td>
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</tr>
<tr>
<td>Right caudal FFA</td>
<td>142/59a</td>
<td>.012a</td>
<td>+38 − 61 − 23</td>
<td>n.t.</td>
<td>4</td>
<td>Face preferential</td>
</tr>
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<td>Right rostral FFA</td>
<td>71a</td>
<td>.009a</td>
<td>+32 − 50 − 19</td>
<td>n.t.</td>
<td>3.6</td>
<td>Face preferential</td>
</tr>
<tr>
<td>Right dIPFC</td>
<td>225</td>
<td>.063</td>
<td>+40 +21 +31</td>
<td>n.t.</td>
<td>4.6</td>
<td>−</td>
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<tr>
<td><strong>(D) Covert recognition</strong></td>
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<tr>
<td>Previously recognized faces–recently famous faces</td>
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<td>Right caudal FFA</td>
<td>45a</td>
<td>.042</td>
<td>+38 − 61 − 23</td>
<td>n.t.</td>
<td>4.1</td>
<td>Face preferential</td>
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<tr>
<td>Right dIPFC</td>
<td>237</td>
<td>.022</td>
<td>+42 +27 +30</td>
<td>n.t.</td>
<td>4.9</td>
<td>−</td>
</tr>
<tr>
<td>Right sPL</td>
<td>485</td>
<td>&lt;.001</td>
<td>+27 − 65 +45</td>
<td>n.t.</td>
<td>4.1</td>
<td>−</td>
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</tbody>
</table>

a When indicated, multiple comparisons correction was performed across voxels defined by the localizers. Talairach coordinates are reported after having converted the activation foci into MNI space (see Materials and methods for details).
b When available, coordinates for the previously defined functional areas by Sorger et al. (2007) are recalled (n.r.: not reported, n.t.: not tested). The reported t local is the Student t score found to be maximal for the voxel local maximum at the mentioned coordinates. iOG: inferior occipital gyrus. Other conventions, same as Fig. 1.
locus rostrally in the defined FFA and another one in a more caudal location of FFA (Fig. 1C). Also noticeable was an additional larger activation, visible in the right middle frontal gyrus (dILPFC − Fig. 1C). No other significant difference was found at the cluster level, but interestingly some voxels in the left OFA reached the statistical threshold ([t(13) = 4.0, p < .001]. In the PF−RF contrast (Table 1D), an additional activation in the right posterior superior parietal cortex was noted. With respect to the PF−UF contrast, only the caudal part of FFA was found to be activated in this contrast ([t(13) = 3.98, p < .001].

Finally, no suprathreshold activation (p > .05) was observed in the RF−UF contrast at the cluster level, either for whole brain or the ROIs analysis.

Parameter estimates and the 90% confidence intervals are shown in Fig. 1D, illustrating the level of activation obtained for the face conditions compared to rest. Strikingly, only marginal differences were found between the levels of activation of UF and RF in the ROIs considered. When compared to baseline, activation levels in both rostral and caudal foci were about 1.8 times greater during the PF condition than during the RF condition, and remained around 1.5 times greater for PF compared to RF in the rostral FFA and 1.7 times greater in the caudal FFA. A similar effect was also evidenced for the left OFA (1.6 and 1.4 times greater for PF than UF and RF respectively). By contrast, the right vLOC, the dLOC (not illustrated), and the lateral temporal foci (not illustrated) showed no measurable differential activation in relation to the familiarity content of the faces.

3.3. ERP analysis

Electrical responses to PF and UF are shown in Fig. 2A for a selection of 8 posterior electrodes (see central inset for electrode location). A maximum positivity was reached at 710–120 msec over all posterior leads, consistent with a P1 response. This was followed by an N170 response that peaked at 180 msec over the right temporal leads (see electrode T6 vs T5). The scalp topography maps for the early P1, N1 and P2 components are different from the patterns normally observed in healthy controls, showing a right lateralization. However, it should be noted that P.S. had previously undergone craniotomy and thus presents bone gaps in her skull which are known to produce alterations in the electrical potentials measured at the surface of the scalp.

Visual inspection of the grand average ERPs revealed a period between around 450–600 msec over anterior electrodes during which PF and UF differed (Fig. 2C). A time-frame-by-time-frame t-test was performed between 0 and 800 msec, in which PF and UF were compared at every electrode using the epochs as dependent samples. Only time frames in which a threshold of p < .05 was reached for at least 10 consecutive time frames in at least 5 adjacent electrodes were taken into consideration. Using this stringent criterion of significance, a difference between conditions appeared over a group of anterior leads between 520–570 msec with famous faces showing a more positive deflection. The graph in Fig. 2B (left) illustrates the results of this point wise t-test for all 109 electrodes across time. The right panels in Fig. 2B illustrate the location of the electrodes that reached the p < .05 cut-off level at 550 msec (top), along with the t-values (bottom) at that same time point, mapped over the scalp surface (colour code is from blue to red for values t = −2.1 to t = 2.92). Fig. 2C illustrates the traces for PF and UF on two frontal sites (FP1 and its anterior midline neighbouring electrode).

4. Discussion

The neural substrates of covert recognition in prosopagnosia were investigated by comparing fMRI and ERP responses to familiar and unfamiliar faces in a patient (P.S.) suffering from severe acquired prosopagnosia. Our analysis showed that both the BOLD and ERP responses to faces that were known prior to the onset of prosopagnosia, differed from the responses to unknown faces and recent celebrities. This occurred despite the fact that she was incapable of identifying the stimuli and that she had no overt sense of familiarity when seeing them. Increases in fMRI activation for previously known faces were observed in a right-lateralized network involving the functional right FFA, as well as the dorso-lateral prefrontal and superior parietal cortex. Furthermore, ERPs collected in a separate session with the same stimuli confirmed the presence of differences between PF and UF in a time window situated around 550 msec over the anterior leads.

The existence of covert recognition of faces in prosopagnosias has already been reported on several occasions using different methods. In one behavioural study by De Haan et al. (1987), the prosopagnosic patient P.H. was found to be able to match pairs of pictures of famous persons significantly faster than unknown persons, again despite any lack of overt knowledge of the individuals. In another task, the investigators presented written names of politicians and pop stars, asking the patient to categorise them into their appropriate occupational category. They observed that P.H. was faster when categorising names that were accompanied by photographs of matching persons than if the photographs represented persons from a different occupational category. In addition, when the patient was asked to learn to associate names with faces, learning was better when the names actually did correspond to the face presented, than when the names and faces bore no relation.

In a separate study, Young et al. (1988) performed a semantic priming task in which healthy controls as well as patient P.H. were asked to determine whether written names were familiar or not. Here again, when the names were preceded by a picture of a related face, response times were found to be faster.

In these different investigations, an influence of familiarity on performance was observed despite the fact that prosopagnosia precluded any awareness of facial identity, thereby demonstrating the existence of covert recognition of identity. Since P.S. showed evidence of differential brain activation for familiar faces, the question arises whether she might also show behavioural evidence of covert recognition. We carried out 3 separate tasks (unpublished data) with P.S. in the course of this study which all failed to show any differences in performance with regard to familiarity. Indeed, neither an interference task (adapted from De Haan et al., 1987), nor a semantic priming task (adapted from Young et al., 1988), nor still an adaptation of an attentional blink task requiring gender discrimination in famous and unknown faces (Jackson
and Raymond, 2006) revealed any impact of face familiarity on performance.

On the one hand, P.S.’s lack of behavioural signs of covert processing might not seem surprising. Indeed, covert processing has been reported in associative prosopagnosics, while apperceptive prosopagnosics, such as P.S., are less likely to show covert recognition (see e.g., Schweinberger and Burton, 2003 for a review). On the other hand, this observation is clearly at odds

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**Fig. 2** — ERP results. (A) A subset of 4 left and 4 right electrodes around T5 and T6 showing the first ERP components (P100, N170 and P2) to PF and UF. The ERPs for PF and UF are illustrated in black and brown lines respectively. Notice the absence of an N170 component on the left sites contrasting with the ERP over the right leads. (B) The left graph illustrates the result of a point-wise t-test performed on all electrodes for each time frame. Significant differences (coloured squares, defined at $p < .05$ for at least 10 consecutive time frames and five adjacent electrodes) are found at around 550 msec on frontal sites (green and red colours). The right panel illustrates the p map (above) with sites showing significant differences at 550 msec in red, and the t-map (below) illustrating the distribution of the t-values between −2.1 (blue) and 2.92 (red). (C) Illustration of electrode FP1 and its nearest anterior midline neighbour showing a difference between conditions of 1.4 μV (PF: black lines; UF: brown lines).
with the imagery findings which provide evidence of differential processing for familiarity at the neural level. One possible explanation could be that FFA activation varies gradually, with activity at weaker levels being insufficient for behavioural signs of covert processing to be seen, with these appearing only at higher levels of activation than that observed in P.S. Conscious awareness would then only appear when a sufficiently strong neural response is present. This hypothesis would concur with neural network accounts of covert processing which suggest that implicit recognition may result from residual activation of parts of the face processing network that are still functional (Farah et al. 1993). However, it may also be the case that other additional networks are necessary for behavioural signs of covert recognition to appear. The lack of a control group in our study prevents us from supporting either of these two views. Indeed, it is whether P.S.’s FFA activation is similar to, or weaker than, that expected in healthy controls.

The role of the ventral pathway in visual awareness has been disputed. Several investigations in healthy subjects have suggested that conscious perception gives rise to an increase in the activity of stimulus-specific visual occipito-temporal areas, whether the stimuli are objects (Grill-Spector et al., 2000), words (Dehaene et al., 2001) or faces (Moutoussis and Zeki, 2002). Regarding faces more specifically, the role of the core areas (Haxby et al., 2000) in overt recognition of specific identities has been recently investigated and confirmed (Grill-Spector et al., 2004; Henson et al., 2003; Rotshtein et al., 2005). For instance, Grill-Spector et al. (2004) presented faces as well as other classes of objects to healthy participants in an event-related fMRI paradigm and asked them to detect the category of stimuli (e.g., face vs texture, or bird vs texture), and in addition to identify a specific target within the category (e.g., Harrison Ford vs other faces; or a pigeon vs other birds). A greater FFA response was found for detected compared to non-detected faces. Of particular interest, and in line with our study, the identification of a specific face also correlated with an increase in the FFA response, consistent with the view that it is involved in the conscious identification of specific individuals.

Other neuroimaging studies of face recognition, which did not specifically seek to investigate conscious detection of familiarity, also noted activations in the lateral middle fusiform gyrus (as well as in the inferior lateral prefrontal cortex, and the lateral and medial temporal cortex), when subjects became aware of an identity, especially when very familiar faces were used, by opposition with newly-learned experimental ones. These studies used stimuli, which contained inherent biographical long-term components, either because they represented personal acquaintances (Nakamura et al., 2000; Taylor et al., 2009), including one’s own face (Sugiyama et al. 2008; Taylor et al., 2009), or because they were celebrities known through the media (Sergent et al., 1992; Hoffman and Haxby, 2000; Simon et al., 2001). These investigations consistently showed, in addition to FFA activation, the recruitment of a large scale distributed network for recognition, and possibly identification, of highly-familiar faces (Haxby et al., 2000; Ishai et al., 2005). Thus, a large body of evidence suggests that FFA is recruited during face recognition and might be more specifically involved in visual awareness of identities.

However, conflicting evidence is now appearing suggesting that the involvement of FFA may not be sufficient for awareness to arise. Recent converging fMRI and ERP studies have used masked priming to investigate non-conscious processing of identity. In a typical paradigm, a face prime is presented, followed by the target which is either the same face or a different one, and to which the participant must respond. The prime can be masked such that it is not consciously perceived by the viewer. In this latter case, despite the fact that subjects are unaware of the face prime, their response to the target face is influenced by the presence of the prime (Henson et al., 2008; Kouider et al., 2009). An fMRI procedure carried out using this paradigm (Kouider et al., 2009) revealed that activity in the FFA, as well as in other characteristic face-preferential areas, was reduced for a face that was preceded by a same-face prime compared to a different-face prime. In another event-related fMRI investigation, an increase in FFA activation was found in response to a previously encoded face compared to an unknown one, whether or not it had been consciously identified (Lehmann et al., 2004). These studies suggest that FFA activity may be modulated by identity, even when the stimulus is not consciously perceived, arguing against the view that its activity is sufficient for awareness to take place (e.g., Grill-Spector et al., 2004).

Prosopagnosia provides a good model to investigate unconscious identification of identity as this disorder is characterised by a lack of overt knowledge regarding the identity of a face. Functional MRI studies in these persons are thus critical to determine whether FFA is involved in unconscious identification. Prior case reports have all exploited the popular repetition suppression/adaptation effect (Grill-Spector et al., 1999; Desimone, 1996; Miller et al., 1991), which is akin to repetition priming (Schacter and Buckner, 1998; Buckner et al., 1995; Begleiter et al., 1995), and which consists in comparing fMR responses to repeated and non-repeated (i.e., novel) faces. In congenital forms of prosopagnosia, the presentation of novel faces yields a normal adaptation in FFA following repetition, as observed in healthy controls, (Avidan et al., 2003). By contrast, the few studies carried out with acquired prosopagnosics failed to reveal similar effects (i.e., with patient P.S. (Schiltz et al., 2006) or with patient D.F. (Steeves et al., 2006)), although Schiltz et al. (2006) actually found a trend towards adaptation for repeated faces in P.S.’s remaining (right) FFA (Experiment 1). Repetition suppression studies have therefore failed to provide evidence of covert recognition in acquired prosopagnosia.

In the electrophysiological domain, a related paradigm, repetition priming, has been studied in healthy subjects, in whom ERPs to primed and unprimed faces were compared. Several studies have shown that responses to two consecutive presentations of a same face, compared to presentations of two different faces produce differential effects over temporoparietal leads between 200 and 300 msec. This response has been termed the visual memory potential or N250r (Begleiter et al., 1995; Schweinberger et al., 1995; Schweinberger et al., 2002).

Recent studies of the N250 suggest that it might reflect stored perceptual representations of known faces. Tanaka et al. (2006) compared the N250 in response to the
participant’s own face, a face that had to be learned as well as unknown faces. The subject’s own face produced a marked N250, contrary to the unknown faces. Interestingly, the learned target face was initially not different from non-target faces, however over time, the N250 for this learned target increased to the level of the subject’s own face. In a subsequent study (Kaufmann et al., 2009) the N250 was found to be maintained even for different views of a learned face excluding the possibility of a purely perceptual effect for this component. No such early response was observed in P.S. and only a late anterior positivity appeared to distinguish familiar from non-familiar faces.

Evidence of a later component indexing familiar faces has been put forward by a number of other electrophysiological studies. Comparing familiar and unfamiliar faces, Eimer (2000) described an enhanced central negativity between 300 and 500 msec in response to familiar faces, followed by an enhanced positivity after 500 msec (the P600f). In this study, the differences between familiar and unfamiliar faces were processed overtly, but in a second experimental run, in which the subjects’ attention was drawn away from the faces, the N400f was no longer observed, although the P600f remained present. Paller et al. (2000) found that when subjects learned to recognise faces, their subsequent presentation showed positive deflections over centro-parietal leads. Interestingly, half of the learned faces in this study had been presented in association with semantic information. These faces produced a greater positive deflection over anterior electrodes at around 500 msec, than those learned without biographical information. This late anterior positivity results was thus interpreted as the reflection of access to semantic information, although this view was challenged by Kaufmann et al. (2009) who found that semantic information about faces affected a slightly later period (700–900 msec). Tanaka et al. (2006) also noted a late positive deflection (400–600 msec) in response to familiar faces over central leads and suggested that it could be linked to memory processes.

To our knowledge, only two ERP studies have investigated the response to famous and unknown faces in prosopagnosia, one of which also found evidence of a late response. Eimer (2000) compared the ERP response to familiar and unfamiliar faces in P.H.D., a patient with acquired prosopagnosia. In this patient no ERP differences were found between the two types of faces. By contrast, in another patient, P.C., Renault et al. (1989) observed differences between familiar (including celebrities) and unfamiliar faces, peaking between 700 msec and 800 msec with a central distribution. As was the case for P.S., patient P.C. had undergone previous craniotomy, consequently rendering impossible any meaningful interpretation of the topography of the scalp potentials. Nevertheless, this finding, along with ours in P.S., suggests that covert processing in prosopagnosia occur only within the relatively late time window, although its interpretation remains unclear even in healthy controls (Paller et al., 2000; Tanaka et al., 2006; Kaufmann et al., 2009). Nevertheless, in P.S., fMRI activation was found only in FFA and dIPFC. Associated with the anterior EEG modulations, the results would suggest that the differences at around 500 msec might reflect the response of the frontal component of the network.

This dIPFC activation evokes primarily an involvement of the attentional network commonly seen to affect the activity of visual areas in a variety of tasks (Kanwisher and Wojcikul, 2000; Kastner and Ungerleider, 2000; Corbetta and Shulman, 2002). Selective attention is known to modulate FFA activity when subjects orient their attention to faces (Wojcikul et al., 1998; O’Craven et al., 1999; Furey et al., 2006), as well as when they are asked to search for specific identities (Haxby et al., 1994; Hoffman and Haxby, 2000). Thus it could be that the effect observed here is the result of a greater attentional mobilisation towards known faces. However, P.S.’s inability to identify familiar faces is undeniable. In addition, P.S. was not informed of the precise aim of the experiments at the time they were performed and the task demands were orthogonal to the familiarity parameter. Consequently, any attentional bias towards famous faces would still necessarily imply that covert identity recognition took place. The activity in the fronto-parietal areas must therefore also occur as a corollary of covert recognition, possibly as a stimulus-driven control of attention, which could act as a circuit breaker depending on stimulus salience (Corbetta and Shulman, 2002; Palermo and Rhodes, 2007), although further studies would be needed to confirm this hypothesis.

4.1. Conclusion

The presentation of previously familiar and non-familiar faces to a brain-damaged patient who was unable to process identity overtly revealed differences in ERPs at around 550 msec, as well as changes in fMRI activation in several right-lateralized cortical regions. These results provide evidence for non-conscious processing of familiarity in a patient with prosopagnosia that relies on a component of the core system for face processing, namely, the FFA. The data suggest in addition that the FFA may not be sufficient to produce conscious face recognition. Finally, our findings suggest that it is necessary to distinguish paradigms that use highly familiar faces predating the onset of prosopagnosia, from those involving the repetition of unfamiliar ones, when exploring covert recognition in these patients.

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We are grateful to P.S. for her patience and willingness to perform the experiments we carried out in this study.


