9 Clarifying the functional neuro-anatomy of face perception by single case neuroimaging studies of acquired prosopagnosia

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Abstract

In this paper I review the neuroimaging studies carried out over the past few years on a brain-damaged patient presenting a face-selective recognition deficit (acquired prosopagnosia), the patient PS. These studies show that (1) in rare cases such as PS, a right inferior occipital lesion damaging the occipital face area (OFA) but sparing the adjacent non-face preferential area of the ventral lateral occipital complex (vLOC) can lead to prosopagnosia without object agnosia; (2) preferential responses to faces in the fusiform gyrus ('fusiform face area', 'FFA') can be observed despite a lesion encompassing the lower-level ipsilateral OFA, suggesting that there is a direct pathway in the normal brain from early visual cortices to the 'FFA' to categorize face stimuli at the basic level; (3) while categorization of the stimulus as a face can be preserved behaviorally and in the 'FFA' response, fMR-adaptation studies show that individual representations of faces are not extracted properly in the 'FFA' following acquired prosopagnosia. Based on these observations, I suggest a reformulation of current hierarchical neuro-functional models of face identity processing. Initial categorization of the visual stimulus as a face could take place in the right 'FFA' following direct striate/extrastriate inputs, bypassing the OFA. This first representation would then be refined to achieve a full individual face representation, a process that depends critically on reentrant in-

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teractions with lower-level visual areas, mainly of the right hemisphere (OFA). Altogether, the studies reviewed here illustrate how combining functional imaging and lesion studies in a single-case approach can greatly contribute to our understanding of the neuro-anatomy of face processing in the human brain.

9.1 Introduction

Today the question of how the human brain perceives and recognizes faces is widely investigated, in particular by means of functional neuroimaging studies of the healthy brain. Since the earliest studies in this field using positron emission tomography (PET, Sergent et al., 1992) and functional magnetic resonance imaging (fMRI, Puce et al., 1995), they aim at (1) localizing the brain areas involved in face processing, (2) characterizing the nature of face representations and processes in these areas, and (3) clarifying how these regions interact with each other while we process faces.

In this chapter, I would like to illustrate how functional neuroimaging single case studies of brain-damaged patients suffering from face recognition impairments, prosopagnosia, may help to reach these goals, beyond the information provided solely by neuroimaging studies of the healthy brain. After briefly reviewing the contributions of neuroimaging studies of face processing in the normal brain, I will present the functional neuroimaging studies carried out over the past five years by my colleagues and me on a remarkable case of acquired prosopagnosia, the patient PS (Rossion et al., 2003). In this chapter I hope to convince the reader that such neuro-functional investigations of single cases of brain-damaged prosopagnosic patients can be an extremely rich source of information to draw our map of the functional neuro-anatomy of face processing in the human brain.

9.2 Neuroimaging studies of face perception in the healthy brain

Justine Sergent and her colleagues (1992) initiated the neuroimaging studies of face processing in the healthy brain using PET. These studies confirmed the right hemispheric dominance in processing faces that had been long reported by lesion analyses of cases of prosopagnosia (Hécaen and Angelergues, 1962) and divided visual field studies (Levy et al., 1972). These studies also confirmed the involvement of the fusiform and parahippocampal gyri during face processing, two areas that had been identified as being critical for face processing from lesion studies (Meadows, 1974; Damasio et al., 1982). Subsequent research using fMRI concentrated on the visual areas responding more to faces than pictures of other objects, irrespective of the task, (e.g. Puce et al., 1995) and singled out a functional area of a few mm3 in size, showing the strongest preferential response to faces, in the lateral part of the right middle fusiform gyrus, the FFA (Kanwisher et al., 1997; McCarthy et al., 1997). As demonstrated by many subsequent studies, the right FFA is in fact only one of three bilateral spots of preferential activations to faces over other object categories that are systematically observed in the human visual system, the others being localized posteriorly in the inferior occipital cortex (occipital face area, OFA, e.g. Gauthier et al., 2000a), and in the posterior part of the superior temporal sulcus (pSTS; e.g. Puce et al., 1998) (Figure 9.1a). While these areas respond also to many object categories (e.g. Avidan et al., 2002; Grill-Spector et al., 2006a), they are the only visual areas that consistently show a preference for face stimuli in fMRI. According to Haxby and colleagues (2000), these three areas form the 'core' system for face perception, providing inputs to an extended system, i.e. to temporal and prefrontal regions involved in emotional and semantic processing associated with person recognition (Figure 9.1b). These areas, which are bilateral but present a strong right hemispheric dominance on average (e.g. Kanwisher et al., 1997; Rossion et al., 2000a; see Figure 9.1a), are defined functionally (faces vs. object categories; or vs. scrambled faces, preserving all low-level visual features of face stimuli): they are located outside of the retinotopic visual cortex and their borders are not defined anatomically (Halgren et al., 1999). They also present a large inter-individual variability in terms of location, spatial extent, and hemispheric dominance (see Rossion et al., 2003).

Many studies have shown that these areas, in particular the FFA and OFA, are involved in discriminating individual face exemplars. The strongest evidence for this individual face coding comes from so-called fMRI adaptation studies, in which the neural response to a given stimulus is reduced when the stimulus is repeated (Grill-Spector and Malach, 2001; Grill-Spector et al., 2006b). If this adaptation is released when two different stimuli are presented repeatedly as compared to the repetition of the exact same stimulus, then one can assume that the populations of neurons in this area can differentiate the two stimuli. Release from adaptation to face identity (i.e. face A followed by face B vs. face A followed by face A) is found in all three functional areas, in particular in the OFA and FFA, strongly supporting their role in representing individual faces (e.g., Gauthier et al., 2000a; Eger et al., 2004; Schiltz et al., 2006; Gilaie-Dotan and Malach, 2007; for pSTS evidence, see Winston et al., 2004).

Even though the preferential response to faces of these areas is undisputed, it has been shown that the FFA also responds differently to distinct object categories (e.g., Haxby et al., 2001; Grill-Spector et al., 2006a), and can show increased activation to nonface objects of expertise (e.g., car pictures in car experts, Gauthier et al., 2000b). This indicates that the popular "face area" tag is incorrect and quite unfortunate, and suggest that the FFA is not a module for face perception: it carries out certain perceptual processes that are most important – perhaps critical – for faces but these processes can potentially be applied to other nonface object stimuli following expertise training, even in adulthood.

Most recent fMRI studies performed in the normal brain have attempted to clarify the nature of the face representations and processes in these areas (e.g., Eger et al., 2004; Winston et al., 2004; Fang et al., 2007; Chen et al., 2007). Directly related to some aspects of face perception that are highly documented by behavioral evidence (Sergent, 1984; Young et al., 1987), it has been shown for instance that in the "face areas", in particular in the right FFA, the perception of a facial feature is dependent of the presence and location of the other features ("holistic face representation", Schiltz and Rossion, 2006). Other studies have shown that the FFA was highly sensitive to inversion of individual faces (Yovel and Kanwisher, 2005; Mazard et al., 2006), in line with behavioral observations (Yin, 1969); and that faces are represented in this

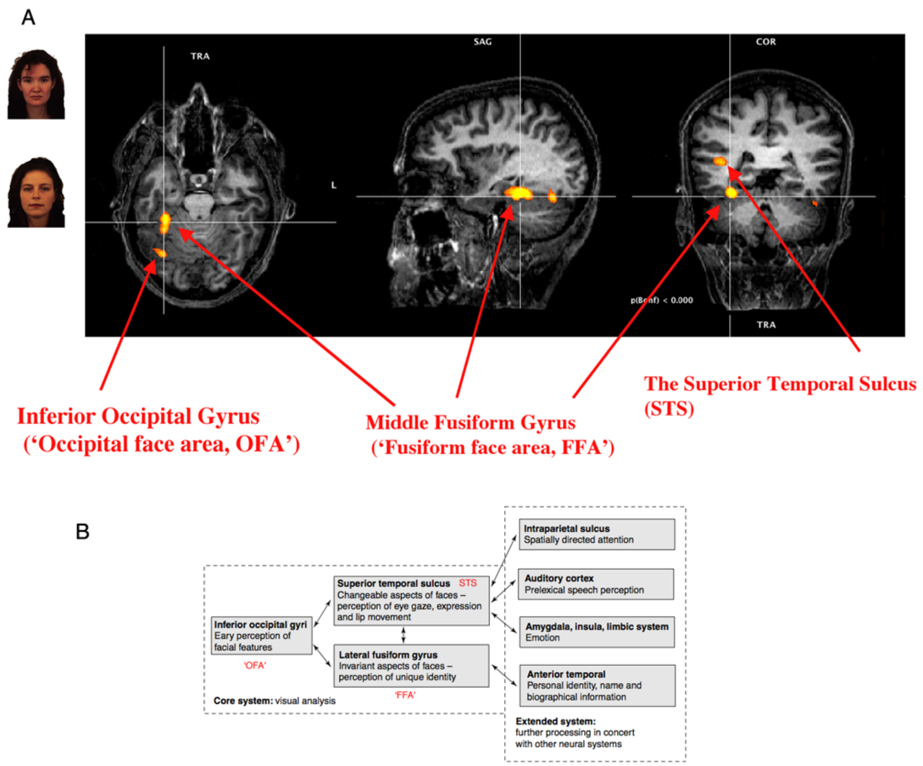

Figure 9.1. A. The three functional areas forming the core system of face perception in the normal human brain (Haxby et al., 2000). These areas respond more to faces than any other object categories. They are illustrated here in the right hemisphere, in a single normal brain, during a functional face localizer contrast (faces vs. objects). B. The three visual areas incorporated in a 'core' system of face perception in the normal human brain as proposed by Haxby et al., 2000, and connected to brain areas in the temporal, parietal, and prefrontal lobes devoted to complex person recognition functions (Figure adapted from Haxby et al., 2000 with permission).

area with respect to a central tendency or prototype (Loffler et al., 2005), as is also described behaviorally (Rhodes et al., 1987; Valentine, 1991)

In summary, in a relatively short amount of time, functional neuroimaging studies of the normal brain have offered a relatively precise neuroanatomical map of face perception. However, the precise function(s) of the "face areas" with respect to face perception are still hotly debated, and their critical role in face perception, as well as their functional interactions, remain largely unknown.

9.3 Understanding how the human brain process faces by combining lesion studies and functional neuroimaging

By itself, functional neuroimaging in the healthy brain is unable to indicate whether the areas activated during the presentation of face stimuli are necessary for their successful perception. To clarify this question, the identification of the localization of the lesions causing prosopagnosia, may be of fundamental importance. The first cases of acquired prosopagnosia – i.e. the inability to recognize faces despite intact intellectual function and preserved low-level visual processes – were described in the 19th century (Wigan, 1844; Quaglino and Borelli, 1867) and the term prosopagnosia (from the greek, "prosopon", for face and "a-gnosia", without knowledge) was introduced by Bodamer in 1947 (see Ellis and Florence, 1990). The majority of cases of prosopagnosia are due to (right) posterior cerebral artery infarcts (see Goldsmiths and Liu, 2001) and the major complaint of these patients is in recognizing previously seen (i.e. familiar) faces and in learning new faces. However, as far as acquired prosopagnosia is concerned, even so-called associative prosopagnosic patients appear to have deficits at perceiving correctly an individual face. Hence, they fail at matching different pictures of unfamiliar faces, or when they succeed they use extremely slow and painstaking procedures (Levine and Calvanio, 1989; Davidoff and Landis, 1990; Farah, 1990; Delvenne et al., 2004; Bukach et al., 2006). Thus, while it is clearly acknowledged that low-level sensory deficits cannot explain prosopagnosia (Ettlinger, 1956; de Haan et al., 1995) and that there is a great amount of variability in terms of functional impairments among prosopagnosic patients (e.g., Schweich and Bruyer, 1993; Sergent and Signoret, 1992), I will refer in this paper to prosopagnosia as a deficit of face perception, which is inevitably associated with the inability to recognize faces. While prosopagnosic patients can usually classify a visual stimulus as a face (face detection), they have difficulties in deriving a full percept of an individual face.

In principle, lesion analyses of prosopagnosia should be of great interest to understand the neural basis of face perception. However, relying on this lesion method (i.e. correlating neuroanatomical data and clinical symptoms, Damasio and Damasio, 1989) as a means to establish the neuroanatomical basis of prosopagnosia is associated with a number of weaknesses, most notably a lack of precision due to the extent and variability of functional and anatomical impairments of the patients (e.g., Sergent et al., 1992). Another difficulty is that brain regions which may appear structurally intact and thus not considered to be critically associated with the impaired function(s) in a prosopagnosic patient may in fact be functionally depressed because they do not receive normal inputs from lesioned regions (diaschisis, see Price and Friston, 2002a). An illustration of this phenomenon was provided early on by Sergent and Signoret (1992), who reported a case of prosopagnosia with no structural damage to the right parahippocampal gyrus. Yet, a PET measurement of the patient's brain indicated a functional depression of this region, presumably because this area was deprived of normal inputs from other lesioned parts of the cortex. Thus, any attempt at correlating behavioral deficits of the patient due to the hypofunction of the hippocampal gyrus with visible structural damage would have been flawed. However, this observation highlights a potential interest

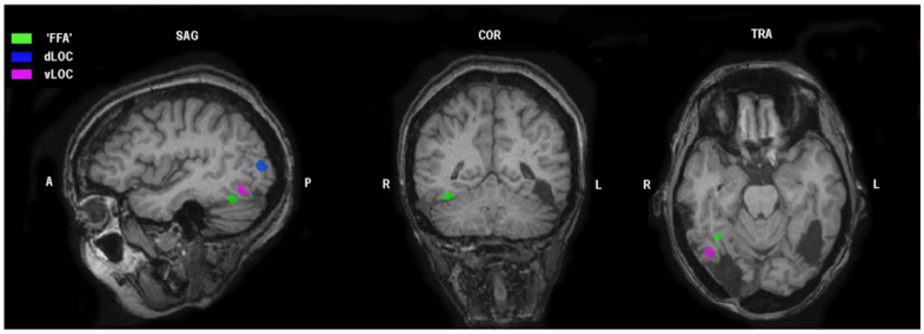

Figure 9.2. Localization of PS' lesions with respect to the right FFA and LOC complex (vLOC= ventral part; dLOC= dorsal part). Note that the lesion that is instrumental in causing the prosopagnosic deficit in the right hemisphere, encompassing the right OFA, is very close to the vLOC region. It is likely that in most cases of prosopagnosia following right posterior damage, both the OFA and vLOC are damaged, causing impairments for both face and object recognition.

in studying brain-damaged prosopagnosic patients with functional neuroimaging: such studies may not only improve the accuracy of associations between function and brain localizations, but they may also offer a powerful tool to investigate the relationship(s) between brain areas identified in the normal brain, and to test hypotheses regarding their functional connectivity (see Price et al., 2001; Price and Friston, 2002a). For instance, if the OFA is truly the front-end of the core face perception system, as suggested by Haxby and colleagues (2000; Figure 1), then a lesion to this area should prevent the flow of information to higher visual areas such as the FFA and the pSTS. In fact, this is precisely the opportunity to test this hypothesis that was offered to my colleagues and me a couple of years ago when we met the patient PS, a particularly interesting case of acquired prosopagnosia.

9.3.1 PS, a case of acquired pure prosopagnosia

The case of the patient PS has been described in detail in several publications over the past few years (Rossion et al., 2003; Caldara et al., 2005; Schiltz et al., 2006; Sorger et al., 2007; Dricot et al., in press) and I will thus concentrate here on the main aspects of her neuropsychological profile. PS is a right-handed female born in 1950 who sustained a severe closed-head injury (she was hit by a bus) in 1992 which left her with damaged brain tissue in the lateral part of the occipital and temporal lobes, bilaterally, as well as in the anterior part of the left cerebellum. Her largest lesion extends from the posterior part of the right inferior occipital gyrus to the posterior fusiform gyrus. The left hemisphere lesion is more anterior and covers a large part of the middle fusiform gyrus (Figure 9.2). The exact localization of the lesions and their relationships to the prosopagnosic deficit have been described and discussed in detail (Sorger et al., 2007).

Several years after her accident, following spontaneous recovery and neuropsychological reeducation training, PS still presents a massive prosopagnosia, being unable to recognize both famous people and familiar people from their faces. Her deficit at face recognition is particularly severe, PS reporting several instances of failure to recognize extremely familiar persons from their face in real life situations (her daughter, her husband, close friends, etc.). This pattern is commonly reported by brain-damaged cases of acquired prosopagnosia and it contrasts with the excellent person recognition abilities of PS from people's voices for instance, but also from other visual cues such as the clothes, the gait, size and posture of familiar individuals.

Behavioral investigations carried out several years after PS's accident (i.e. from 2000 onward, see Rossion et al., 2003) have largely confirmed her prosopagnosia. For instance, she could classify as famous only 14 people's photographs out of 60 that she knows very well by their name, and she could identify only four of them. She is impaired at old/new face recognition tests on unfamiliar faces, and also at matching different pictures of unfamiliar faces either presented on the same or different viewing conditions (viewpoint, lighting changes, etc.). Her score at the Benton face discrimination test (Benton and Van Allen, 1968) is extremely low (27/54)[1] and she is particularly slowed down at this test and at other computer tests requiring to match/discriminate individual faces (Rossion et al., 2003; Schiltz et al., 2006). Hence, she is clearly unable to derive a full perceptual representation of an individual face. Yet PS is not impaired or slowed down at categorizing a face as a face, even in impoverished contexts requiring an integration of features at the basic level (e.g., Mooney faces), or in detecting a face stimulus in a visual scene presented briefly (Busigny and Rossion, in preparation).

Unlike most other cases of prosopagnosia, PS does not complain at all of object recognition difficulties. Her recognition of the colorized Snodgrass and Vanderwart's object set (Rossion and Pourtois, 2004) is perfect and fast and she performs in the normal range at matching pictures of common or novel objects (Rossion et al., 2003; Schiltz et al., 2006). This preserved function is also found in subordinate categorization and fine-grained discriminations (Rossion et al., 2003; Schiltz et al., 2006).

To determine the nature of PS's facial representations, we tested her by means of a response classification method revealing facial information randomly across spatial locations of the face (the bubbles technique, Gosselin and Schyns, 2001; for the origin of this random aperture method to isolate diagnostic face information, see Haig, 1985). In this study (Caldara et al., 2005) the patient PS had to learn 10 photographs of individual faces (2-3 hours of learning and frequent refreshers) and then to identify these faces individually during thousands of trials. On every single trial the face photograph was revealed through a number of apertures ("bubbles") randomly located on the face. Performance of the patient was maintained at 75% by increasing or decreasing the number of bubbles throughout the experiment, collecting images corresponding to correct and incorrect responses (Gosselin and Schyns, 2001). Unsurprisingly, PS required a much larger amount of bubbles (i.e., information) to perform the task at the same level as normal participants. More interestingly, response classification images, contrasting correct and incorrect trials, showed that the patient did not use information located on the eyes area at all, relying almost exclusively on the lower part of

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[1] A more recent testing (2006) showed a much better score (39/54), even though it was still below normal range, but with extremely slow response times (37min ± 34 secs to complete the test, mean age-matched control: 6min ± 77 secs: Busigny and Rossion, in preparation).

the face for correct face identification (mouth and lower external contours; see Figure 9.6). In contrast, normal participants relied primarily on the eyes area of the face, with a preference for the right eye (i.e. left visual field; see also Gosselin and Schyns, 2001). These observations of a massive impairment at extracting diagnosticity from the face's eye region may be a characteristic feature of prosopagnosia, as indicated by the recent observations of difficulties at discriminating pictures of unfamiliar faces differing by the eyes but not the mouth in another brain-damaged case of prosopagnosia (Bukach et al., 2006). Most recently, we have showed that PS's failure to extract and represent diagnostic information on the eyes of faces extends to the identification of personally familiar faces (Ramon and Rossion, 2007). Eye movement recordings during familiar face identification also show a dominance of the number of fixations to the mouth area of the face relative to the fixations on the eyes (Orban de Xivry et al., in revision) in contrast with typical viewers' eye movement patterns (Figure 9.2). We are currently exploring the nature of this bias towards the mouth at the expense of the eyes in prosopagnosia and its functional significance (see Caldara et al., 2005; Ramon and Rossion, 2007), but in this chapter I will concentrate on the neural basis of PS's prosopagnosia.

9.3.2 The necessary role of the right OFA for face perception

Where are PS's brain lesions located relative to the areas that respond preferentially to faces (Figure 9.1)? Her largest lesion is located in the right hemisphere and concerns a substantial part of the inferior occipital cortex (Figure 9.2; see also Sorger et al., 2007). Based on the well-known right hemispheric prevalence in causing prosopagnosia and the absence of preferential response to faces in the vicinity of the right inferior occipital lesion for PS (Rossion et al., 2003), we hypothesized that the absence of right OFA activation was instrumental in causing PS's face perception impairment. This observation was later supported by a report showing that the site of maximal overlap of lesion localization in several cases of prosopagnosia concerns exactly the lateral part of the right inferior occipital cortex, where the right OFA is usually located (Bouvier and Engel, 2006). Hence, even though a complementary role of the left hemisphere in face processing functions should never be neglected (Sergent, 1988) and may possibly account in part for PS's face perception impairment (see Sorger et al., 2007), there is now converging evidence that the lateral part of the right inferior occipital cortex, including the OFA, is a necessary component of the intact face perception system.

9.3.3 Why so few cases of pure prosopagnosia? Insights from neuroimaging

As indicated above, PS can be defined as a pure case of prosopagnosia, an impairment at face recognition without object recognition difficulties. Very few of such cases have been reported previously (e.g., De Renzi, 1986; De Renzi and di Pellegrino, 1998; Henke et al., 1998; Sergent and Signoret, 1992) and it is fair to say that they were not investigated thoroughly for object recognition so that the issue of a deficit restricted to the category of faces has remained largely debated in the literature (e.g., Damasio et al., 1982; Gauthier et al., 1999). I have no doubts that other such cases of pure acquired prosopagnosia, although extremely rare, will be reported with adequate testing in the literature in the years to come and will clarify this issue once and for ever. Yet, it remains that the large majority of prosopagnosic patients present deficit for both face and object recognition (e.g., Barton et al., 2002; Bouvier and Engel, 2006; Clarke et al., 1997; Damasio et al., 1982; Farah, 1990; Gauthier et al., 1999). Why is it the case? Here the functional neuroimaging studies of the patient PS provide some interesting clues.

In normal viewers there is an area in the lateral occipital complex (LOC, Figure 9.2) showing greater fMRI response to pictures of objects (including faces) than scrambled objects (Malach et al., 1995) which does not show systematic larger responses to certain object categories than others. It is located anteriorly to retinotopic visual areas extending in two anatomically segregated subregions both ventrally (vLOC) on the lateral bank of the fusiform gyrus and dorsally (dLOC) (Figure 9.2). These areas, in particular the vLOC, have been directly correlated with object perception (e.g., Avidan et al., 2002; Grill-Spector et al., 2000; James et al., 2000). The role of the vLOC in the discrimination of individual object exemplars has also been supported by fMRI-adaptation studies showing a larger response in this region to novel objects than to repeated objects (Avidan et al., 2002; Grill-Spector et al., 1999; Sayres and Grill-Spector, 2006).

Interestingly, in PS's brain, fMRI studies show a right vLOC area of normal size and height of signal, lying just next to the lesion that damaged the right OFA (Figure 9.3; see Sorger et al., 2007). One intriguing possibility is that the sparing of the right vLOC may be critical in accounting for PS's preserved object recognition and discrimination abilities. However, given the proximity of the right vLOC and OFA, it is likely that many acquired cases of prosopagnosia, in particular the patients who suffer from a right posterior artery infarct, will have *both* the OFA and at least a substantial section of the vLOC damaged by the lesion. For instance, the patient DF (Milner et al., 1991) is massively impaired at face and object recognition following lesions of the main part of the OFA *and* the vLOC in both hemispheres (James et al., 2003).

These observations suggest that prosopagnosia is most often associated with object recognition deficits (visual agnosia) because of right inferior occipital and occipitotemporal lesions damaging both the vLOC and part of the OFA/FFA complex (Figure 9.2). However, a lesion of the right OFA sparing the right vLOC, as in the case of PS, may lead to an isolated deficit at face perception. This observation will need complementary evidence from other brain-damaged cases but it has the merit of offering a tenable anatomical solution to this long debate regarding the very existence of acquired prosopagnosia with normal object recognition (e.g., Ellis and Young, 1989): in most cases, a right hemisphere lesion damaging the OFA will also encompass a substantial part of the vLOC of the same hemisphere, causing object perception impairments. In addition, neuropsychological evidence also indicates that object perception is less lateralized than face perception, with cases of visual agnosia generally presenting bilateral lesions (Farah, 1990). Hence, a unilateral right hemispheric lesion damaging the right OFA and the vLOC but sparing the homologous areas of the left hemisphere may cause prosopagnosia but leave object perception less impaired or even unimpaired. In other words, while there may be multiple pathways for normal object perception and recognition (e.g., Humphreys and Riddoch, 1984) face perception appears to rely on

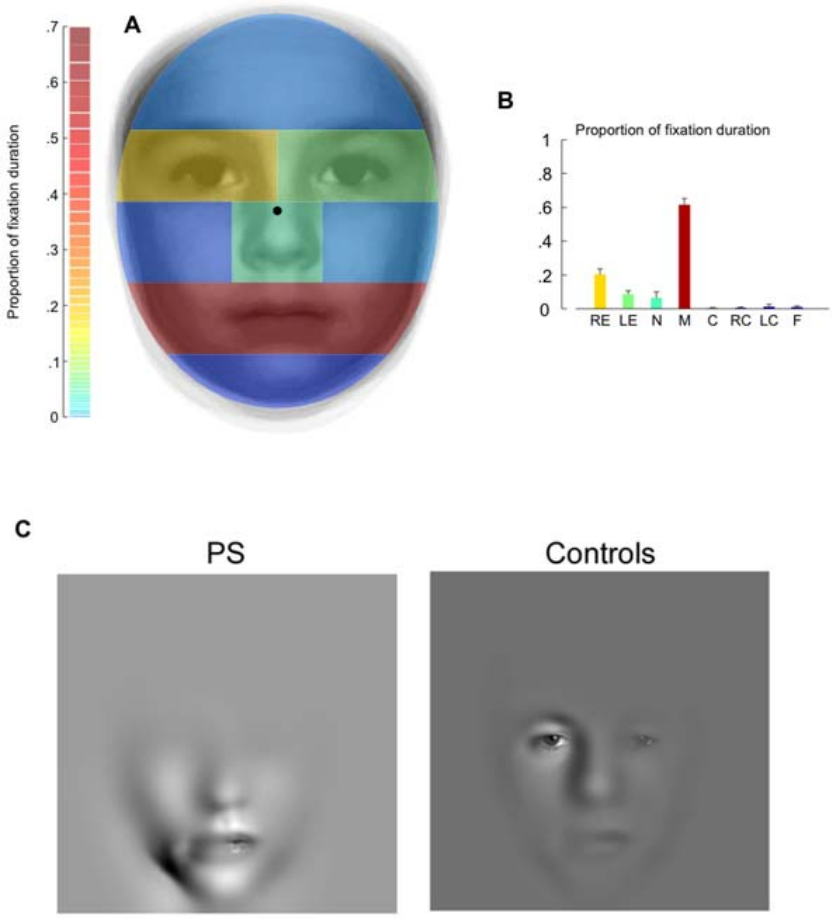

Figure 9.3. Representation of the different regions scanned by PS during her identification task of familiar faces, showing the massive dominance of the mouth over all other areas of the face. Note that the eyes are fixated also, showing that PS does not avoid looking at this region of the face spontaneously. However, the eye region appears to carry less diagnostic information for PS. The regions are superimposed on the average picture from all children face used in the experiment (Orban de Xivry et al., submitted). The color of each scoring regions corresponds to the proportion of fixation duration yielded by the colour bar on the left of the panel. The black dot corresponds to the fixation point displayed just before the picture. B: Histogram of the inter-child mean (± 0.95 confidence interval) proportion of fixation duration for each scoring region. RE: Right Eye; LE: Left Eye; N: Nose; M: Mouth; C: Chin; RC: Right Cheek; LC: Left Cheek; F: Forehead. C: Classification images for PS and controls obtained following her identification task on learned faces presented through bubbles apertures (Caldara et al., 2005). In contrast to controls, PS relied heavily on the mouth to recognize the faces. She also needed many more apertures than control participants to perform the task at the same level (see Caldara et al., 2005).

expert processes and more specialized areas, located largely in the right hemisphere. This lack of degeneracy (Edelman, 1978; Tononi et al., 1999) in the visual system for face perception may be a negative consequence of our expert processing skills for this category.

9.3.4 FFA without OFA, evidence for a direct pathway for basic face categorization

The previous section has underscored the important role that fMRI (compared to conventional structural MRI) can play in revealing the functional integrity of brain regions that might be potentially damaged in prosopagnosic patients. However, the case of the patient PS has proved most interesting when asking questions about the functional connectivity between visual areas responding preferentially to faces.

While the right posterior lesion of PS's brain damaged the territory of the OFA, we noticed that the middle and anterior sections of the fusiform gyrus, exactly where the right FFA is usually disclosed in normal participants when comparing the response to faces and objects (Figures), was intact in PS's brain. This pattern of damaged and spared brain tissue in a case of prosopagnosia offered us a unique opportunity to test one of the key features of the neuro-functional model proposed by Haxby et al. (2000): the hypothesis that the OFA is the front end of the system, providing the early inputs to higher visual areas such as the FFA and pSTS (Figure 9.1b). If this simple hierarchical model was correct, the destruction of the right OFA should have prevented face preferential activation in higher visual areas of the FFA and pSTS.

However, in contrast to the model, our first fMRI investigation of the patient PS (Rossion et al., 2003), using a simple face localizer experiment, showed a very clear preferential activation for faces in the middle fusiform gyrus (i.e. right FFA) in the absence of any face preferential activation around the lesioned area of the right inferior occipital cortex (i.e., no right OFA) (Figure 9.4). Hence, we found that the right middle fusiform gyrus may show a larger response for faces than objects (FFA), without getting any inputs from the ipsilateral OFA!

This observation suggests that in the normal brain the FFA may potentially be activated preferentially for faces through a direct pathway initially independent from the face preferential activation observed in the posteriorly located area in the inferior occipital cortex, that is the OFA. This initial proposal (Rossion et al., 2003) has been reinforced by a number of subsequent observations:

- The activation of the right FFA for the patient PS has been replicated countless times, in different laboratories, with 4 different scanners (1.5T and 3T) and different acquisition parameters (block design or event-related paradigms) (Rossion et al., 2003; Schiltz et al., 2006; Sorger et al., 2007; Dricot et al., in press). It is extremely robust.

- Compared to normal participants in our experiments, the FFA of the patient PS is in the normal range in terms of size and localization (see Rossion et al., 2003; Sorger et al., 2007).

- The amplitude difference between faces and objects is in the normal range for

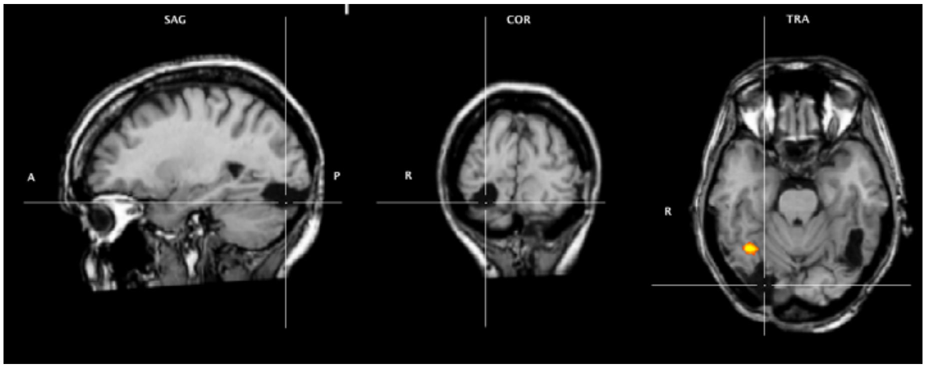

Figure 9.4. PS's main lesion, thought to be instrumental in causing her prosopagnosia, concerns the right inferior occipital cortex and posterior part of the fusiform gyrus (cursor), encompassing the OFA. This lesion does not prevent a preferential activation for faces in the right middle fusiform gyrus (FFA; here as the result of a combined analysis of six functional localizer runs, contrasting faces and object pictures in a face localizer contrast, see Sorger et al., 2007 for details).

PS's FFA (Rossion et al., 2003), even though it can be in the lower range in some experiments, perhaps because of an absence of release from identity adaptation in her FFA (see below).

- The FFA activation in the patient PS's brain is observed whether the patient is impaired at performing the task (e.g., one back face matching task) or can perform the task normally (e.g., color detection task; see Rossion et al., 2003; Schiltz et al., 2006; Dricot et al., in press).
- Besides the right FFA activation, the right pSTS also shows preferential activation for faces, in the absence of OFA inputs (Figure 9.5) (Sorger et al., 2007).
- PS's right FFA activation does not appear to originate from face preferential inputs coming from the OFA of the left hemisphere (e.g., through transcallosal connections): it is larger and peaks earlier for contralateral than ipsilateral face stimulation (Figure 9.6; Rossion et al., in preparation).
- Finally and most importantly, the FFA activation with no evidence for OFA activation has been also observed in another case of (prosop)agnosia due to bilateral damage to the inferior occipital cortex, the patient DF (Steeves et al., 2006). This is an important observation for two reasons. First, the damaged area that is common for both PS and DF is the right OFA, supporting the critical role of this region. Second, the left OFA is damaged in DF's brain, ruling out a contribution of the other hemisphere to the right FFA.

Overall, these observations of a right FFA activation without ipsilateral OFA in two brain damaged cases suggests that, in the normal brain, the FFA may potentially be

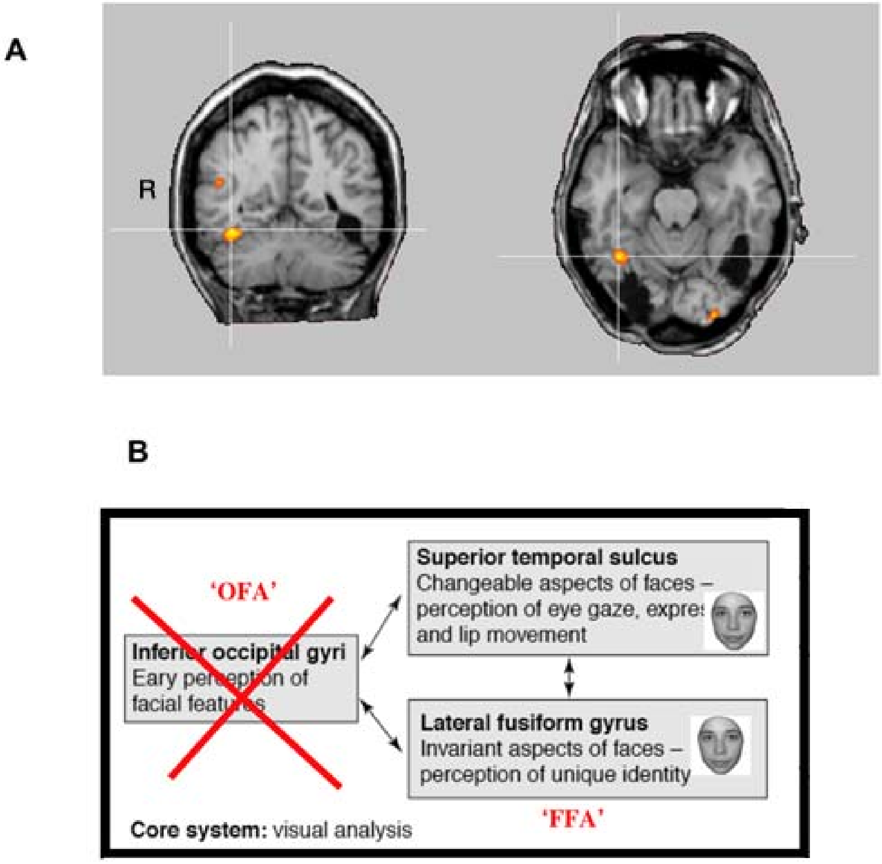

Figure 9.5. Face preferential activations in the patient PS's brain on coronal and transversal views. The cursor is located on the right FFA activation. Note the pSTS activation on the coronal view, and the left OFA activation on the transversal view (see Sorger et al., 2007 for details). Lateralization experiments, as well as Granger causality mapping suggest that the left OFA activation originates from the right FFA activation (see text). B: Schematic representation of PS's right hemisphere lesion on the neuro-functional model of face processing proposed by Haxby and colleagues (2000). PS's lesion damaged the cortical territory of the right OFA, and there is no evidence of face preferential activation around that area. This does not prevent face preferential activation to arise in both the right FFA and pSTS of the same hemisphere, suggesting that the onset of these anterior activations is independent of normal activation in the right OFA, against a simple hierarchical feedforward model of face processing.

activated preferentially for faces independently of inputs coming from the posteriorly located area, the OFA, in contrast to the initial proposal of a simple hierarchical feed-forward model of face perception (Haxby et al., 2000). That is, both the OFA and the FFA are activated in parallel in the normal brain, independently from each other, such that a lesion to one of the areas does not prevent the face preferential activation in the other area. Alternatively, and more intriguingly, the FFA may be activated before any putative contribution from the OFA, and the functional relationship between the two areas goes in the other direction (FFA to OFA), at least for the initial face preferential response. That is, the onset of OFA activation in the normal brain may originate from FFA input. If the second hypothesis is correct, then a patient with a right FFA lesion should not present any OFA activation. This is precisely what we recently observed with the (prosop)agnosic patient NS reported earlier (Delvenne et al., 2004): while the territory of the right OFA appears structurally intact in this patient's brain activation pattern, and show a large response to visual stimuli, there was no evidence of a preferential response to faces in this posterior location, in the absence of a right FFA (Figure 9.7). However, contrary to the observations of an FFA activation made with the patient PS, this can be considered as a null result and should be treated with caution before converging evidence is found.

To clarify further the source of the preferential activation for faces in the fusiform gyrus of the patient PS, we have recently applied Granger Causality Mapping (GCM) (Roebroeck et al., 2005) to a face localizer experiment of the patient PS. This has led to two interesting observations. First, we found that the right FFA activation for faces was influenced posteriorly only by a region of the ipsilateral primary visual cortex (V1, see Figure 9.8; Dricot et al., in preparation). This finding suggests a relationship between V1 and the right middle fusiform gyrus, possibly accounting for the FFA activation in PS's brain. It is in agreement with the evidence of direct projections from V1 to V4 and from V2 to the posterior part of the infero-temporal cortex in the monkey brain (TEO; Nakamura et al., 1993). In humans, diffusion tensor imaging (DTI) studies have not reported direct anatomical connectivity between V1 and the FFA in the majority of brain connectivity patterns tested but direct connections between early visual areas V3 and V3a and the FFA (Kim et al., 2006). Second, in addition to the right hemisphere V1-FFA relationships that we identified using Granger causality, there was a dominant influence of the right FFA towards several posterior regions: the right lateral ventral occipital cortex (vLOC), next to the lesion, and several areas in the left hemisphere, including the left OFA (Dricot et al., in preparation). Obviously, the right OFA cannot be included in this network because it is damaged in the patient's brain. However, preliminary analyses using Granger Causality in normal participants tested during face processing tasks also suggest a dominant influence of the right FFA towards the ipsilateral OFA (Dricot et al., in preparation). Considering these observations altogether, the right FFA activation may indeed reflect an early stage of processing, possibly following direct early visual inputs in primary visual area or extrastriate cortex, and influencing in turn several ispilateral and contralateral posterior areas.

To summarize, the neuroimaging investigations carried out mainly on the prosopagnosic patient PS and reinforced by studies of other brain-damaged cases of prosopagnosia strongly suggest that in the normal brain: (1) the posteriorly located right OFA is a necessary component of the face perception system; (2) the anteriorly located FFA,

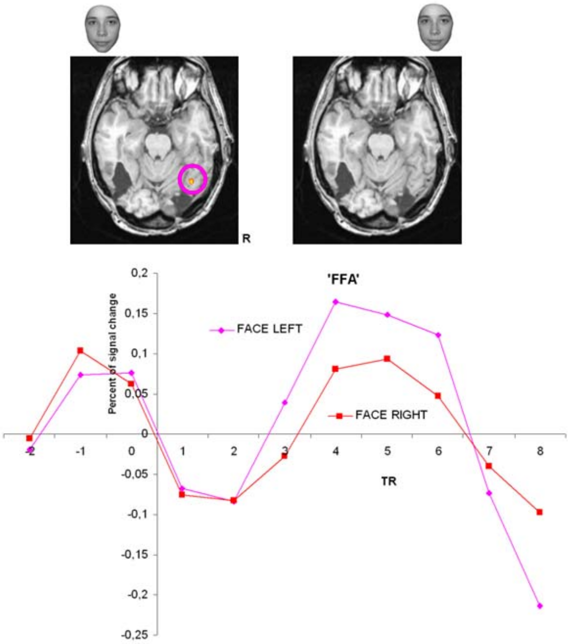

Figure 9.6. The right FFA of the patient PS is activated earlier and larger for contralateral presentation of faces (the right hemisphere is on the right here, for sake of clarity) than ispilateral presentation, against the hypothesis that the right FFA activation originates from transcallosal connections from left posterior visual areas (e.g., left OFA).

also a necessary component of the face perception system, can be activated through a direct pathway from early visual areas, bypassing the OFA; (3) face preferential response in the OFA may either originate from early visual inputs also, or may depend on inputs from the ipsilateral FFA.

9.3.5 Holistic and fine-grained discrimination of individual faces: a role for an FFA-OFA reentrant loop?

How can a patient like PS be deeply prosopagnosic and yet show a preferential response for faces in the FFA (and in the pSTS) that looks perfectly normal in terms of localization, size and height of the differential fMRI signal between faces and objects? To understand this apparent paradox, one should be reminded that the FFA activation emerges by differentiating pictures of faces and non-face object categories (a face localizer), something that the patient PS is perfectly able to do behaviorally (e.g., Schiltz et al., 2006). Like other cases of prosopagnosia, her difficulties are apparent when she has to process individual exemplars of faces: either discriminate different individual faces, or recognize an individual familiar face. Hence, populations of neurons in her

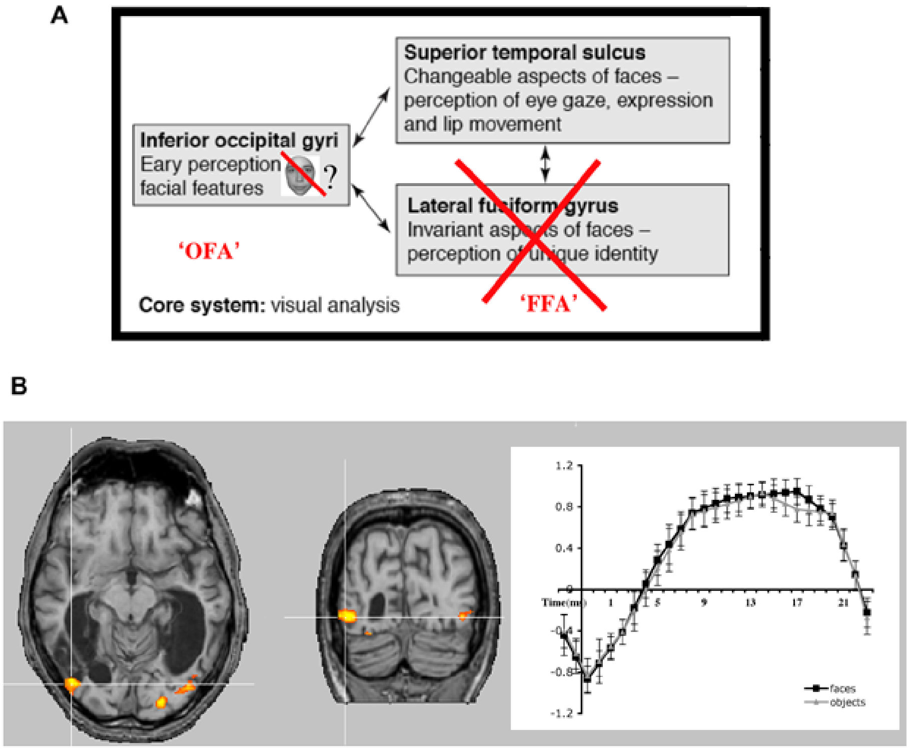

Figure 9.7. The patient NS (Delvenne et al., 2004) is an acquired case of visual agnosia and prosoagnosia, presenting lesions to the right middle fusiform gyrus, as well as the parahippocampal gyrus, bilaterally. A. In the right hemisphere, his lesion damages the whole territory of the right FFA, but largely sparing the right inferior occipital cortex, as represented schematically here onto Haxby et al. (2000) neuro-anatomical model of face perception. However, when performing the exact same face localizer experiment as the patient PS (parameters in Schiltz et al., 2006) there was no evidence for any face-preferential activation three face localizer runs, besides a small spot of activation in the pSTS ($p<0.05$, uncorrected). This absence of face-preferential activation was not due to a lower signal in visual areas, which were activated for both faces and objects above the fixation cross baseline (here the percent signal change for faces and objects in an area of the right inferior and middle occipital cortex, posterior to the lesioned cortex, activated equally strongly for faces and objects).

FFA can carry out the categorization of the stimulus as a face, even when it is extremely simplified or degraded (Figure 9.9). However, unlike neurons in the same area of the normal brain, they may just be unable to code for individual faces.

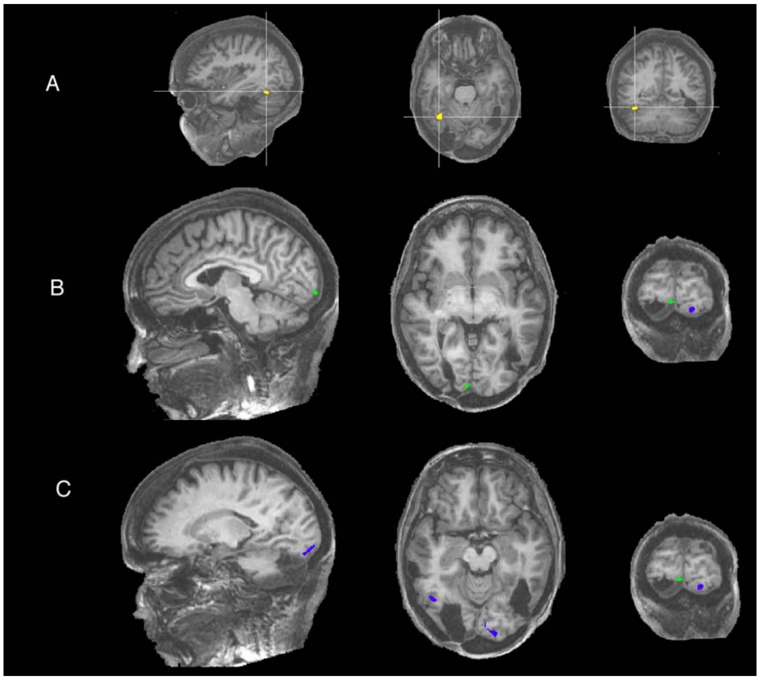

Figure 9.8. Granger causality (Roebroeck, Formisano and Goebel, 2005) was applied to a face localizer experiment with the patient PS. A: Above: The right FFA as activated in a face localizer is taken as the , searching across the whole brain for regions influencing and being influenced by the right FFA. B. The main site of influence to the right FFA during the presentation of faces (but not objects) was located in the ipsilateral primary visual cortex (in green color, 6, -92, -11). C. In blue, regions receiving direct influences from the right FFA, controlaterally in the left hemisphere (including the left OFA) and in the right vLOC. (from Dricot et al., in preparation).

A FFA that does not discriminate individual faces

To test the intriguing hypothesis that cells in PS's FFA may be unable to code for individual faces, PS and control participants were presented with blocks or pairs of identical face stimuli in an fMRI machine, as compared to the successive presentation of different face stimuli. Whereas neural activation was lower for repeated facial identities in the right FFA of normal participants consistent with many studies (e.g., Gauthier et al., 2000a; Grill-Spector and Malach, 2001; Eger et al., 2004; Gilaie-Dotan and Malach, 2007), there was no significant difference in the level of activation for the patient PS whether different or identical face identities were presented successively (Schiltz et al., 2006; see Figure 9.10). That is, despite showing a larger response to faces than objects in the normal range, PS's right FFA showed an absence of face identity adaptation effect. To be more accurate, the level of signal in PS's right FFA was as large as in normal participants when identical faces were presented repeatedly but failed

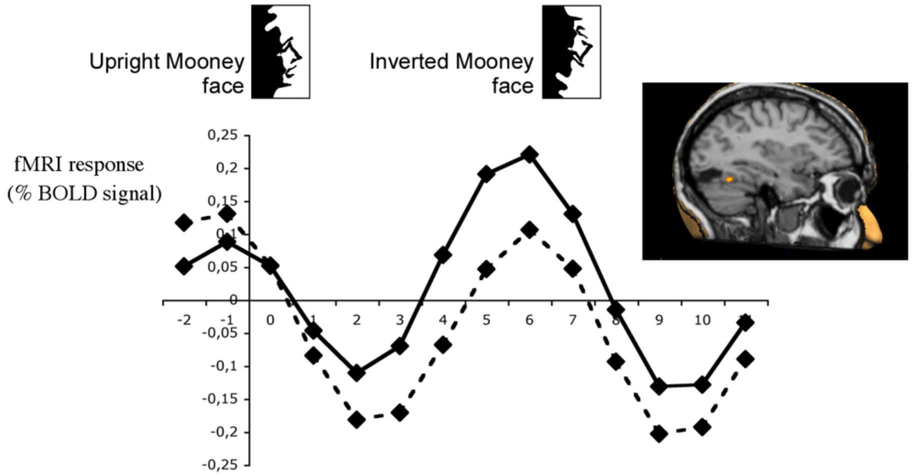

Figure 9.9. The right FFA of the patient PS is activated for pictures of Mooney faces, in line with her preserved behavioral ability to categorize a face as a face (Schiltz et al., 2006), to detect faces in visual scenes presented rapidly and to perceive faces in these two-tone images. (scale in TR, one TR = 1250 ms).

to show a release from adaptation when different faces were presented (Figure 9.10).

Hence, contrary to what our initial observations suggested, PS's right FFA does not work normally: while being involved in the categorization of the stimulus as a face (as opposed to other objects), the signal in this area does not carry sufficient coding information to discriminate individual faces. Originally, these observations were made during an orthogonal task that the patient was able to perform as well as normal participants (color detection task, see Schiltz et al., 2006), both in a block design and an event-related (ER) paradigm. Interestingly, they stand out even during an ER individual face discrimination task in the scanner for which the patient performs well below controls and more slowly but better than at chance (Dricot et al., in press). Again, these results have been recently replicated with the patient DF, also showing (bilateral) FFA activation without release to face identity adaptation (Steeves et al., 2007).

This observation of a dissociation, in the same brain area, between an intact face categorization and an impaired face individualization has several theoretical consequences. First, the anomalous activation to conditions with different faces in the FFA of the prosopagnosic patient PS, in line with her behavioral impairment, points towards a critical function of this region in individual face perception. Second, and most importantly, these observations suggest that successful individual face perception in the FFA may require the right OFA to be intact: without a contribution of the right OFA, which is also showing face identity adaptation effects in the normal brain (see Schiltz et al., 2006), the coding for facial identity is impaired. This is observed in fMRI-adaptation paradigms, as described above, but also in the face localizer experiment where different facial identities are presented: initially, neural activation to faces in the right FFA

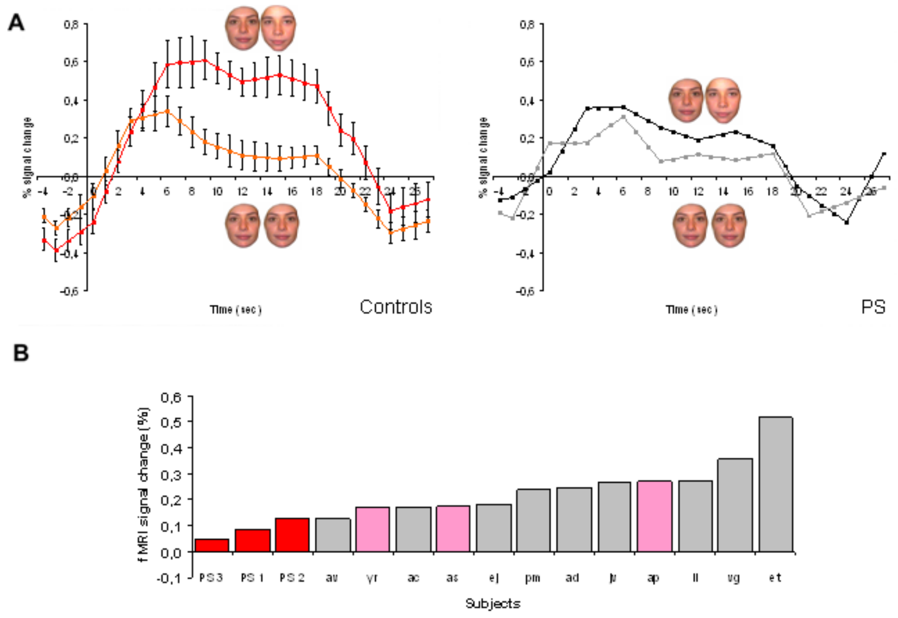

Figure 9.10. Lack of release from identity adaptation effect for the prosopagnosic patient PS in the right FFA (adapted from Schiltz et al., 2006). A. Left: Activation in normal subjects is larger when pictures of different faces are presented successively during a block (18 seconds, 18 different face stimuli) than when the same facial identity is repeated throughout the block. Right: For the patient PS, the two conditions do not show a significant difference: there is a lack of release from identity adaptation in the right FFA. B. Adaptation indexes (different – same faces / sum) for the patient PS (replicated two times, 3 x 3 runs) and for each normal participant in the same experiment (in pink color: aged-matched controls).

of PS is as large or even larger than in the normal brain but the BOLD response is not sustained and drops down below normal range (Figure 9.11). Hence, averaging over the entire time-window of activation for faces may mask any difference between PS's and normal participants' right FFA during a face localizer (Rossion et al., 2003). However, a closer look at the time-course of activation, in particular when long stimulation blocks and recording epochs are used, reveals an abnormally functioning FFA in the patient's brain. We have attributed this non-sustained response of the FFA to the lack of reentrant inputs from the OFA which contribute to individualization of the face representations in the normal brain (see the discussion section in Schiltz et al., 2006). According to this hypothesis, the FFA of the patient PS may show a normal response profile in simple face detection tasks (e.g., Figure 9.9), but is likely to shown smaller or abnormal responses relative to controls when individual faces have to be discriminated and should benefit from the OFA inputs (a so-called dynamic diaschisis effect, Price et

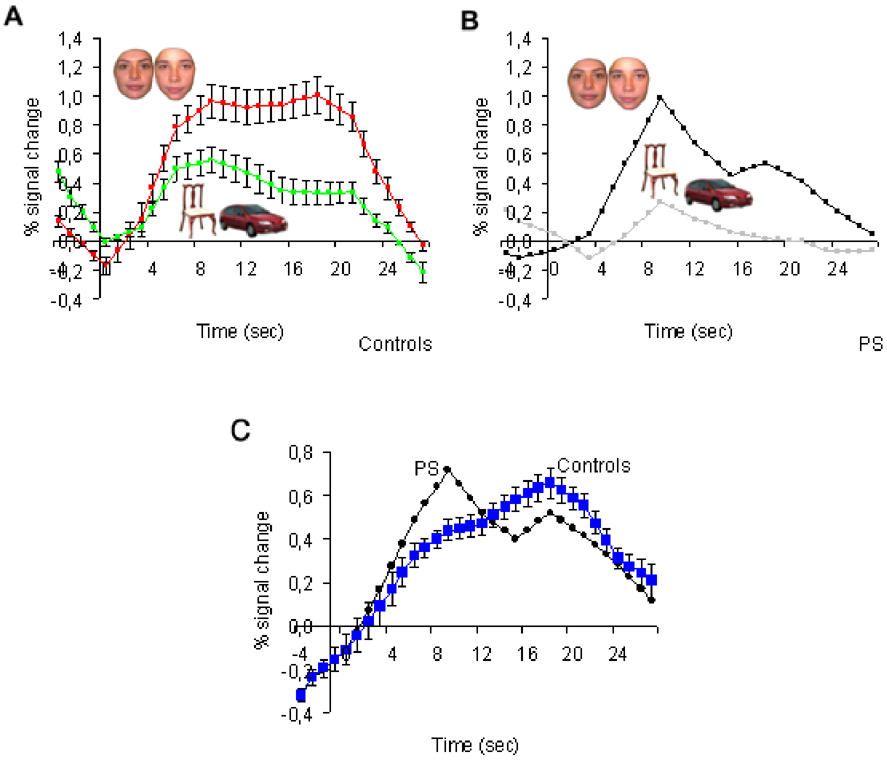

Figure 9.11. Typical BOLD signal in the right FFA observed for a face localizer (TR 3000 ms; blocks of 18 secs, see methods in Rossion et al., 2003; Schiltz et al., 2006) for normal participants (A) and the patient PS (B). Note that relative to controls the BOLD response is not sustained for PS when different faces are presented. However, subtracting the reponse to object stimuli from the response to face stimuli leads to a an overall response in the normal range for PS when the whole time-course is considered (Rossion et al., 2003). The lack of sustained activation, presumably because of identity adaptation in the absence of OFA inputs, would cause a significant decrease of the differential response to faces for PS, only apparent with long stimulation blocks (figure adapted from Schiltz et al., 2006).

al. 2001).

To summarize, we have shown that the preferential activation for faces in the lateral part of the right middle fusiform gyrus ('rFFA') can arise in the absence of face preferential inputs coming from posterior areas such as the right OFA. However, without any contribution from the right OFA, the activation level in the 'rFFA' when different faces are presented drops down to the level of identical faces.

The neural microgenesis of face perception

Based on these observations, we suggest reformulating the neuro-functional organization of face perception in the human brain, to incorporate the following elements (see Figure 9.12; Rossion, in press). Following early processing in striate and extrastriate visual areas, face stimuli would activate high-level visual areas of the fusiform gyrus (and possibly pSTS) through a direct pathway, leading to the earliest face preferential response at a relatively anterior location in the ventral visual stream (FFA). Neurons in this non-retinotopic visual area have presumably a relatively large receptive field, as in the area TE of the monkey IT (between 30 and 50 degrees, Boussaoud et al., 1991), allowing an initial representation of the whole face stimulus, even when it is perceived out of the foveal view (i.e. a face popping out, somewhere in the visual scene). This initial representation would be rather coarse, sufficient for accurate detection and categorization of the stimulus as a face for instance, but insufficient for the fine-grained analysis required to identifying the particular person whose face is presented. This process is preserved for the patient PS who shows normal behavioral and neural face categorization/detection function even for degraded high-contrast stimuli such as Mooney faces (Figure 9.9). However, in the normal brain following this initial categorization process, the face representation would be progressively refined to allow the extraction of local features and their integration to form a full percept of an individual face supporting identification (a structural encoding code, according to the terminology of Bruce and Young's (1986) functional model of face processing). This is where lower-visual areas such as the OFA may be called upon during this microgenesis of face perception (Sergent, 1986). That is, through reentrant signaling, the higher order face-sensitive populations of neurons in the FFA may lead to or enhance face preferential responses in lower level visual areas i.e. the OFA, where populations of neurons with smaller receptive fields would help refining the face representation. In other words, global and coarse information in higher visual areas would serve as a header to set up the processing of fine information related to facial identity in lower visual areas. Given their smaller receptive fields, neurons in the OFA may be fine-tuned to subserve such fine discrimination, which are critical in real life situations (e.g., recognizing the same identity across age differences, changes in lighting, discriminating siblings or twins, etc.). Reentrant connectivity between the two areas would then support the full extraction of individual face representations (Figure 9.2).

If we consider patients such as PS the initial categorization of the stimulus as a face in the right FFA, which allows her to categorize faces vs. objects to detect faces in visual scenes, or even to perceive a whole Mooney face stimulus, cannot be followed by an integration with lower visual areas in the right hemisphere to refine the initial face representation. Consequently, there is an absence of facial identity discrimination in the FFA of PS, and a decrease of the hemodynamic FFA response in the absence of sustained reentrant interactions with the right OFA (Figures 9.10 and 9.11).

This proposal of a neural microgenesis of face perception, starting with a coarse categorization in high visual areas followed by a refinement through reentrant interactions with lower visual areas (Rossion et al., 2003), is in agreement with the presence of massive cortical bi-directional connections (Felleman and Van Essen, 1991) and the hypothesis of reentrant phasic signaling between areas of the visual cortex (Edelman,

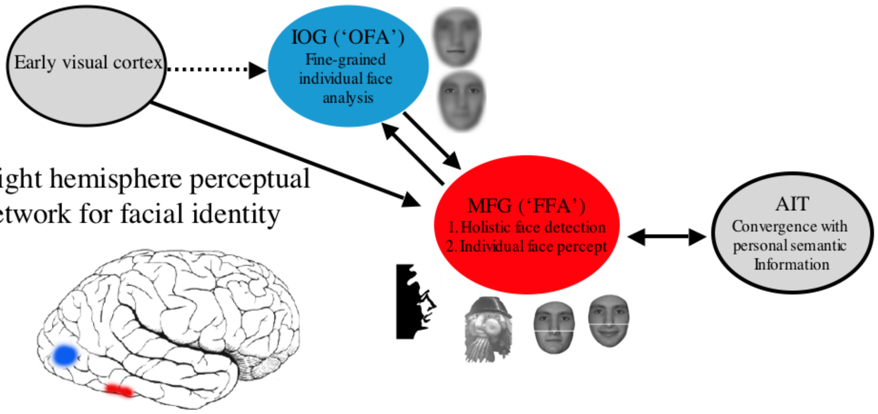

Figure 9.12. Reformulating the neuro-functional organization of face perception in the human brain. Following early visual analysis, visual stimuli are detected as whole faces in high visual cortices (1): in the middle fusiform gyrus (MFG), leading to preferential activation for these stimuli (FFA). The crude representation of the face stimulus is then refined through reentrant interactions with lower visual areas (2), leading to a face preferential activation in the inferior occipital gyrus (IOG, OFA). This refinement allows the extraction of a full percept of an individual face. A lesion of the OFA does not prevent face preferential activation in the FFA but leads to an absence of individual face adaptation effects in this area.

1978, 1993). It is a proposal that is not particularly challenging or novel, but is inspired from several sources. Starting with Mumford (1992), a number of authors have indeed suggested that through feedback connections, higher level perceptual computations and representations that involve high resolution details, fine geometry and spatial precision may involve lower visual areas (Mumford, 1992; Bullier et al., 2001; Lee et al., 1998; Galuske et al., 2002). These proposals have perhaps been more extensively formulated in the reverse hierarchy theory (RHT) of visual perception proposed by Hochstein and Ahissar (2002). According to RHT, explicit perception begins at high-level visual cortex, representing the gist of the scene or an object at the basic level. This is performed on the basis of a first order approximation of low-level inputs. The details are not represented at this stage, and the representation is then refined by recruiting lower visual areas, with smaller receptive fields neurons, through feedback connections. RHT has been derived from perceptual learning experiments and has been proposed to account for many phenomena of vision and attention such as the initial and fast perception of object categories (including face detection), feature search "pop out" effects and whole superiority effects (see Hochstein and Ahissar, 2002).

The revised cortical model of face perception proposed here is largely in agreement with this RHT framework. In fact, faces are perhaps the best candidates for a coarse-whole to fine-parts scheme: faces are often detected very far away, out of foveal vision and/or with their features too small to resolve. Hence, a whole face stimuluscan be detected without and before any detailed analysis and decomposition of the individual features (Sergent, 1986; Loftus and Harley, 2004). In visual scenes, faces can be detected extremely rapidly (Rousselet et al., 2003). More to the point, a whole face is perceived readily even when there are no facial features, or when they are not easily discernable, such as in a painting of the 16th century artist Giuseppe Arcimboldo (e.g., "The Vegetable Gardener") or in a two-tone Mooney face (Figure 9.9). Besides being compatible with multiple sources of evidence, an initial, rapid, feedforward categorization of the stimulus as a face followed by reentrant interactions with lower visual areas is thus (eco)logically valid and highly plausible. Moreover, this initial categorization and the reentrant interactions between high and low level visual processes would probably take place predominantly in the right hemisphere for faces, consistent with the evidence of the early face categorization and individual discrimination effects are observed most significantly in this hemisphere (Jacques et al., 2007).

With respect to the RHT, the present proposal differs according to at least two aspects. First, in order to obtain a first approximation of the visual stimulus in high level visual areas it may not be necessary for the feedforward initial processing of visual information to go through the hierarchy of visual areas, as proposed in the RHT framework. That is, direct connections from low-level visual areas such as V1/extrastriate cortex to high-level visual areas such as the FFA can bypass the hierarchy of intermediate visual areas, including the OFA (Figure 9.12). Otherwise, there would not be any activation of the FFA in brain-damaged patients with posterior occipital lesions such as PS and DF. Second, and this is a related point, it may be incorrect to refer to a feedback from the FFA to the OFA, as we initially proposed (Rossion et al., 2003). Rather, the initial input to the OFA could possibly originate from the FFA or the two areas may exchange information largely in parallel. Consequently, rather than feedback, it would be more appropriate to hypothesize the presence of phasic reentrant connections (Edelman, 1978, 1993) between these areas, as leading to a full individual face percept.

Interestingly, this revised neural model of the microgenesis of face perception is also largely compatible with neurophysiological evidence. For instance, single cell recordings in the monkey brain have shown that the representation of faces in IT which emerges rapidly (70-130 ms, average latency 100 ms in the monkey brain, Kiani et al., 2005) is that of a global face stimulus which cannot be decomposed in parts without altering the cell's response (Desimone et al., 1984; Wang et al., 1996). The very same neurons in these areas appear to carry out both coarse and fine-grained categorization of faces at different time-scales (100-150 ms, Sugase et al., 1999). Event-related potential (ERP) recordings on the human scalp as well as the latency of saccadic reaction times also indicate that objects and faces are detected in visual scenes well before a perceptual decision at 150 ms (Thorpe et al., 1996; Rousselet et al., 2003; Kirchner and Thorpe, 2006). ERPs indicate that segmented faces are reliably discriminated from other object categories at about 130 ms (onset of occipito-temporal N170 peak; see Rossion and Jacques, in press for a review), and recent evidence collected in our laboratory indicates that individual representations of faces are discriminated slightly later, at about 160 ms, within the time window of the same component (Jacques and Rossion, 2006; Jacques, d'Arripe and Rossion, 2007). Thus, overall, a reasonable amount of evidence supports the possibility of a rapid coarse categorization of the face stimulus in high level visual areas such as the right fusiform gyrus (FFA) followed by a refinement through reentrant interactions with lower visual areas, in particular the ipsilateral OFA.

To be fair and complete it is necessary to mention and discuss the potential evidence against the view advocated here and which would rather support a hierarchical feedforward two stages model, with an initial face categorization in posterior lower visual areas such as the OFA followed by individual face representations in the FFA. For instance, using fMRI adaptation to facial identity, Rotshtein et al. (2005) showed that the OFA was more sensitive to the physical aspects of the face stimulus than the FFA. Following an earlier work that we performed with morphed individual faces in PET (Rossion et al., 2001) these authors used fMRI to show release from adaptation to two faces that differed physically in the OFA, regardless of whether the subject perceived the two faces as being two photographs of the same person or of different identities. This finding contrasts with the FFA, which showed release from adaptation when the two pictures of faces were perceived as different identities but not when they were perceived as the same identity. This evidence was taken in favor of a hierarchical model of face processing in the ventral stream, with only the FFA but not the OFA being sensitive to individual representations of faces. However, as we indicated previously (Schiltz et al., 2006), the presence of a fine discrimination sensitivity (release from adaptation when 2 faces slightly differ physically) in the OFA is compatible with our findings and with the view advocated here. Furthermore, while our model calls upon reentrant interactions between these areas (Figure 9.2), it is also in favor of a higher level of abstraction in the FFA than the OFA, following the initial input to the face system in the FFA. As a matter of fact, holistic representations are stronger in the FFA than the OFA in particular in the right hemisphere (Schiltz and Rossion, 2006). The only finding in the study of Rotshtein et al. (2005) that is difficult to reconcile with our view is that of an absence of release from adaptation when the faces differ only physically in the FFA. This would indeed suggest that this area does not discriminate highly similar faces, even following reentrant inputs from the OFA. In this context, it is interesting to note that a recent fMRI study using morphed faces did not replicate this latter observation of Rotshtein et al.'s (2005) study: the FFA (and the OFA) was sensitive to small physical differences between the faces along a morphed continuum, mirroring subject's discrimination abilities (Gilaie-Dotan and Malach, 2007).

More recently, Fairhall and Ishai (2007) applied Dynamic Causal Modeling (DCM) to fMRI data during face processing to investigate the connectivity between these areas. These authors reported a predominantly feedforward connectivity between the OFA and FFA which could be interpreted as being in disagreement with the model outlined on Figure 9.12. However, unlike Granger Causality, DCM is a modeling method that requires specific hypotheses. Thus, the brain regions included in the model, the anatomical connectivity between them and the modulations by experimental conditions have to be specified (Penny et al., 2004). In line with Haxby et al.'s (2000) earlier proposal, Fairhall and Ishai (2007) constrained their model by considering the OFA as the entry node of the system, such that the functional connections tested mediated the propagation of face-selective responses in the OFA around the face system. The model is thus biased, even though the authors mention that there was no evidence for a potential contribution of backwards connections from the FFA and STS to the OFA to the model. This purely hierarchical feedforward interpretation, without any feedback, is rather surprising, given that there should certainly be important feedback connections between these areas, consistent with the presence of massive reentrant connections in the visual system (Felleman and Van Essen, 1991). Furthermore, the regions of interest defined by Fairhall and Ishai (2007) were obtained after contrasting faces and scrambled faces, and may thus contain a large number of voxels that do not respond preferentially to faces (over objects), but simply to shape information (i.e. LOC), making it difficult to compare with our proposal. While it would be interesting to apply DCM to appropriate fMRI data to test the functional pathways leading to face preferential responses, there are probably better ways to test the model, as described below (see also Rossion, in press). In particular, the finding of a dominant OFA to FFA functional relationship by Fairhall and Ishai (2007) does not rule out the view advocated here that the initial activation for faces emerges in the FFA through a rapid direct pathway, bypassing the OFA. When the two areas then interact with each other, it may well be that a substantial directional relationship takes place in the posterior-anterior (OFA to FFA) direction. In the absence of precise timing information, as could be collected from MEG studies or neurophysiological recordings in the monkey face-selective patches of activation (see below), this issue is difficult to clarify.

Finally, while the view advocated here is compatible with a number of sources, it disagrees with other purely hierarchical computational models of face processing such as the HMAX architecture proposed by Riesenhuber and colleagues (Riesenhuber and Poggio, 1999; Jiang et al., 2006). While this hierarchical model may perhaps account for some characteristics of face processing obtained from both behavioral and neuroimaging signals (Jiang et al., 2006), it cannot account for the observations of an activation of the FFA without a posterior OFA, as observed in the cases of PS and DF. Being based on a simple combination of features through several stages of increasing complexity, it is also at odds with several phenomena characterizing normal face perception, such as the perception of faces made of non-face features (e.g., Arcimboldo's paintings). In addition, it cannot account for the observation that inversion affects more the perception of spatial relationships between facial features than local information on these features (e.g., Freire et al., 2000; Goffaux and Rossion, 2007)[2], and with the widely acknowledged norm-based coding of individual faces (e.g., Rhodes et al., 1987; Leopold et al., 2001). My view is that this hierarchical computational architecture will need to be substantially revised to incorporate top-down connections and processes, or it will prove increasingly incompatible with numerous neural and functional key aspects of face perception (i.e. the whole before the parts, see Sergent, 1986).

All in all, I believe that there is currently no substantial evidence against the neuro-functional framework proposed here from neuroimaging studies of brain-damaged patients, which is rather in agreement with the very nature of face perception.

To conclude this section, I have derived from the neuroimaging studies of brain-damaged patients (mainly PS) the proposal that there is a direct feedfoward activation from V1/extrastriate areas to the right FFA, which bypasses the visual areas located along the hierarchy in the ventral stream. This early face preferential activation is that of a global percept, allowing fast categorization of the stimulus as a face. However, the

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[2] Rather than revising their model, Riesenhuber and colleagues have questioned the fact that inversion affects more the perception of distances between features than local features (Riesenhuber et al., 2004). However, their observations contrast with a wide body of evidence and appear to be due to methodological shortcomings in their study (see Goffaux and Rossion, 2007).

first face representation is too coarse for perceptual tasks requiring the extraction of a more detailed individual representation. In the normal brain, the face representation is thus progressively (i.e. within tens of milliseconds, between 100-200 ms following stimulus onset) refined, calling upon lower-visual areas through reentrant interactions. This may cause the emergence or increase of face preferential responses in the OFA, in the normal brain. This process cannot take place in the patients PS and DF, who present damage to the inferior occipital cortex, without any evidence of OFA activation. Consequently, these patients are severely impaired at perceiving individual faces.

This proposal is consistent with several sources of evidence, as reviewed above, but is inconsistent with a strict hierarchical view of the face processing pathway as initially suggested (Haxby et al., 2000) and often taken for granted in the literature. Direct tests of this proposal inspired by neuroimaging studies of brain-damaged patients should benefit from independent work using this approach (i.e. combining functional neuroimaging and lesion studies). Further evaluation of the model may also come from two different methods in future investigations. First, transcranial magnetic stimulation (TMS) could be used to interrupt the flow of information coming out of the identified right OFA in individual brains. In many participants of our experiments, the OFA appears to be located close to the external surface of the cortex suggesting that it should be possible to create relatively selective temporary interruption of cortical function in this area. Behaviorally, disrupting the processing of information in the right OFA using TMS should leave intact face detection but rather cause impairments in individual face discrimination and recognition tasks. This has been recently reported by Pitcher et al. (2007) in an rTMS and dual pulse TMS study, even though these authors used an average localization rather than individually defined 'OFAs', making it difficult to ensure that they truly affected the OFA area in all of their participants. Furthermore, if repetitive TMS coupled with fMRI (e.g., Bestmann et al., 2004; Sack et al., 2007) is applied to the OFA territory, one should still observe a normal onset of preferential activation for faces in the ipsilateral FFA, which may nevertheless not be as sustained as without TMS, due to the lack of reentrant OFA inputs. This is a direct and strong prediction of the model outlined on Figure 9.2.

Another promising method to test the directionality and the time-course of the OFA-FFA interaction (or of "face areas" in general) during normal face processing is fMRI recordings in the monkey brain (Logothetis et al., 2001). Using this method, several studies have identified similar areas of face preferential response in the monkey occipito-temporal cortex (Tsao et al., 2003; Pinsk et al., 2005). Electrophysiological recordings have shown a high face-selectivity of the neurons responses (Tsao et al., 2006) in 3 patches located in the STS, emerging at a latency of. about 100 ms, as in traditional IT recordings. However, there was no information reported in these studies about possible differential time courses of neural activation in different face patches, and the relationship between these areas and the human FFA and OFA remains unclear. Nevertheless, the discovery of these face-selective small regions in fMRI recordings in the monkey brain may offer the exciting opportunity to create animal models of prosopagnosia, by lesioning these regions selectively and temporarily (e.g., through cooling methods, see Hupé et al., 2001) to investigate their functional connectivity. Insofar as the non-human primate face perception system is highly homologous to humans, I would again predict that anterior areas can show a preferential response to faces independently of such responses in lower visual areas.

9.4 Conclusions and future directions

Of the most important observations made principally but not exclusively on the brain-damaged prosopagnosic patient PS, I can summarize the following:

(1) The preferential response to faces in the inferior occipital cortex, termed the OFA, is not an epiphenomenon. It is usually neglected in the neuroimaging face literature, which concentrates most often exclusively on the FFA (e.g., Kleinschmidt and Cohen, 2006). Yet the OFA appears to play a critical role in face perception. A lesion of the right OFA is instrumental in causing cause prosopagnosia.

(2) A lesion of the right FFA may also cause prosopagnosia, a suggested by others (Barton et al., 2002), and there is also evidence that prosopagnosia can follow more anterior temporal structures sparing both the FFA and OFA structurally (e.g., Bukach et al., 2006; Gainotti et al., 2003). However, a conventional structural imaging approach is not sufficient to derive conclusions about the critical sites causing prosopagnosia because there is a large amount of interindividual variability in the localization functional areas. Most importantly, functional imaging may reveal abnormal face processing in areas left intact by the lesions, because they are deprived of inputs from other areas.

(3) A lesion of the right OFA will usually concern the ventral part of the lateral occipital complex (vLOC) as well, causing impairments for both face and object perception. In rare cases such as PS, the damage has spared the vLOC, leading to prosopagnosia without object agnosia.

(4) Even without any contribution of the right OFA, the right FFA may yet show intact categorization of the visual stimulus as a face suggesting direct striate/extrastriate inputs, bypassing the hierarchy of visual areas. This initial representation can be that of a whole face. This contradicts a view according to which the OFA would be the necessary "front end" of the face perception system, extracting facial features first (Haxby et al., 2000).

(5) Without reentrant inputs from the right OFA, the FFA is unable to derive a full perceptual representation of an individual face. Discriminating individual unfamiliar faces can be achieved to a certain extent by acquired prosopagnosic patients but the FFA plays little or no role in this function if deprived of OFA inputs.

Collectively, these studies show that there is a network of visual areas with a right hemispheric dominance that is involved in deriving full perceptual representations of individual faces, a function that is fundamental for our social interactions. A subset of these areas show a preferential response to faces, such as the right FFA and the OFA and appear to be critical for this function. Obviously, a large number of questions remain open, both about the neuro-functional organization of the patient PS' and other acquired prosopagnosic patients, as well as about the functional neuro-anatomy of face perception in the normal brain: e.g., Why is the FFA not recruited at all for individual face perception without the OFA, even though the patient can perform individual face discrimination above chance level? Is the vLOC or other areas coding for residual individual face discrimination in prosopagnosia by means of low-level analysis of single face features such as the mouth (see Dricot et al., in press)? Why is there no sign of functional reorganization in PS's brain? Where is the initial FFA activation coming from both in the normal brain and in patients such as PS and DF? What is the role of the left hemisphere, in particular the left FFA and OFA, in normal face perception? Besides the right OFA, whose lesion is instrumental in causing prosopagnosia, which are the other regions – such as the right FFA and anterior temporal areas – that are also necessary to subtend normal face perception?

Answering these questions will be fundamental to establish the neural dynamics of face perception at the system level in the human brain. While there are certainly multiple methods of cognitive neuroscience that will contribute to reach this goal, I hope to have provided a convincing illustration that a fruitful and inspiring approach in this field is the combination of functional imaging with the study of brain-damaged cases of prosopagnosia. Because acquired prosopagnosic patients with well preserved low-level visual processes are extremely rare, present a large degree of variability in terms of their functional and neural impairments, and need to be characterized in depth for these studies, I advocate a single-case approach as described here rather than studies which treat variable patients as a group. In line with a cognitive neuropsychology approach at the functional level (Caramazza, 1986; Shallice, 1988), this single-case methodology can constrain and inspire neuro-functional models of normal face processing. This methodology is important not only to characterize the function(s) of brain areas and to clarify the necessity of certain areas for a given function but also to understand the functional connectivity between brain areas. Using this approach for a number of years, my colleagues and I have derived here a number of predictions about the functional neuro-anatomy of face perception. Even if these predictions and the simple scheme proposed here are proved wrong by future investigations, the approach itself should not be abandoned, as it is undoubtedly a powerful source of inspiration for deriving hypotheses about how the human brain perceives faces.

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