

Faculté de psychologie et des sciences de l'éducation

Neuro-imagerie de la reconnaissance des visages chez les sujets sains et le patient neurologique

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LISTE DES ABREVIATIONS

AiT	Cortex Inféro-Temporal Antérieur
BOLD	Blood Oxygenation Level Dependant
DCM	Dynamic Causal Modelling
DTI	Diffusion Tensor Imaging
FDR	False Discovery Rate
FFA	Fusiform Face Area
GCM	Granger Causality Map
GLM	General Linear Model
ICA	Independant Component Analysis
ILF	Faisceau Longitudinal Inférieur
IRM (MRI)	Imagerie par Résonance Magnétique (Magnetic Resonance Imaging)
IRMf (fMRI)	Imagerie par Résonance Magnétique Fonctionnelle (Functional Magnetic Resonance Imaging)
IT	Cortex Inféro-Temporal
LOC	Lateral Occipital Complex
OFA	Occipital Face Area
PCA	Principal Component Analysis
pIT , cIT et aIT	Posterior, Central et Anterior Inferotemporal Cortex
SEM	Structural Equation Modelling
STS	Superior Temporal Sulcus

TE	Temporo (division cytoarchitecturale de IT, partie antérieure)
TEO	Temporo-occipital (division cytoarchitecturale de IT, partie postérieure)
TEP (PET)	Tomographie par Emission de Positrons (Positron Emission Tomography)

1. INTRODUCTION GENERALE

Dans la plupart des thèses portant sur la reconnaissance des visages, se trouvent en introduction des justifications brillantes, savantes et parfois amusantes sur les raisons qui ont poussé les chercheurs à s'intéresser à un domaine qui semble si naturel et donc si facile : le traitement de la reconnaissance des visages. Beaucoup soulignent l'importance fondamentale des visages dans la relation aux autres. Même si Shakespeare dans Macbeth nous rappelle qu''Il n'y a pas d'art pour découvrir sur le visage les dispositions de l'âme'', il est vrai que dès l'enfance, nous inférons à partir des visages qui nous entourent toutes sortes d'informations non verbales essentielles dans notre relation à l'autre : plutôt basiques comme l'âge et le sexe et assez personnelles comme la beauté jusqu'à des impressions plus complexes comme l'intentionnalité de la personne à notre égard. Parfois stéréotypées ou erronées, ces inférences nous permettent pourtant d'agir rapidement et souvent efficacement. Cette expertise que nous avons développée et qui nous a amené à traiter les visages avec une facilité apparente repose cependant sur une architecture neuro-anatomique plus complexe qu'il n'y parait.

Décrire le traitement des visages peut se faire selon différentes « unités » ou niveaux *anatomiques* et *fonctionnels* de catégorisation, de la plus petite, « l'unité moléculaire » à la plus haute, « l'unité sociale » en passant par « l'unité cellulaire », « corticale » et « comportementale ». Notre travail basé sur l'Imagerie cérébrale structurelle et Fonctionnelle par Résonance Magnétique (IRM et IRMf) s'est particulièrement attaché à l'aire corticale. Nous nous sommes intéressé d'un point de vue *anatomique* à la définition et à la localisation des régions sensibles aux visages. D'un point de vue *fonctionnel*, nous nous sommes intéressé aux rôles de ces régions et à leur connectivité. Les unités plus petites ont néanmoins toujours éclairé voire dirigé notre travail que ce soit au niveau « moléculaire » (du point de vue *anatomique* les photorécepteurs et du point de vue *fonctionnel* la transduction du signal lumineux) ou au niveau « cellulaire » (du point de vue *anatomique* les neurones et/ou cellules gliales et du point de vue *fonctionnel*: les champs récepteurs simples,

complexes, hypercomplexes, la rétinotopie et les connexions afférentes/efférentes de ces neurones). L'enregistrement cellulaire chez le primate non humain a évidemment inspiré bien des études IRMf. De même, les études IRMf ont utilisé largement dans leurs paradigmes expérimentaux différents effets classiques de la neuropsychologie des visages (effet d'inversion, effet composite, effet d'expertise, etc.,…) qu'on pourrait voir comme les composants *anatomiques* de « l'unité comportementale » possédant des avantages *fonctionnels* de rapidité de traitement. Finalement, ces effets neuropsychologiques ont été également étudiés au niveau cortical -en IRMf- en fonction de la race, de l'âge ou encore du sexe (sorte « d'*anatomie* » de « l'unité sociale » influençant nos interactions et notre *fonctionnement* en société).

Notre dissertation comprendra deux chapitres principaux, l'un reprenant le contexte théorique et en particulier l'état de la connaissance de la neuro-anatomie fonctionnelle des visages, l'autre reprenant notre contribution empirique à la description de cette organisation.

Dans le chapitre 1, nous aborderons les différentes techniques du niveau cortical mais aussi cellulaire qui ont apporté des avancées à la compréhension de la reconnaissance des visages : l'anatomopathologie, l'étude animale, en particulier l'enregistrement cellulaire, et les différentes techniques d'imagerie cérébrale. Nous le terminerons par la proposition d'un modèle de la reconnaissance des visages qui s'oppose au modèle hiérarchique classique.

Dans le chapitre 2, nous présenterons nos travaux en IRMf étayant ce modèle. Plus de 150 sujets ont bien voulu que nous les « scannions » souvent à plusieurs reprises. Qu'ils soient remerciés encore une fois… Ce chapitre comprendra 6 parties.

La première abordera la question fondamentale du rôle et du choix d'un « localizer » visage, soit un paradigme expérimental permettant de définir quelles sont les régions qui sous-tendent réellement la perception des visages. Nous y présenterons notre propre localizer et les résultats de son utilisation pour une série importante de sujets droitiers.

La deuxième comparera des sujets droitiers et gauchers au niveau de leurs réseaux visages au moyen de ce même localizer.

La troisième comparera une patiente (PS) ayant perdu la faculté de reconnaître les visages à un groupe de sujets contrôles droitiers en ce qui concerne la détection de visages (pouvoir dire que cette forme est un visage).

La quatrième comparera la même patiente à un groupe de sujets contrôles mais cette fois au niveau de la reconnaissance individuelle de visages (pouvoir dire de quel visage il s'agit).

La cinquième décrira l'utilisation du même paradigme chez une autre patiente ne reconnaissant ni les objets, ni les visages (DF).

La sixième montrera finalement des résultats en connectivité *fonctionnelle* chez PS et des sujets contrôles droitiers. La description de la patiente PS y sera complétée par les résultats obtenus par une technique de connectivité *anatomique* « Diffusion Tensor Imaging » (DTI).

2. CONTEXTE THEORIQUE : Que sait-on de la neuro-anatomie fonctionnelle du traitement des visages ?

2.1. Les sources de connaissance

C'est seulement depuis une vingtaine d'années, d'abord avec la Tomographie par Emission de Positrons (TEP ; Sergent et al., 1992, Haxby et al., 1994) et ensuite avec l'Imagerie par Résonance Magnétique Fonctionnelle (IRMf ; Clark et al., 1996 ; Puce et al., 1996; Kanwisher et al., 1997) que les études d'imagerie cérébrale fonctionnelle ont été mises à contribution pour la compréhension et la description de la neuro-anatomie du traitement des visages chez des sujets sains ou cérébro-lésés. Auparavant, les informations quant à ce réseau ne découlaient principalement que de l'étude de la corrélation anatomo-clinique essentiellement de patients incapables de reconnaître des visages (Wigan et al., 1844 ; Quaglino & Borelli, 1867 ; Jackson, 1872 ; Wilbrand, 1892 pour les premières études décrivant le trouble dans la seconde moitié du 19^{ième} siècle ; Bodamer et al., 1947 pour la définition du terme « prosopagnosie » du grec prosopon, le visage et a-gnosis, l'absence de reconnaissance). Dans les années 70 (Gross et al., 1972) se sont ajoutés les enregistrements cellulaires dans le cortex inféro-temporal du primate non humain. Ce chapitre donne un aperçu historique des connaissances actuelles avec un accent tout particulier sur l'imagerie cérébrale et la cohérence de ses résultats avec les deux autres grandes sources d'informations.

2.2. Les corrélations anatomo-cliniques

Bien que l'échelle spatiale des corrélations anatomo-cliniques soit assez large de par l'étendue et la variabilité des lésions et que les troubles associés soient parfois incomplètement étudiés (en particulier au niveau de la pureté de la prosopagnosie), elles sont néanmoins importantes dès lors qu'il faut juger de la nécessité et/ou de la suffisance d'une région cérébrale[1]. L'« agnosie

[1] Remarquons que la "Transcranial Magnetic Stimulation" (TMS) qui consiste à stimuler électriquement des « unités » du système nerveux (aires cérébrales), est une méthode qui découle de cette philosophie.

des physionomies » définie en 1947 par Bodamer comme la prosopagnosie (Rondot et al., 1967) est généralement associée à des lésions occipito-temporales (Damasio et al., 1982). Plus précisément, les lésions se retrouvent essentiellement au niveau des gyri lingual, occipital inférieur, fusiforme postérieur et antérieur ou encore parahippocampique. Au niveau de la latéralisation, elles présentent une dominance droite (Michel et al., 1989). De plus, des lésions uniquement à droite peuvent entraîner des prosopagnosies (Landis et al., 1988 ; Sergent & Signoret, 1992) et sont donc une condition suffisante à son apparition. Vu la rareté des prosopagnosies sur lésions gauches, 4 cas recensés sur une centaine de cas dont 3 gauchers (Eimer & McCarthy, 1999 ; Mattson et al., 2000, Barton et al., 2008) et un patient épileptique (Wright et al., 2006), on peut penser que c'est aussi une condition nécessaire. En effet, on le verra dans notre contribution expérimentale, le réseau visage des gauchers est très particulier et ne présente pas une latéralisation droite marquée comme celle retrouvée chez les droitiers (voir aussi Willems et al., 2009) et Wright et al. (2006) rapportent que les crises d'épilepsie récurrentes avant l'ablation du centre épileptogène situé dans le gyrus fusiforme gauche de leur patient ont pu engendrer des lésions miroirs à droite. En outre, dans une des plus importantes études vu le nombre de prosopagnosiques intégrés (100 prosopagnosiques y sont référencés), Bouvier & Engel (2006) soulignent aussi clairement une dominance droite des lésions. Pour les 52 prosopagnosiques pour lesquels ils disposaient des anatomies correctes et comparables, ils ont établi en effet des cartes superposant toutes les lésions où cette latéralisation droite apparaissait évidente (Figure 1). Ils montrent ainsi des zones lésionnelles non contiguës appuyant l'existence d'un réseau visage (voir point 2.4). La correspondance maximum entre tous les patients se trouve en outre dans le lobe occipital inférieur.

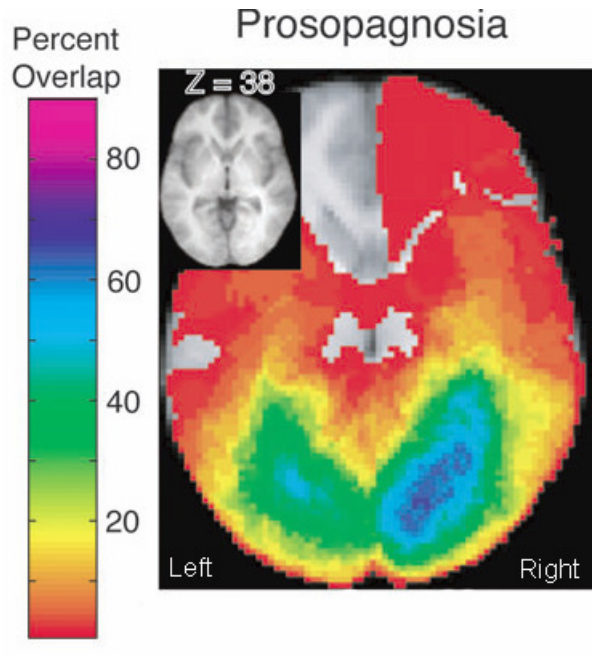


Figure 1. (D'après Bouvier & Engel, 2006). Superposition des anatomies de 52 patients prosopagnosiques. La correspondance maximum entre les lésions de ces patients se trouve dans le lobe occipital inférieur droit.

2.3. Les études chez l'animal

L'enregistrement cellulaire chez l'animal et le primate non humain en particulier a été une des techniques les plus marquantes dans la compréhension non seulement du cortex visuel primaire (V1), secondaire (V2) et extrastrié mais jusqu'à l'entièreté de la voie ventrale avec l'enregistrement dans le cortex inféro-temporal (IT), extrémité de la voie ventrale. L'information visuelle parcourt un trajet depuis la rétine grâce au nerf optique et au tractus optique (après le chiasma optique) en grande majorité jusqu'au niveau du corps genouillé latéral et au niveau du tubercule quadrijumeau antérieur et du prétectum. Chez les primates, le corps genouillé latéral comporte 6 couches de cellules. Les deux couches les plus ventrales (couches 1 et 2) reçoivent principalement des fibres en provenance des cellules ganglionnaires de type M de la rétine (système magnocellulaire, voie rapide, transportant plutôt l'information en provenance de la périphérie rétinienne et par leur champ récepteur large plutôt sensible à l'analyse du mouvement et aux relations spatiales). Les 4 couches les plus dorsales (de 3 à 6) reçoivent quant à elles des fibres venant des cellules ganglionnaires de type P (système parvocellulaire, voie plus lente, transportant plutôt l'information en provenance du

centre de la rétine et par leur champ récepteur étroit plutôt sensible à l'analyse fine des formes et de la couleur). Les informations des deux systèmes sont ainsi traitées en parallèle dans des couches différentes du corps genouillé latéral. Les tuberculules quadrijumeaux antérieurs (et pretectum) sont, quant à eux, plus impliqués dans des connexions régulant les réactions d'orientation des yeux, de la tête et du corps ou dans des réactions d'éveil.

L'information visuelle quitte les corps genouillés latéraux depuis leurs surfaces postérieures dorsolatérales par les radiations optiques en un faisceau temporal et dorsal jusqu'à V1, le cortex visuel primaire. Les deux systèmes, magno- et parvocellulaires, y aboutissent dans des sous-couches différentes de la couche IV de V1. Le champ visuel supérieur se retrouve dans la lèvre calcarine inférieure et le champ visuel inférieur dans la lèvre calcarine supérieure. V1 présente l'organisation corticale classique en colonnes corticales abondamment étudiée notamment par Hubel & Wiesel (1969) dans le cortex visuel. Chaque colonne (entre 300 et 600 μm, Horton et al., 2005) répond ici à une région particulière de l'espace visuel et à une orientation particulière d'une barre lumineuse ou à un intervalle de fréquences spatiales, une hypercolonne désignant un ensemble complet de colonnes reprenant toutes les orientations ou fréquences possibles pour les deux yeux. Cette sensibilité des colonnes à des caractéristiques différentes (forme, couleur, mouvement etc.,…) se retrouve sur V2 qui reçoit les afférences majoritairement de V1[2]. Après V2, deux grandes voies principales traitent l'information visuelle : la voie dorsale et ventrale (Goodale et al., 1992 ; voir Goodale et al., 2004 pour une revue) : la première dédiée à l'action projetant vers le cortex pariétal postérieur (par V3 et MT, aire temporale moyenne) et la seconde fournissant une représentation détaillée du monde permettant des tâches de reconnaissance et d'identification et aboutissant (par V4) dans le cortex inféro-temporal. Avant d'aborder plus en détails ce dernier, soulignons encore que cette organisation quoique hiérarchique (l'information visuelle et son traitement se

[2] Les axones de la cellule IV de V1 se projettent principalement sur les neurones des couches II et III et de là partent les connexions avec les autres aires corticales. Via les couches V et VI, des connexions sont cependant également établies avec des structures sous-corticales, thalamiques, mésencéphaliques et pontiques.

complexifient en effet à chacune des étapes) présente non seulement des connexions ascendantes (feedforward) mais aussi descendantes (feedback). De même, il existe des connexions entre des régions éloignées ainsi qu'au sein même des régions. Le système est aussi massivement parallèle. Bullier et al. (2001) ont par exemple montré l'interaction rapide de la voie dorsale sur la voie ventrale par l'intermédiaire de connexions descendantes sur V1 et V2 guidant la voie ventrale dans sa reconnaissance d'objets. Hochstein et al. (2002) ont par ailleurs souligné l'importance de ces connexions descendantes dans la reconnaissance même de l'objet. Ils appuient la conception de la vision de « la forêt avant les arbres » contrairement à la vue hiérarchique classique initialisée par Hubel & Wiesel (1968) et reprise par Felleman & VanEssen (1991). Leur théorie dissocie la vision « at a glance » et la vision « with scrutinity » mais en associant la première à des mécanismes de hauts niveaux tandis que la seconde reflète des représentations de bas niveaux, les deux se déroulant quasi en parallèle. La perception initiale, explicite, se ferait dans les aires de haut niveau à large champ récepteur dans une sorte d'intégration approximative des inputs de très bas niveau. Elle redescendrait ensuite le long de la voie ventrale via les connexions descendantes pour y interpréter les informations détaillées qui s'y trouvent (en « remontant » la voie ventrale) tout en confirmant ou corrigeant la vision initiale grossière (Figure 2). Des études en « Diffusion Tensor Imaging » (DTI) réalisées chez l'homme ont d'ailleurs tenté de montrer l'existence de connexions reliant les régions de bas niveaux (V3 ; Kim et al., 2006 ou V2, Catani et al., 2003) directement, sans passer par la voie hiérarchique, notamment vers une région du gyrus parahipocampique sensible aux objets et permettant sans doute cette vision « at a glance » dans les régions supérieures. Remarquons finalement que dès le début des années 2000 (ou même avant, voir Jones et al., 1997) les modèles purement hiérarchiques (Biederman, 1987 ; Riesenhuber & Poggio, 1999) sont un peu délaissés[3] dans les modèles computationnels de détection d'objets et de visages pour être remplacés par des

[3] Il y a encore des développeurs qui utilisent des modèles hiérarchiques (Ulman, 2007 par exemple).

modèles mêlant les approches ascendantes et descendantes beaucoup plus efficaces dès qu'il y a des images bruitées ou incomplètes.

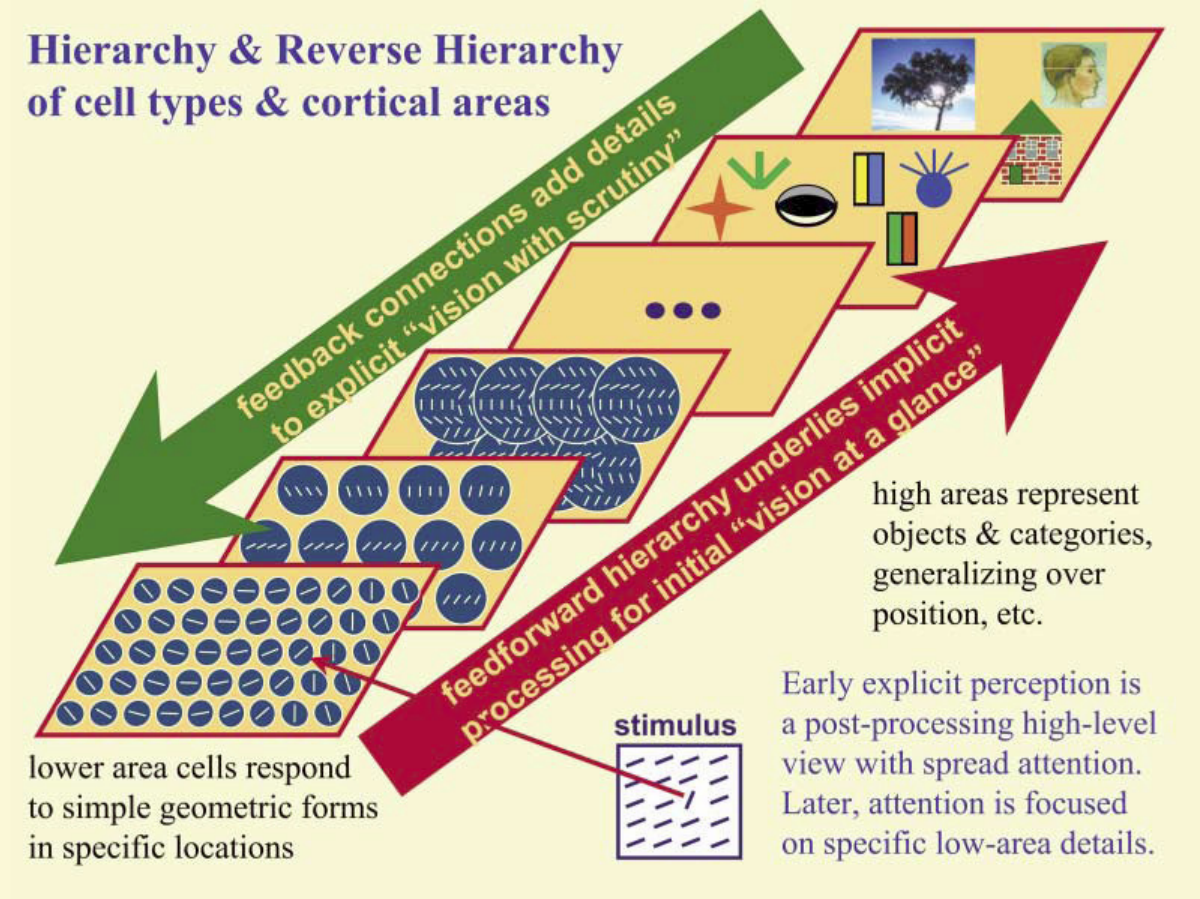


Figure 2. (D'après Hochstein et al., 2002). La perception initiale explicite réalisée dans les aires de hauts niveaux sur base d'information des aires de bas niveaux (V1 et V2) éclaire la voie ascendante de l'information visuelle. ''*Life can only be understood backward, but it must be lived forward*'' Kierkegaard.

2.3.1. Le cortex inféro-temporal

Depuis plus de 40 ans déjà avec les premières études de Gross et al. (1972), des cellules répondant de manière non rétinotopique contrairement aux aires striées (V1) et extra-striées à des objets moyennement complexes ont été trouvées dans le cortex inféro-temporal du singe. Leurs propriétés fonctionnelles ont été étudiées abondamment par la suite (Perrett et al., 1992 ou Gross, 1992 et Tanaka et al., 2003 ont fait plusieurs revues de littérature sur ces cellules). Une large proportion de ces cellules répondent de manière invariante à la taille des stimuli (Tanaka et al.,

1991) ou à leur position dans le champ visuel (avec cependant une réponse modulée en fonction de la distance à la fovéa ou du contexte, Wang et al., 1998). De même, certains neurones conservent leur sélectivité à la forme quelle que soit la façon dont elle est définie [luminance, texture mouvante etc., (Ito et al., 1994)]. Logothetis et al. (1994) ont montré qu'ils pouvaient adapter leur sélectivité en fonction d'un apprentissage ou de la difficulté. Finalement, Tanaka et al. (1991) ont montré que le codage d'un objet repose sur l'activité distribuée de plusieurs colonnes corticales du cortex inféro-temporal et non sur une seule, chaque objet pouvant avoir certaines colonnes communes avec d'autres objets.

2.3.2. Les cellules visages

Le cortex inféro-temporal (IT) a été classiquement divisé en une région postérieure (pIT ou TEO, temporo-occipital) et deux régions plus antérieures (cIT, central-IT et aIT, anterior-IT, l'ensemble formant TE, temporal) bordant le sillon temporal supérieur (STS). TE et le STS sont connectés depuis V1, V2, V4 et TEO suivant une hiérarchie classique mais on trouve également des connexions directes depuis V4 (Zhong et al., 2003). C'est au niveau de ces régions qu'on retrouve également la plus grande proportion de cellules visages chez le singe (Baylis et al., 1987) et Tsao et al. (2003) considèrent TE et la partie ventrale du STS comme les régions où l'on trouve l'équivalence de la région visage du gyrus fusiforme humain de par la sensibilité à l'identité (soit la fameuse ''Face Fusiform Area'' ou ''FFA'' définie par Kanwisher et al. en 1997). En 2008, Tsao et al. utilisant cette fois-ci l'IRMf chez le singe montrent plus précisément trois groupes de « face patches » dans le cortex occipito-temporal (organisé suivant un axe postéro-antérieur : « posterior, middle et anterior face-patch ») et soulèvent l'existence d'une région sensible aux visages plus antérieure que la ''FFA'', associée elle au « middle face patch » du singe[4]. Ils montrent également que les cellules de cette région répondent majoritairement de manière sélective aux visages ce qui, on le montrera au point 2.4.2.1., n'est cependant pas en contradiction avec l'activité préférentielle

[4] Tsao et al. dans un souci d'établir un parallélisme entre les régions visages du singe et de l'homme, ont dans leur étude scanné également des sujets humains et montrent chez certains d'entre eux cette région antérieure (voir 2.4.2.2.).

aux visages de la région équivalente chez l'homme trouvée en imagerie cérébrale. Il y aurait enfin une dominance droite pour ces « face patches » (Zangenehpour & Chaudhuri, 2005). En outre, Tanaka (1991) a montré que l'on ne pouvait décomposer le visage en stimuli plus simples sans réduire l'activité cellulaire et Perrett et al. (1992) que, lorsque les traits sont réarrangés à l'intérieur du visage, la cellule diminue aussi son activité. Le visage est traité comme un ensemble global consistant en un arrangement précis de traits faciaux en accord avec les effets comportementaux classiques de la reconnaissance des visages chez l'homme tels que l'effet de supériorité du tout sur les parties (whole part advantage ; le fait que la reconnaissance du visage en entier est supérieure à la reconnaissance d'un trait isolé, Tanaka & Farah, 1993) ou l'effet composite (le fait que la reconnaissance de la partie supérieure d'un visage est plus altérée lorsque la moitié inférieure d'un autre visage est alignée avec elle plutôt que décalée, Young et al., 1987). Il semble aussi que la majorité des cellules visages codent essentiellement une vue particulière du visage (face ou profil par exemple, avec l'organisation classique en colonne corticale) et diminuent d'activité quand on s'en éloigne (Perrett et al., 1991, 1998) et que très peu répondent de manière équivalente à toutes les vues (avec un temps de latence d'ailleurs plus grand pour celles dont c'est le cas, Perrett et al., 1991). Perrett et al. (1982) puis Baylis et al. (1985) ont montré également que les cellules visages répondaient à un nombre important de visages évoquant donc un codage distribué d'un visage particulier au travers d'une population de neurones. Par contre, dans la partie dorsale du STS (voire même aussi déjà dans le fond du STS ou dans sa partie ventrale), se trouvent des cellules visages cette fois sensibles à l'expression faciale (Sugase et al., 1999). Tsao et al. (2008) relèvent aussi la présence d'une région visage droite dans le cortex préfrontal du macaque dédiée, selon eux, à guider la réponse comportementale aux informations faciales. Leur étude est d'ailleurs la première à utiliser l'IRMf pour scanner le cortex préfrontal du singe et guider les choix de l'emplacement de ses électrodes. Dans une autre étude combinant IRMf et enregistrement cellulaire, Freiwald et al. (2009) montrent dans TE (dans le middle face patch) des cellules sensibles au visage en entier et

des cellules sensibles à certains traits. Celles-ci ne présentent cependant une modulation d'amplitude que si le trait est « à la bonne place » d'un template global du visage à l'endroit.

2.4. L'imagerie cérébrale

2.4.1. Description méthodologique

La tomographie à positron (TEP) depuis 25 ans déjà et l'imagerie fonctionnelle par résonance magnétique (IRMf) depuis 20 ans ont permis néanmoins des avancées spectaculaires dans la compréhension de l'organisation anatomique de la reconnaissance des visages, quoiqu'étant toutes deux des méthodes indirectes de l'activité cérébrale. Brièvement, le principe physique de l'imagerie par résonance magnétique ou l'IRM est d'envoyer une combinaison d'ondes électromagnétiques inoffensive à haute fréquence à l'intérieur du cerveau et de déterminer la composition chimique et donc la nature des tissus biologiques en mesurant le signal réémis par certains atomes (comme l'hydrogène). L'IRMf permet de caractériser l'activité cérébrale en mesurant des paramètres vasculaires grâce à l'utilisation d'outils mathématiques spécifiques et précis d'analyse de signal permettant d'identifier des régions cérébrales particulièrement actives lors de la réalisation d'une tâche. Pendant la séance IRM, un individu sain ou atteint d'une lésion cérébrale va réaliser différents types de tâches, et son activité cérébrale sera mesurée. A titre d'exemples, on peut mesurer l'activité cérébrale lorsqu'on écoute un son, mémorise une information, lit un texte, reconnaît un visage, manipule des objets, etc. Son grand avantage sur la tomographie à positrons [outre l'amélioration des résolutions spatiales (jusqu'à des voxels d'un mm^3 pour la fMRI vs 25 mm^3 pour la TEP - un voxel étant un pixel volumétrique) et surtout temporelle (de 1.5 à 6 secondes vs 2 minutes) permettant des paradigmes plus souples] est bien sûr qu'elle ne nécessite pas l'injection d'un produit radioactif , la TEP reconstruisant l'image de l'activité cérébrale grâce aux émissions produites par les positrons issus de la désintégration de ce

produit[5]. La résolution spatiale de ces deux techniques est évidemment bien inférieure à la résolution spatiale de l'enregistrement cellulaire mais plutôt que de considérer cela comme un désavantage, il faut garder en mémoire que cela permet, de manière non invasive, d'enregistrer l'activité d'une population de cellules donnée directement sans devoir l'inférer à partir d'un seule cellule et que l'ensemble du cerveau peut être pris en compte rendant possible directement la comparaison et la corrélation des activités de différentes populations.

Avant d'aborder l'état actuel des connaissances sur le réseau visage et son historique, il nous parait important de souligner les grandes questions ou principes des études en IRMf.

2.4.1.1. The "Blood-Oxygenation-Level-Dependant effect" (BOLD effect)

Il est important de bien réaliser que les images d'activités que l'on obtient en IRMf sont une mesure très indirecte de l'activité neuronale. Ce que l'on mesure, c'est le changement dans les concentrations d'hémoglobine désoxygénée (en tenant compte du flux et du volume sanguin) qui est un corrélat physiologique de la consommation d'oxygène, elle-même un corrélat de l'activité neuronale entraînée par les processus sensitifs, moteurs ou cognitifs. Dans la plupart de nos chapitres expérimentaux, nous présenterons des tracés du changement dans le signal IRMf, soit la réponse hémodynamique. De manière générale, l'interprétation des signaux en imagerie repose sur le fait que plus une augmentation du signal apparaît, plus le neurone décharge et qu'un maintien du signal apparaît quand l'activité neuronale se maintient (Heeger et al., 2000). De plus, dans nos expériences, nous avons appliqué les règles classiques de l'IRMf postulant que la réponse hémodynamique est la même quelles que soient les régions. Le lien exact entre l'activité neuronale et la réponse Bold est cependant très loin d'être aussi simple et de nombreux papiers récents ont été

[5]Remarquons cependant que l'IRMf, contrairement à la TEP, est sensible aux artefacts de susceptibilité. La susceptibilité magnétique d'un tissu correspond à l'aimantation interne de ce tissu induite par un champ magnétique externe. A l'interface entre 2 régions (air-os / tissu) ayant des susceptibilités magnétiques différentes, il existe des distorsions du champ magnétique externe à l'origine d'une éventuelle perte de signal. Le lobe temporal antérieur est par exemple une région difficile à étudier en IRMf.

jusqu'à questionner l'existence d'une réponse Bold sans réponse neurale et la réelle localisation de l'activité neuronale (Sirotin et al., 2009 ; Devor et al., 2008) ou postuler que le signal Bold reflétait plus l'activité synaptique que le taux de décharge des neurones (Lauritzen, 2008). Il est certain que les modèles de couplage neurovasculaire choisis influencent l'interprétation des données de l'imagerie (Logothetis, 2008 ; Lauritzen et al., 2005) et que les études couplant l'enregistrement cellulaire et l'IRMf chez l'animal éveillé apporteront sans aucun doute des précieuses indications quant au réel couplage (Sirotin & Das, 2009). Finalement remarquons que la réponse Bold peut varier très fort d'une session IRMf à l'autre même chez un sujet identique avec un paradigme identique suivant l'état de fatigue ou la prise de café par exemple (Liu et al., 2004) rendant indispensable la normalisation des données et compliquant parfois le choix des seuils statistiques d'activation (voir partie expérimentale).

2.4.1.2. L'adaptation

Un paradigme abondamment utilisé en IRMf est le paradigme d'adaptation. L'idée de base est que lorsqu'on présente de manière répétée le même stimulus au sujet, la réponse à ce stimulus diminue. La réduction de la réponse hémodynamique lors de la présentation répétée de la même caractéristique d'un stimulus dans une région cérébrale donnée et l'augmentation/la reprise de l'activation quand on modifie à nouveau cette caractéristique du stimulus indique que cette région est sensible à cette caractéristique. Cette approche utilisée la première fois par Grill-Spector et al. (2001) a permis de montrer par exemple certaines régions sensibles à la forme, à l'illumination et le point de vue d'un objet ou de l'identité faciale mais l'indépendance à la taille et à la position. L'échelle temporelle de présentation et en particulier la durée de la phase d'adaptation (durée de présentation du même stimulus) influençant l'adaptation, il faut toutefois garder à l'esprit que l'absence d'un effet ne peut pas toujours être interprété comme une non sélectivité de la région à un stimulus donné et qu'en particulier un null-effet chez les patients nécessite qu'aucun des sujets contrôles ne présentent ce null effect pour pouvoir être interprété correctement. Remarquons que

comme la réponse Bold, le lien entre l'adaptation et l'activité neuronale est aussi forcément sujet à débat (voir Grill-Spector et al., 2006a pour une revue des modèles sous-jacents) et qu'ici aussi l'enregistrement cellulaire conjoint à l'IRMf permettrait de mieux en définir la cause neuronale. La répétition d'un stimulus peut par exemple donner des changements à une échelle temporelle donnée et pas à une autre, induire des changements dans la dynamique neuronale dans des régions plus tardives, altérer la modulation de la réponse neuronale etc. (Krekelberg et al., 2006).

2.4.1.3. Les types de paradigmes en IRMf

Dans le champ des visages, la plupart des études d'IRMf qui ont été réalisées ont porté sur la localisation et le rôle des régions visages en se basant sur des méthodes d'analyses univariées bien que les outils et les méthodes disponibles en neuro-imagerie soient beaucoup plus diversifiés.

Les études en IRMf peuvent se diviser en deux approches complémentaires : les études de localisation d'activité proprement dite (en analyse univariée OU multivariée) et les études de connectivité (qui sont par définition des analyses multivariées, c'est-à dire des analyses où chacun des voxels n'est plus considéré individuellement).

Les études de localisation se subdivisent en deux grands groupes :

- Les études par régions d'intérêt qui consistent à regarder des effets expérimentaux uniquement dans certaines régions définies parfois anatomiquement ou le plus souvent fonctionnellement par « *Localizer* ». Ces derniers sont des paradigmes expérimentaux relativement courts (d'une dizaine de minutes) servant à identifier fonctionnellement chez chacun des participants d'une étude des régions distinctes du cortex telles les aires du langage, de la reconnaissance des visages, du traitement spatial etc., qui peuvent varier en localisation anatomique à travers les sujets. L'espace fonctionnel est plus adéquat que l'espace anatomique pour y étudier par la suite des hypothèses fonctionnelles et certaines régions fonctionnellement définies peuvent être des composants de modèles

neuropsychologiques à tester. De plus, la limitation du nombre de voxels à prendre en compte (quelques centaines de voxels par rapport à une dizaine de milliers de voxels) augmente la puissance statistique. Bien sûr, il est impératif que la définition fonctionnelle soit la plus adéquate et complète possible pour permettre ensuite l'étude des régions trouvées au niveau de l'expérience proprement dite. Par exemple, quel est l'effet de la familiarité (expérience proprement dite mêlant visages inconnus et familiers) dans le réseau visage défini en comparant l'activité entre la présentation de visages et d'objets. Remarquons encore que dans des études de groupe, ce type de paradigme permet de définir les régions propres à chacun des sujets et d'y définir leur propre effet expérimental avant de les regrouper.

- Les études en « *Whole brain* » qui regardent les effets expérimentaux partout dans le volume cérébral enregistré. L'avantage est un aperçu complet des données, le désavantage étant une perte de puissance statistique et une plus grande difficulté à comparer certaines régions importantes dans les processus cognitifs étudiés.

Historiquement donc (Kanwischer et al., 1997) et habituellement, la grande majorité des études en IRMf dans le champ des visages, utilisent des analyses univariées et des localizers (voir Berman et al., 2010 pour une large revue). Friston et al. (2006) et Saxe et al. (2006) ont largement débattu de la pertinence de ce choix, Friston et al. (2006) soulignant essentiellement le risque de méconnaitre les interactions éventuelles entre la tâche expérimentale et le localizer. Lorsqu'on utilise un localizer il y a un risque de passer à côté de régions importantes si la localisation des régions activées par la tâche expérimentale diffère de celle du localizer. En revanche, Saxe et al. (2006) défendent l'utilisation de localizers pour leur rapidité, leur simplicité (un localizer imbriqué dans l'expérience selon un désign factoriel alourdit le processus expérimental et en diminue la puissance statistique) et leur définition globale du réseau. Sans rentrer en détail dans ce débat, nous pensons comme Saxe et al. (2006) qu'il est utile, lors de chaque expérimentation sur les visages, de

prévoir 10 minutes pour un localizer indépendant. Néanmoins, nous pensons que les deux analyses suivantes sont indispensables et complémentaires : regarder l'effet expérimental dans toutes les régions d'intérêt trouvées grâce au localizer mais également regarder en analyse « whole-brain » (conseillée par Friston et al., 2006) l'effet expérimental en ne se servant du localizer que pour la compréhension du rôle des régions trouvées en « whole-brain » et cela aussi bien au niveau du groupe que du sujet individuel.

Les études de connectivité entre les régions cérébrales se subdivisent également en deux grands groupes :

- Les études de connectivité fonctionnelle ne permettant pas de conclusions sur les directions des connexions et,
- les études de connectivité effective qui permettent elles, d'étudier la direction.

Chaque type d'études peut également être divisé en deux groupes :

- les méthodes dites *Data driven* classiques (méthodes plutôt exploratoires)
    - <u>en connectivité fonctionnelle :</u> par exemple les classificateurs [analyses en composants principaux (PCA) ou indépendants (ICA) ; Formisiano et al., 2004] qui peuvent être appliqués sans que des modèles de l'activité cérébrale soient disponibles. Ces méthodes, selon nous, ont surtout de l'intérêt lorsque l'on n'est pas certain d'avoir affaire à une réponse hémodynamique classique ou/et par exemple que l'on n'est pas certain de la durée d'un état cognitif particulier que l'on voudrait étudier, ce qui n'est pas vraiment le cas dans le champ des visages. Kriegeskorte et al. (2007) qui en défendent l'approche ont d'ailleurs eu bien des difficultés à montrer en IRMf haute résolution que la ''FFA'' présentait un pattern d'activation différent pour deux visages différents (les seuls stimuli de leur étude !) et était donc sensible à l'identité comme d'autres l'avaient prouvé plus facilement au moyen de paradigme

d'adaptation (Schiltz et al., 2006). Un autre exemple d'études de connectivité fonctionnelle : les études en resting-state commencent à abonder en neuro-imagerie et consistent à analyser les corrélations dans les oscillations du signal Bold pendant que le sujet est inactif dans le scanner. Zhang et al. (2009) dans le champ des visages montrent ainsi un réseau de régions visages préactivé comprenant le gyrus fusiforme postérieur ou moyen, le sillon temporal supérieur et le gyrus occipital moyen.

- en connectivité effective : essentiellement des méthodes autorégressives et linéaires comme celles basées sur les « Granger causality » (Roebroeck et al., 2005, 2009 ; voir notre chapitre expérimental 6) qui pour une région donnée indiquent la direction d'influence entre cette région et tous les autres voxels ou des méthodes développées sur l'analyse de cohérence (Sun et al., 2004).

- les méthodes dites *Hypothèse driven* qui se situent dans le cadre des statistiques bayésiennes (donc non exploratoire) : sur base de ce qu'on voit dans les données, on évalue quelle hypothèse est la plus probable parmi celles que l'on a posées au départ ; sur base de certains symptômes, pour donner un exemple médical : fièvre, maux de tête et de ventre, on compare la probabilité que ce soit une grippe par rapport à une indigestion. Ces méthodes sont donc fortement dépendantes des a priori des auteurs.

  - en connectivité fonctionnelle : certaines études en resting-state utilisent des résultats DTI comme a priori par exemple (Teipel et al., 2010). Tous les classificateurs peuvent être aussi contraints en fonction d'hypothèses préalables (Lu et al., 2005).

  - en connectivité effective : essentiellement les études en « dynamic causal modelling »[6] (DCM ; Friston et al., 2000) qui testent des modèles hypothétiques spécifiques aux tâches et stimuli. On y compare des modèles décrits par un système

[6] Une autre méthode, le « structural equation modelling » (SEM) est parfois aussi utilisée mais est moins appropriée que le DCM pour l'IRMf car le lien entre la réponse neuronale et la réponse hémodynamique n'y est pas directement modélisée.

non linéaire : input-state-output où les états sont des régions d'intérêt et où on regarde trois paramètres : l'influence des inputs (design expérimental, attention) sur ces états, la connectivité intrinsèque entre les états et finalement l'influence des inputs sur la modulation de la connectivité intrinsèque (termes bilinéaires qui sont fonction des états et des inputs). En fait, on a un couplage de base entre les régions et on regarde l'influence sur ce couplage du design expérimental et de facteurs généraux (comme l'attention, la fatigue etc.) qui sont vus comme des perturbations des états et de la dynamique neuronale à travers le système. Le gros problème de ce type d'approche qui malheureusement est la plus courante parmi les rares études de connectivité effective dans le champ des visages est le nombre trop élevé de paramètres libres dans le modèle mathématique sous-jacent et donc l'obligation de le restreindre pour éviter des calculs ingérables. Le nombre de régions et le nombre de connexions introduits dans le modèle sont réduits et laissés au bon vouloir du chercheur…. Par exemple, Fairhall & Ishaï (2007) dans une étude cherchant à définir les sens d'influence dans différentes régions visages ne rentrent dans leur modèle qu'un nombre limité de régions (absence des régions striées et extra-striées) et, de plus, ne définissent pas correctement ses régions. Les résultas des études DCM (voir la description du réseau au point 2.4.2.) dans le champ des visages sont donc à prendre avec beaucoup de réserve.

2.4.1.4. Les études anatomiques : volumétrie (ou épaisseur corticale) et DTI

Les études volumétriques ou d'épaisseur corticale

Ces méthodes mesurant avec le plus de précision possible la substance grise sont assez peu utilisées dans le champ des visages. Elles sont en général utilisées pour étudier la plasticité cérébrale dans le cadre d'apprentissage [par exemple Mechelli et al. (2004) qui montrent un accroissement dans V5 et dans le sillon intrapariétal gauche lors de l'apprentissage de la jonglerie

chez des adultes] ou dans le cadre d'analyse de patients afin de corréler avec précision les lésions et de les mettre en rapport avec leurs troubles cognitifs [par exemple, Geuze et al. (2008) qui montrent un cortex préfrontal amoindri chez les soldats victimes de stress post-traumatique]. Les seules et très rares études où apparaissent des volumétries sont celles qui étudient la corrélation entre le nombre de voxels activés de la ''FFA'' par exemple et des tests comportementaux où elles interviennent dans la normalisation de l'activité de la région par rapport à son volume [voir par exemple, Goloraï et al. (2007) dans une étude développementale de la ''FFA'']. Vu le niveau d'expertise déjà élevé de la reconnaissance de visages et les rares cas de prosopagnosie acquise, les études uniquement volumétriques ne sont pas les plus pertinentes dans un premier temps.

Quoique pas très nombreuses dans le champ des visages, les études en DTI sont par contre idéales pour détecter d'éventuelles lésions dans la matière blanche chez certains patients prosopagnosiques sans lésions apparentes (Thomas et al., 2008).

Les études DTI

La technique de DTI permet de fournir des informations sur la matière blanche grâce aux propriétés intrinsèques des molécules d'eau. En particulier la tractographie à partir de données DTI permet de révéler la trajectoire de ces fibres blanches. Dans le tissu cérébral, les molécules d'eau ne diffusent pas dans toutes les directions mais sont contraintes par leur environnement (notamment les fibres axonales). Leur diffusion correspond à une diffusion anisotropique caractérisée par deux mesures, une diffusivité moyenne (Mean Diffusivity, MD) indépendante de la direction et l'anisotropie (Fractional Anisotropy, FA) qui estime la directionnalité de cette diffusion c'est-à-dire si elle a une orientation préférentielle (Mori & Zhang, 2006). Au moment de l'acquisition, des gradients de champs de différentes directions sont appliqués et plus ces directions sont variées, plus précises seront les deux mesures dans chacun des voxels. Selon notre expérience, un minimum de 30 directions est requis dès lors que l'on veut tracer le trajet des fibres (soit faire une tractographie). Les algorithmes de tracking retracent ensuite le chemin des fibres à travers les voxels grâce aux

valeurs de FA : soit de manière déterministe c'est-à-dire en considérant essentiellement une seule direction possible par voxel, soit probabiliste en propageant les fibres le long de directions (non fixées) suivant une loi de probabilité. Ces dernières méthodes tentent d'établir une probabilité d'existence d'un faisceau reliant deux régions données. Elles sont plus efficaces dans les voxels où il y a croisement compliqué de fibres ou un bruit exagéré car la FA y chute fortement et le tracking déterministe s'y stoppe fréquemment. Cependant ces méthodes probabilistes sont très lentes (plus de 24 heures pour un patient) et sont peut-être plus utiles quand le tracking s'intéresse avant tout aux courtes fibres en U plutôt qu'aux longs faisceaux connectant des gyri assez éloignés.

Si à notre connaissance, aucune étude ne détaille avec précision le réseau de fibres blanches du réseau visages, combinée avec des études en connectivité effective, cela permettrait pourtant d'avoir des indications précieuses sur la dynamique de la reconnaissance des visages (voir notre chapitre expérimental 7).

2.4.1.5. Les types de design en imagerie fonctionnelle

Comme nous venons de le dire, la plus grande proportion d'études en IRMf sont des analyses univariées reliant dans chaque voxel l'activité au design expérimental. Ceux-ci sont de deux types : en « block » ou en « event-related » design[7]. Le premier consiste en une présentation alternative d'une ou plusieurs conditions d'une dizaine de secondes. Le second consiste en une présentation randomisée d'évènements uniques soit lentement (avec un intervalle assez long entre chaque évènement pour que la réponse hémodynamique suite à la stimulation retombe à son niveau de base), soit rapidement ce qui entraîne la nécessité de démêler les réponses hémodynamiques. Le « block design » est évidement non adéquat si l'on veut trier les évènements en fonction de la réponse du sujet mais il présente un avantage au niveau de la détection des régions. Il est plus efficace en terme de résolution spatiale. L' « event-related design » est quant à lui plus efficace pour

[7] Des designs mixtes peuvent être aussi envisagés et sont constitués d'événements discrets mais qui interviennent dans le contexte d'autres facteurs expérimentaux qui eux varient suivant une structure en « blocks design » (Huettel et al., 2003)

suivre l'évolution de l'activité au cours du temps et donc en terme de résolution temporelle. Dans le champ des visages, classiquement, les localizers sont donc en « block design » pour détecter le réseau visage et l'expérience proprement dite en « event-related design ».

2.4.1.6. Les études de groupe et de cas unique

Avant d'aborder le réseau visage proprement dit, il est bon de souligner qu'une particularité de ce travail est qu'à l'image des méthodes de corrélations anatomo-cliniques, il montre l'avantage de l'IRMf dans l'étude de cas unique pour la compréhension de la neuro-anatomie fonctionnelle de la reconnaissance des visages. L'étude de cas unique peut sembler surprenante en imagerie cérébrale mais on le verra dans notre partie expérimentale, elle est méthodologiquement possible sous certaines conditions et est en fait une source d'inspiration et de mise en relief du fonctionnement chez l'individu sain.

2.4.2. Le réseau neuronal impliqué dans la perception des visages

Si la plupart des traitements sur les visages sont rapides, efficaces et ne demandent pas d'apprentissage, il ne faut pas oublier que le visage est un stimulus visuel complexe en 3D fait de traits externes (cheveux, forme globale du visage…) et internes (yeux, nez, bouche…) qui varient localement en forme et en propriétés de surface (couleur, texture de la peau…). Ces traits forment une structure globale qui permet de les définir comme formant un visage et de guider l'identification quelles que soient les conditions externes (d'éclairage, de point de vue, de distance, de coiffures …) ou internes (d'expressions, d'âge). Un réseau visage efficace doit être capable d'extraire une représentation individuelle de chaque visage rencontré.

2.4.2.1. La ''Fusiform Face Area'' (''FFA'')

Les premières études de la neuro-anatomie fonctionnelle des visages ont commencé avec Sergent et al. (1992). Le champ était relativement libre puisque à ses débuts, les premières études en imagerie cérébrale (en TEP) se basèrent sur la théorie et en particulier sur les modèles cognitifs de

l'époque (modèle de Bruce & Young, 1986) issus des études comportementales classiques. Très ambitieux et brillants, ces travaux fouillés souffraient malheureusement du problème de la nouveauté de la démarche et des limites techniques. S'opposant à cette philosophie enthousiaste, les études de Puce et al. (1995), Kanwisher et al. (1997) et Mc Carthy et al. (1997) choisirent une approche beaucoup plus simple se dirigeant plutôt de l'expérimentation et de l'exploratoire (non sans certains problèmes méthodologiques…) vers la théorie avec bien entendu la fameuse ''FFA'' de Kanwisher et al. (1997). L'impact de ce célébrissime papier dans la littérature visage (cité et recité dans toutes les études d'imagerie mettant en scène des visages) marque non seulement les esprits par le baptême de la région du gyrus fusiforme répondant plus aux visages qu'aux objets mais aussi parce que pour la première fois, une étude est divisée en deux parties claires : une dédiée à la définition et à la localisation d'une région d'intérêt, l'autre dédiée au testing d'autres stimuli ou tâches dans cette région. La partie localizer est très simple et indépendante de la tâche. Une quinzaine de sujets sont amenés à regarder passivement une alternance de blocs de 30 secondes de visages et d'objets. L'analyse est faite à seuil extrêmement sévère et consiste juste à regarder quels sont les voxels activés de manière consistante à travers les sujets. A $p < 0.0001$, une et une seule région apparaît selon Kanwisher et al. (1997): la ''FFA'' (Figure 3) soit une 100e de voxels dans le gyrus fusiforme moyen droit à 40 -55 -10 (coordonnées Talairach) chez 12 sujets[8].

[8] Kanwisher et al. (1997), étrangement partiaux, ne reprennent que les 5 meilleurs sujets pour tester leurs effets expérimentaux dans leur ''FFA''….

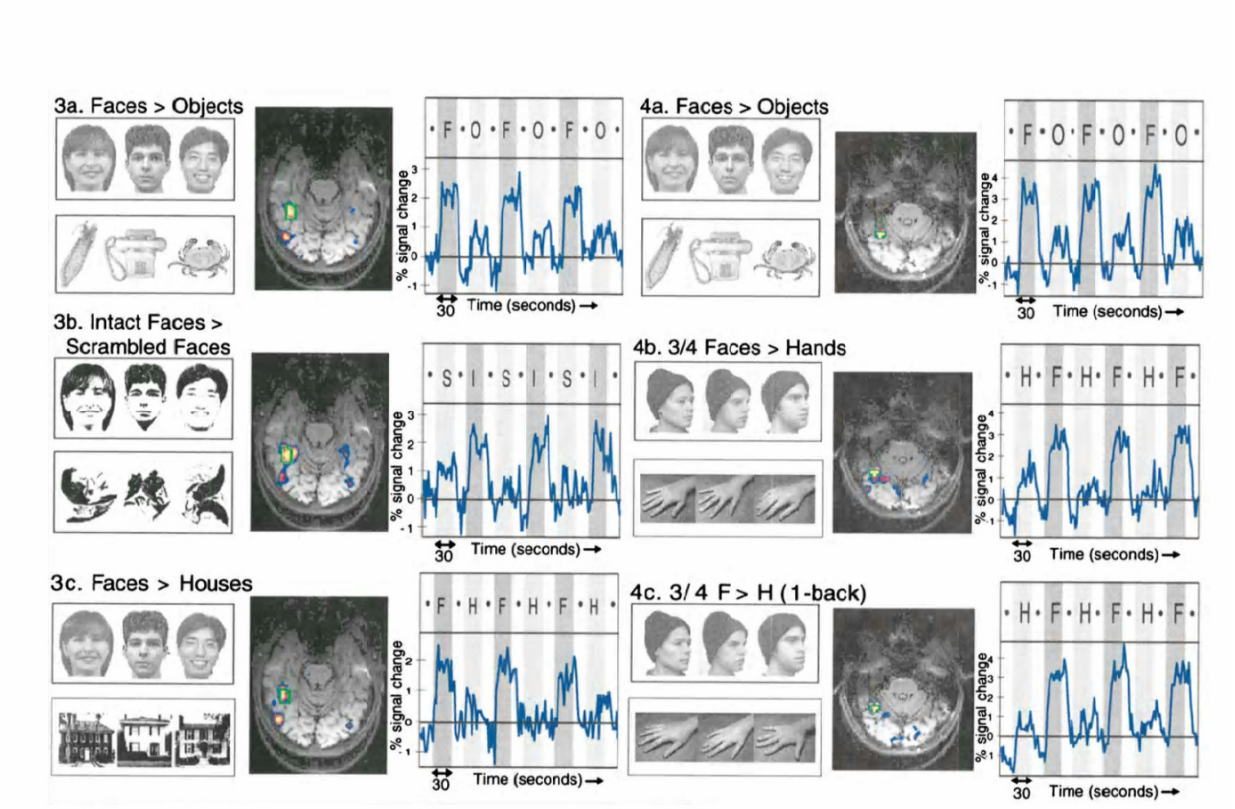


Figure 3. (D'après Kanwisher et al., 1997.) Définition de la ''FFA'' (entourée en vert). Remarquons qu'il y a d'autres zones activées chez chacun des deux sujets présentés.

Cependant, quand on regarde plus en détails les cartes individuelles des sujets, il apparaît d'autres régions. Mais, moins fortement consistante au niveau de la localisation (voir notre partie expériementale), Kanwischer et al. (1997) en font l'impasse pour soutenir une position modulaire forte reconnue par la suite comme erronée de par l'existence d'un réseau cortical beaucoup plus large et marquant une préférence (pas une exclusivité) pour les visages. Par exemple, chez 8 sujets on trouve une activation du STS, chez 7 une activation dans le fusiforme gauche et chez 4 une activation dans le gyrus occipital inférieur, régions reconnues plus tard comme faisant partie du réseau visage (Haxby et al., 2000). De plus, à cette époque, une trentaine de papiers TEP ou IRMf existaient déjà dans le champ des visages[9] et une dizaine montraient déjà une activation dans le

[9] Même si certains n'utilisaient les visages que comme outil pour comprendre les mécanismes de la mémoire (Dolan et al, 1996).

gyrus fusiforme mais avec des designs plus compliqués, sans tenir de position théorique forte ou sans faire un choix très restrictif dans le choix de la ou des régions à présenter.

Sergent et al. (1992) sont en réalité les premiers à avoir montré que la présentation de visages par rapport à des objets (vivants ou non) activait des régions occipito-temporales essentiellement à droites (dont le gyrus lingual, occipital inférieur et fusiforme). Leur première étude en TEP était cependant très, trop, complète car combinant différentes conditions (objets, visages, sinusoïdes) à différentes tâches (orientation de sinusoïdes, catégorisation de genre, identification, catégorisation d'objets, vivants ou non) et ne permettait pas une isolation parfaite d'un seul de ces facteurs. Dans une logique exploratoire, ils reprennent toutes les régions activées mais si l'on regarde attentivement, ils trouvent quand ils comparent les visages aux objets et aux sinusoïdes une région en 37 -55 -11 (coordonnées Talairach) sensible aux visages, soit la même région que Kanwisher et al. (1997). Surtout, Sergent est de manière générale une source d'inspiration pour les chercheurs dans le champ des visages car contrairement à Kanwisher qui a plutôt eu tendance à le restreindre, elle l'a enrichi de ses intuitions et expérimentations. Par exemple, Sergent a l'idée dès 1986 (Sergent, 1986) d'une microgenèse de la perception du visage allant d'un traitement grossier et global vers un réaffinement de la représentation du visage, s'opposant donc à une vision uniquement hiérarchique de la perception d'un visage. Elle soulève aussi (Sergent et al., 1992) l'existence d'une certaine dissociation entre le traitement des émotions et celui de l'identification et dans ses travaux par TEP sur la prosopagnosie, elle initie les études de cas uniques en imagerie (Sergent et al., 1992) et attire l'attention sur l'importance des phénomènes top-down.

Haxby et al. (1994) dans une étude TEP et Clark et al. (1997) en IRMf montrent aussi dans un design (Figure 4) comparant une condition de matching (choix entre deux visages extraits du test de Benton ; Benton & Van Allen, 1972) à une tache sensorimotrice (le sujet répond alternativement à droite et à gauche) une région activée dans le gyrus fusiforme. Cependant, le seuil non sévère

choisi par les auteurs entraîne des activités nombreuses essentiellement dans le cortex occipito-temporal qui seront d'ailleurs à la base de la définition par Haxby et al. (2000) d'un réseau visage complexe en réponse à Kanwisher et al. (1997).

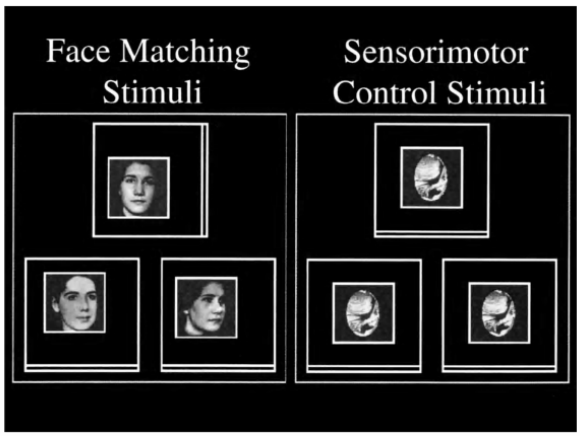


Figure 4. (D'après Haxby et al., 1994). Design utilisé dans son expérience en TEP : tâche de matching pour les visages et simple pression du boitier réponse à droite et à gauche dans la tache sensorimotrice.

De même, d'autres auteurs, Dolan et al. (1996), Courtney et al. (1996) et McCarthy et al. (1997) dans des études TEP ou IRMf destinées à investiguer les zones activées dans des tâches de mémoire et utilisant des stimuli faciaux trouvent tous le gyrus fusiforme.

Finalement citons encore Puce et al. (1996) qui comparant des visages, des chaînes de caractères et des textures égalisés en luminance et en contraste trouvent à droite deux régions activées : la "FFA" en 30 -54 -20 (coordonnées Talairach) mais aussi une autre région activée entre le gyrus fusiforme postérieur et le gyrus occipital inférieur en 36 -66 -17 (coordonnées Talairach) définie plus tard par Gauthier et al. (2000a) comme l' ''Occipital Face Area'' ou "OFA".

2.4.2.2. Les autres régions

Après 1997, les plus de 1000 études IRMf se sont attachées soit à définir de manière la plus précise possible le réseau visage au moyen de localizers soit se sont essayées à définir les rôles précis de ces régions.

Au cours du temps, un réseau plus vaste de régions répondant aux visages a donc été mis à jour. En 1998, Puce et al. montrent l'activation de la partie postérieure du sillon temporal supérieur (STS) au mouvement de la bouche et à la direction du regard. Comme on l'a dit, en 2000(a), Gauthier et al. définissent également une région du gyrus occipital inférieur (l' ''OFA'') activée préférentiellement pour les visages de la même manière que la ''FFA''. Cette aire, on le verra dans notre partie expérimentale, est cependant très loin d'être aussi stable et unique que la ''FFA'' et est plus sensible aux paradigmes expérimentaux (tâche ou stimulus). Les 3 aires, ''FFA'', ''OFA'' et STS seraient activées bilatéralement mais avec une dominance droite plus marquée et sont définies par Haxby et al. (2000) comme le cœur du réseau de traitement perceptif des visages (Figure 5 et 6). Les représentations des visages qui y seraient élaborées serviraient d'input aux aires plus impliquées dans le traitement émotionnel (les aires limbiques), sémantique (pôle temporal antérieur), de la parole (cortex auditif) ou de l'attention spatiale (sillon intra-pariétal). Parmi ces régions, certaines sont d'ailleurs assez systématiquement rapportées comme sensibles aux visages : les amygdales (Tovée et al., 1998) ou beaucoup plus récemment le pôle temporal antérieur[10] [Nestor et al., 2008 (50 -9 -28 -coordonnées Talairach) ; Kriegeskorte et al., 2007 (38 -2 -38 -coordonnées Talairach) ; Tsao et al., 2008 ; Pinsk et al., 2009 ; Rajimehr et al., 2009 encore que les régions décrites par ces trois derniers groupes d'auteurs semblent moins antérieures et moins latérales] et feraient donc partie du système « étendu ». L'ensemble est très bien décrit par l'expression du papier de Tovée (1998) : la ''FFA'' « with a little help from his friends » permet la reconnaissance des visages. Rajoutons finalement que Tsao et al. (2008) et Pinsk et al. (2009) trouvent comme nous des activités dans le cortex frontal (voir notre partie expérimentale) en rapport avec le contrôle comportemental vis-à-vis des informations faciales. Schiltz et al. (2010) trouvent que les activités dans ces régions sont corrélées avec la difficulté d'une tâche traitant des visages. On le verra cependant dans notre partie expérimentale, le fait de définir fonctionnellement les régions visages

[10] Le pole temporal antérieur est une région dont le rôle dans le traitement des visages a été (et est encore) sans doute négligé de par sa situation anatomique. C'est en effet une des régions où il est le plus difficile d'obtenir un signal car les artéfacts de susceptibilité y sont très importants.

entraîne des variations individuelles en terme de taille, de nombre et de localisation, variations individuelles pouvant elles-mêmes être plus ou moins importantes selon le type de région (voir aussi Pinsk et al., 2009). Weiner et al. (2010) dans un papier tout récent soulignent comme nous l'importance de tenir compte des variations individuelles et de développer une méthode consistante de localisation des régions visages. Mais contrairement à nous et dû au choix de ses stimuli qui ne permet pas un contrôle des propriétés de bas-niveau, Weiner et al. (2010) ne trouvent pas une (ou des) ''OFA''(s) de haut niveau dans la partie postérieure du cortex occipito-temporal (voir notre partie expérimentale, chapitre 1).

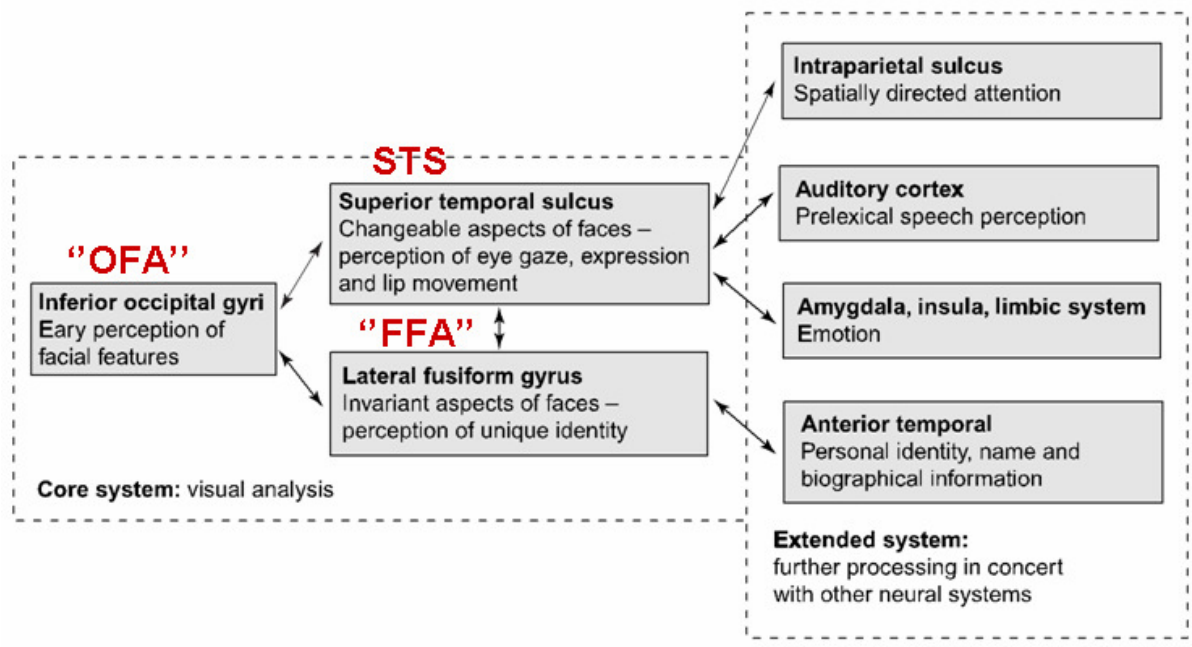


Figure 5. (D'après Haxby et al., 2000). Modèle hiérarchique de la reconnaissance des visages. Aires activées de façon préférentielle lors du traitement perceptif des visages. Ce sont des aires définies fonctionnellement non rétinotopiques et que l'on ne peut identifier a priori sur des images anatomiques. Nos chapitres expérimentaux montreront la grande variabilité individuelle de ces régions (en particulier des ''OFA''). Ces régions ne sont pas continues mais présentent des démarcations réelles (Spiridon et al., 2006).

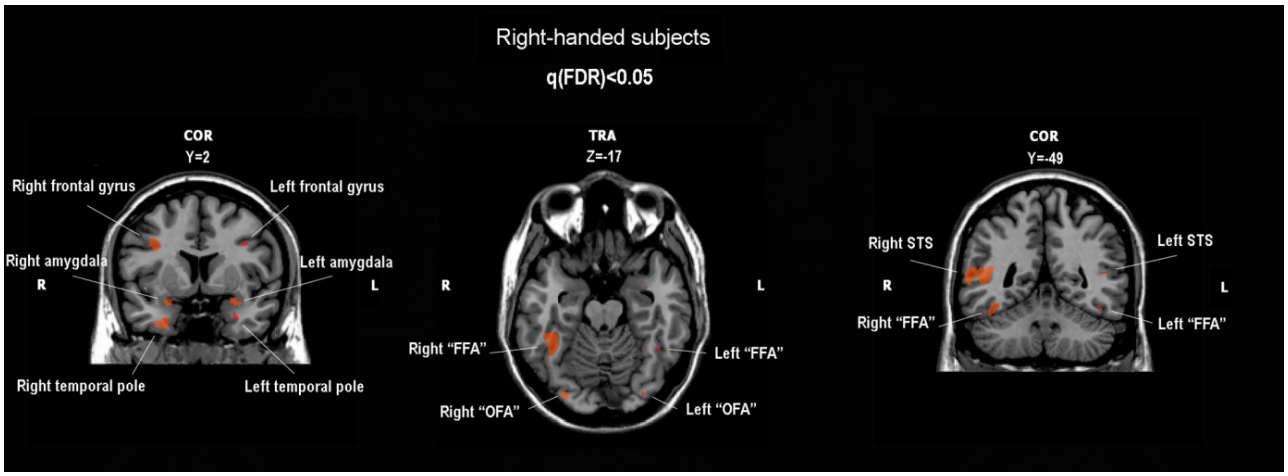


Figure 6. Régions activées chez 40 sujets droitiers lors de la comparaison de visages à des objets en conjonction avec la comparaison de visages à des visages brouillés. (Dricot et al., submitted, chapitre 1 de notre partie expérimentale).

2.4.2.3. Le rôle des régions

La modularité

C'est évidemment la ''FFA'' qui a été la plus étudiée d'une part suite à son importante stabilité à travers les expériences (Berman et al., 2010) et d'autre part par sa « participation » au débat de la modularité de la reconnaissance des visages.

Certains auteurs actuels collaborateurs de Kanwisher (Kleinschmidt et al., 2006 ; Yovel et al., 2006, Spiridon et al., 2002) défendent d'ailleurs toujours cette vision modulaire d'un système qui ne traiterait que la catégorie faciale s'opposant à d'autres auteurs comme Gauthier et al. (2000b) qui défendent plutôt l'existence d'un réseau non pas spécifique à une catégorie mais à un traitement particulier de stimuli lié à l'expertise ou Haxby et al. (2000) et plus tard Weiner et al. (2010) qui penchent vers un réseau de reconnaissance d'objets et de visages distribué et commun en partie soit un codage distribué des catégories d'objets visuels. Selon eux, des régions qui ne répondraient pas préférentiellement à une catégorie d'objet pourraient cependant jouer un rôle dans l'identification d'un stimulus de cette catégorie (pour les objets dans la ''FFA'' et pour les visages dans les régions objets). En tous les cas, on le verra dans notre partie expérimentale, à l'échelle de l'aire cérébrale il n'y a vraisemblablement pas et sûrement pas au niveau de la 'FFA'' une aire ne répondant qu'aux

stimuli faciaux. Par contre, conformément aux études chez le singe (Tsao et al., 2006) ou des études en haute résolution chez l'homme (Grill-Spector et al., 2006b), il est possible que dans une aire cérébrale donnée soit entremêlés des sous-populations de taille plus grande qu'une colonne corticale répondant de manière sélective soit aux visages (sous-populations les plus nombreuses) soit aux objets (sous-populations les moins nombreuses) conformément à Haxby et al. (2000) et leur codage distribué. Weiner et al. (2010) développent d'ailleurs l'idée d'un modèle hybride entre modularité et codage distribué. Ces mélanges de sous-populations empêchent par contre de se prononcer définitivement sur la possibilité d'une région visage sensible surtout à l'expertise visuelle très grande et naturelle pour les visages plutôt que pour les stimuli per se (Gauthier et al., 2000b) car les effets d'expertise visuelle dans la ''FFA'' sont assez faibles (Rhodes et al., 2004) et instables (OpdeBeeck et al., 2008) et pourraient reposer sur les sous-populations d'objets de la ''FFA''. Il faudra attendre des études plus complètes en IRMf de hautes résolutions pour clarifier la question et l'étendre au STS et à l' ''OFA''. Remarquons finalement que si peu d'études IRMf ont été faites chez l'enfant, Golorai et al. (2007) ont cependant montré une corrélation entre l'accroissement en volume de la ''FFA'' au cours du développement et les performances dans des tâches de reconnaissances de visages. La taille de la ''FFA'' chez l'adulte n'a, par contre, pas de corrélation avec les performances (Golorai et al., 2007).

L'identité dans le système central

Si à notre connaissance nous sommes les premiers à avoir montrer chez un patient grâce à des données IRMf (voir notre partie expérimentale, chapitre 3 et 4) une dissociation entre la dynamique et les substrats neuronaux de la détection de visages par rapport à l'identification, la sensibilité à l'identité des visages a elle été souvent étudiée. A l'aide des paradigmes d'adaptations décrits au point 2.4.1.2. ou à des classificateurs (Kriegeskorte et al., 2008), elle a été montrée dans la ''FFA'' et l' ''OFA'' (Schiltz et al., 2006 ; Gauthier et al., 2000a ; Andrews et al., 2004 ; Fox et al., 2009) qui coderaient donc les aspects stables et invariants des visages et l'activité de ces régions

montrerait d'ailleurs une corrélation avec les performances [e.g. (Eger et al., 2004b; Gauthier et al., 2000b; Gilaie-Dotan & Malach, 2007; Grill-Spector et al., 2004; Loffler et al., 2005; Rotshtein et al., 2005; Schiltz & Rossion, 2006 et 2010)]. Ces deux régions seraient impliquées dans l'individuation. Bien sûr, les effets d'adaptation peuvent être différents d'une région à l'autre et rien ne dit que les deux régions soient sensibles au même niveau (haut ou bas) de l'information. Rotshtein et al. (2005) ont par exemple montré à l'aide de morphing que la récupération après l'adaptation n'est présente dans la ''FFA'' que lorsqu'il y perception d'un changement d'identité faciale contrairement à l' ''OFA'' sensible aux changements physiques du morphing même s'il ne « traverse pas la frontière » d'une identité nouvelle. De même Eger et al. (2004) ont montré que la ''FFA'' s'adaptait invariablement à la fréquence spatiale (de hautes vers basses ou l'inverse) alors que l' ''OFA'' était sensible au changement de fréquence. L'étude de Rotshtein et al. (2005) n'a cependant jamais été répliquée dans notre laboratoire et une autre étude montre l'inverse avec une ''FFA'' sensible à des changements sans qu'il y ait une perception d'un changement d'identité (Gilaï-Dotan & Malach, 2007). Quant à l'étude de Eger et al. (2004), ils utilisent une comparaison visages-visages brouillés pour localizer les régions visages et l' ''OFA''qu'ils définissent peut donc être une région ne répondant pas préférentiellement aux visages. Cette région pourrait être le LOC (Lateral Occipital Complex, Malach et al., 1995) qui montre une réponse plus élevée pour les objets que pour les objets brouillés mais sans plus d'activité pour une catégorie que pour l'autre et qui présente une adaptation aux changements physiques (Avidan et al., 2002; Grill-Spector et al., 1999; Sayres & Grill-Spector, 2006).

Le STS a quant à lui et conformément aux études animales été reconnu comme activé préférentiellement par l'aspect dynamique des visages comme l'expression (Winston et al., 2004 ; Fox et al., 2009) et le mouvement des yeux (Hoffman & Haxby, 2000 ; Puce et al., 1998) plutôt qu'à l'identité.

Le codage des représentations faciales

Une autre hypothèse comportementale élaborée par Rhodes et al. (1987) puis Valentine (1991) a également été testée mais malheureusement de manière inappropriée en IRMf. Selon Rhodes et al. (1987), le codage des visages s'effectue dans un espace multidimensionnel dont le centre, la norme, serait une sorte de moyenne de tous les visages que l'on a rencontrés (avec un poids plus grand pour les visages habituels) et les autres visages se coderaient par rapport à cette norme. Loffler et al. (2005) semblent le montrer dans une étude où les visages proches de cette norme sont ceux qui activent le moins la ''FFA'' et où, plus on présente des visages éloignés de cette norme, plus la ''FFA'' est active. En fait, c'est une simple erreur expérimentale et de design qui provoque ce résultat car en fait, c'est à un phénomène d'adaptation que l'on a affaire comme le montre d'ailleurs le papier déjà cité plus haut de Gilaï-Dotan & Malach (2007). Si la méthode utilisée ne permet pas de valider la théorie de Rhodes et al. (1987) : les visages sont codés par leur déviation par rapport à la norme), elle ne permet pas non plus de l'invalider. Le débat reste ouvert.

En fait, une condition avec des visages très différents les uns des autres entraîne plus de récupération après l'adaptation qu'une condition avec des visages qui sont plus semblables les uns aux autres. L'utilisation de l'effet d'inversion (le fait que présenter un visage à l'envers perturbe sa reconnaissance contrairement aux autres objets, Yin et al., 1969) en est un autre exemple (Mazard et al., 2006 et Yovel et al., 2005). Les visages présentés à l'envers quoique différents sont perçus comme plus semblables que des visages différents présentés à l'endroit, la ''FFA'' présentant moins d'activité dans le second cas. Dans le cas des mêmes visages, la différence se marque peu même si un visage à l'endroit seul active plus la ''FFA'' qu'un visage à l'envers, ce dernier activant la ''FFA'' au même titre que des traits de visages isolés l'activent (Harris & Aguirre, 2008; Liu et al., 2009; Yovel & Kanwisher, 2004). Cependant, ces expériences ne donnent pas directement des informations sur le codage et sur la réalité du pattern d'activation représentant des visages.

D'autres études en imagerie (Schiltz et al., 2010) ont par ailleurs permis d'étayer l'hypothèse d'un codage holistique principalement dans la ''FFA'' grâce à un autre effet comportemental : l'effet composite. Celui-ci, on l'a vu, décrit le fait que la reconnaissance de la partie supérieure d'un visage est plus altérée lorsque la moitié inférieure d'un autre visage est alignée avec elle plutôt que décalée (Young et al., 1987). Cela requiert la perception simultanée de différents traits du visage [ou quasi simultanée, Anaki et al. (2007) et Singer & Sheinberg (2006) ont montré que l'effet se maintient dans un intervalle de +/- 200 ms avant la présentation de la partie inférieure]. Schiltz et al. (2010) démontrent dans leur étude que cette perception holistique est présente dans la ''FFA'' ce qui va d'ailleurs de pair avec le fait qu'on y trouve des neurones à champ récepteur large probablement sensible au visage en entier comme chez le primate non humain (Desimone et al., 1984). La perception d'un visage et son identification nécessitent à la fois le traitement du visage en entier et des détails permettant cette identification. Toute perturbation de cette capacité à percevoir plusieurs éléments en même temps entraînerait une chute de performances. Cette étude montre justement que lorsqu'on demande un traitement sur une partie du visage, les neurones de la ''FFA'' ne peuvent faire autrement que d'être influencés par les autres parties du visage au moins si la présentation du visage est habituelle et non inversée par exemple (Schiltz et al., 2006 ; Rossion, 2008). D'autres études s'attachant aux relations spatiales et distances entre traits du visages aboutissent d'ailleurs aux mêmes conclusions (Goffaux, et al., 2009; Rhodes et al., 2009 ; Rotshtein et al., 2007). En utilisant des stimuli jouant sur les distances entre les traits, ils soulignent l'impact dans la ''FFA'' de ces variations. Goffaux et al. (2009) précisent de plus que les distances verticales entre les traits sont plus affectées par l'inversion que les horizontales dans la « FFA » droite que partout ailleurs. Rotshtein et al. (2007) et Rhodes et al. (2009) quant à elles rapportent des effets similaires dans le gyrus occipital inférieur mais pas dans le STS.

En ce qui concerne la familiarité proprement dite, Gobbini & Haxby dans leur revue du sujet (2007) soulignent l'existence de connexions étroites entre la perception, le réseau de connaissance

sur la personne et l'aspect émotionnel. Les résultats controversés entre les études sur l'impact de la familiarité dans la voie ventrale seraient dus selon eux aux différents feedbacks des réseaux émotionnels et communément rapportés comme activés (par exemple la jonction pariéto-temporale et le cortex para-cingulaire) lorsque nous réalisons par exemple des processus qui nous aident à identifier l'état mental de l'autre personne ou à raisonner sur les états émotionnels et cognitifs de notre entourage et cela quelle que soit la tâche spécifique. Ces régions moduleraient l'activité dans les régions visages classiques suivant la tâche (indépendante de la familiarité ou reconnaissance active) et les stimuli (visages célèbres, familiers, émotionnellement proches…) expliquant pourquoi certains trouvent moins d'activité pour les visages célèbres qu'inconnus dans la ''FFA'' (Gobbini et al., 2004) ou familiers qu'inconnus (Rossion et al., 2001) et d'autres plus d'activités pour les familiers (Henson et al., 2000). La sensibilité aux points de vue d'un visage dépendrait de plus de la familiarité de ce visage : au plus le visage est familier, au plus la ''FFA'' s'adapterait aux différentes vues du visage (Eger et al., 2005 ; Ewbank et al., 2008) encore que ce résultat soit aussi controversé (Pourtois et al., 2004). Il est vrai que cet effet a été testé avec des visages célèbres et en ce qui concerne la dernière étude les images choisies pour les célébrités sont des images très stéréotypées et quasi iconiques[11]. Par contre, au niveau de régions plus antérieures du lobe temporal, on observe généralement des augmentations d'activité consistantes dans la littérature (Leveroni et al., 2000 ; Gorno-Tempini et al., 1998) en réponse à des visages familiers. La familiarité jouerait aussi sur l'usage d'un autre aspect important des visages dans leur traitement : l'information « de surface » soit sa couleur et sa texture. Vuong et al. (2005) montrent que l'on se baserait plus sur cette information lorsque l'on traite des visages familiers. Cependant, de manière générale (Jiang et al., 2009), dans les régions visages droites, les informations de structure et de forme joueraient plus dans la reconnaissance des visages que les informations de surface ; ce qui

[11] Les photos choisies sont en effet elles-mêmes célèbres et connues.

serait consistant avec l'importance de l'effet holistique à droite. A gauche, les deux seraient traités de manière plus équilibrée (Jiang et al., 2009).

Finalement, notons encore que si la "FFA" est, on vient de le voir, sensible à la perception holistique d'un individu et qu'elle participe au codage de l'identité, elle peut très bien participer aussi à une détection holistique d'un visage : des auteurs ont par exemple montré que la ''FFA'' était sensible à une structure générale d'un visage (Liu et al., 2009 ; Caldara & Seghier, 2009 ; Hasson et al., 2001 ; voir aussi notre partie expérimentale) voire à une structure qui en partagerait les caractéristiques de symétrie et d'organisation (Caldara et al., 2006). Cette structure générale d'un visage détectable rapidement serait déjà possible avec les basses fréquences spatiales présentes dans le stimuli visage et donc à une échelle relativement grossière (Goffaux et al., 2006). La vision humaine décompose l'input rétinien en deux types d'information : l'orientation et les fréquences spatiales. Goffaux et al. (2010) dans une étude cherchant à montrer comment ces informations sont intégrées, utilisent deux types de stimuli (visages et visages brouillés) à différentes fréquences spatiales (dont des basses et des hautes, Figure 7) avec différentes durées de présentation (70, 150, 300 ms). Ils trouvent dans la ''FFA'' droite mais pas dans l' ''OFA'' droite ni dans les régions sensibles aux objets (LOC ; Lateral Occipital Complex, Malach et al., 1999) et uniquement pour les visages, une sensibilité significativement plus élevée pour les basses fréquences spatiales que les hautes fréquences spatiales avant 70 ms et un rapport inversé à 150 ms. Goffaux et al. (2010) confirment ainsi l'idée de Sergent (1986) d'une microgenèse de la perception du visage allant d'un traitement grossier et global vers un réaffinement de la représentation du visage tout en précisant cette dynamique temporelle du traitement des visages fonction de la fréquence spatiale. La résolution spatiale de l'IRMf ne permet évidemment pas de descendre au niveau cellulaire, tout en notant que Sugase et al (1999) avaient montré chez le singe des neurones déchargeant avec des latences différentes d'abord à l'information globale d'un visage (catégorisation) puis +/- 50 ms après à des informations fines sur l'identité et l'émotion. Comme nous l'avions dit dans notre point

2.3, Freiwald et al. (2009) trouvent par ailleurs chez le singe dans TE, en plus des cellules sensibles au visage en entier, des cellules sensibles à certains traits qui ne présentent une modulation d'amplitude que si le trait est « à la bonne place » d'un template global du visage à l'endroit. Tsao et al. (2008) soulignent aussi l'utilité du mécanisme de détection agissant comme un filtre spécifique au domaine (ici les visages) qui accomplirait une ségrégation (isolement du visage par rapport au fond, tâche bien difficile pour beaucoup d'algorithmes de reconnaissance faciale) et faciliterait le contrôle des cellules destinées à l'identification proprement dite (regroupées en région visage pour plus de facilité).

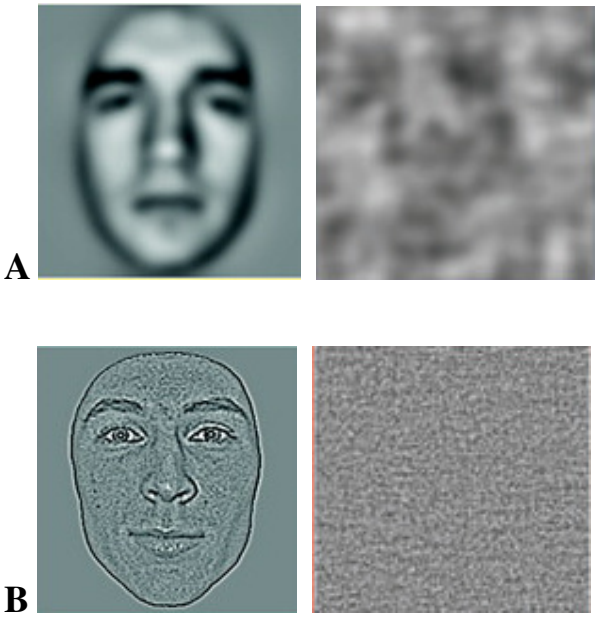


Figure 7. (D'après Goffaux et al., 2010). Exemple de stimuli utilisés : A. Stimuli (visages et visages brouillés) en basses fréquences spatiales (2 à 8 cpi, cycles par image) B. Stimuli (visages et visages brouillés) en hautes fréquences spatiales (32 à 128 cpi, cycles par image). Tous les stimuli ont été égalisés en termes de luminance et contraste (voir Goffaux et al., 2010 pour les détails).

2.4.2.4. La connectivité des régions visages

Modèles de la reconnaissance des visages

Au-delà de la nature des représentations faciales, une autre question importante est le fonctionnement et l'organisation des interactions entre régions.

Modèle de Bruce & Young (1986)

A la base du modèle de Haxby et al. (2000) introduit au point 2.4.2.2. et développé ci-dessous, Bruce & Young (1986) (Figure 8) se sont attachés à développer un modèle fonctionnel hiérarchique pour expliquer les traitements perceptifs et cognitifs impliqués dans la reconnaissance des visages. Deux questions essentielles y sont abordées : la nature des *''codes d'informations''* utilisés dans le traitement des visages et les composants fonctionnels responsables de la génération de ces différents codes et de leur accès. Les codes y sont au nombre de 7 : un *''pictorial code''* (code pictural) qui est comme une photo, un moment particulier dépendant de la lumière, de l'angle de vue, de l'expression etc., un *''structural code''* (code structural) qui capte les aspects essentiels de la structure du visage pour le distinguer des autres, un *''visually derived semantic code''* (code sémantique visuel) qui contient les informations sémantiques dérivées des informations visuelles (l'âge, le sexe, l'apparence d'honnêteté ou d'intelligence), un *''identity-specific semantic code''* (code sémantique de l'identité) lié à l'identité de la personne (métier, adresse, etc.) et qui a une relation arbitraire avec la forme physique du visage, un *''name code''* (code nominal) qui est le code de sortie permettant de générer un nom, soit une étiquette arbitraire pouvant être difficile à retenir, un *''expression code''* (code de l'expression) qui analyse les formes et les postures des traits du visage et qui permet de catégoriser quelqu'un comme triste ou joyeux par exemple et enfin, un *''facial speech code''* (code du discours facial) qui est l'analyse du mouvement des lèvres et de la langue lorsque la personne parle. S'il n'est pas certain que les deux derniers codes soient utiles à la reconnaissance de la personne, c'est l'accès à l' ''identity-specific semantic code'' qui permet de savoir si l'on a reconnu la personne. Notons également que Bruce & Young (1986) précisent qu'il pourrait y avoir un code structural distinct pour les visages familiers et non-familiers et qu'un visage familier serait géré par l'interconnexion de codes structuraux pour des angles de vue distincts et indépendants de l'expression. De plus, certains codes structuraux coderaient la configuration

globale tandis que d'autres coderaient des signes distinctifs particuliers. Un visage serait reconnu comme familier quand il y aurait apparemment entre la représentation codée et le code structural stocké.

La figure 8 reprend les composants fonctionnels gérant ces codes :

- le structural encoding (le *''pictural code''* en serait une entrée) produit un set de descriptions du visage qui inclut des descriptions centrées sur l'observateur fournissant l'information pour l'analyse des expressions (*''expression code''*) et l'analyse du discours facial (*''facial speech code''*) et des descriptions abstraites de la configuration globale et des traits fournissant l'information pour les unités de reconnaissance faciale (*''structural code''*). Les représentations produites par cette unité sont donc par la suite processées dans 3 systèmes séparés.

- les Face Recognition Units (FRUs) stockent les codes structuraux. Chaque unité contient les codes structuraux décrivant un visage connu. Quand un visage est vu, les inputs fournis par l'encodage structurel sont comparés aux FRUs. La force du signal envoyé vers les étapes suivantes dépend du degré de ressemblance entre ces deux représentations. Le niveau d'activation des FRU peut être amorcé indirectement par un effet de contexte ou directement par un effet de récence . Les FRUs sont au niveau de la familiarité.

- les Person Identity Nodes (PINs) contiennent les codes *''sémantiques des identités spécifiques''*. Ils sont activés par les FRUs et il y a un PIN pour chaque personne connue. Les FRUs ne répondent qu'aux visages tandis que les PINs répondent aux visages, aux voix, aux noms, aux vêtements, etc. Les PINs permettent d'atteindre la reconnaissance de la personne et pas seulement des visages. Les PINs sont au niveau de l'identification.

- le Name Generation (*''name code''*) est atteint uniquement via le PIN. C'est le niveau de la dénomination.

- le Directed Visual Processing permet la reconnaissance passive d'un visage sans passer par l'information sémantique. Il permet d'encoder (*''pictural code''*, *''structural code''* et *''visually derived semantic codes''*) et de comparer des visages non familiers.

- le Cognitive System contient toutes les informations associatives et épisodiques qui se trouvent en dehors des PINs. Il reçoit des informations de tous les niveaux antérieurs et permet de rediriger l'attention vers les autres composants du sytème.

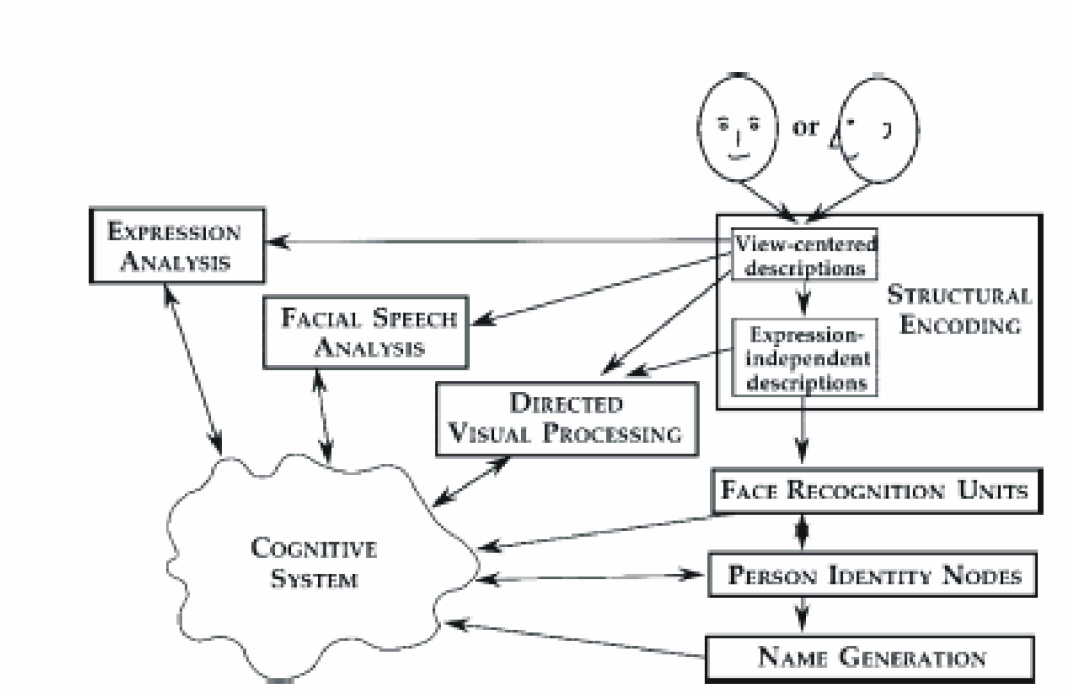


Figure 8. (D'après Bruce & Young, 1986). Modèle cognitif et fonctionnel hiérarchique des traitements perceptifs et cognitifs impliqués dans la reconnaissance des visages et des informations liées à la personne.

Ce modèle permet d'expliquer certaines difficultées de la vie quotidienne chez les sujets sains comme le sentiment de familiarité mais l'incapacité d'identifier la personne et à fortiori de récupérer son nom (FRUs fonctionnant correctement mais l'accès aux PINs déficient) ou la capacité d'identifier la personne mais l'incapacité de retrouver son nom (FRUs et PINs fonctionnant bien mais perte de l'accès au nom). De plus, la possibilité de fournir le nom d'une personne sans retrouver aucune information sur cette personne n'arrive jamais et appuie la hiérarchie des composants.

Au niveau des patients, ce modèle explique l'existence de dissociations entre la reconnaissance des visages et des expressions faciales et entre l'analyse du discours facial et des autres aspects du visage (Sergent & Poncet, 1990). De même, des études conportementales confirment ces dissociations comme par exemple celle de Young et al. (1986) qui montre que la familiarité et le priming facilitent la performance des tâches d'identification mais pas de traitement des expressions. Les études chez l'animal révèlent finalement des cellules visages sensibles à l'expression faciale distinctes des cellules visages sensibles à l'identité (Sugase et al., 1999 ; Hasselmo et al., 1989).

Cependant, ce modèle ne prend pas position sur l'existence d'une étape de détection de visages (« le visage est-il d'abord classé comme un visage ? ») préalable éventuellement à l'entrée dans le système de reconnaissance des visages et ne précise pas la spécificité de ses composants (« les codes structuraux des visages sont-ils différents, plus holistiques par exemple, que les codes structuraux des objets ? »).

Modèle de Haxby et al. (2000)

Ce modèle introduit au point 2.4.2.2. (Figure 5) tente d'accorder le modèle de Bruce & Young (1986) avec les différentes régions visages trouvées lors des études d'IRMf. Plus précisément, Haxby et al. (2000) s'attachent à montrer quelles régions sous-tendent les différents aspects cognitifs de la perception et de la reconnaissance des visages. Le réseau neuronal responsable du traitement des visages est divisé en cœur du réseau neuronal comprenant les ''FFA''s, ''OFA''s et STSs activés bilatéralement mais avec une dominance droite plus marquée et en un système étendu plus impliqué dans le traitement émotionnel, sémantique, de la parole ou de l'attention spatiale.

Le cœur du réseau est, selon eux, organisé de manière hiérarchique au sens où l' ''OFA'' servirait d'input à la fois à la ''FFA'' et au STS. Cette dissociation fonctionnelle entre ces deux

dernières régions a été étayée, on l'a vu, par l'observation des patients, les études comportementales et l'IRMf. Haxby & Hoffman (2000) le montrent, eux-mêmes, dans une étude mesurant comment l'attention sélective soit sur la direction des yeux soit sur l'identité module la réponse aux visages dans ces régions. Par contre, la hiérarchisation n'est qu'une supposition basée sur la localisation anatomique des 3 régions. De plus, leurs propres données (Haxby & Hoffman, 2000) laissent penser que l' ''OFA'' jouerait un rôle plus important dans l'identification que dans la perception du sens du regard.

Le système étendu :

D'autres régions participent à la perception des visages dans la mesure où elles sont recrutées pour traiter les informations basées sur les visages.

La lecture labiale active les régions associées au traitement auditif de la parole. Elle active d'ailleurs les aires auditives même en l'absence de son (Calvert et al., 1997) ce qui souligne l'activité coordonnée entre le STS activé lors de l'analyse visuelle du mouvement des lèvres et le gyrus temporal supérieur activé lors de l'analyse des phonèmes.

La perception des expressions faciales active le système limbique (notamment l'insula et l'amygdale) associé au traitement des émotions. La perception de visages non neutres active les régions associées avec l'émotion portée par le visage. Morris et al. (1996) démontrent par exemple l'activité de l'amygdale lors de la perception de visages inquiets.

La perception du mouvement des yeux active les régions pariétales associées à l'attention spatiale[12]. L'activité du sillon intrapariétal augmente quand l'attention est portée sur la direction du regard plutôt que sur l'identité et en particulier quand la direction du regard est incongruente avec la direction de la tête. L'attention spatiale est en effet alors dirigée vers l'endroit « regardé » (Haxby & Hoffman, 2000).

[12] Les régions « frontal eyes fields » sont aussi probablement activées dans le réseau de l'attention spatiale.

Finalement, si l'association entre un visage et une identité unique paraît reposer sur l'activité dans l' ''OFA'' et la ''FFA'', la reconnaissance de ce visage comme quelqu'un qui nous est familier activerait le lobe temporal antérieur (Sergent et al., 1992), région également activée lors de la perception de noms connus par exemple (Gorno-Tempini et al., 1998), ce qui soulignerait son rôle dans les représentations sémantiques, biographiques et autobiographiques.

Toutes les régions supplémentaires font donc aussi partie d'autres systèmes neuronaux qui sous-tendent d'autres fonctions cognitives que la reconnaissance des visages proprement dite et qui agissent de concert avec le cœur du réseau pour faciliter la reconnaissance précise du mouvement de la bouche, des expressions et de la direction du regard.

Hiérarchisé comme le modèle de Bruce & Young (1986), celui d'Haxby et al. (2000) regroupe cependant la perception des expressions et du mouvement labial (et y ajoute celle du mouvement des yeux) dans une représentation commune des aspects variables du visage indépendante de la représentation de l'identité. Cette représentation des aspects variables du visage faciliterait la communication sociale. Les deux représentations élaborées dans le cœur du système visage serviraient d'entrée au système étendu décrit ci-dessus. Le degré réel de séparation de ces différentes régions fonctionnelles reste cependant incertain et il est probable que les interactions soient plus importantes que ce modèle laisse supposer. La séquence temporelle des traitements des deux représentations et les feedbacks éventuels des composants du système étendu restent aussi assez imprécis. De plus, comme dans le modèle de Bruce & Young (1986), celui d'Haxby et al. (2000) fait l'impasse sur la possibilité d'une dissociation entre la détection et l'identification d'un visage en ne traitant que le niveau de l'identification.

Rossion (2008) (Figure 9) introduisant cette dissociation développera en réponse à Haxby et al. (2000) un modèle où le cœur du réseau n'est plus hiérarchisé mais où l'activité de la ''FFA'' est préalable à l'activité de l' ''OFA''.

Avant de l'aborder plus en détail, soulignons que Gobbini et Haxby (2007) ont eux-mêmes révisé leur modèle mais sans modifier le cœur hiérarchisé ou la fonctionnalité générale. Cette révision se penche plus en détail sur la reconnaissance des visages familiers. Elle y développe le rôle de la réponse émotionnelle indispensable dans la reconnaissance de la personne et souligne que l'apparence visuelle des individus que l'on connait n'est qu'un aspect de la connaissance que l'on a de la personne (au même titre que son caractère, les intentions qu'on lui suppose et les informations bibliographiques). Le système étendu est enrichi de nouvelles régions telles le cortex paracingulaire antérieur, la jonction temporopariétale (impliqués dans le rappel des intentions, attitudes, et état mental de la personne) et le précuneus (impliqué dans la mémoire épisodique). La modulation des trois régions du cœur du système de traitement des visages par la familiarité dépend notamment du type de familiarité et du feedback des amygdales[13].

Modèle de Rossion (2008)

Le système de traitement perceptif des visages comprendrait une voie directe depuis les aires visuelles précoces vers la ''FFA'' droite (aux champs récepteurs larges), sans passage par les régions visage postérieures, permettant la détection holistique relativement grossière du visage (catégorisation holistique). Une boucle réentrante avec une région postérieure spécifique aux visages (''OFA'', aux champs récepteurs plus étroits) servirait ensuite pour affiner la représentation au niveau individuel (individualisation analytique) et permettre une identification holistique qui ré-émergerait dans la ''FFA'' (individualisation holistique). Les deux phénomènes de détection et

[13] Thorpe et al. (2007) ont montré que lorsqu'un visage et une autre image sont présentés de part et d'autre du point de fixation, une saccade oculaire peut être déclenchée en direction du visage en moins de 100 ms même si la cible est sensée être l'autre image. Il serait donc possible que les visages impliquent un traitement automatique et pré-attentif et que les visages aient un accès direct à certaines structures sous-corticales (en particulier, l'amygdale). Morris et al. (1999), à la suite d'une étude en IRMf (1998) montrant l'activité de l'amygdale par des stimuli émotionnels non conscients, ont proposé l'existence d'une voie rapide entièrement sous-corticale, thalamo-amygdalienne, dédiée au traitement des stimuli émotionnels. VanRullen & Reddy (2008) soulignent cependant qu'une telle voie n'est à ce jour pas prouvée car les données les plus probantes en faveur de ce « raccourci » de la reconnaissance visuelle proviennent de paradigmes IRMf, pour lesquels l'ordre d'activation des différentes aires n'est pas facilement connu, de par la faible résolution temporelle de la méthode. De plus d'autres auteurs rapportent d'ailleurs que l'activation de l'amygdale lors de la présentation inconsciente de visages émotionnels est accompagnée d'activations importantes de la voie ventrale du cortex visuel.

d'individualisation holistique prendraient corps dans la même région mais avec des timings différents. Remarquons que ce modèle n'exclut pas la possibilité de connexions des aires primaires à des régions postérieures et donc un chemin parallèle plus hiérarchique.

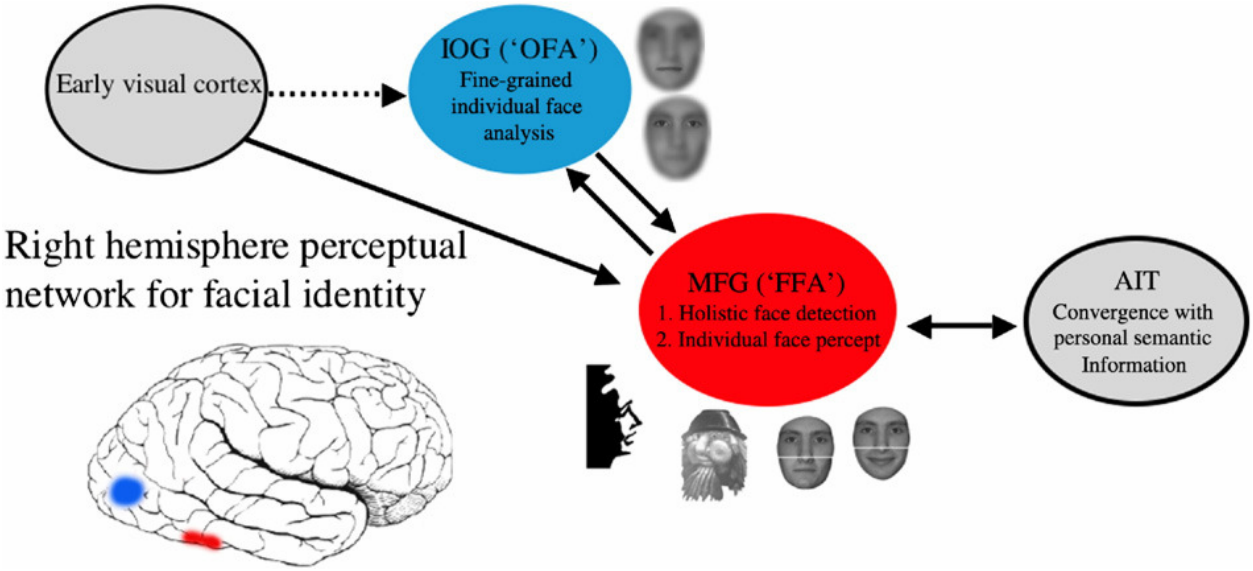


Figure 9. (D'après Rossion, 2008). Modèle non hiérarchique de l'organisation neuro-anatomique de la perception des visages.

Notons que ce modèle «coarse-to-fine» s'est inspiré des travaux de Sergent (1986) pour qui la représentation initiale grossière du visage est réaffinée grâce à l'accès aux détails en «haute résolution » au niveau des traits du visage mais aussi de leur configuration. Il est aussi en accord avec les travaux d'Hochstein & Ahissar (2002) développé au point 2.3. et compatible avec la présence de connexions bidirectionnelles corticales massives (Felleman et Van Essen, 1991) et l'hypothèse d'un signal phasique réentant entre les différentes aires du cortex visuel (Edelman, 1978 ; Edelman, 1993). De manière semblable, un certain nombre d'auteurs dans le domaine de la reconnaissance d'objets ont d'ailleurs suggéré qu'elle impliquait un retour de l'information visuelle des aires corticales de haut niveau vers les aires visuelles inférieures pour donner du sens aux détails «haute résolution » (Bullier et al., 2001 ; Galuske et al., 2002 ; Mumford, 1992 ; Lee et al., 1998 ou encore Bar, 2003 qui met lui l'accent sur le rôle du cortex préfrontal dans cette facilitation).

Informations apportées par l'imagerie cérébrale dans le testing des modèles

On a vu plus haut, (point 2.4.1), les différentes méthodes possibles pour estimer directement la connectivité entre régions cérébrales au moyen de l'IRM. Malheureusement, suite à l'influence massive des études par région d'intérêt dans le champ des visages et à la nouveauté de ces méthodes dont certaines en sont encore à la mise au point technique, assez peu d'études de connectivité existent dans la littérature qui explorent les aspects plus dynamiques de la reconnaissance des visages et en particulier qui étudient la connectivité dans les régions centrales du traitement des visages (connectivité entre les ''FFA''s, les ''OFA''s et le STS). Les études s'intéressent plutôt :

- aux aspects mnésiques qu'aux aspects perceptifs de la reconnaissance des visages. Majerus et al. (2007) et Rissman et al. (2008) étudient par exemple la connectivité (corrélation d'activité entre régions) du réseau visage avec le sillon intra-pariétal gauche (selon eux un modulateur général d'attention) dans différentes tâches mnésiques sur du matériel visuel dont les visages ne sont qu'un exemple parmi d'autres. (Connectivité fonctionnelle, « Data-driven » ; voir point 2.4.1.)

- à la connectivité comme critère diagnostique par exemple de la maladie d'Alzheimer (Bokde et al., 2006 par des corrélations d'activité). (Connectivité fonctionnelle, « Data-driven » ; voir point 2.4.1.)

- A l'amygdale et aux relations de celle-ci au reste du cerveau et du réseau visage en fonction de l'âge et du traitement des émotions négatives (St-Jacques et al., 2008), de la peur (Vuillemier et al., 2007) ou du caractère agressif (Passamonti et al., 2008). Ces études montrent que le traitement émotionnel peut affecter l'activité de toutes les régions visages et plaident pour une moins grande ségrégation entre les processus d'identification et de traitement émotionnel. La vision d'un visage effrayé augmenterait par exemple l'activité dans la ''FFA'' par rapport à un visage neutre et la connectivité amygdale-gyrus fusiforme

se renforcerait (Vuillemier et al., 2007) en plus d'autres modulations provenant des réseaux fronto-pariétaux. (Connectivité fonctionnelle, « Data-driven » ; voir point 2.4.1.).

En fait, quasi les seules études de connectivité s'intéressant à la façon dont les régions centrales sont connectées sont des études en DCM (Friston et al., 2003 ; voir point 2.4.1.) donc en connectivité effective qui teste des modèles hypothétiques spécifiques aux tâches et stimuli. Le nombre de régions et le nombre de connexions introduits dans ces modèles sont souvent, on l'a dit, réduits et laissés au bon vouloir du chercheur et les résultats sont à prendre avec réserve. Summerfield et al. (2006) ont ainsi montré que, lorsqu'une décision perceptuelle doit être prise à propos d'un visage, la connectivité top-down depuis le cortex fronto-ventral vers le gyrus fusiforme augmente. Mechelli et al. (2004) l'avaient d'ailleurs aussi trouvé dans le cas de la génération mentale d'images de visages mais avaient aussi souligné l'augmentation de la connectivité depuis les zones visuelles extra-striées jusqu'au cortex préfrontal dans la perception de visages. De manière plus controversée, Fairhall & Ishaï, (2007), se basant sur le modèle de Haxby et al. (2000), présentent des données où le réseau visage central est organisé de manière hiérarchique (''OFA'' vers ''FFA'' et ''OFA'' vers STS, Figure 10) et où la ''FFA''[14] exerce une influence sur le système étendu (suivant les définitions du modèle de Haxby et al., 2000). Le traitement des visages non émotionnellement neutres augmenterait en effet la connectivité entre la ''FFA'' et l'amygdale tandis que les visages célèbres entre la ''FFA'' et le cortex orbito-frontal. Le problème de cette étude est le choix des régions introduites dans le modèle : difficile de tester la réalité d'un modèle hiérarchique ou non si d'abord des régions plus primaires n'y sont pas intégrées et ensuite si les régions retenues ne sont pas correctement choisies. En effet, l' ''OFA'' choisie est définie à partir d'une comparaison visages moins visages brouillés, comparaison non contrôlée pour la forme et succeptible de ne pas être spécifique aux visages (la coordonnée rapportée dans ce papier pour cette région : 41 -77 -1, coordonnées Talairach correspond d'ailleurs dans nos propres expériences à une

[14] Le modèle est surtout marqué à droite car à gauche, seuls 5 sujets sur les 10 ont pu être inclus dans l'étude, les autres n'ayant pas assez d'activité à gauche.

région…objet). L'influence de la ''FFA'' sur l' ''OFA'' rapportée par Rotshtein et al. (2008) est d'ailleurs nettement supérieure à l'influence réciproque de l' ''OFA'' sur la ''FFA'' (respectivement t=6.1 p<0.01 et t=2.8 p<0.05) dans une autre étude de connectivité effective en DCM où le choix de l' ''OFA'' est très différent de Fairhall & Ishaï (2007) car spécifique aux visages.

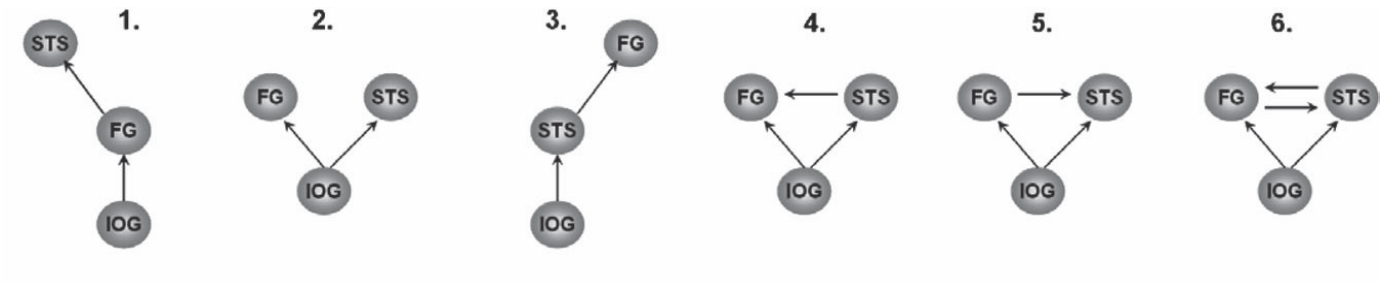


Figure 10. (D'après Fairhall & Ishaï, 2007). Les 6 modèles du système central (défini par Haxby et al., 2001) comparés dans l'étude (FG pour ''FFA'' et IOG pour ''OFA''). Le modèle 2 est parmi ceux proposés (et parmi ceux proposés uniquement), le modèle le plus probable. Les connexions sont testées dans les deux sens et c'est, selon les auteurs, la voie hiérarchique qui prime (t=2.4 p<0.05 sur t=0.1 p=0.5). Malheureusement, non seulement l'IOG testé n'est pas une région visage mais en plus il n'y a pas de modèle reprenant une éventuelle connexion depuis le gyrus lingual par exemple ou V1 ou V2 vers la ''FFA''.

Remarquons que les études en DTI qui permettent de souligner les potentielles connexions entre les aires cérébrales du traitement des visages, ont trouvé des candidats possibles pour des voies directes depuis des aires visuelles précoces (le gyrus lingual par exemple) à la ''FFA'' (Catani et al., 2003) ou depuis V3 vers la ''FFA'' (Kim et al., 2006).

Pour rappel, les fibres blanches sont divisées en fibres associatives (courtes en U et longues), commissurales (corps calleux, commissure antérieure et postérieure) et de projection (capsule interne, corona radiata, corticospinale, corticobulbaire, corticopontique et corticothalamique). Les fibres associatives longues comprennent le cingulum, le faisceau unciforme, les faisceaux longitudinaux supérieur et inférieur (ILF) et les faisceaux occipito-frontaux supérieurs et inférieurs.

Peu d'études ont étudié la connectivité anatomique du réseau visage en DTI. Kim (Kim et al., 2006) a pourtant montré en combinant une étude fMRI et DTI chez 4 sujets une connexion entre les aires V1/V2 et la 'FFA' chez 2 de ces sujets[15] et une connexion entre V3 et la 'FFA' chez tous. Cependant, les données DTI n'ont été acquises qu'avec 12 directions et un seul run par sujet ce qui nous semble peu. Thomas (Thomas et al., 2008) a par ailleurs montré une réduction avec l'âge de la substance blanche du faisceau occipito-frontal inférieur corrélé à une chute de performance dans le traitement des visages mais ne s'est pas intéressé aux connexions occipito-temporales du réseau. Catani (Catani et al., 2003) s'est lui intéressé à ces connexions mais n'a pas combiné son étude à des données fMRI. Il prouve toutefois l'existence chez l'homme de connexions directes (l'ILF) depuis les aires V2, V4 ou encore depuis le gyrus lingual vers le cortex temporal (dont des fibres collatérales aboutissent dans le gyrus fusiforme et probablement la 'FFA'), donc distinctes des connexions associatives courtes, sérielles et hiérarchiques (Figure 11). Ces deux types de connexions, l'un rapide l'autre plus lent peuvent facilement être mis en rapport avec les résultats de Goffaux (Goffaux et al., 2010) qui montre une sensibilité significativement plus élevée pour les basses fréquences spatiales que les hautes fréquences spatiales des visages avant 70 ms et un rapport inversé à 150 ms et de Sugase (Sugase et al., 1999) qui trouve chez le singe des neurones déchargeant avec des latences différentes d'abord à l'information globale d'un visage (catégorisation) puis +/- 50 ms après à des informations fines sur l'identité et l'émotion.

[15] Mais le seuil est faible pour un des deux sujets.

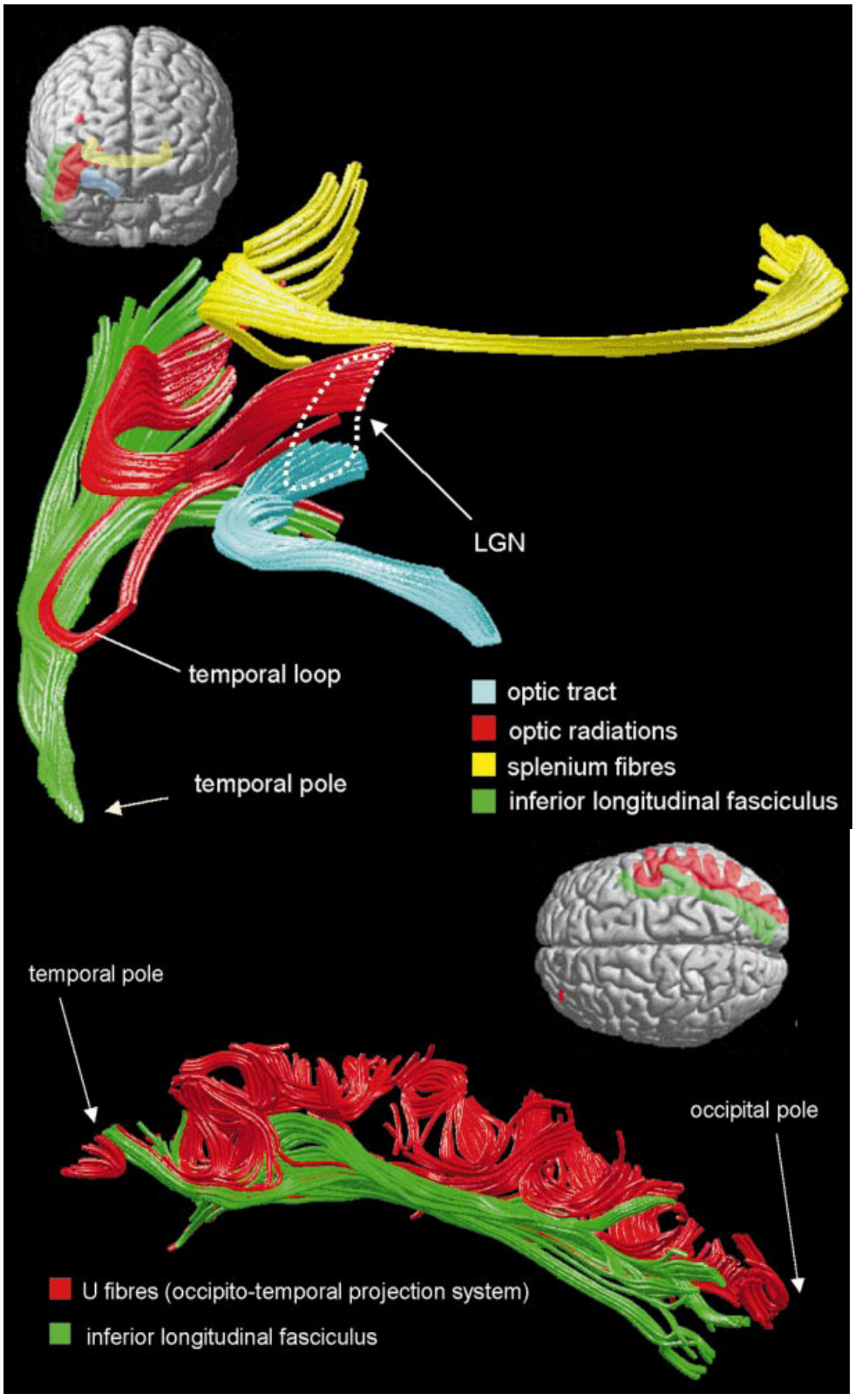


Figure 11. (D'après Catani et al., 2003). Description des voies visuelles. Après le chiasma optique, le tractus optique se projette sur le corps genouillé latéral. De là, partent les radiations optiques jusqu'au cortex visuel primaire. L'ILF et

les fibres courtes connectent ensuite ces aires primaires et/ou secondaires vers le cortex temporal, l'un rapidement et les autres plus lentement.

Zhang et al. (2009) ont par ailleurs montré, par des études de connectivité fonctionnelle en resting state, l'existence d'un réseau d'aires visages connectées préalablement à toute stimulation et comportant principalement le gyrus fusiforme (droit mais aussi gauche[16] par le corps calleux) et le cortex visuel primaire.

Nous espérons donc que la dominance du modèle hiérarchique d'Haxby et al. (2000) diminuera dans les études de connectivité. Ce modèle est sous l'influence du modèle de Bruce & Young (1986) et des études en IRMf par régions d'intérêt. Aucune étude de la connectivité ''OFA'' – ''FFA'' n'y est rapportée et le sens ''OFA'' vers ''FFA'' est pour le moins hypothétique. L'originalité du modèle tient plus dans la dissociation de l'aspect identitaire (''FFA'') et émotionnel (STS) du traitement des visages qui, elle, est étayée par l'expérimentation. D'une manière générale aussi, nous espérons que les modèles computationnels de réseaux de neurones non hiérarchiques[17] dans le domaine des visages qui s'appuient sur des études en IRMf et qui associent des modèles biologiquement plausibles et à large échelle pourront bénéficier du développement des études de connectivité fonctionnelle et effective (déjà en 1999, Horwitz et al. en soulignait l'intérêt). Une étude chez le singe combinant la fMRI et des microstimulations électriques (Moeller et al., 2008) dédiée à l'étude de la connectivité entre les différentes régions chez le singe a d'ailleurs souligné la présence et le rôle primordial des connexions descendantes.

2.4.2.5. Les études de cas uniques en IRMf

Certes, les études comparatives anatomo-cliniques avaient, on l'a vu, apporté des informations non négligeables malgré la variabilité des lésions et des atteintes comportementales (Farah et al., 1990) dans la localisation des régions visages (dominance droite, importance des gyri

[16] Sans préciser si ses participants étaient droitiers ou gauchers.
[17] Summerfield et al. (2006) parlent de « predictive coding » pour souligner l'importance des influences top-down dans la reconnaissance des visages.

lingual, occipital inférieur, fusiforme postérieur et antérieur ; Damasio et al., 1982 ; Sergent et al., 1992, Bouvier & Engel, 2006). Toutefois, utiliser l'IRMf chez les patients prosopagnosiques permet d'aller plus loin dans la compréhension de la dynamique normale des régions visages saines. Nous n'avons d'ailleurs travaillé qu'avec des prosopagnosies acquises et jamais avec des prosopagnosies développementales ou congénitales (soit un mauvais développement du système de reconnaissance des visages ; Berhmann et al., 2005) car il nous paraît difficile d'en tirer des conclusions sur le fonctionnement « normal » de la reconnaissance de visages. Il est en effet délicat de situer ces ''patients'' par rapport à des personnes situées au plus bas d'une courbe de Gauss représentant les capacités de reconnaissance de la population. Une étude intéressante de Degutis et al. (2007) a cependant montré qu'entraîner des patients souffrant de prosopagnosie congénitale augmentait la connectivité entre la ''FFA'' et l' ''OFA''. De même, nous ne nous sommes pas intéressé aux prosopagnosies progressives car associées à des démences, elles ne peuvent pas être considérées comme des prosopagnosies pures. Les études en IRMf de patient souffrant de prosopagnosie acquise dépassent la simple localisation anatomique en permettant de faire le tri, c'est-à-dire, entre fonctionnellement normales ou non, des régions apparemment anatomiquement non lésées. Comparer les réseaux déficitaires de ces cas uniques à des groupes contrôle permet al.ors de contraindre les différents modèles de connectivité des régions du réseau visage sain. Une partie importante de notre travail expérimental a d'ailleurs été l'acquisition chez des patients prosopagnosiques de données d'imagerie fonctionnelle. La patiente PS (voir Sorger et al., 2007 pour une description des lésions de la patiente ou notre partie expérimentale), prosopagnosique pure (Busigny et al., 2010) a ainsi été largement étudiée et scannée. PS présente la particularité de conserver une activité préférentielle aux visages au niveau de la ''FFA'' droite classique tout en étant lésée anatomiquement (et fonctionnellement, PS n'a pas de ''OFA'' droite de par cette lésion) au niveau du gyrus occipital inférieur (Rossion et al., 2003a). Ce cas (confirmé par un autre cas par la suite, patiente DF ; Steeves et al., 2006 pour une description du cas, ou voir notre partie

expérimentale) a largement inspiré et/ou renforcé Rossion (2008) dans sa vision du modèle neurofonctionnel de la reconnaissance des visages et nous a confortée dans la vision d'un modèle non simplement hiérarchique de la reconnaissance des visages.

2.5. Introduction aux chapitres expérimentaux

2.5.1. Description des chapitres

Dans la première partie de cette présentation, nous avons tenté de présenter un aperçu historique des connaissances sur la neuro-anatomie fonctionnelle de la représentation des visages essentiellement sur la base des études en IRMf en nous attachant toutefois à montrer qu'elles n'étaient pas en contradiction avec les données chez le primate et celles venant de la comparaison anatomo-clinique. Sous-jacente à ces données et contrairement au modèle hiérarchique classique présenté par Haxby et al., (2000) (Figure 5), notre partie expérimentale tentera d'étayer un autre modèle, non hiérarchique (Rossion, 2008 ; Figure 9) (voir le point 2.4.2.4. pour la description de ces modèles).

Dans notre premier chapitre expérimental, nous aborderons tout d'abord la question des régions visages activées par la perception des visages et en particulier nous montrerons la plus grande difficulté à définir l' ''OFA'' que la ''FFA''. Contrairement à la ''FFA'' en effet, le choix des stimuli et du paradigme expérimental entraîne des variations dans la localisation de la région appelée ''OFA'' à travers les études et entraîne donc des variations à des degrés divers de la spécificité (de haut et bas niveaux) aux visages de la région trouvée et appelée ''OFA''. Nous montrerons qu'il est possible de trouver une région plus postérieure que la ''FFA'' qui présente une sélectivité de haut niveau aux visages et qui est plus tardive que la ''FFA''. Cette ''OFA'' semble donc un bon candidat pour être celle du modèle de la 9.

Le second chapitre comparera des sujets droitiers et gauchers au niveau de leurs réseaux visages au moyen du même localizer que celui du chapitre 1 et justifiera que les rares cas de

prosopagnosies après lésions gauches se trouvent chez des gauchers. Nous montrerons des différences dans le degré de latéralisation des réseaux visages droitiers et gauchers et questionnerons la pertinence du modèle de la Figure 9 chez les gauchers.

Les chapitres 3, 4 et 5 appuieront la dissociation entre détection holistique et individualisation holistique.

En l'occurrence, le troisième chapitre comparera la patiente prosopagnosique pure (PS) à un groupe de sujets contrôles droitiers en ce qui concerne la détection de visages (pouvoir dire que cette forme est un visage). On verra que la patiente qui possède une ''FFA'' structurellement et fonctionnellement intacte catégorise un visage de la même façon que les contrôles.

Par contre, le chapitre 4 comparera la même patiente à un groupe de sujets contrôles mais cette fois au niveau de la reconnaissance individuelle de visages (pouvoir dire de quel visage il s'agit). On verra que la patiente ne présente pas dans sa ''FFA'' de sensibilité à l'identité des visages retrouvée dans la ''FFA'' des contrôles (qu'on reliera au fait de son absence d' ''OFA''). On montrera par contre et en accord avec le codage distribué (Haxby et al., 2001) qu'elle présente dans sa ''FFA'' une sensibilité à l'identité des objets et dans son LOC (Lateral Occipital Complex, région sensible à la forme des objets mais sans spécificité à l'une ou l'autre catégorie ; Malach et al., 1999) épargné par la lésion, une sensibilité à certains traits du visage expliquant ses capacités très résiduelles et analytiques de reconnaissance de visages (axées sur la bouche).

Le chapitre 5 décrira l'utilisation du même paradigme chez une autre patiente prosopagnosique et agnosique cette fois (DF qui présente des lésions occipitales majeures comprenant et l' ''OFA'' et le LOC) et montrera aussi une ''FFA'' bien présente mais déficiente dans l'identification des visages et cette fois également des objets.

Le chapitre 6 présentera finalement des résultats en connectivité effective chez PS et des sujets contrôles droitiers, soulignant l'influence directe des aires précoces vers la ''FFA'' et de la

''FFA'' vers l' ''OFA''. Ce chapitre décrira également chez la patiente PS, grâce à de la DTI, le chemin anatomique possible depuis ses aires visuelles précoces jusqu'à sa ''FFA''.

2.5.2. Définitions particulières

Analyse de bas niveau (or low-level analysis) :

Une analyse est dite de *bas niveau* si elle repose essentiellement sur des caractéristiques fréquentielles telles que les couleurs ou la fréquence spatiale.

Analyse de haut niveau (or high-level analysis) :

Une analyse est dite de *haut niveau* si elle repose essentiellement sur des traits catégoriels tels que la forme.

Exemples :

Un contraste entre des visages et des voitures par exemple varie selon les deux niveaux d'analyse : il y a un changement de forme (changement de haut niveau) et un changement de fréquences spatiales et de couleurs (changement de bas niveau). Un contraste entre des visages intègres et des visages brouillés (ne possédant plus l'information de forme) mais conservant les mêmes propriétés fréquentielles ne varie plus selon les caractéristiques de bas niveau qui sont ainsi contrôlées.

Sensibilité (or sensitivity) :

Une région cérébrale est dite *sensible* à une caractéristique ou à une catégorie (par exemple les visages) si elle s'active à la présentation d'exemplaires présentant cette caractéristique ou de cette catégorie (par exemple un visage).

Spécificité (or specificity) :

Une région cérébrale est dite *spécifique* (ou ‘’plus’’ spécifique) à une caractéristique ou à une catégorie (par exemple les visages) si elle s’active de manière exclusive (ou ‘’plus’’ importante) à la présentation d’exemplaires présentant cette caractéristique ou de cette catégorie (par exemple un visage) plutôt qu’à la présentation d’exemplaires de caractéristique différente ou d’une autre catégorie (par exemple une voiture).

Exemples:

Si une région s’active à la fois pour le contraste entre des visages et des visages brouillés et pour le contraste entre des objets et des objets brouillés, la région sera sensible à la fois aux visages et aux objets mais ne sera pas spécifique aux visages. De même si une région s’active à la fois pour le contraste entre des visages et des objets et pour le contraste entre des visages brouillés et des objets brouillés, elle ne sera pas spécifique à l’analyse de haut niveau d’un visage.

3. Contribution empirique

3.1. Defining face perception areas in the human brain: a large-scale fMRI localizer study[18]

3.1.1. Abstract

A whole network of human brain areas showing larger response to faces than other visual stimuli has been identified using fMRI. Most studies identify only a subset of this network, by comparing the presentation of faces to all kinds of object categories mixed up, *or* to scrambled faces, using different statistical thresholds. Given these different approaches, the set of face-preferential network can be artificially overextended or minimized, both at the local (size of areas) and global (number of areas) levels. Here we performed a meta-analysis of the data of forty right-handed subjects, tested with a new whole-brain localizer controlling for both high-level and low-level differences between faces and objects. Faces (F), objects [cars (C)]and their phase-scrambled counterparts (SF and SO) were used in a 2x2 block-design. Random group-level and single-subject analyses were made. A conjunction contrast [(F-SF) and (F-O)] identified 6 areas: ''FFA'', ''OFA'', amygdala, pSTS, AiT (anterior infero-temporal cortex) and thalamus, who all but amygdala showed a strong dominant right lateralization. Interestingly, the ''FFA'' showed the least face-specific response of all these areas: it presented a significantly larger response to O than SO and was also sensitive to low-level properties of faces (SF>SO). These observations were confirmed by the single-subject analysis, which nevertheless highlighted a large amount of variability in terms of number, height, extent and spatial localization of the face-preferential areas. An earlier BOLD onset response to faces in the right ''FFA'' than all other areas reinforces the view that face-preferential responses may emerge first in the right ''FFA'' as compared to the ''OFA''. Overall, this study helps understanding the extent and specificity of the face network in

18 Cette section est une version remise en page et complétée d'un article soumis à Human Brain Mapping avec le même titre de Laurence Dricot, Bernard Hanseeuw et Bruno Rossion.

the human brain, and provides a well-balanced functional localizer to identify and characterize its properties.

3.1.2. Introduction

The perception and recognition of faces are the objects of intense research in Cognitive Neuroscience. In particular, the localization of this complex function in the human brain is highly investigated. Understanding of the neural basis of face recognition started in the middle of the 19th century, with the description of patients presenting difficulties at recognition of faces following brain damage (Quaglino and Borelli, 1867; Wigan, 1844). The study of this syndrome, prosopagnosia (Bodamer, 1947), has for long been the only source of information about the neural basis of face recognition. Correlation between, on the one hand, the behavioural impairments related to the inability to recognize faces and, on the other hand, the localization of lesion, offered the first opportunity to identify cortical areas the damage of which produces prosopagnosia. Patients with prosopagnosia present either bilateral or unilateral right hemisphere damage[19], in different areas of the ventral occipital and temporal cortices, in particular the lingual, fusiform and parahippocampal gyri, as well as the anterior temporal pole (Bouvier and Engel, 2006; Damasio et al., 1982; Hécaen and Anguerlergues, 1962; Meadows, 1974; Sergent and Signoret, 1992). Hence, neuropsychological investigations of such patients revealed early on the dominance of the right hemisphere in face recognition (Hécaen and Anguerlergues, 1962), and pointed to a critical role of multiple occipito-temporal cortical areas for this function (Sergent and Signoret, 1992).

However, for a number of reasons (large size and variability of the lesions, potential effects of these lesions on the integrity of other areas, …), the precise definition of the cortical areas involved in the normal recognition of faces in humans, their function, and whether these areas are uniquely devoted

[19] Only a few cases of prosopagnosia have been reported with a unilateral left-sided lesion but all these patienst were left-handed (Barton, 2009; Mattson et al., 2000), with the exception of one case of a patient with epilepsy, for which the functional integrity of the right occipito-temporal cortex remains unclear (Wright et al., 2006).

to the processing of faces remained largely unclear before the advent of functional neuroimaging (Sergent and Signoret, 1992).

Starting with the seminal work of Justine Sergent and colleagues (1992) using positron emission tomography (PET) in the early nineties, a wealth of neuroimaging studies have since been carried out, mainly with functional magnetic resonance imaging (fMRI), allowing a definition of the brain areas particularly involved in face perception in the normal healthy brain. Even though there were already a large number of published neuroimaging studies of face perception already at the time, both with PET and fMRI (e.g., Haxby et al., 1994; Puce et al., 1995), a landmark paper in this field is the study reported by Kanwisher et al. (1997). This study introduced the (face) localizer approach in neuroimaging, comparing the presentation of (blocks of) faces *vs.* nonface objects stimulation while keeping task constant. This procedure isolated a single area in the middle section of the right hemisphere lateral occipito-temporal cortex (fusiform gyrus) that responded more to faces than objects. Both the approach and the area identified in most individual brains, the "fusiform face area" (''FFA'') (Kanwisher et al., 1997), have had a major influence in this area of research over the past fifteen years (e.g., see the reviews of Berman et al., 2010; Kanwisher and Yovel, 2006). In most current neuroimaging studies of face perception, researchers conduct an independent experiment to localize the ''FFA'' in each individual brain. Once the area is defined, its response properties can then be tested in an other experiment by manipulating face (or nonface) stimuli and tasks of interest in a constrained way.

However, even if one acknowledges the interest or even the necessity of such a face localizer approach to clarify the neural substrates of human face perception (see the debate by Friston et al., 2006; Saxe et al., 2006), there are several methodological issues that need to be considered when using such an approach because they can greatly influence the definition of the area(s) involved in face perception. There are at least four main methodological issues that arise when defining a face localizer.

First, the *kind of stimuli* that are compared to faces in a functional localizer: objects from multiples categories (chair, table, ball, scissors,…), (phase-)scrambled faces, or exemplars from a single nonface object category (e.g., pictures of different houses). Usually, only one of these three comparisons is performed, and the three kinds of comparisons have been performed in different face localizer studies (e.g., Kanwisher et al., 1997; Ishai et al., 2005; Haxby et al., 1999 respectively). Yet, these different comparisons can lead to highly different definitions of the ''FFA'' and other putative face-sensitive ares) (i.e., localization, magnitude and extent).

Second, the *task* that participants have to perform in the face localizer should be considered. Most of the time either passive viewing or a one-back task (detecting immediate repetition of the exact same stimulus in a train of stimuli) is used. Berman and colleagues (2009) recently addressed the impact of these two factors on the activation to faces in the fusiform gyrus. They concluded that, as far as the ''FFA'' is concerned, the task was not a major factor accounting for localization differences. However they found that the kind of stimuli compared to faces greatly influenced the extent, strength and reliability of the ''FFA''. Unfortunately, the authors did not provide with a recommended way of localizing the ''FFA'' in the human brain. Most importantly, they restricted their analysis to the ''FFA'', a point which leads to the third and fourth issues to consider when using a face localizer approach.

A third issue is whether the whole brain, or only a portion of it as (in the original Kanwisher et al., 1997' study), should be considered. While scanning the whole brain allows identification of sensitivity to faces without a priori localization constraints, it requires longer recording time and thus potentially less power to disclose and characterize local sensitivity to faces (i.e., in the ''FFA'').

Fourth and most importantly, the statistical criteria used to define the voxels presenting a larger response to faces than comparison stimuli have a huge impact on the outcome of a face localizer. As a matter of fact, Kanwisher et al. (1997) reported only *one* cortical area (the ''FFA'')

whose response was larger for faces than control stimuli, contrary to previous neuroimaging studies (e.g., Sergent et al., 1992). This is because Kanwisher et al. (1997) restricted their recording to a small portion of the brain and used a quite conservative statistical threshold. In fact, as pointed out early on by Tovée (1998) and in agreement with the above-cited studies on acquired prosopagnosia (see Rossion, 2008), the ''FFA'' certainly needs "a little help from its friends" to carry a complex function such as face perception. Nowadays, it is widely acknowledged that in each individual human brain there are multiple areas, of different sizes and distributed across the whole brain, that respond more to faces than nonface visual stimuli (e.g., Fox et al., 2009; Haxby et al., 2000; Ishai, 2008; Rajimehr et al., 2009; Tovée, 1998; Tsao et al., 2008; Weiner and Grill-Spector, 2010). Specifically, these areas concern the posterior part of the inferior occipital cortex ("Occipital Face area", ''OF''A, e.g., Gauthier et al., 2000a), and of the superior temporal sulcus (pSTS, e.g., Puce et al., 1998), the anterior infero-temporal cortex or temporal pole (AiT) as reported mainly in PET studies (e.g., Sergent et al., 1992) but also more recently in fMRI studies (Kriegeskorte et al., 2007; Rajimehr et al., 2009) and the amygdala (e.g., Morris et al., 1996). Interestingly, recent fMRI studies carried out in the individual monkey brain also point to a network of areas responding more to faces than nonface visual stimuli, and distributed in the occipital, temporal and prefrontal cortices (Pinsk et al., 2009; Tsao et al., 2006; 2008).

Considering these observations, the community of researchers inside or outside of this field may be under the impression that the question of localization of face perception is largely solved: there is a set of well identified areas involved particularly in face perception. Researchers should now focus entirely on defining the respective functions of these localized areas and how they are connected anatomically and interact functionally. However, and unfortunately, the reality is rather different. That is, the issues raised above about the ''FFA'' (comparison stimuli, task, statistical threshold, brain volume considered) remain entirely valid, and are multiplied by the fact that instead of having to deal with a single area, there is a whole set of areas responding preferentially or

specifically to faces in the human brain. In particular, the critical question of which control visual stimuli should be compared to faces, and consequently whether this cerebral network is artificially overextended or not (Wiggett and Downing, 2008) has not yet been addressed satisfactorily.

In the present study, we addressed some of the methodological issues raised above – and draw their theoretical implications - by performing a large-scale whole-brain investigation (40 participants) with a factorial face localizer design in which faces are compared to both a familiar nonface object category and to phase-scrambled faces. This paradigm allows controlling for low-level responses to faces and assess the degree to which a preferential response to face stimuli in a given area is (1) truly face specific (i.e., the area does not respond to nonface objects at all) and (2) driven entirely by high-level features of a face (i.e., does not respond more to scrambled faces than scrambled nonface objects). It corresponds to two runs of about 10 minutes each, as typically performed in face localizer experiments when researchers ought to test for the sensitivity of face areas to other experimental manipulations, and it allows localizing areas sensitive to object shape also (LOC, Grill-Spector and Malach, 2004; Malach et al., 1995).

3.1.3. Materials and Methods

3.1.3.1. Participants

Forty right-handed participants [age=25.8 +/- 5.55; 31 women; Edinburgh Inventory (Oldfield 1971)] were tested. None of them had a history of neurological or vascular disease, head injury or alcohol abuse, nor did they display cognitive complaints. The participants gave their informed written consent prior to the behavioral and fMRI experiments. The study conformed to the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Department of the University of Louvain.

3.1.3.2. Experimental procedures

Stimuli

Four categories of stimuli were used: photographs of Faces, Cars, and their phase-scrambled versions: Scrambled Faces and Scrambled Cars (Figure 1. 1).

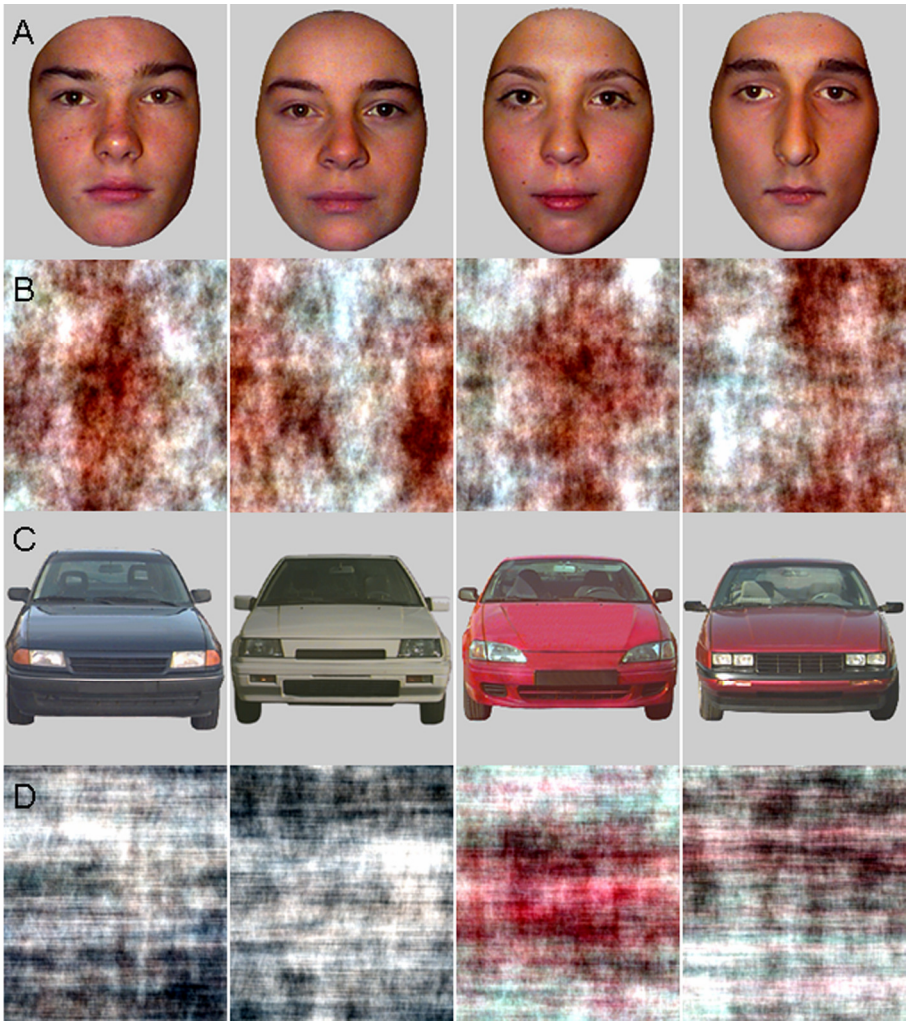


Figure 1. 1. Stimuli: Faces (A), Cars (C), and their phase-scrambled versions: Scrambled Faces (B) and Scrambled Cars (D).

The Face condition consisted of 43 pictures of faces (22 females) cropped so that no external features (hair, etc.) were revealed. All the faces were shown in frontal view. There were inserted in a gray rectangle to form a rectangular image (Figure 1. 1). Similarly, the Car condition consisted of

43 pictures of different cars in a full-front view also embedded in a gray rectangle. Faces and cars were presented in color and equalized in luminance. The scrambled stimuli were made using a Fourier phase randomization procedure [FFT with phase replaced by phase of a uniform noise (amplitude conserved in each frequency band (see e.g. Sadr and Sinha 2004)] that yields images preserving the low-level properties of the original image (i.e. luminance, contrast, spectral energy…), while completely degrading any category-related information (Figure 1. 1). Pictures of faces/cars and the phase scrambled face/car pictures subtended equal shape, size and contrast against background.

Rather than using multiple object categories mixed up in a block, as performed in many studies including previous studies of our laboratory (see table 1 in Berman et al., 2010), here a single object category – cars - was used to compare to faces. Indeed, comparing objects from multiple categories to a single category (faces) has serious limitations because visual homogeneity of the stimuli within a block is then much larger for faces than objects. It follows that a one-back task is much easier for objects than faces, a factor that may cause an increase of attention for faces in such face localizer paradigms. Here pictures of cars were used as the single object category, for several reasons: cars are a set of mono-oriented objects, they form a highly familiar and visually homogenous category, and they have multiple parts, just like faces (‘‘internal’’: lights, radiator grill, window, bumper; ‘‘external’’: mirrors, wheels, …). Also, pictures of cars have been used as control stimuli of faces in numerous behavioral (e.g., Yin et al., 1969) and neuroimaging studies (e.g., Gauthier et al., 2000b; Grill-Spector et al., 2004), and these pictures in particular have been used in several of our previous studies (Busigny and Rossion, 2010; Rossion and Curran, 2010; Schiltz et al., 2006). Here, cars will be referred to as objects (O) in contrast to faces (F), and their scrambled versions (SF, SO).

Paradigm

Participants performed two runs of 11 min duration. In each run, there were 6 blocks of 18 sec duration for each of the 4 types of stimuli. Blocks were separated by a baseline condition (cross fixation) of 9 secs. In each block, 24 stimuli of the same condition were presented (750 ms per stimuli, no ISI) on a black background screen. This gave a total amount of 144 stimuli per category per run. The stimuli and the fixation cross were presented centrally, but stimulus location varied randomly in x (6%) and in y (8%) direction at each presentation (5.5° and 6.2° as visual angle degrees in the x and y direction, average location is centred). In each block, among the 24 stimuli of the same condition, 2 or 3 consecutive repetitions of the exact same stimulus were integrated (target trials) and participants performed a one-back identity task (15 targets for each condition per run).

Imaging acquisition parameters

Functional MR images of brain activity were collected using a 3T head scanner (Siemens Allegra, Siemens AG, Erlangen, Germany), with repeated single-shot echo-planar imaging: echo time (TE) = 50 ms, flip angle (FA) = 90°, matrix size = 64x64, field of view (FOV) = 224x224 mm², slice order descending and interleaved, slice thickness = 3.5 mm. Repetition time (TR) was 2250 ms, 36 slices (the whole brain is scanned 293 times per run, 48 times per condition per run). A three-dimensional (3D) T1-weighted data set encompassing the whole brain was acquired to provide detailed anatomy (1 mm^3) thanks to aADNI sequence (TR = 2250 ms, TE = 2.6 ms, FA =9°, matrix size = 256 × 256, FOV = 256 × 256 mm^2, 192 slices, slice thickness = 1 mm, no gap, total scan time = 8 min 5.

3.1.3.3. Data analysis of the imaging experiments

Preprocessing

The fMRI signal in the different conditions was compared using BrainVoyager QX (Version 1.9.10, Brain Innovation, Maastricht, The Netherlands). Prior to analysis, the functional data sets

were subjected to a series of preprocessing operations. Preprocessing consisted of a linear trend removal for excluding scanner-related signal, a temporal high-pass filtering applied to remove temporal frequencies lower than 3 cycles per run, and a correction for small interscan head movements by a rigid body algorithm rotating and translating each functional volume in 3D space. The data were corrected for the difference between the scan times of the different slices. Data was not smoothed in the spatial domain. In order to be able to compare the locations of activated brain region across participants all anatomical as well as the functional volumes were spatially normalized (Talairach and Tournoux 1988) and the statistical maps computed were overlaid to the 3D T1-weighted scans in view to calculate Talairach coordinates for all relevant activation clusters. Subsequently, the functional data were analyzed using one multiple regression model (General Linear Model; GLM) consisting of predictors, which corresponded to the particular experimental conditions of each experiment. The predictor time courses used were computed on the basis of a linear model of the relation between neural activity and hemodynamic response, assuming a rectangular neural response during phases of visual stimulation (Boynton et al. 1996). All coregistrations were done manually and the corrections of the movement were optimized (sinc interpolation, only one run rejected out of 80, so that only one run was available for one subject).

Statistical analyses and contrasts of interest

We performed both a random effect group analysis, and a random effect analysis based on definition of areas in each individual participant. In the group analysis, we performed 5 contrasts of interests. The main contrast of interests were the interaction [(F-O) – (SF-SO)] and conjunction [(F-O) and (F-SF)] contrasts. These contrasts were aimed at isolating the areas responding more to faces than non-faces objects, and for which this difference could not be accounted for by low-level visual parameters. In addition, we used the single contrasts (F-O) as performed in the large majority of face localizer studies (either with multiple object shapes or one object category, see e.g., Loffler et al., 2005 or Gauthier et al., 2000b; for a larger list see Berman et al., 2010) and the contrast (F-FS),

which is used in a number of studies also (e.g., Eger et al., 2004; Ishai et al., 2006). Finally, we also identified areas that responded to shape (e.g., LO) by the contrast O-SO. Given that the conjunction contrast proved to be the most interesting to reveal the network of areas involved in face perception in the group analysis, we performed the individual participant analysis with this contrast.

Statistical threshold for definition of areas

At the group level, two procedures were used to define the areas of interest. First, a conservative *identical* statistical threshold was used to identify the areas. A threshold of q(FDR)<0.001, which activated the whole visual cortex including the ventral and dorsal pathways when all the conditions were compared together to the baseline (one large cluster of +/- 80 000 voxels around V1) was chosen. Second, the size of the ''FFA'' was fixed at 500 mm^3 to measure the peak of activation in this area (t) and in other face-preferential areas.

In the individual participant analysis, we used the conjunction contrast [(F-FS) and (F-O)] and fixed the size of the ''FFA'' at 200 mm^3 to identify the other face-sensitive regions (see Fox et al., 2009 for a similar approach with 50 mm^3 cluster size of ''FFA'').

Bold latency mapping

Finally, to compare the time-course of activations across regions (Formisano and Goebel, 2003), we calculated for each of them the bold estimation of the onset time of the response to first face in each block of faces (432 trials in total) using a piece-wise linear trapezoidal model for the response without forcing a return to baseline (interpolation factor 2; Richter et al., 2000).

3.1.4. Results

3.1.4.1. Behavioural data

Behavioural data of 4 participants in the one-back task was not recorded. Overall, participants performed the task quite well in all condition (mean accuracy rates: 96.48% +/-1.84%; mean response times: 544.76ms +/-63.24ms).

A 2 (Category: Faces vs. Objects) x 2 (Shape: Scrambled vs. non-scrambled) ANOVA with 36 participants was performed on accuracy rates. There was no effect of category ($F_{1,35}$= 1.08; p=0.305), but a highly significant effect of shape ($F_{1,35}$= 35.21; p<0.0001), due to a lower performance for scrambled stimuli. There was also a significant interaction between shape and category ($F_{1,35}$ =13.13; p<0.001), due to the relatively low performance for scrambled objects (95.45%+/-1.81%; Supplementary Figure 1. 1. A). Post-hoc between Faces and Scrambled Faces (t_{35}=1.87, p=0.07) or Faces and Objects (t_{35}=-1.98, p=0.06) just failed to reach significance.

With respect to response times (RT), there was a main effect of category ($F_{1,35}$=19.35; p<0.0001), participants performing the task faster for objects than faces (Supplementary Figure 1. 1. B), and of shape ($F_{1,35}$=4.34; p=0.044), with slower responses for scrambled stimuli. These main effects were qualified by a significant interaction between the two factors ($F_{1,35}$= 10.26; p<0.003), because participants were the fastest for non-scrambled objects (547.20ms+/-63.57ms). There was no difference between Faces and Scrambled Faces in terms of response speed (t_{35}=0.16; p=0.87), but a difference between Faces and Object (t_{35}=5.58, p<0.0001).

<u>Comparison with one-back task in a face localizer with multiple objects:</u>

In a typical face localizer neuroimaging study, contrasting faces and objects from multiple categories, the one back task is much more difficult for faces than non face objects. For instance, in a typical size group of 15 right-handed participants taken from a previous study (Dricot et al., 2008), there was a highly significant difference between faces and objects both in accuracy

(t_{14}=5.12, p<0.0002) and correct RTs (t_{14}=6.25, p<0.00002). In comparison, in the face localizer of the current study, a bootstrap analysis which takes 10.000 times 15 participants out of 36 randomly leads to an average t=1.28 (NS, p=0.220019; SD of t values = 0.71) for accuracy and t=3.90 (p<0.0016; SD of t values = 1.0578) for RTs (Supplementary Figure 1. 2.). Hence, although the current localizer is not perfectly equalized for differences of performance in the one-back task between conditions in terms of RTs (repeated objects being detected faster than faces), it represented a significant improvement in comparison with the traditional face localizer used in such studies.

3.1.4.2 Neuroimaging results

Random analysis

Single Contrasts: Faces vs. Scrambled faces / Faces vs. Objects

At q(FDR)<0.001 (t=5.22,), we report 12 clusters for the contrast F-SF (Table 1. 1. A.) and 17 clusters for F-O (Table 1. 2. A.). We made the following observations:

Table 1. 1 A. Talairach locations of all the regions found in the random analysis for the 40 right-handed subjects.

Contrast: F-SF

at q(fdr)<0.001:	Talairach Coordinates:			Cluster size:
	x	Y	z	mm^3
Right fusiform gyrus in temporal and occipital lobe (‘‘FFA’’ and ‘‘OFA’’ mixed)	36	-57	-15	**3589**
Right superior temporal sulcus	47	-57	15	**66**
Right (middle) superior temporal sulcus	46	-40	10	**71**
Right amygdala	20	-6	-9	**1229**
Right perirhinal cortex (BA 38)	28	-4	-27	**22**
Right hippocampus	32	-23	-6	**35**
Right thalamus (pulvinar)[20]	8	-28	1	**52**
Right gyrus rostral	0	41	-5	**19**
Left fusiform gyrus (BA 20 or 37) = left ‘‘FFA’’	-37	-42	-17	**468**
Left fusiform gyrus or inferior occipital gyrus (BA 19) = left ‘‘OFA’’	-38	-74	-12	**737**
Left amygdala	-23	-5	-9	**1022**
	-9	-73	7	**91**
Left cuneus (BA 17)				

[20] The spatial resolution is not precise enough to be sure that it is really the pulvinar.

Table 1. 2. A. Talairach locations of all the regions found in the random analysis for the 40 right-handed subjects. Contrast: F-O

at q(fdr)<0.001:	Talairach Coordinates:			Cluster size:
	x	y	z	mm^3
Right fusiform gyrus (BA 37) = right ‘‘FFA’’	40	-44	-16	**331**
Right inferior occipital gyrus (BA 18) = right ‘‘OFA’’	25	-88	-10	**571**
Right superior temporal sulcus	48	-48	8	**624**
Right amygdala	19	-6	-9	**630**
Right perirhinal cortex (BA 38)	25	0	-28	**32**
Right precentral gyrus (BA 6)	42	0	34	**1395**
Right superior frontal gyrus (BA 6)	3	4	52	**19**
Right thalamus (pulvinar)	5	-26	-1	**331**
Right thalamus (ventro-lateral part)	11	-13	13	**53**
Right thalamus (medial dorsal part)	1	-12	11	**61**
Right internal capsule	22	-23	-2	**20**
Left inferior occipital gyrus (BA 18) = left ‘‘OFA’’	-20	-90	-12	**819**
Left amygdala	-21	-5	-9	**429**
Left lingual gyrus (BA 17)	-7	-95	-2	**17**
Left thalamus (pulvinar)	-8	-25	-5	**17**
Left cerebellum	-12	-64	-40	**26**
Cerebellum (oculomoteur vermis)	-3	-60	-24	**1140**

1. When faces are compared to scrambled faces, there is a large cluster in the right ventral stream that encompasses the whole right fusiform gyrus (Figure 1. 2. A.). There is no distinction between the “traditional” ‘‘OFA’’ and ‘‘FFA’’. Increasing the statistical threshold to p(Bonferoni corrected)<0.5 allows a separation between the anterior and posterior parts of the fusiform, but other areas that are often found relevant for face processing (e.g., pSTS) are no longer significant.

2. There is a right hemispheric dominance for both F-O (75% of voxels, without cerebellum) and F-SF (69%).

3. Face-sensitive activations extend largely to the cerebellum for the contrast F-O, but not for F-SF.

4. When the two maps are superimposed (Figure 1. 2. A.) to each other, the right ‘‘FFA’’ as defined by (F-SF) encompasses the ‘‘FFA’’ defined by F-O. There is good overlap between the

pSTS as defined in the two contrasts. However, there is no overlap at all between the large right hemisphere cluster in the ventral stream defined by (F-SF) and the right ‘‘OFA’’ as defined by (F-O). That is quite sensible since one is not face specific (F-SF) and the other is not high-level (F-O).

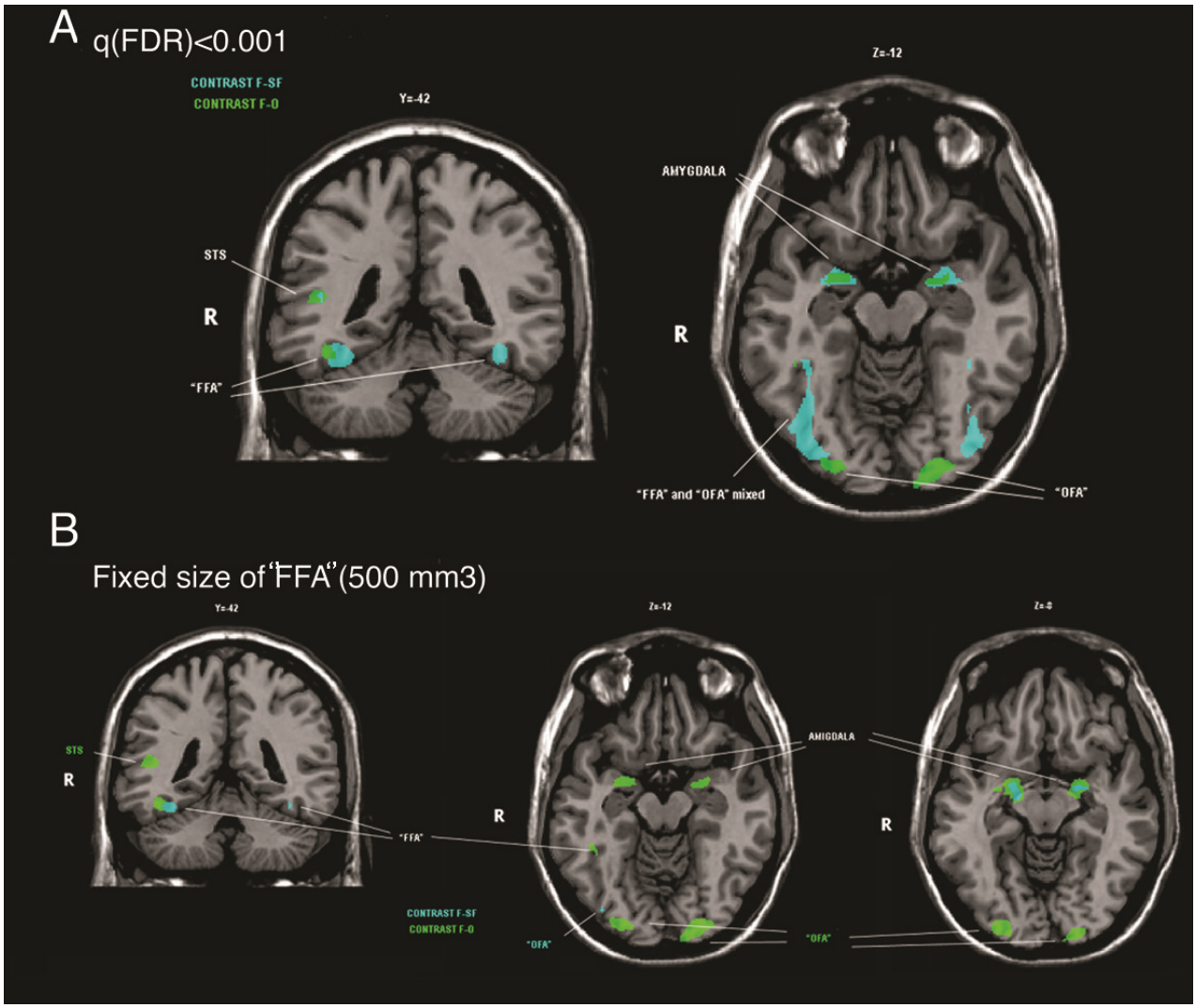


Figure 1. 2. A. Comparison of the activation maps when performing faces *vs.* objects (F-O) and faces *vs.* scrambled faces (F-SF). Note the large ventral occipito-temporal activations observed for faces *vs.* scrambled faces, a comparison that is used in many studies to define “face-specific” areas such as the FFA and OFA (e.g., Fairhall & Ishai, 2007). The overlap of the activation maps is quite good at the level of the FFA and amygdala, but the OFA as defined by the 2 contrasts do not correspond to the same area at all. **B**. Same comparison as in A, but obtained when a Fixed size of FFA (500 mm^3) is used for the two contrasts. When the two maps are superimposed to each other, the right FFA as defined by (F-SF) encompasses again the right FFA defined by F-O. There is good overlap between the pSTS as defined in the two contrasts. However, there is still no overlap at all between the right OFA as defined by (F-SF) and (F-O).

When a fixed size of ‘‘FFA’’ was used (+/- 500 mm^3) for the two contrasts, we identified 5 clusters for F-SF (‘‘FFA’’=498 mm^3; t = 7.45) (Table 1. 1. B.) and 19 (‘‘FFA’’=504 mm^3; t=4.83) for F-O (Table 1. 2. B.). We made the following observations:

Table 1. 1. B. Talairach locations of all the regions found in the random analysis for the 40 right-handed subjects.

Contrast: F-SF

when a right ‘‘FFA’’ of 500 mm^3 is considered:	Talairach Coordinates:			Cluster size:
	x	y	z	mm^3
Right fusiform gyrus (BA 20 or 37) = right ‘‘FFA’’	35	-41	-18	**498**
Right inferior occipital gyrus (BA 19 or 18) = right ‘‘OFA’’	36	-79	-12	**21**
Right amygdala	18	-7	-8	**96**
Left fusiform gyrus (BA 20 or 37) = left ‘‘FFA’’	-36	-42	-16	**20**
Left amygdala	-20	-6	-8	**54**

Table 1. 2. B. Talairach locations of all the regions found in the random analysis for the 40 right-handed subjects.

Contrast: F-O

when a right ‘‘FFA’’ of 500 mm^3 is considered:	Talairach Coordinates:			Cluster size:
	x	y	z	mm^3
Right fusiform gyrus (BA 37) = right ‘‘FFA’’	40	-44	-16	**504**
Right inferior occipital gyrus (BA 18) = right ‘‘OFA’’	25	-88	-10	**847**
Right superior temporal sulcus	49	-49	7	**1346**
Right amygdala	20	-6	-9	**849**
Right perirhinal cortex (BA 38)	25	0	-28	**87**
Right precentral gyrus (BA 6)	43	0	34	**2102**
Right superior frontal gyrus (BA 6)	3	4	52	**49**
Right hippocampus	31	-22	-5	**24**
Right thalamus (pulvinar)	5	-26	-1	**474**
Right thalamus (ventro-lateral part and medial dorsal part mixed)	4	-13	11	**303**
Right internal capsule	21	-23	-2	**43**
Right cerebellum	5	-64	-33	**29**
Left inferior occipital gyrus (BA 18) = left ‘‘OFA’’	-20	-90	-12	**1113**
Left amygdala	-21	-5	-10	**578**
Left lingual gyrus (BA 17)	-7	-95	-2	**90**
Left thalamus (pulvinar)	-9	-24	-5	**46**
Left cerebellum	-12	-65	-39	**85**
Left cerebellum	-18	-63	-41	**19**
Cerebellum (oculomoteur vermis)	-3	-61	-24	**1915**

5. For F-SF, this method differentiates between the ‘‘FFA’’ and the ‘‘OFA’’ but other face-sensitive areas may not be disclosed (e.g., pSTS).

6. When the two maps are superimposed (Figure 1. 2. B.) to each other, the right ‘‘FFA’’ as defined by (F-SF) encompasses once again the ‘‘FFA’’ defined by F-O. There is good overlap between the pSTS as defined in the two contrasts. However, there is no overlap at all between the right ‘‘OFA’’ as defined by (F-SF) and (F-O).

7. Furthermore, the ‘‘OFA’’s as defined in F-SF and F-O do not appear to present the same response properties (Figure 1. 3.; Table 1. 3.). The ‘‘OFA’’ found in (F-SF) responds to object structure, largely independently of the category (O-SO: $p<0.000000$). Even a non-independent F-O contrast with respect of the area’s definition failed to reach significance ($p=0.165319$). In contrast, the more posterior area identified by (F-O) (Figure 1. 3.) responds highly to scrambled stimuli, and more to scrambled faces than objects (SF-SO, $p<0.006771$).

3.1. Characterizing the face processing network in the human brain: a large-scale fMRI localizer study

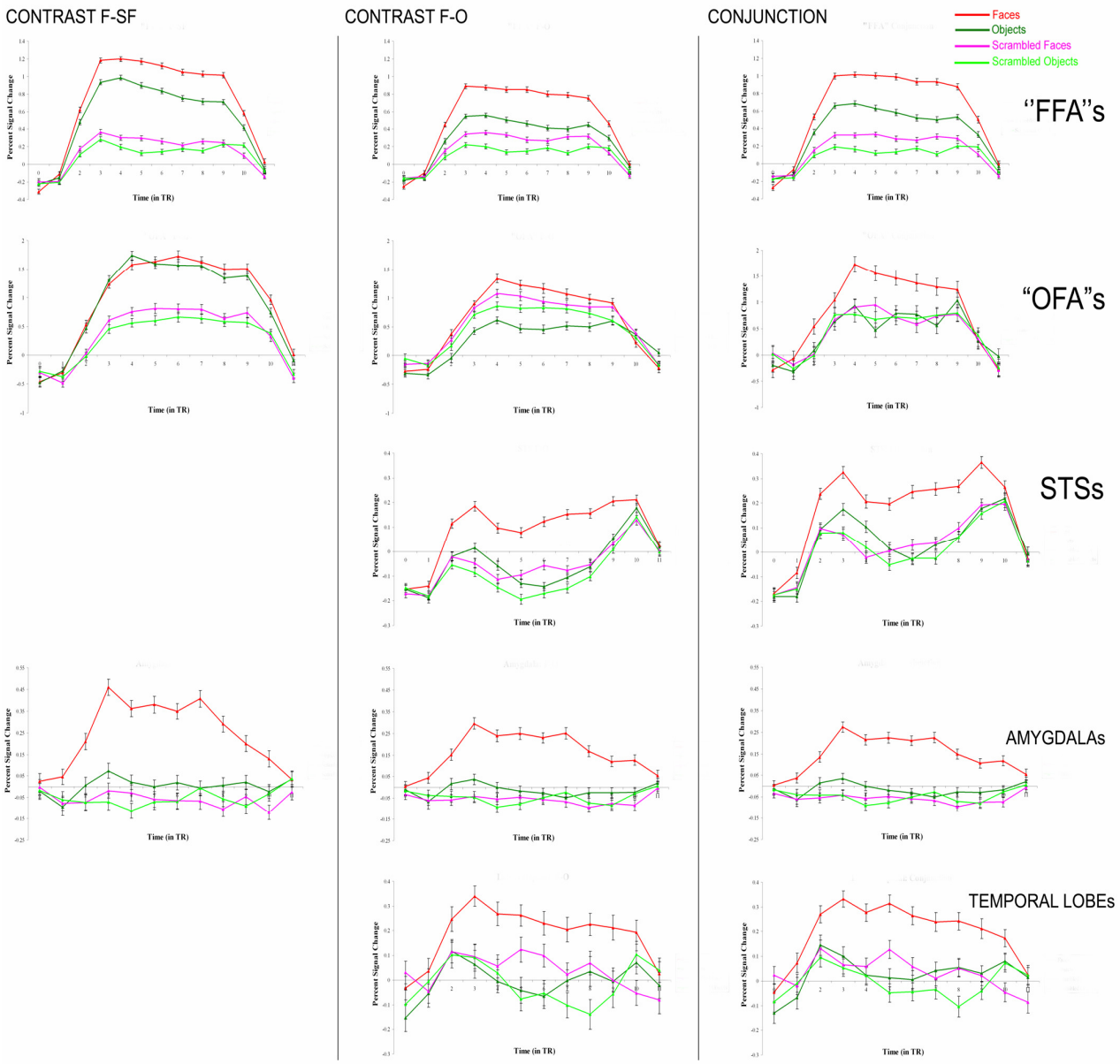


Figure 1. 3. Signals percent changes for the clusters of the core and extended system for the 3 following contrasts: F-SF (''FFA''= 498 mm³; t=7.45), F-O (''FFA''= 504 mm³; t=4.83) and the conjunction contrast (''FFA'' = 501 mm³; t=4.29). Note that the ''FFA'', irrespective of the contrast used, responds highly to nonface objects, and also shows a larger response to scrambled faces than scrambled pictures of cars. The "OFA" defined in the 3 contrasts are different areas showing completely different response properties (contrary to the other regions). This illustration indicates that comparing the behavior of this area across studies when it is defined by the different contrasts is inadequate. The ''OFA'' identified in the conjunction contrast responds above baseline for all conditions, but it is not more sensitive to low-level aspects of faces (scrambled faces) than objects, and does not respond more to objects than scrambled objects either. Thus, paradoxically, the OFA appears to show a more specific response to faces than the ''FFA''.

8. There is a right hemispheric dominance for F-O (77% without cerebellum) and F-SF (89%).

9. For the other face-sensitive clusters (Figure 1. 3.; Table 1. 3.) identified at that threshold, the response properties are quite equivalent between the two contrasts.

Table 1. 3. Comparison between the 3 contrasts: F-O, F-O and the conjunction for the core and extended system found at size of ‘‘FFA’’ equivalent.

		F-SF		F-O		SF-SO		O-SO	
		t	**p**	**t**	**p**	**t**	**p**	**t**	**p**
Right ‘‘FFA’’ Found with	**F-SF**	14.528	0.000000	5.42	0.000003	3.741	0.000589	18.509	0.000000
	F-O	8.597	0.000000	9.859	0.000000	5.287	0.000005	7.307	0.000000
	Conjunction	9.866	0.000000	8.583	0.000000	5.093	0.000009	9.287	0.000000
Right ‘‘OFA’’ Found with	**F-SF**	9.236	0.000000	1.414	0.165317	2.995	0.004750	10.581	0.000000
	F-O	3.569	0.000970	7.843	0.000000	2.86	0.006771	-3.841	0.000439
	Conjunction	5.737	0.000001	5.926	0.000000	0.826	0.414073	0.171	0.865143
Right STS Found with	**F-SF**	/	/	/	/	/	/	/	/
	F-O	7.193	0.000000	9.943	0.000000	5.964	0.000001	4.01	0.000266
	Conjunction	7.417	0.000000	7.616	0.000000	2.675	0.010868	1.993	0.053245
Right amygdala Found with	**F-SF**	11.421	0.000000	10.967	0.000000	-0.163	0.871186	2.628	0.012209
	F-O	10.834	0.000000	10.462	0.000000	-0.375	0.709587	2.037	0.048502
	Conjunction	11.041	0.000000	10.647	0.000000	-0.407	0.685873	2.068	0.045351
Right temporal pole Found with	**F-SF**	/	/	/	/	/	/	/	/
	F-O	5.312	0.000005	7.493	0.000000	2.233	0.031358	2.11	0.041320
	Conjunction	6.795	0.000000	7.781	0.000000	1.934	0.060348	3.128	0.003321

Objects – Scrambled objects

10. We found 3 clusters at q(FDR)<0.001 (Supplementary Figure 1. 3.; Supplementary Table 1. 1.): the right middle occipital gyrus (BA 19) which is the right dorsal posterior vertex of LO, one large right region encompassing the right fusiform gyrus, parahippocampus gyrus and inferior occipital gyrus corresponding to the right ventral posterior vertex of LO and ventral anterior vertex mixed and one large left region encompassing the left fusiform gyrus, parahippocampus gyrus and inferior occipital gyrus corresponding to the left ventral posterior vertex of LO and ventral anterior vertex and left dorsal posterior vertex mixed [Grill-Spector and Malach (1999), lateral occipital complex=LOC= 3 vertices: dorsal and ventral posterior vertex (LO) and ventral anterior vertex (PF/Loa)]. There is a slight right hemispheric dominance for O-SO (55% of voxels, excluding the cerebellum). In the ventral LOC cluster, the level of activation is no different for faces and objects (p=0.429823).

Interaction [(F-SF) – (O-SO)]

11. At q(FDR)<0.001 (t=5.22), we found only 4 clusters (Supplementary Table 1. 2.): the right and left amygdalas, the left cuneus and a region of the right inferior occipital cortex which is quite low-level (O+F=SF+SO, p=0.852202). The ‘‘FFA’’ was not identified by this contrast which is emphasizing more the specificity than the sensitivity to faces.

Conjunction [(F-SF) and (F-O)]

The conjunction contrast identified 8 face-sensitive clusters at q(FDR)<0.001 (t=5.09), including the ‘‘FFA’’ and ‘‘OFA’’ (Table 1. 4. A.). There was a strong right hemispheric dominance, with only the amygdala identified in the left hemisphere.

Table 1. 4. A. Talairach locations of all the regions found in the random analysis for the 40 right-handed subjects.

Contrast: CONJUNCTION: (F-O) and (F-SF)

at q(fdr)<0.001:	Talairach Coordinates:			Cluster size:
	x	y	z	mm^3
Right fusiform gyrus (BA 37) = right ''FFA''	39	-44	-16	**152**
Right inferior occipital gyrus (BA 18) = right ''OFA''	29	-85	-11	**7**
Right superior temporal sulcus	46	-41	10	**76**
Right (lateral) superior temporal sulcus	57	-51	9	**13**
Right amygdala	19	-6	-9	**625**
Right hippocampus	30	-22	-5	**8**
Right thalamus (pulvinar)	8	-29	1	**26**
Left amygdala	-21	-5	-9	**446**

Lowering the statistical threshold to obtain 500 mm^3 in the middle right fusiform [t = 4.29; q(FDR)<0.01] identified 16 clusters (Figure 1. 4.; Table 1. 4. B.), and allowed us to make the following observations:

Table 1. 4. B. Talairach locations of all the regions found in the random analysis for the 40 right-handed subjects.

Contrast: CONJUNCTION: (F-O) and (F-SF)

when a right ''FFA'' of 500 mm^3 is considered:	Talairach Coordinates:			Cluster size:
	x	y	z	mm^3
Right fusiform gyrus (BA 37) = right ''FFA''	38	-43	-17	**501**
Right inferior occipital gyrus (BA 18) = right ''OFA''	29	-84	-12	**169**
Right superior temporal sulcus	48	-48	9	**1089**
Right superior temporal sulcus	40	-53	16	**19**
Right amygdala	20	-6	-9	**1144**
Right perirhinal cortex and fusiform gyrus (BA 38)	28	0	-28	**178**
Right precentral gyrus (BA 6)	34	2	34	**8**
Right precentral gyrus (BA 6)	34	5	28	**33**
Right hippocampus	31	-23	-5	**41**
Right thalamus (pulvinar)	6	-29	1	**149**
Right thalamus (lateral genicule nucleus)	9	-23	-5	**12**
Right thalamus (medial dorsal part)	1	-16	7	**14**
Left amygdala	-21	-6	-10	**846**
Left cuneus (BA 17)	-8	-74	7	**58**
Left thalamus (medial dorsal part)	-1	-11	7	**12**
Cerebellum (oculomoteur vermis)	-2	-56	-23	**102**

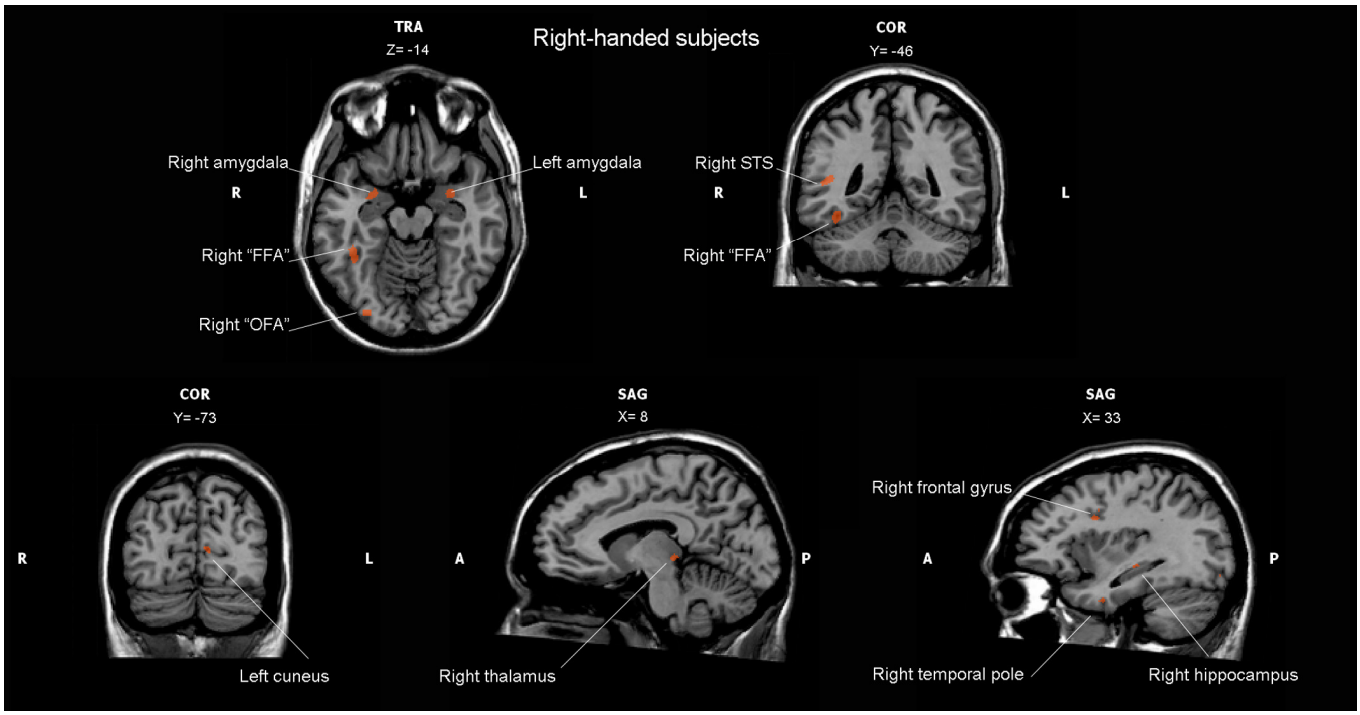


Figure 1. 4. Group analysis (random effect) revealing the set of face-preferential areas at a conservative statistical threshold (fixed size of FFA = 500 mm3, t=4.29) in the conjunction contrast: [(F-SF) & (F-O)]. Note the right hemispheric dominance for the areas usually disclosed (''FFA'', ''OFA'', pSTS), but also for face-preferential activations observed in the anterior temporal lobe, prefrontal cortex and hippocampus.

12. There is a strong right hemispheric dominance (79% of voxels, excluding cerebellum[21]) and neither ''FFA'' nor ''OFA'' were found in the left hemisphere.

13. In the right hemisphere, we identify the 3 clusters of the "core system" devoted at the visual analysis (Haxby et al., 2000): the right middle fusiform gyrus (BA 37) or ''FFA'', the right inferior occipital gyrus (BA 18) or ''OFA'', and the pSTS. We also find 3 clusters of the extended face processing system: the right amygdale, the left amygdala, and the right AiT (right perirhinal and fusiform cortex, BA 38). (Figure 1. 4.).

[21] With cerebellum, we have 72.87% (if we consider separately men and women, we have 72.10% for men and 73.09% for women).

14. Among all the areas identified (Figure 1. 3.; Table 1. 3.) the ‘‘FFA’’ is the least face-specific, in the sense that it responds also strongly to non face objects (O-SO, $p<0.000001$). Moreover, it responds also highly to low-level characteristics of faces (SF-SO, $p<0.00001$). Note that these contrasts are not independent of the area's definition, which minimized the response to O and SF. Hence, the sensitivity to objects and scrambled faces, relative to scrambled objects, is even more remarkable.

15. In contrast, the ‘‘OFA’’ identified responds to all stimuli, but does not show any difference of activation for O *vs.* SO ($p=0.865143$). Moreover, its sensitivity to faces cannot be accounted at all by low-level visual properties (SF - SO, $p=0.414073$; Figure 1. 3.). Among the other face-preferential areas identified, there were small but significant effects of O-SO in the right amygdala and AiT ($ps<0.05$), and in the right STS for SF-SO ($p<0.01$) (all other $ps>0.05$).

16. The conjunction analysis also disclosed a number of other potentially interesting face-sensitive clusters (Figure 1. 4., Figure 1. 5.; Table 1. 4. B., Table 1. 4. C.) in the right prefrontal cortex (NS for SF-SO and O-SO) at the junction between the Precentral Gyrus and Inferior frontal Gyrus (Operculum part), in the dorsal part of the right middle hippocampus (NS for SF-SO and O-SO), in the pulvinar (NS for SF-SO and O-SO). There was also a small cluster close to the left primary visual cortex V1 [left cuneus (BA 17)] where all conditions were deactivated compared to baseline, but the deactivation was less pronounced for faces, and one cluster in the cerebellum.

3.1. Characterizing the face processing network in the human brain: a large-scale fMRI localizer study

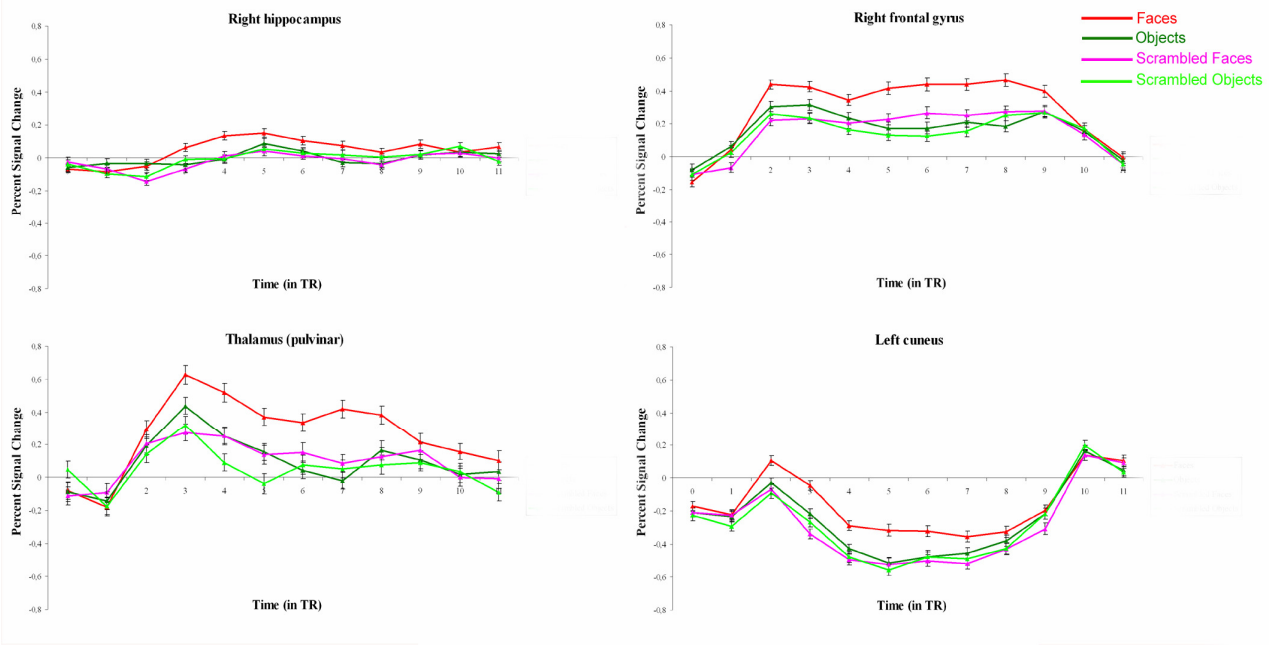


Figure 1. 5. Signals percent changes for the clusters belonging not to the core and extended system for the conjunction contrast (F-SF) and (F-O) (‘‘FFA’’ = 501 mm³; t=4.29).

Table 1. 4. C. Face’s specificity for the regions found in the random analysis for the 40 right-handed subjects. Contrast: CONJUNCTION: (F-O) and (F-SF)

when a right ‘‘FFA’’ of 500 mm^3 is considered:	SF-SO t	SF-SO p	O-SO t	O-SO p
Right fusiform gyrus (BA 37) = right ‘‘FFA’’	5.093	*0.000009*	9.287	*0.000000*
Right inferior occipital gyrus (BA 18) = right ‘‘OFA’’	0.826	*0.414073*	0.171	*0.865143*
Right superior temporal sulcus[22]	2.675	*0.010868*	1.993	*0.053245*
Right amygdala	-0.407	*0.685873*	2.068	*0.045351*
Right perirhinal cortex and fusiform gyrus (BA 38)	1.934	*0.060348*	3.128	*0.003321*
Right precentral gyrus (BA 6)[23]	1.916	*0.062708*	0.648	*0.521084*
Right hippocampus	-0.873	*0.387931*	0.171	*0.865175*
Right thalamus (pulvinar)	1.752	*0.087565*	1.819	*0.076573*
Left cuneus (BA 17)	-1.248	*0.219490*	1.255	*0.216956*
Left amygdala	0.140	*0.889644*	2.645	*0.011713*

[22] For the other more little STS we have the same behaviour except for SF-SO which is not significant (t=1.612, p<0.115060)

[23] The two clusters together.

17. When considering the whole primary visual cortex (V1), defined anatomically (1, -88, 2; 4750 voxels), there was more activation for phase-scrambled than non scrambled stimuli (SF+SO>F+O, p<0.000000[24]). However, there was also a higher sensitivity to low-level properties of faces (F>O, p<0.000000; SF>SO, p<0.000145; Supplementary Figure 1. 4.) probably due to top-down selection or inhibition of non pertinent information or restriction to one part of the visual field.

18. Finally, in order to disclose face-sensitive areas in the left hemisphere, the statistical threshold has to be reduced substantially. At q(FDR)<0.05 (t=3.38), we find 10 additional clusters[25], including 7 clusters in the left hemisphere (Table 1. 4. D.).

Table 1. 4. D. Talairach locations of the NEW[26] regions found in the random analysis for the 40 right-handed subjects when the threshold is minimum. Contrast: CONJUNCTION: (F-O) and (F-SF)

at q(fdr)<0.05 (right ''FFA'' = 1212 mm^3)	**Talairach Coordinates:**			**Cluster size:**
	x	**y**	**z**	**mm^3**
Left fusiform gyrus (BA 37) = left ''FFA''	-39	-40	-20	**18**
Left fusiform gyrus (BA 37) = left ''FFA''	-42	-49	-17	**10**
Left inferior occipital gyrus (BA 18) = left ''OFA''	-30	-84	-13	**100**
Left superior temporal sulcus	-44	-48	10	**18**
Left perirhinal cortex and fusiform gyrus (BA 38)	-28	2	-25	**19**
Left precentral gyrus (BA 6)	-35	4	31	**62**
Left hippocampus	-22	-22	-4	**20**
Right cuneus (BA 17)	10	-68	7	**140**
Precuneus	2	-58	37	**148**
Inferior rostral gyrus	2	41	-5	**17**

[24] But SF>SO>F>O, the 3 beeing significant: t=4.21, t=5.60, t=8.08 respectively.

[25] We find also more activity in the cerebellum and in the thalamus (left and right).

[26] Except thamamus' and cerebellum's regions.

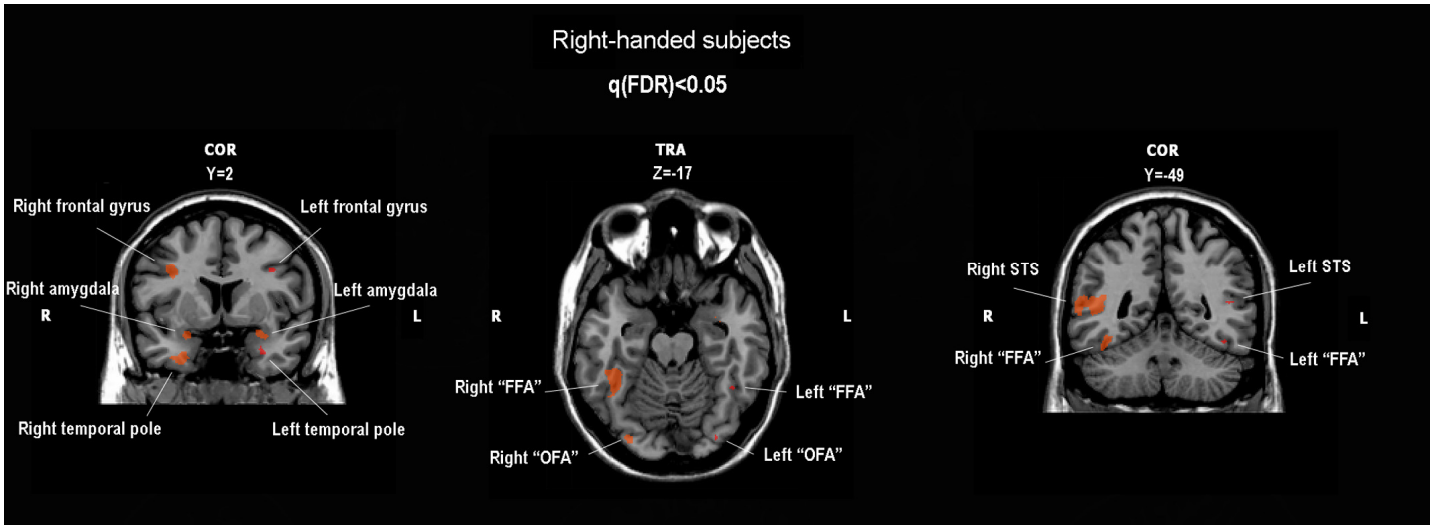


Figure 1. 6. Activation map at the limit of q(FDR)<0.05 (t=3.39) for the conjunction contrast: (F-SF) and (F-O). Group analysis (random effect) revealing the set of face-preferential areas at the limit of q(FDR)<0.05 (t=3.39) in the conjunction contrast: [(F-SF) & (F-O)]. Note the right hemispheric dominance (in size) for the areas usually disclosed (''FFA'', ''OFA'', pSTS), but also for face-preferential activations observed in the anterior temporal lobe, prefrontal cortex and hippocampus.

19. These 7 face-sensitive areas all have homologous regions in the right hemisphere, activated at a more severe threshold (Figure 1. 6.; Table 1. 4. D.). Among these clusters, we found 2 small significant clusters in the left fusiform gyrus (BA 37) of 18 mm^3 and 10 mm^3, which could both correspond to the left ''FFA'' [the global size (28 mm^3) =2.3% of the right ''FFA'''s size at this q(FDR) threshold (1212 mm^3 in the right middle fusiform)], 1 cluster in the left inferior occipital gyrus (BA 18) of 100 mm^3, corresponding to a left ''OFA'' [=15.1% of the right ''OFA'' size (662 mm^3)], and a small cluster in the STS of 18 mm^3[=0.4% of the right STS's size (4730 mm^3)]. Other clusters were found in the left precentral gyrus [BA 6, 62 mm^3 =12.6% of the right equivalent region's size (491 mm^3)], anterior inferior temporal cortex [BA 38, 19 mm^3 =2.5% of the right

equivalent region's size (748 mm³)], and left hippocampus [20 mm^3 =11.2% of the right equivalent region's size (178mm³)][27].

20. Face-preferential areas of the left hemisphere show more or less the same response profile as their right homologous areas (Figure 1. 7.; Table 1. 4. E.). The left ''FFA'' responds significantly to non face objects (O-SO: p<0.00081) and its preferential response to faces is partly driven by low-level features (SF-SO: p<0.000001). Apart for the left ''OFA'', which also shows lower significant responses for the same contrasts (O-SO p<0.017137; SF-SO, p<0.008861), the other face-sensitive areas of the left hemisphere (pSTS, amygdala and AiT) seem to present a truly (or at least higher) specific response to the high-level characteristics of faces (Table 1. 4. E.).

Table 1. 4. E. Face's specificity for the additional regions found in the random analysis for the 40 right-handed subjects when the threshold is minimum. Contrast: CONJUNCTION: (F-O) and (F-SF)

	SF-SO t	**SF-SO p**	**O-SO t**	**O-SO p**
Left fusiform gyrus (BA 37) = left ''FFA''[28]	3.632	*0.000808*	6.601	*0.000000*
Left inferior occipital gyrus (BA 18) = left ''OFA''	2.764	*0.008661*	2.478	*0.017637*
Left superior temporal sulcus	0.999	*0.324024*	2.842	*0.007094*
Left perirhinal cortex and fusiform gyrus (BA 38)	0.908	*0.369229*	1.036	*0.306659*
Left precentral gyrus (BA 6)	0.565	*0.575010*	1.196	*0.238779*
Left hippocampus	1.013	*0.317228*	1.100	*0.277910*

[27] The 3 other clusters are: 1 cluster of 140 mm³ in the right cuneus and one in the precuneus (148 mm³) where the condition F is less desactivated than the other conditions and one central cluster in the inferior rostral gyrus (17 mm³).

[28] Two clusters together

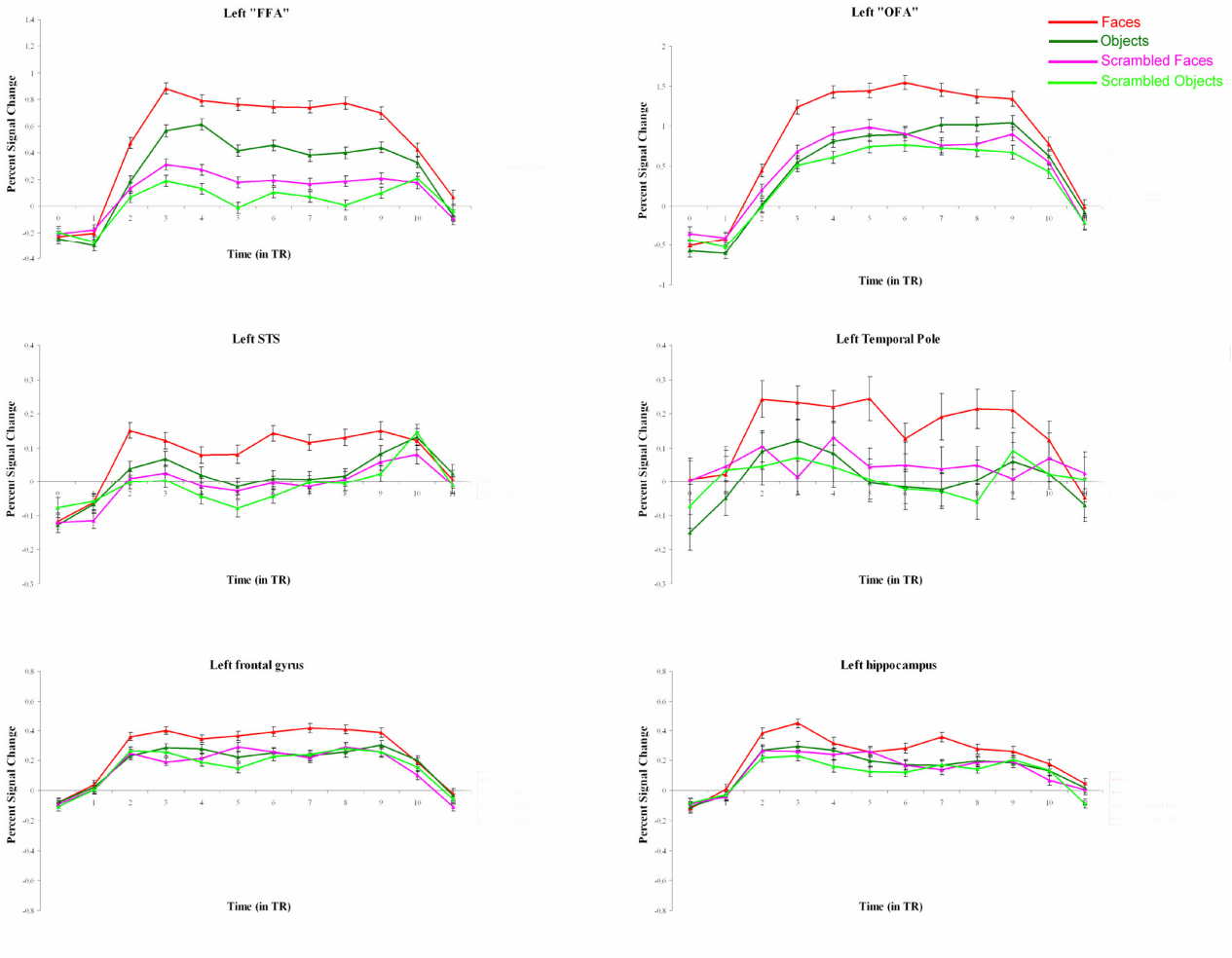


Figure 1. 7. Signals percent changes for the new regions found in the random analysis when the threshold is minimum [conjunction contrast (F-SF) and (F-O) at the limit of q(FDR)<0.05 (t=3.39)]. The left ''OFA'' like the right ''OFA'' (Figure 1. 3.) responds above baseline for all conditions, but it is not more sensitive to low-level aspects of faces (scrambled faces) than objects, and does not respond more to objects than scrambled objects either. Thus, in the left hemisphere as in the right one, the left ''OFA'' appears to show a more specific response to faces than the left FFA.

Conjunction (O-F) and (O-SO)

21. This analysis at q(FDR)<0.001 (t=5.09) revealed 3 clusters (Supplementary Table 1. 3.) which are the right parahippocampus gyrus, the right inferior occipital gyrus (BA 18 or 19) and a huge cluster encompassing the left parahippocampus gyrus until the left inferior occipital gyrus (BA 18 or 19). There is a left hemispheric dominance (64% of total voxels), which is due to the right dominance of faces (O-SO alone: 45% of left voxels).

In summary, there were a number of interesting observations from the group analysis of this factorial localizer paradigm. **First,** a conjunction contrast [(F-O) and (F-SF)] appears to be optimal in revealing the set of areas particularly involved in face processing. This contrast identifies the ‘‘FFA’’ better than an interaction contrast [(F-O) - (SF-SO)], given that the ‘‘FFA’’ responds largely to objects and to low-level properties of faces, which are given a too strong weight in the interaction contrast. **Second,** there are clear advantages in using such a conjunction contrast as compared to the individual F-O and F-SF contrasts, which are traditionally used. While these contrasts give rise to largely overlapping ‘‘FFA’’s, the definition of the other areas of the set can vary greatly, in particular the ‘‘OFA’’. This observation has important consequences because it indicates that it is not the same region that is identified in different studies as the ‘‘OFA’’, and which is sometimes compared across studies for its response properties (see general discussion). **Third,** there is a strong RH dominance in the set of areas responding preferentially or specifically to faces. Yet, the corresponding face-preferential areas (‘‘FFA’’, ‘‘OFA’’, pSTS, AiT, amygdala, frontal gyrus) are found in the left hemisphere when lowering the statistical threshold, with a remarkable homology. Given that we reported only the statistical analysis at the group level at this stage, it may be that the smaller activation for faces in the left hemisphere is due to one of several factors, or a combination of factors: a general decrease in height of the signal in these left hemisphere areas, or a decrease specific to faces, or more variance in the height of the signal across subjects or yet more variance in the spatial localization of these areas across subjects. We will address this issue below. **Fourth,** importantly and surprisingly, we found that the ‘‘FFA’’, if anything, shows the least face-specific response compared to the other areas: it responds largely to nonface objects too, and is also sensitive to low-level properties (e.g., spatial frequencies) of faces.

Individual subject analysis

In the individual participant analysis, we used the conjunction contrast [(F-FS) and (F-O)] and fixed the size of the ‘‘FFA’’ (right middle fusiform gyrus, BA 37) at 200 mm^3 to identify the

other face-sensitive regions (see Fox et al., 2009 for a similar approach with 50 mm^3 cluster size of ‘‘FFA’’). At this threshold, 4 participants only out of 40 did not present a significant activation in the ‘‘FFA’’ ($t<1.97$) and were not taken into consideration. We made the following observations:

1. There is a huge amount of variability between individual participants in terms of the level of activation of their fusiform gyrus in response to faces. The average t value was at 4.33 with a standard deviation of 1.23.

2. The number of areas identified (Supplementary Table 1. 5. A. and 1. 5. B.) at that criterion (fixed ‘‘FFA’’ size), and their spatial distribution also vary a lot across participants. The correlation between the t value at the ‘‘FFA’’ fixed and the number of whole brain ($\rho=-0.39$, $p<0.02$) explained only 15% of the variance between subjects. The remaining variance must thus be accounted for by the individual variability of the face network (see below).

<u>The fusiform gyrus</u>

<u>The right fusiform gyrus</u>

3. With respect to the right ‘‘FFA’’ found at 200 mm^3 in 36 individual participants, we observed for 15 of these 36 participants a second smaller area ($t_{14}=8.79$, $p<2.2EX-7$ between the right ‘‘FFA’’ and this second area for the 15 subjects) activated in the anterior fusiform (BA 20) (different than AiT; Figure 1. 8.). This region contains 70.40 mm^3+/-69.13 mm^3 in the 15 subjects. For 6 of the 36 participants, we also found a second spatially distinct face-sensitive area in the middle fusiform gyrus (48 mm^3+/-45.86.13 mm^3 in the 6 subjects, $t_5=6.64$, $p<0.0006$ between the right ‘‘FFA’’ and this second area in the middle fusiform gyrus for the 6 subjects). In two participants, the three clusters could be identified and well separated spatially. The total number of voxels which were face-sensitive in the right middle fusiform gyrus for the 36 participants was: 215.44 mm^3+/-31.57 mm^3.

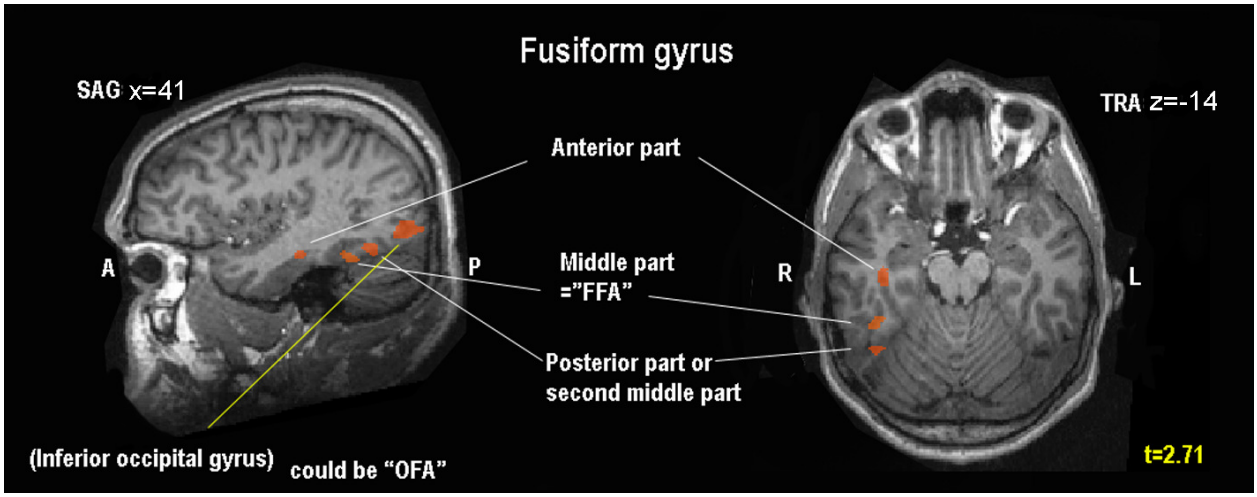


Figure 1. 8. One subject showing 4 significant (and well separated spatially) clusters in the conjunction contrast [(F-SF) & (F-O)] in the ventral stream, with one cluster in between the ''FFA'' and ''OFA'' (also identified by Weiner & Grill-Spector, 2010) and one cluster anterior (BA 20, different than AiT), to the usual localization of the ''FFA''.

4. The anterior fusiform face-sensitive area found in 15 participants has a higher degree of high-level face-specificity than the ''FFA''. The contrast SF-SO is not significant (t_{14}=1.63, p=0.125, random effect in ROI analysis) contrary to the right ''FFA'' (t_{14}=2.64, p<0.019, random effect in ROI analysis) and the difference between the two regions is significant (t_{14}=1.75, p<0.05). The contrast O-SO is significant for the two regions (t_{14}=6.35, p<0.000018 for the anterior region and t=9.67, p<0.000000 for the ''FFA'', random effect in ROI analysis) but higher for the "''FFA''" than for the anterior region (t_{14}=2.97, p<0.005).

<u>The left fusiform gyrus</u>

5. A left ''FFA'' (BA 37) is found in 31 participants (mean size: 149.46 mm^3+/-229.31 mm^3 in the 31 subjects). For 14 of these 31 participants, we also find a second area in the anterior fusiform (BA 20) (102,21mm^3+/-164.04 mm^3 in the 14 subjects, this region is not smaller in size than the left ''FFA''; t_{13}=0.76, p=0.23 between the left ''FFA'' and this second area for the 14 subjects). In three of these 31 participants, there is also an second area in the middle fusiform gyrus (30.67mm^3+/-7.23 mm^3 in the 3 subjects; t_2=5.06, p<0.018). The total

amount of voxels in the left middle fusiform gyrus calculated on the whole group of 36 participants is: 150.89 mm^3+/-218.25 mm^3.

6. The left anterior fusiform face-sensitive area found in 14 participants has a higher degree of high-level face-sensitivity than the left ‘‘FFA’’. The contrast SF-SO is not significant (t_{13}=0.91, p=0.381, random effect in ROI analysis) contrary to the left ‘‘FFA’’ which is significant (t_{13}=2.181, p<0.048) and the difference between the two regions is significant (t_{13}=1.74, p<0.052). The contrast O-SO is significant for the two regions (t_{13}=5.00, p<0.000243 for the anterior region and t_{13}=5.502, p<0.000102 for the ‘‘FFA’’) without difference between the two regions (t_{13}=1.28, p=0.116).

<u>If we compare the right and the left hemispheres:</u>

7. The left ‘‘FFA’’ is smaller in size than the right ‘‘FFA’’ (t_{35}=1.740, p<0.045). However, there is no difference for the anterior fusiform (t_{35}=-0.52, p=0.303). The lateralization of the ‘‘FFA’’ (number of voxels in the right middle fusiform/ number of voxels in the left and right middle fusiform) is 71.02% +/-25.83, which is not different than of mean value considering all areas of the network (67.91% +/- 18.70) (t_{35}=-1.02, p=0.157). The lateralization of the anterior region is 50.54% +/-44.61% on 22 subjects (14 subjects has no anterior regions), which is lesser than of mean value considering all areas of the network (67.91% +/- 18.70%) (t_{21}=2.18, p<0.020).

8. The left ‘‘FFA’’ found in 31 participants has a higher degree of high-level face-sensitivity than the right ‘‘FFA’’. The difference between the two regions for the contrast SF-SO is significant (t_{30}=1.71, p<0.048). 7 subjects have the two anterior fusiform activated (right and left): there is no difference between the two sides for the contrast SF-SO (t_6=0.778, p=0.233) but there is a difference for the contrast O-SO (t_6=2.23, p<0.030). To summarize the contrast SF-SO is significant for the right ‘‘FFA’’ and not for the 3 others regions (left ‘‘FFA’’ and

the right and left anterior regions) and the contrast O-SO is significant for the 4 regions but significantly lesser for the right anterior region in comparison to the 3 others.

9. Interestingly, the disparity in spatial localization is greater in the left than the right ‘‘FFA’’. We find a significant difference when we compare the distances for each right ‘‘FFA’’ from the centre of the all 36 right ‘‘FFA’’s (centre is the mean Talairach coordinates) to the distances for each of the 31 left ‘‘FFA’’s from the centre of the 31 left ‘‘FFA’’s (t_{65}=1.67, p<0.050 ; Figure 1. 9.). We don’t find the same for the anterior region (t_{27}=0.30, p=0.38).

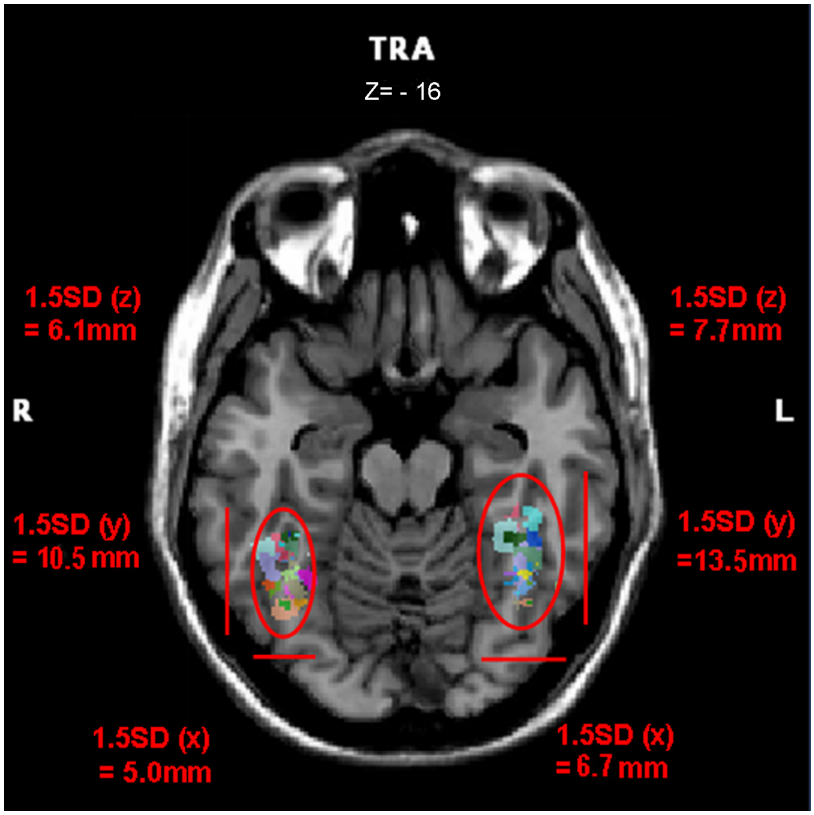


Figure 1. 9. Disparity in spatial localization for the right and left ‘‘FFA’’s. There a significant difference when we compare the distances for each right ‘‘FFA’’ from the centre of the all 36 right ‘‘FFA’’s (centre is the mean Talairach coordinates) to the distances for each of the 31 left ‘‘FFA’’s from the centre of the 31 left ‘‘FFA’’s (t_{65}=1.67, p<0.050).

The inferior occipital cortex

10. At fixed (200 mm^3) size of right ‘‘FFA’’, and considering all the clusters found in the posterior part of the fusiform gyrus (in the occipital lobe, BA 19) and in the inferior occipital gyrus (BA 18 or 19), we found at least one right face-sensitive area for 27 participants and one left area for 24 participants. 20 participants have regions in both hemispheres and 5 in none of the sides. In the right hemisphere, 10 participants have two face-sensitive clusters in the occipital lobe, and 2 participants have 3 clusters. In the left hemisphere, 4 participants have 2 clusters and one has 3 clusters. All these spatially distinct regions could be considered as ‘‘OFA’’s and 30% of the subjects could have more than one right ‘‘OFA’’ and 8.33% more than one left ‘‘OFA’’s (Figure 1. 10.).

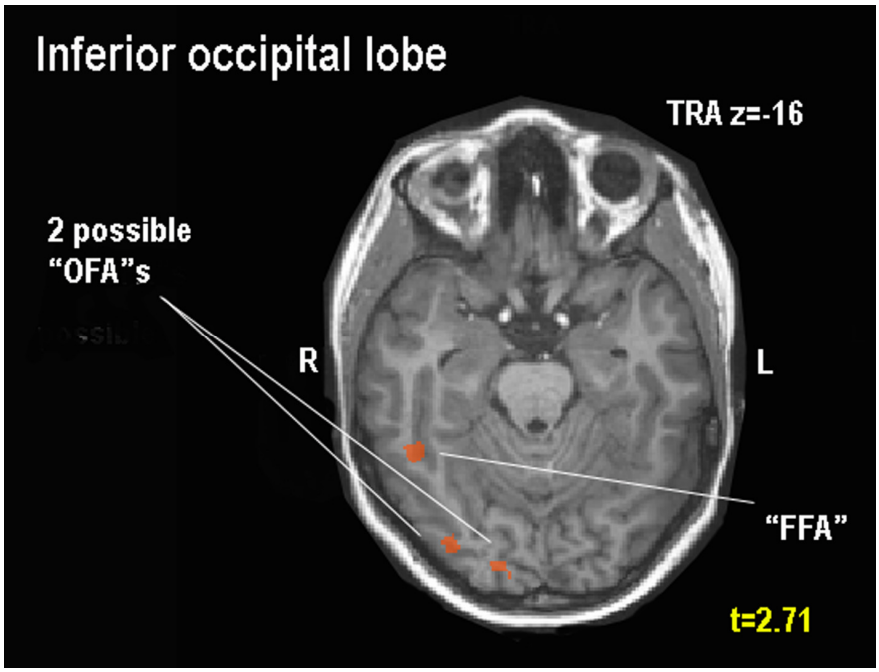


Figure 1. 10. Subject with two right areas activated in the inferior occipital gyrus. The clusters could be identified wand well separated spatially and both of them could be considered as ‘‘OFA’’s.

11. The difference between the sum of all face-sensitive voxels in the right and left hemispheres is almost significant (right: 104.06 mm^3 +/-274.02 mm^3; left: 112.75 mm^3 +/-358.28 mm^3, t_{35}=1.47, p=0.075 if we consider all the 36 subjects and right: 162.32 mm^3 +/-201.86 mm^3; left: 78.11 mm^3 +/-109.82 mm^3, t_{19}=1.67, p=0.056 if we consider the 20 subjects having regions on both sides).

12. Interestingly (see Table 1. 5. for the size of the regions), we found for 8 subjects one area activated in the right posterior part of the fusiform gyrus (9 on the left), for 12 subjects one area in the right inferior occipital gyrus, BA 19 (11 on the left), and for 20 subjects one area in the right inferior occipital gyrus, BA 18 (10 on the left). This spatial dominance of the right inferior occipital gyrus explains why only this region is found in the random analysis. If we compare the size of the areas activated in the 3 right regions [Anova 1*3] we found a significant difference ($F_{2,37}$=3.28, p<0.044) due to the larger size of the region found on the BA 18 (t_{35}=2;35, p<0.016 with the BA 19 and t_{35}=2;35, p<0.016 with the right fusiform posterior). We don't find difference between the left regions ($F_{2,27}$=0.003, p=0.997). If we compare the right and the left side for all the subjects, we found only a difference between the right and left BA 18 (t_{35}=2.35, p<0.016) and not between the right and left posterior fusiform (t_{35}=0.27, p=0.395,) and between the right and left BA 19 (t_{35}=-2.27, p=0.394). The lateralization of the ''OFA'' (number of voxels in the right / number of voxels in the left and right) is 61.50% +/-38.79% which is not different than of mean value considering all areas of the network (66.77% +/- 18.81%) (t_{31}=-0.914, p=0.184).

Table 1. 5. At fixed (200 mm^3) size of right ‘‘FFA’’, all the clusters found in the posterior part of the fusiform gyrus (in the occipital lobe, BA 19) and in the inferior occipital gyrus (BA 18 or 19) for the 36 subjects of the individual analysis.

	Right posterior fusiform gyrus		**Right inferior occipital gyrus, BA 19**		**Right inferior occipital gyrus, BA 18**		**Total in right**	
Number of subjects	8		12		20		27	
Mean size and standard-deviation (mm^3)	114,43	*+/-112,72*	45,08	*+/-54,30*	109,52	*+/-167,82*	140,08	*+/-184,81*
Mean size and standard-deviation on the 36 subjects (mm^3)	22,89	*+/-66,32*	15,46	*+/-37,75*	65,71	*+/-139,75*	104,06	*+/-170,21*

	Left posterior fusiform gyrus		**Left inferior occipital gyrus, BA 19**		**Left inferior occipital gyrus, BA 18**		**Total in left**	
Number of subjects	9		11		10		24	
Mean size and standard-deviation (mm^3)	80,50	*+/-140,00*	61,73	*+/-134,69*	70,78	*+/-82,59*	85,22	*+/-131,03*
Mean size and standard-deviation on the 36 subjects (mm^3)	18,40	*+/-72,19*	19,40	*+/-78,62*	18,20	*+/-50,89*	56,00	*+/-113,11*

13. We can notify that the region found in the right BA 18 (20 participants)[29] has a high degree of high-level face-sensitivity. The contrast SF-SO is not significant (t_{18}=0.944, p=0.360, random effect in ROI analysis). The contrast O-SO is significant (t_{18}=3.012, p=0.008, random effect in ROI analysis) but lesser than the right ''FFA'' of the 20 subjects (t_{19}=2.09, p<0.025). On the equivalent left region (8 subjects), the mean t is at 0.175 for the contrast SF-SO but not significantly lesser than the left ''FFA'' (t_7=1.24, p=0.129). The contrast O-SO is at 3.544 and is lesser than the left ''FFA'' of the 8 subjects (t_7=1.90, p<0.050).

14. There is no difference between disparities in spatial localization: t_{15}=0.99, p=0.17 for the posterior part of the fusiform gyrus, t_{21}=0.09, p=0.47 for the inferior occipital gyrus, BA 19 and t_{28}=0.83, p=0.21 for the inferior occipital gyrus, BA 18.

<u>The STS</u>

15. We found activity in the STS for 24 participants out of 36 and in the left posterior STS for 13 subjects but we find often different clusters in the superior temporal sulcus per subject. 10 subjects have activity on the both side. If we consider the global number we found a mean of 228.75 mm^3 +/-337.33 on the right for the 24 subjects and a mean of 137.85 mm^3 +/-217.91 on the left for the 13 subjects. The left STS is very smaller in size than the right STS (t_{35}=2.83 p<0.004 for the 36 subjects in total and t_9=2.3, p<0.023 for the 10 subjects having STS on both sides). The lateralization of the STS (number of voxels in the right / number of voxels in the left and right) is 76.85% +/-36.28 which is more than of mean value considering all areas of the network (64.65% +/- 18.82%) (t_{26}=1.90, p=0.034) (9 subjects have none region). If we looked more in details we found that for our 24 participants having activities in the right STS, 6 subjects have two regions, 3 have 3, 2 have 4 and 1 have 5 on the right posterior STS (Talairach coordinates y<-35). Like for the

[29] We didn't analyse the other regions in random effect (number of subjects<10).

''OFA''s is not easy to choose which cluster to consider as the STS (Figure 1. 11.). More, 8 of the 24 have also activities in a more right anterior part (Talairach coordinates y>-35) of the STS (3 of the 8 have 2 regions). For our 13 subjects having activities in the left STS, 4 participants have 2 regions, one have 3 and one have 4 in the left posterior STS (Talairach coordinates y<-35). None of them have activities in the anterior part (Talairach coordinates y>-35) of the left STS.

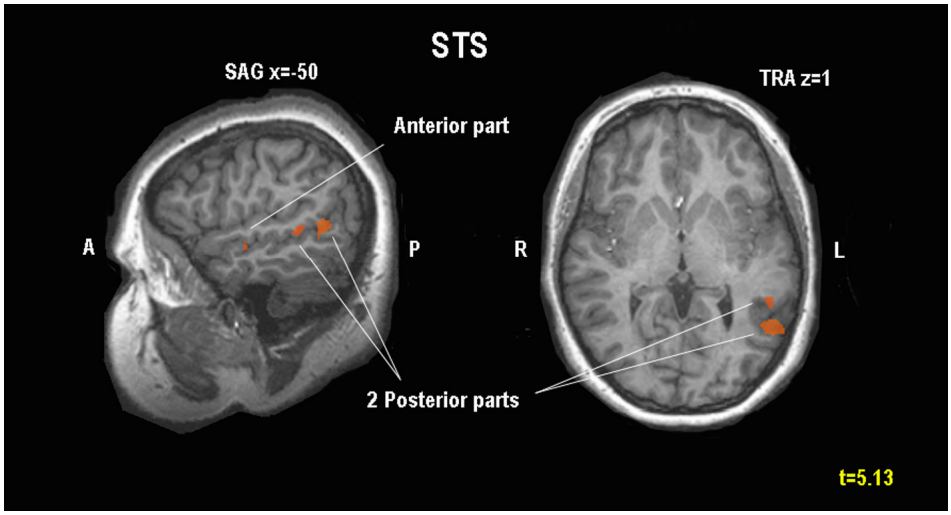


Figure 1. 11. Subject with left areas activated in STS. One (or two) region is (are) the classical pSTSs and the other one is activated in the anterior part of the STS.

16. The right STS has a high degree of high-level face-sensitivity. The contrast SF-SO is not significant (t_{23}=1.20, p=0.217, random effect in ROI analysis). The contrast O-SO is significant (t_{23}=7.173, p=0.000000, random effect in ROI analysis) but lesser than the right ''FFA'' of the 24 subjects (t_{23}=7.30, p<9.84EX-8). The left STS presents the same high degree of high-level face-sensitivity. The contrast SF-SO is not significant (t_{12}=-1.22, p=0.247, random effect in ROI analysis). The contrast O-SO is significant (t_{12}=2.24, p<0.045, random effect in ROI analysis) but lesser than the right ''FFA'' of the 13 subjects (t_{12}=4.99, p<0.00016, paired t-test), lesser than the left ''FFA'' (only 12 participants of the 13 have a left ''FFA'', t_{11}=9.18, p<8.63EX-7), and lesser than the right STS (10 participants of the 13 have a right STS, t_9=2.131, p<0.031).

There is no difference between the disparity in spatial localization: t_{35}=-1.16, p=0.13, for the posterior part of STS.

Other areas

17. With respect to the other areas of the network identified in the random analysis, there were very few clusters found at the individual participant level: bilateral amygdala in 1 out of 36 participants, right AiT (right perirhinal and fusiform cortex, BA 38) in 8 participants (97.75 mm^3 +/-160.45 mm^3) and left AiT in 4 participants (mean of 52.75 mm^3 +/-64.38 mm^3). Two of these participants presented bilateral AiT activations. Face-sensitivity in the precentral gyrus (BA 6) was found for 9 participants in the hemisphere right (24.44 mm^3 +/-39.33 mm^3) and 2 of these participants also presented a cluster in the left homologous region (mean of 21.00 mm^3 +/-28.28 mm^3). We notice only for one subject an activation in the right hippocampus and for 3 subjects one activation in the left cuneus (BA 17, mean of 31.33 mm^3 +/-12.01 mm^3). This means that these regions are slightly but consistently activated in face processing. There is no difference between the disparity in spatial localization: t_9=-1.44, p=0.09 for the precentral gyrus but there is one for the AIT: t_{10}=4.31, p<0.0005.

Bold latency mapping (Figure 1. 12., Table 1. 6.)

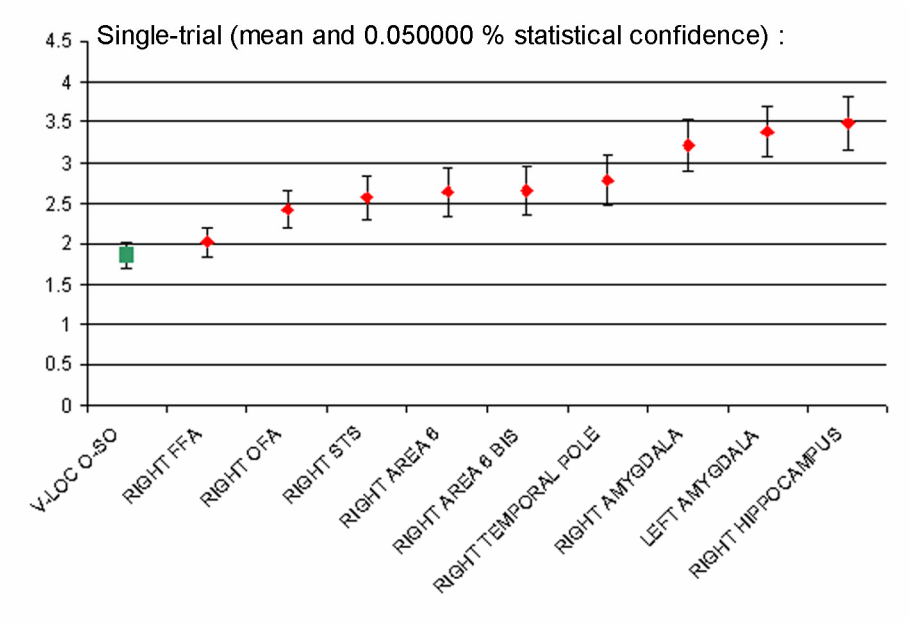


Figure 1. 12. Results of the bold latency mapping analysis. Onset time of the response to first face in each block (432 trials in total) across the areas of the core and extended face network [conjunction contrast, t = 4.29; q(FDR)<0.01] and in the posterior ventral part of the LO (Grill-Spector and Malach, 1999), area not specific for faces. Among all areas responding preferentially to faces, the right FFA shows the earliest onset response, significantly before the OFA (t_{18}=4.00, p<0.0008). It is activated as early as the ventral part of the LO complex (t_{18}=-1.880, p=0.076).

When the onset time of the response to first face in each block (36 subjects, 12 trials per subject, 432 trials in total) is compared across the regions of the core and extended face network [conjunction contrast, t = 4.29; q(FDR)<0.01], the right ‘‘FFA’’ is the fastest region of the face network even before the ‘‘OFA’’ (t_{18}=3.96, p<0.0005) and is activated as fast (t_{18}=-1.880, p=0.0764) as the ventral posterior part of the LO complex (Grill-Spector and Malach, 1999), region not specific for faces. This early response of the ‘‘FFA’’ is associated with a lower variance across trials (see Table 1. 6.). In order to take this issue into account we chose only the 20 subjects with one ‘‘OFA’’ defined in the inferior occipital gyrus (BA 18). The right ‘‘FFA’’ is yet the fastest

region of the face network (2.35 +/-0.17 s and 2.53 +/-0.15 for the ‘‘OFA’’) but the p is only almost significant due to the lesser number of subjects (p<0.09).

Table 1. 6. Comparison of the bold estimation of the onset time of the response to first face in each block of faces (480 trials in total) for each region of the core and extended network found with the conjunction (F-O) and (F-SF).

Regions of the core and extended network (random analysis)	**Onset (second) [Single-trial (mean and 0.050000 % statistical confidence)]**		**Distance from the calcarine (mm) (x=0 y=-75 z=5)**
Right ‘‘FFA’’	2.017	0.182	54
Right ‘‘OFA’’	2.428	0.237	35
Right STS	2.561	0.273	55
Right area 6	2.632	0.297	89
Right area 6 BIS	2.649	0.299	90
Right temporal pole	2.786	0.303	86
Right amygdala	3.211	0.314	73
Left amygdala	3.384	0.310	74
Right hippocampus	3.487	0.335	61
*v-LOC **	*1.860 (faces)* *1.808 (objects)*	*0.162* *0.158*	*42*

*region found with the contrast O-SO. (F-O not significant)

3.1.5. General discussion

In this large-scale fMRI face localizer study, we made a number of observations that may be important both for methodological (optimization of the face localizer approach) and theoretical (neural basis of face recognition) reasons. We discuss these two issues in turn.

3.1.5.1. Methodological issues

Optimization of face localizers

Functional localizers are widely used in neuroimaging studies of high level vision, and in face perception studies in particular, in order to define functional areas of interest that can be further tested for their response properties. We would like to argue that the functional localizer used in the present study presents several interests, when compared to functional localizers used in previous studies.

First, by performing the conjunction of two contrasts (F-SF and F-O), it allows controlling *simultaneously* for high-level (shape-specific) and low-level characteristics of faces. Following Kanwisher et al. (1997), most studies define the ‘‘FFA’’ and other face-preferential areas by comparing directly faces to objects, without taking into account their low-level differences (see Berman et al., 2010, Table 1). Hence, these studies include in their ROI definition some voxels that may not be sensitive to face representation *per se*, but to low-level properties that intrinsically differ between faces and objects (e.g., spatial frequencies, Bosworth et al., 2006; Keil, 2008; 2009; Keil et al., 2008). Other studies identify these areas by contrasting faces to scrambled faces only (e.g., Eger et al., 2004; Ishai et al., 2006; Fairhall and Ishai, 2007; see Berman et al., 2010, Table 1). This latter definition is simply inappropriate if one wants to make inferences about areas specifically or even preferentially involved for faces, because the areas identified may respond equally large if pictures of nonface objects are contrasted to their scrambled counterparts (i.e., the LOC). As our observations indicate (see also Berman et al., 2010), these two different procedures (S-SF or F-O) do not affect the localization of the ‘‘FFA’’’s center of activation to a great extent (Figures 1. 2. and 1. 3.). However, its size may change substantially, and separating the ‘‘FFA’’ from the ‘‘OFA’’ may be difficult with the contrast F-SF unless one uses a very conservative threshold. Moreover, other face-preferential areas may vary tremendously in terms of localization and significance. Finally, we note that while others (Yue et al, 2006) have used conjunction contrasts as used here, they did not use phase-scrambled stimuli in which face and object features cannot be identified, and which do not contain any information about shape.

A second interest of the present localizer is that rather than contrasting faces to multiple objects mixed up in the same condition, it relies only on a single category for comparison. This approach avoids the bias of having a much larger variability in shape, color and texture in the object condition compared to the face condition. We chose to use cars as the category of comparison to faces, for a number of reasons detailed in the methods section, and which make cars excellent

control stimuli in our opinion (better than pictures of houses, which are commonly used in such studies). Admittedly, there are also some limitations due to this particular choice of cars as a category. For instance, one cannot exclude that the voxels identified as responding preferentially to faces here also respond strongly to living things in general. Moreover, it would be wise to ensure that subjects of a given study are not experts in recognizing makes of cars, since their ‘‘FFA’’ might be smaller when contrasting faces to cars (Gauthier et al., 2000b; Xu et al., 2005).

Third, and this is related to the previous point, this localizer can be done with an active one-back task, which allows monitoring subjects' level of attention during the task, and is certainly preferable to passive viewing. Moreover, comparing faces to multiple objects in a one back task, as in Kanwisher et al. (1997) and many subsequent studies, is problematic because performing a one-back task is much easier for objects differing in shape, color, texture than for the more visually homogenous faces. Since these areas increase their level of activation with subjects' level of attention to faces (e.g., Gentile and Jansma, 2010; Wojciulik and Kanwisher, 1998), using a (one-back) task that is harder for faces than objects may artificially inflates the face-preferential response of the areas. Hence, equalizing as much as possible the level of difficulty of the one-back task for faces and control objects is important. Here, with a normal sample of subjects for an fMRI experiment, the performance is almost equal for faces and cars in the one-back task (subjects are still slightly faster for cars). Hence, contrary to face localizers that contrast faces to multiple objects in a one-back task, differences in activation cannot be attributed to differences in task difficulty but to real differences in the representation of different visual categories.

Fourth, while quite well controlled, the present localizer appears to also show robustness and sensitivity in terms of identifying the different areas of interest, across the whole brain. With the scanning parameters on a 3T scanner, it provides 48 measures of the entire brain by condition. In individual subjects, the two runs recorded allow performing the following contrast: [(F-SF run1 and

F-SF run2) and (F-O run1 and F-O run2)]. This procedure cancels a large part of the noise and inconsistencies between runs (as noted by e.g., Duncan et al., 2009).

Fifth, the same localizer can be used to define general object areas (LOC, Lateral Occipital Complex, Malach et al., 1999) by means of the contrast O-SO (rather than O-F, which is sometimes used to define the LOC, e.g., Andrews et al., 2004).

All in all, considering these issues, we argue that the version of the face localizer introduced in the current study present a number of advantages over the localizer procedures used in previous fMRI studies.

Interindividual variance and ROI definition

At the group level, the set of areas responding preferentially to faces is easily identified by the conjunction contrast [(F-O) and (F-SF)]: one area in the lateral part of inferior occipital gyrus (‘‘OFA’’), one in the middle fusiform gyrus (‘‘FFA’’), one or possibly two in the superior temporal sulcus (pSTS), one in the medial part of the infero-temporal cortex, the amygdala, as well as activations in the hippocampus and the precentral sulcus (Figures 1. 4. and 1. 6.). All these areas show a much stronger face preferential response in the right than the left hemisphere, but when the statistical threshold is less conservative they are found in both hemispheres at homologous locations (Figure 1. 6.).

These areas are identified in a group analysis because they show a strong preferential response to faces that cannot be accounted for by low-level features, but also because they are activated by all, or at least a large subset, of the subjects. Moreover, in order to disclose these activations at the group level there must be a sufficient overlap between the localization of face-preferential activation in the different individual brains. These factors all play a role in accounting for the magnitude of face preferential activation in these areas in a group analysis. For instance, face preferential activation in the amygdalas is difficult to disclose at the individual level (significant in

only 1 subject out of 40 here), but since there is a much smaller variance across individual brains in the localization of this area than for the ‘‘FFA’’ for instance, a highly significant face preferential response in the amygdalas is observed at the group level. More generally, the present study shows that there is a huge amount of inter-individual variance in terms of statistical threshold, spatial extent and localization of the face-preferential areas across participants.

In addition, a substantial number of participants present face preferential responses in more than one area in the inferior occipital gyrus, in the fusiform gyrus, or in the posterior STS. This variance across subjects in terms of the number of clusters activated cannot be merely accounted for by an overall level of activation, or sensitivity to faces, that also differs across participants. Indeed, the height of the t value (mean 4.24 ± 1.24 SD) in the right ‘‘FFA’’ obtained in the conjunction analysis when the size of the area is fixed at 200mm^3 for each participant accounts only for 15% of the variance in terms of all activated voxels by this contrast. In other words, if a participant presents a particularly highly significant right ‘‘FFA’’, it does not necessarily mean that he/she will present a particularly large number of face-preferential areas, or that other face-preferential areas will also be highly significant compared to other participants of the study: there are genuine differences across individuals in terms of relative sizes of the different face preferential areas in the brain. *Consequently, using the exact same statistical criterion to identify a given area in each individual brain of a group of participants is not be recommended*. If the same conservative statistical threshold is used for all individual brains for instance, the ‘‘FFA’’ or other areas might be identified only in a subset of participants. If a liberal statistical threshold is used, the areas might too large in size in some individual brains, so that they overlap with each other (e.g., ‘‘OFA’’ merged with ‘‘FFA’’, see Figure 1. 2.). Thus, using a different statistical threshold for each individual brain in order to define the ROIs seems to be the correct way of dealing with this issue. Yet, if one wants to use a common threshold, then fixing the size of a given area appears to be the best procedure. We

recommend fixing the right ‘‘FFA’’’ size because it is relatively easily identified in all individual brains (Berman et al., 2010; Fox et al, 2009; the present study).

If needed, the ‘‘FFA’’’ size can be increased in order to identify areas that are less significantly activated such as the AiT or amygdala[30]. Moreover, when several areas are potential candidates for known areas of the “core” and “extended” system (Haxby et al., 2000), the experimenter can use additional criteria to label the areas correctly in individual brains. First, the level of activation for objects and scrambled faces is informative because it differs between the different areas. For instance, the ‘‘FFA’’ responds largely to objects and scrambled faces, while the area in the anterior fusiform gyrus (see below), or the ‘‘OFA’’, do not respond to scrambled faces and only to a small extent to nonface objects. Second, anatomical criteria, such as the spatial relations of the face areas to retinotopic visual areas, as well as to areas responding more to body parts than objects, can also be used (Weiner and Grill-Spector, 2010).

3.1.5.2. Neural underpinnings of face perception

A large set of areas

At the group level, the conjunction of contrasts identified a large set of areas distributed in the right hemisphere, in the inferior occipital cortex (“Occipital Face area”, Gauthier et al., 2000a), the middle fusiform gyrus (“Fusiform Face area”, Kanwisher et al., 1997), the infero-temporal cortex [AiT], the posterior part of the superior temporal sulcus (pSTS, Puce et al., 1998) and the amygdalas (Morris et al., 1996). These areas are well known and were all included in the “core” and “extended” neural face processing system defined by Haxby et al. (2000). These observations thus confirm the large distribution of face representations in the human brain (see also Fox et al., 2009; Ishai, 2008; Tovée, 1998; Tsao et al., 2008; Pinsk et al., 2009; as well as Pinsk et al., 2009; Tsao et al., 2006; 2008 in the monkey brain). All of these areas respond largely to faces and not, or to a very

[30] Note that the amygdala can also be defined anatomically.

small extent, to objects or scrambled faces. The only notable exception is the ‘‘FFA’’, which responds also largely to objects and scrambled faces (see below).

In addition, we also found face preferential activation in the right hippocampus and the prefrontal cortex, the thalamus bilaterally, and the left cuneus. Even though their function may be quite general, these additional areas appear to play a greater role for faces than the objects used in the present localizer,. The area found in the right hippocampus may be particularly involved when using a one-back recognition task with repetition of visual stimuli (Düzel et al., 2003), and has also been disclosed in a previous study during non-conscious face recognition (Henke et al., 2003). The area activated in the prefrontal cortex is located between the precentral gyrus and the inferior fontal gyrus (operculum), and has also been found to be involved during one-back tasks, particularly when object representations need to be updated (Bar et al, 2001; Derrfuss et al., 2005) or when the difficulty related to a face task increases (Schiltz et al., 2010). Activation of the thalamus has often been found in visual attention tasks (Robertson et al., 1993). As for the left cuneus, BOLD signal in this area indicates a smaller deactivation for faces than the other conditions of the study, suggesting that this area is part of a face network pre-activated in ‘‘resting state’’ (Zhang et al., 2009).

The many face-preferential clusters in fusiform, inferior occipital gyrus and superior temporal sulcus

Although this area was not evinced in the group analysis, many participants (60%) presented with another significant cluster in the fusiform gyrus (BA 20), slightly anterior but clearly spatially different than the area identified as the ‘‘FFA’’ (BA 37) in these subjects (Figure 1. 8.). This anterior fusiform face area was bilateral and also showed a more specific response to faces than the ‘‘FFA’’. An anterior face-preferential response has been described in recent studies (Tsao et al., 2008) in many individual brains and labeled the AFP1 (anterior face patch 1). However, it unclear if this area rather referred to the AiT cluster identified also here and in other studies (e.g., Rajimerh et al., 2009; Nestor et al., 2008), whereas it was clearly distinguishable from the AiT here. For a

substantial amount of subjects, we also found two significant clusters in the STS, as also reported in recent studies (Fox et al., 2009; Pinsk et al., 2009), as well as two clusters in the inferior occipital cortex (‘‘OFA’’). The second cluster in the inferior occipital cortex, located in between the ‘‘FFA’’ (middle occipital gyrus, BA37) and ‘‘OFA’’ (inferior occipital gyrus, BA 18), in the posterior fusiform gyrus (pFus) or in the inferior occipital gyrus (BA 19), has also been described previously. However, it has either been combined with the anterior cluster to form the ‘‘FFA’’ (e.g., Grill-Spector et al., 2004), or used as the ‘‘OFA’’ (e.g., Rotshtein et al., 2005: 42, -69, -18 –Talairach coordinates). Recently, two studies defined these areas specifically in the human brain, as ‘‘FFA’’-1 (Pinsk et al., 2009) or pFus (Weiner and Grill-Spector, 2010).

Hence, a simple localizer as used here may already be sufficient to reveal a quite large set of areas showing a preferential (or exclusive) response to faces. The small number of subjects showing many additional areas than the ones identified in the group analysis may just be due to a lack of power with two face localizer runs. If many runs of the same experiment were performed in every single subject, then it is likely that in each individual brain, a set of 6 or more areas responding preferentially to faces would be find in the ventral visual stream only, as in the monkey brain (Tsao et al., 2006; 2008; Pinsk et al., 2009). This observation complicates seriously the definition of the areas of interest in individual participants of a given study (which area “really” corresponds to the ‘‘FFA’’?). With respect to the ‘‘OFA’’-‘‘FFA’’ and the area identified in between the two in the posterior fusiform gyrus, Weiner and Grill-Spector (2010) suggests that anatomical criteria should be used, i.e. a location of these face-preferential clusters with respect to functionally defined retinotopic visual areas. From a theoretical point of view, while the presence of many face clusters or areas all along the ventral stream is in agreement with early PET and intracranial recording studies of face processing (Sergent et al., 1992; Allison et al., 1994; 1999), it raises important issues: why so many areas showing a preferential response to faces? Why are they spatially separated all along the ventral stream?, what are the function(s) of these different areas?

Right hemispheric dominance for face perception across the whole set of areas

The right hemispheric dominance for unfamiliar face perception is now a well-established fact. Acquired prosopagnosia follow either bilateral or right unilateral occipito-temporal lesions (Bouvier and Engel, 2006; Hécaen and Anguerlgues, 1962; Landis et al., 1988). Left unilateral lesions are found in only a handful of cases of prosopagnosia, all left-handed (Mattson et al., 2000; Barton, 2009) but one case with epilepsy (Wright et al., 2006). Multiple sources of evidence ranging from divided visual field studies (Hillger and Koenig, 1991; Parkin and Williamson, 1987), event-related potentials [ERPs, e.g. (Bentin et al., 1996; Rossion et al., 2003b)] or single-cell recordings in the nonhuman primate brain (Perrett et al., 1988) have supported the dominant role of the right posterior visual areas in processing face stimuli [see also (Zangenehpour and Chaudhuri, 2005)]. Neuroimaging studies have also largely supported the right hemispheric dominance for face perception [e.g., (Kanwisher et al., 1997; McCarthy et al., 1997; Sergent et al., 1992)]. Yet, strangely enough, current models of the neural basis of face processing based on neuroimaging (Haxby et al., 2000; Ishai, 2008) do not even consider this RH bias. Moreover, the extent of the RH bias has not been specified by neuroimaging studies, which have either focused on the right ‘‘FFA’’ only (Kanwisher et al., 1997; McCarthy et al., 1997) or on the whole ventro-temporal cortex without distinguishing different areas (Sergent et al., 1992).

It is worth noting that two factors contribute to the massive right lateralization found at the group level here. First, a strong preferential response to faces larger in the right than the left hemisphere for all, or at least a large subset, of the subjects. Second, a larger overlap between the localization of face-preferential activation in the right than in the left different individual brains. Considering these two factors, when one performs a group analysis, the areas that survive a conservative statistical threshold are all localized in the right hemisphere. The only exception is the amygdala, which is found bilaterally (with a right hemisphere advantage also) and for which the spatial disparity factor is not at play.

As our individual analysis indicates, this right lateralization does not only concern the ‘‘FFA’’ (lateralization index: 71%), but also the ‘‘OFA’’ (61%) and the pSTS (77%), the latter showing the strongest lateralization index of all the areas of the network (average, 68%). Moreover, the spatial disparity between the ROI localization of different individual brains appears to be larger in the left than the right hemisphere, at least as far as the ‘‘FFA’’ and AiT are concerned (Figure 1. 9.). This is a novel observation of the present study.

The reason(s) behind this lateralization of function remains somewhat unclear. The classical view holds that the right hemisphere is specialized in holistic processing and the left in analytic processing, with the faces considered as a typical example of a visual stimulus requiring global/holistic/configural perception (Bradshaw and Nettleton 1981; Levy, 1969; Nebes, 1971; Sperry, 1974; for a review see Sergent, 1988). Divided visual field studies have supported this view, whether the face stimuli have to be merely categorized as faces (Parkin and Williamson, 1987; see also Crouzet et al., 2010) or individualized (Hillger and Koenig, 1991; Levy et al., 1972; although see Sergent, 1984). Further studies have shown that the RH specialization for faces is related to the processing of low-spatial frequency information (de Schonen and Mathivet, 1989; Sergent, 1985), which supports holistic processing (Goffaux and Rossion, 2006; Sergent, 1986). Studies of cases of prosopagnosia have also supported this view, since the syndrome is often associated with the inability to process individual faces holistically (e.g., Levine and Calvanio, 1989; Ramon et al., 2010; Sergent and Signoret, 1992; Sergent and Villemure, 1989). More recently, neuroimaging studies have shown that when holistic processing of faces is required or enhanced, the right hemisphere dominance over the left hemisphere increases significantly, in particular at the level of the ‘‘FFA’’ (Dricot et al., submitted; Goffaux et al., 2010; Harris and Aguirre, 2010; Rossion et al., 2000; Schiltz and Rossion, 2006; Schiltz et al., 2010).

Note that all areas showing a preferential response to faces do not have to be involved in holistic face processing to show a RH bias. It may be that there is a right hemispheric bias in the

first area of the network that shows face-preferential response (e.g. the ‘‘FFA’’, see Rossion, 2008, Goffaux et al., 2010, and below), and that this bias is then carried over in the remaining part of the network, at least when faces are not associated with semantic and verbal representations. Finally, with respect to this issue, we also note that a right hemisphere lateralization of the face network is not found in all individual brains, but in an extensive majority of right-handed individuals and a smaller majority of left-handed individuals (see Badzakova-Trajkov et al., 2010). It would be interesting to test in future studies the extent to which behavioral performance in face processing tasks is related to hemispheric dominance as identified in fMRI. Moreover, there is recent evidence that face-preferential activation in the ‘‘FFA’’ is bilateral in left-handers rather than being right lateralized (Willems et al., 2009). We are currently investigating whether this observation holds in the whole network of areas with the functional localizer reported here.

The ‘‘FFA’’ as the least face-specific area of the whole set

The ‘‘FFA’’ is not a face-specific area

The BOLD responses in the different areas revealed a surprising observation: among all areas showing a preferential response to pictures of faces, the area showing the least specific response to faces was the (bilateral) ‘‘FFA’’. This was true both for the group analysis and the individual subjects’ data. Indeed, the ‘‘FFA’’ responded to a large extent to pictures of cars (above baseline and significantly above the response to scrambled cars). This is not a novel observation, as the ‘‘FFA’’ is known to respond to such familiar stimuli as cars from many previous studies (e.g., Dricot et al., 2008; Gauthier et al., 2000b; Grill-Spector et al., 2006; Harel et al., 2010; Peelen et al., 2009; Xu, 2005), and to all kinds of object shapes in fact (e.g., Kanwisher et al., 1997; Ishai et al., 2005; Tsao et al., 2008). Moreover, object-related activation in the ‘‘FFA’’ appears to be functional, since large repetition suppression, or adaptation, effects are also found for nonface objects in the ‘‘FFA’’ (Avidan et al., 2005 ; Dricot et al., 2008 ; Grill-Spector et al., 2001).

The larger response to faces may be due to all voxels in the ‘‘FFA’’ responding more but not exclusively to faces than objects, or to the ‘‘FFA’’ being composed of a subpopulation of voxels responding specifically to faces interspersed with other clusters responding equally strongly to all object categories (Grill-Spector et al., 2006; 2007). Since electrophysiological recordings in a putative homologous area in the monkey brain identifies neurons that respond exclusively to faces (Tsao et al., 2006), it is the latter interpretation that is probably correct. High-resolution fMRI also supports this view (Grill-Spector et al., 2006; 2007). However, a new observation of the present study is that the other areas identified in the face localizer do not present, or to a much small extent, a significant response to pictures of cars. While a BOLD response above baseline was found for cars also in the ‘‘OFA’’ and perhaps in the pSTS, it did not differ between cars and their scrambled counterparts. Thus, contrary to the ‘‘FFA’’, there is a general response to visual stimuli in these areas with a particular increase for stimuli perceived as faces. Moreover, in the pSTS, amygdala and AiT, the response to all other conditions than faces was not even above baseline (Supplementary Table 1. 4.). As acknowledged above, it may be that these areas would show a significant response to other object shapes, for instance pictures of birds or mammals, as used in some studies (Gauthier et al., 2000a, Xu, 2005). A significant response to body parts, which is found in the ‘‘FFA’’ (Chao et al., 1999; Pinsk et al., 2009 ; Tsao et al., 2008; Weiner and Grill-Spector, 2010;), may also be observed in these other areas forming the face network. Nevertheless, with cars, we used a highly familiar and complex control visual stimulus, and yet we did not find much evidence for tuning to these nonface shapes in these other areas.

Considering that the ‘‘FFA’’ is the face-preferential area that shows the least degree of specificity, it is difficult to understand, and somehow regrettable, that so many studies have focused almost exclusively on the ‘‘FFA’’ to address important issues about the nature of face representation (e.g., Kanwisher et al., 1997; 1998; Loffler et al., 2005 ; Yue et al., 2010; Wilkinson et al., 2000). Most importantly, the issue of whether the larger response to faces in areas of the

human brain reflect domain-specific processes or rather flexible processes that can be modulated by visual expertise has often focused exclusively on the ‘‘FFA’’ (Kanwisher, 2000; Tarr and Gauthier, 2000; Kanwisher and Yovel, 2006), which is in fact the area showing evidently the least degree of specialization for faces. To be honest, this focus on a single area has often been advocated by proponents of the domain-specificity view (e.g., Yovel and Kanwisher, 2004), while effects of visual expertise have also been tested in some other areas such as the ‘‘OFA’’ or the anterior fusiform gyrus (e.g., Gauthier et al., 1999). In any case, we believe that the important and yet unresolved question of whether faces are supported by domain-specific neural representations or representations that can accommodate nonface geometries following visual expertise should be considered at the level of the entire network of areas rather than a single area. The present observations in fact suggest that this question might even be more relevant in other areas of the network – who show little or no response to nonface objects in novices – than in the ‘‘FFA’’.

Sensitivity to low-level features of faces in the ‘‘FFA’’

Another interesting observation is that the ‘‘FFA’’, contrary to, or much more than, other face-preferential areas, responds significantly more to low-level features of faces, i.e. phase-scrambled faces, than low-level features of objects, i.e. phase-scrambled cars. This observation cannot be accounted for by the definition of the area because, if anything, the contrast we used selected voxels showing the minimal response to scrambled faces. This is a novel observation of the present study: the ‘‘FFA’’ appears to respond to low-level features that differ between faces and other objects (at least cars). These low-level features cannot be the overall luminance of our set of images, or the size of the stimuli (equalized between conditions). Rather, these low-level features could be of two kinds.

First, differences in amplitude spectrum for face and car images (i.e., amplitude at the different frequencies). It has been shown that faces have specific characteristics in the frequency domain (Bosworth et al., 2006; Keil, 2008; 2009; Keil et al., 2008), and amplitude spectrum (AS)

has been claimed to account for face-specific effects, such as the face pop-out effect in visual search (Vanrullen, 2006, but see Herschler and Hochstein, 2006). AS also appears to contribute to fast saccadic responses towards faces (Crouzet and Thorpe, 2010; Honey et al., 2008), even though phase information (i.e., the structure of a face) accounts for the largest part of such effects (Crouzet and Thorpe, 2010; Morand et al., 2010).

A second low-level characteristic that may contribute to the differences observed in the ‘‘FFA’’ signal between scrambled faces and scrambled cars is color. Even though the role of color in object categorization has been minimized by a number of studies (e.g., Biederman and Ju, 1988), it is clear that color contribute to object categorization at multiples levels (see Price and Humphreys, 1989; Rossion and Pourtois, 2004; Tanaka et al., 2001). With respect to faces, there is evidence that face-specific neurons in the monkey infero-temporal cortex are sensitive to the diagnostic color of faces as a category. If faces are presented in gray-level, or in non-diagnostic color (e.g., a blue face), the cells' response is attenuated and delayed compared to the response to normally colorized faces (Edwards et al., 2003). Here, the scrambled stimuli used preserved the overall color that characterize faces, and which was clearly different than the cars' colors. In fact, if subjects were asked to categorize the scrambled images used in the present experiment according to their category, they would probably rely heavily on color to do the task. Another aspect worth mentioning is that color is certainly more uniform for a car picture compared to a face picture, but the variations of colors *between* items presented in a block were certainly smaller for faces than cars. Unless all stimuli would be presented in grayscale, this parameter is particularly difficult to control, and may also have played a role in the differences observed. An event-related fMRI experiment with the same stimuli would help clarifying and controlling better the contribution of this factor to the effects observed.

Usually, the contribution of low-level parameters to behavioral face categorization is interpreted as evidence for a contribution of low-level visual areas, or pathways, rather than the

dominant classical ventral visual stream (Honey et al., 2008: Vanrullen, 2006). However, the present observations question this interpretation: a high-level visual area such as the ‘‘FFA’’, whose response is driven largely by phase information of the images and which has been associated with the phenomenological perception of a face (e.g., Jiang and He, 2006; Tong et al., 1998), is also particularly sensitive to the low-level features that characterize face stimuli.

Overall, these observations are in agreement with the findings that the ‘‘FFA’’ does not only respond preferentially to the perception of a face *per se*, but is sensitive to low-level features in general, such as size, contrast and position of the (face) stimuli (Yue et al., 2010), as well as to simple characteristics of visual stimuli that are shared by faces (e.g., concentric form, higher number of elements in the top part of the stimulus, see Wilkinson et al., 2000; Caldara et al., 2006, respectively). Unfortunately, most of these previous studies concentrated on the ‘‘FFA’’ only, but did not investigate the response to such manipulations in other face-preferential areas of the network. Here, we found that while the ‘‘FFA’’ was tuned to low-level features of faces (presumably amplitude spectrum and color), other areas of the network responded preferentially to high-level features of faces only: the difference between scrambled faces and scrambled cars was small and even non-significant in many of these areas: ‘‘OFA’’, amygdala, pSTS. Interestingly, and somewhat paradoxically, the ‘‘OFA’’, which is located much more posteriorly than the ‘‘FFA’’, was less sensitive to low-level features of faces than the ‘‘FFA’’. This observation is compatible with the view that the ‘‘FFA’’ may be the earliest area of the network to show a preferential response to faces, an issue that we address below.

The ‘‘OFA’’ and the timing precedence of the ‘‘FFA’’

Even at a conservative statistical threshold, the group analysis identified an area in the lateral inferior occipital cortex of the right hemisphere that responded preferentially to faces, which corresponded well to the ‘‘OFA’’ (also called the inferior occipital gyrus in some studies, e.g., Schiltz and Rossion, 2006; Weiner and Grill-Spector, 2010). The ‘‘OFA’’ has been largely

overlooked by the community of neuroimagers interested in the neural basis of face processing, for several reasons.

First, the influential study of Kanwisher et al. (1997), in which the ‘‘OFA’’ was also visible, focused exclusively on the ‘‘FFA’’, which was considered by the authors as being the single area carrying out face perception. As a result, a large number of subsequent studies interested in understanding the nature of face representation also focused exclusively on the ‘‘FFA’’ (Kanwisher et al., 1998; Loffler et al., 2005, with reviews devoted specifically to this area: Berman et al., 2010; Kanwisher and Yovel, 2006), neglecting the ‘‘OFA’’. Moreover, a number of neuroimaging studies using face localizers are not interested in face processing *per se*, but use the response properties of the most well-known and easily identifiable ‘‘FFA’’ to address other theoretical issues.

Second, the ‘‘FFA’’ is the largest area in size among the area showing a preferential response to faces (e.g., Tsao et al., 2008). In comparison, the ‘‘OFA’’ is smaller in size and is less consistently disclosed in individual brains (e.g., Gilaie-Dotan and Malach, 2007; Rossion et al., 2003). Here, in the right hemisphere, we found the ‘‘FFA’’ in 36 subjects, and the ‘‘OFA’’ in 27 subjects of our individual analysis. The ‘‘OFA’’ is also an area that is less consistent across studies in terms of its average coordinates (compare the ‘‘OFA’’ localization in e.g. Rotshtein et al., 2005 and Rossion et al., 2003). However, even with the less powerful and spatially crude PET method, the ‘‘OFA’’ could already be identified and clearly separated from the ‘‘FFA’’ in the right hemisphere (Rossion et al., 2000). Nowadays, with more powerful magnets and analysis methods, face preferential responses in the inferior occipital cortex are now found consistently, and should no longer be ignored. Moreover, lesion studies suggest a critical role of this area in face processing, with some studies reporting that the largest overlap of lesions causing prosopagnosia falls in the territory of the right ‘‘OFA’’ rather than the right ‘‘FFA’’ (Bouvier and Engel, 2006). Also, transcranial magnetic stimulation (TMS) applied to the right ‘‘OFA’’ (but not the left ‘’OFA’’ or right LOC) affects various aspects of face processing (Pitcher et al., 2007; 2008; 2009; Cohen-

Kadosh et al., 2010). FMRI studies have also identified areas responding preferentially to faces in the occipital cortex of the monkey, which have been related to the ''OFA'' (Tsao et al., 2008; Pinsk et al., 2009).

Here, interestingly, the ''OFA'' showed a higher degree of specificity to face perception than the ''FFA'', since there was no sensitivity to object shape in this area (scrambled cars not different than cars), and no evidence of a preferential response for scrambled faces over scrambled cars. Hence, the ''OFA'' appears to present a higher degree of face specificity than the ''FFA'', with the caveat that we compared faces to only one category (cars, see Weiner and Grill-Spector, 2010). This observation strengthens the claim that face-preferential responses in the inferior occipital cortex need to be taken into account when addressing issues concerning the domain-specificity and nature of face representation in the human brain (Tovee et al., 1998; Rossion et al., 2003)[31].

The contribution of the ''OFA'' to face perception is unclear. According to the classical view of the flow of information in visual cortex, the ''OFA'' would be the first relay of a hierarchy of face processing stages taking place in the ventral stream and beyond (amygdala, prefrontal cortex) (Haxby et al., 2000; Ishai, 2008). In line with this view, some authors have suggested that the ''OFA'' would play a rather low-level role in face processing (Eger et al., 2005; Rothstein et al., 2005). Supporting evidence come from the modelization of effective connectivity by means of DCM, revealing exclusive feedfoward outputs from the ''OFA'' to the ''FFA'' and pSTS within the core aspect of the face perception model (Fairhall and Ishai, 2007). TMS to the ''OFA'' also impairs processing of facial parts in faces if it is applied early on (dual pulses, 60-100 ms, Pitcher et al., 2007). However, the interpretation of these findings is problematic, in particular because of the

[31] Our findings may appear to contradict the statement that the ''OFA'' is the least face-selective area of the whole set (Tsao et al., 2008, Fig. S8; Weiner and Grill-Spector, 2010). However, in the latter study, the authors defined the areas and measured face-preference indexes without considering low-level responses to scrambled stimuli. Given the low-level parameters enhance the preferential response to faces of the ''FFA'' but not the ''OFA'', it is not surprising that Tsao et al. (2008) reached this conclusion, which is technically correct but does not concern the preferential response to face presentations *per se*. Note also that the labeling of this area as an ''OFA'' in Tsao et al. (2008)' study is subject to caution (see Weiner and Grill-Spector, 2010).

‘‘OFA’’ definition in these studies. For instance, Fairhall and Ishai (2007) as well as Eger et al. (2005) defined the ‘‘OFA’’ as a large area of the occipital cortex responding more to faces than scrambled faces (F-SF), as illustrated here in Figure 1. 2. The domain-preference or specificity of this area is unknown in these studies, and according to our observations, it should not have been labeled an ‘‘OFA’’ because it encompasses the whole LOC at least. Thus, it is not surprising that other fMRI studies using DCM have found opposite results than Fairhall and Ishai (2007) with stronger outputs from ‘‘FFA’’ to ‘‘OFA’’ than the opposite during face processing (Rotshtein et al., 2007 who has defined the ‘‘OFA’’ in contrasting high and low spatial-frequency components in faces). Similarly, Pitcher et al. (2007) defined the ‘‘OFA’’ based on an average coordinate of previous studies, ignoring the large amount of interindividual variance in terms of ‘‘OFA’’ localization. More recent TMS evidence collected after individual definition of the ‘‘OFA’’s rather suggests that the early contribution of the ‘‘OFA’’ to face perception is general, with a later response carrying specific information about faces (Pitcher et al., 2010).

However, there is perhaps much stronger evidence against the view that preferential responses to faces in the ‘‘OFA’’ would necessarily precede and lead to ‘‘FFA’’ responses. Most importantly, brain damage to the right inferior occipital cortex, wiping out any face preferential response in this area, does not prevent right ‘‘FFA’’ activation (Rossion et al., 2003). Bilateral ‘‘FFA’’ activation has also been reported in a patient with bilateral inferior occipital lesion and no ‘‘OFA’’s (Steeves et al., 2006). In the normal brain, brief presentation of low-spatially filtered face stimuli activates the right ‘‘FFA’’, while longer durations are necessary to activate the right ‘‘OFA’’ (and other areas) for both low- and high-spatial frequency faces (Goffaux et al., 2010). In the same vein, if face detection is slowed down by gradual rephasing of information in visual scenes (Sadr and Sinha, 2004), face preferential responses emerge first in the right ‘‘FFA’’ and then in the right ‘‘OFA’’ (Jiang et al., 2009). Overall, these and other studies (Dricot et al., submitted) point to a contribution of the ‘‘OFA’’ in face perception that would generally follow rather than precede the

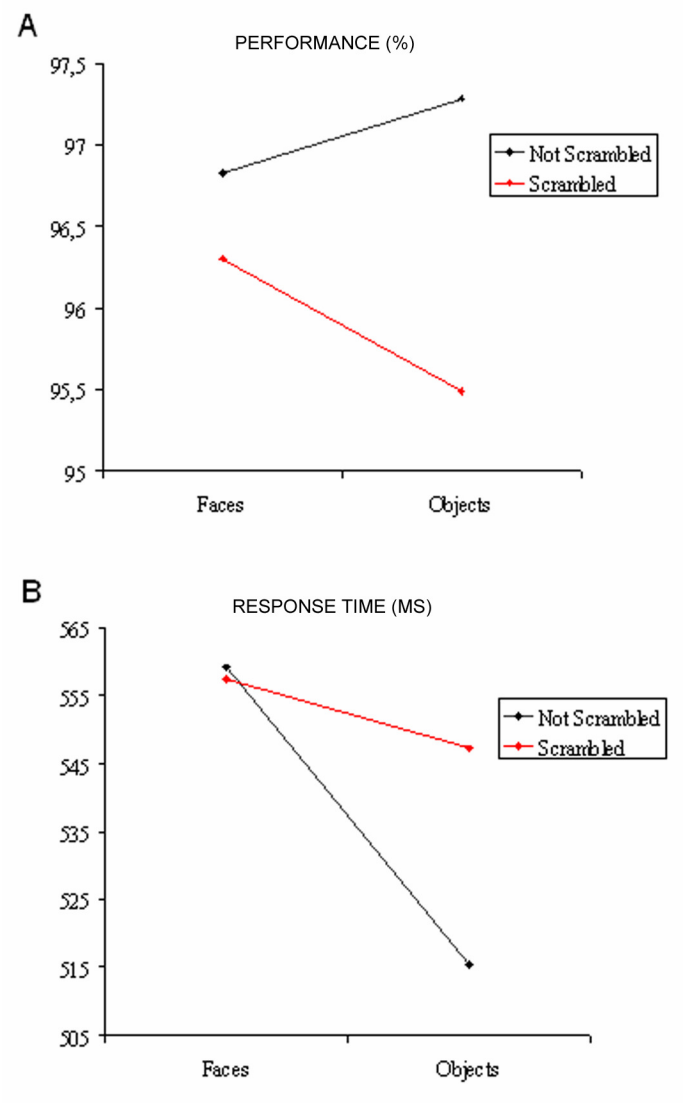
‘‘FFA’’. This view is compatible with a reverse hierarchy of face perception (Rossion et al., 2003; Rossion, 2008) and suggests a direct functional pathway from early visual corticles to hthe middle fusiform gyrus. We would like to argue that the present findings strengthen this view, by showing first that the area that is the most sensitive to low-level visual information, paradoxically, is the most anterior area of the two, the ‘‘FFA’’, and second (2) that the ‘‘FFA’’ onset latency – as estimated by the BOLD latency mapping analysis – precedes significantly the latency of activation of the ‘‘OFA’’. Admittedly, this latter source of evidence should be taken with great care, considering that general differences between areas in terms of vasculature could account for such differences. However, interestingly, the BLM analysis reported a significant delay in the BOLD response of the left ‘‘FFA’’ compared to the right ‘‘FFA’’, two areas that are anatomically analogous, casting doubt on the possibility that such a general factors merely accounts for the effects observed.

3.1.6 Conclusions

We performed a large-scale whole-brain factorial face localizer allowing the control for low- and high-level responses to faces and the measure of the degree to which a preferential response to face stimuli in a given area is truly face specific and driven entirely by high-level features of a face. It corresponds to two runs of about 10 minutes each and it allows localizing regions sensitive to object shape also. At the group and individual subject levels, we report a right hemispheric dominance of the whole face network, which was maximal in the pSTS. The ‘‘FFA’’ showed the least specific response to face representations in the sense that it responded also more to objects than scrambled objects, and more to scrambled faces than scrambled objects. In comparison, the face-preferential responses in the inferior occipital cortex (‘‘OFA’’) presented a more selective response. This sensitivity of the ‘‘FFA’’ to low-level facial features, coupled with its early onset latency in the BOLD response, reinforce the view that it may be the first area of a very large network of areas to present face-preferential responses following visual stimulation.

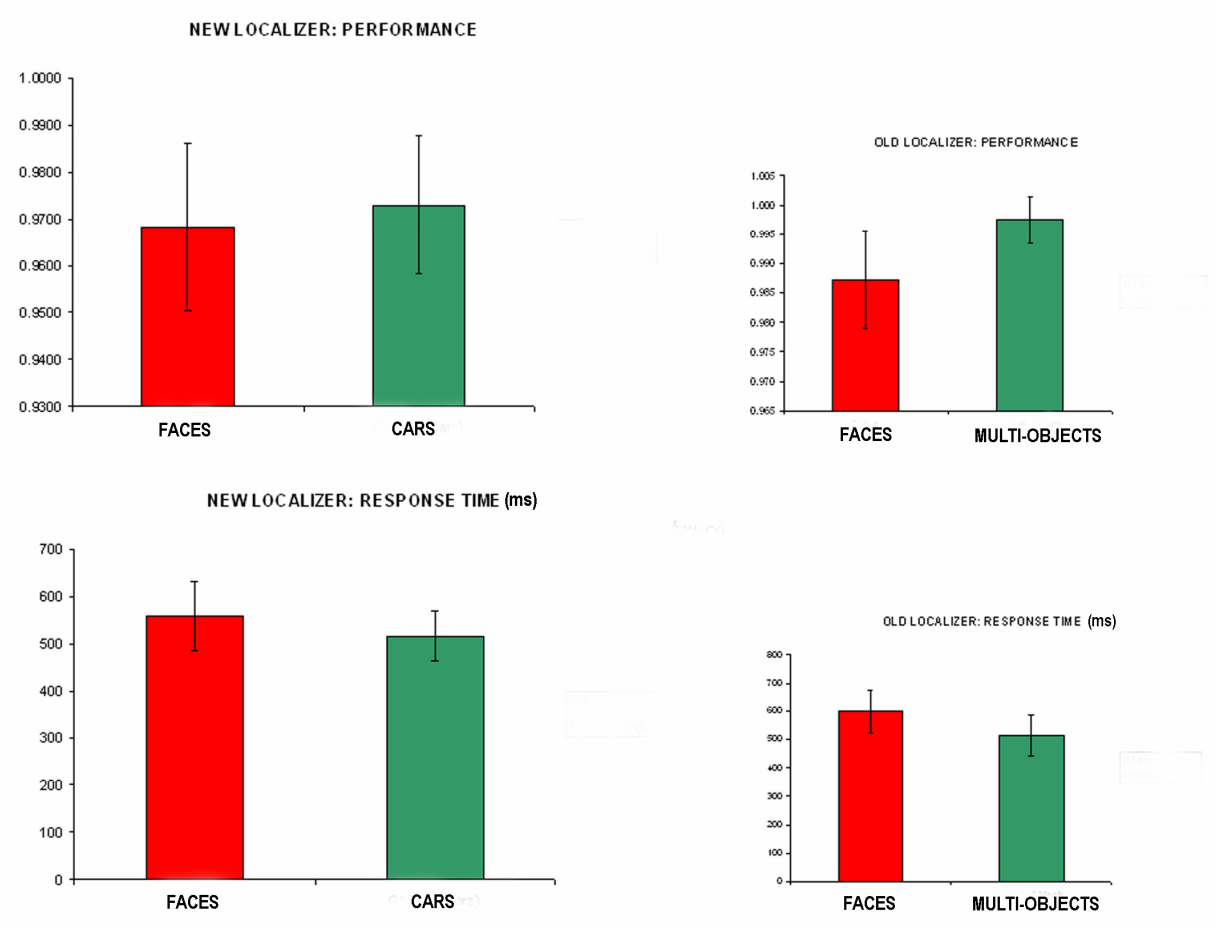
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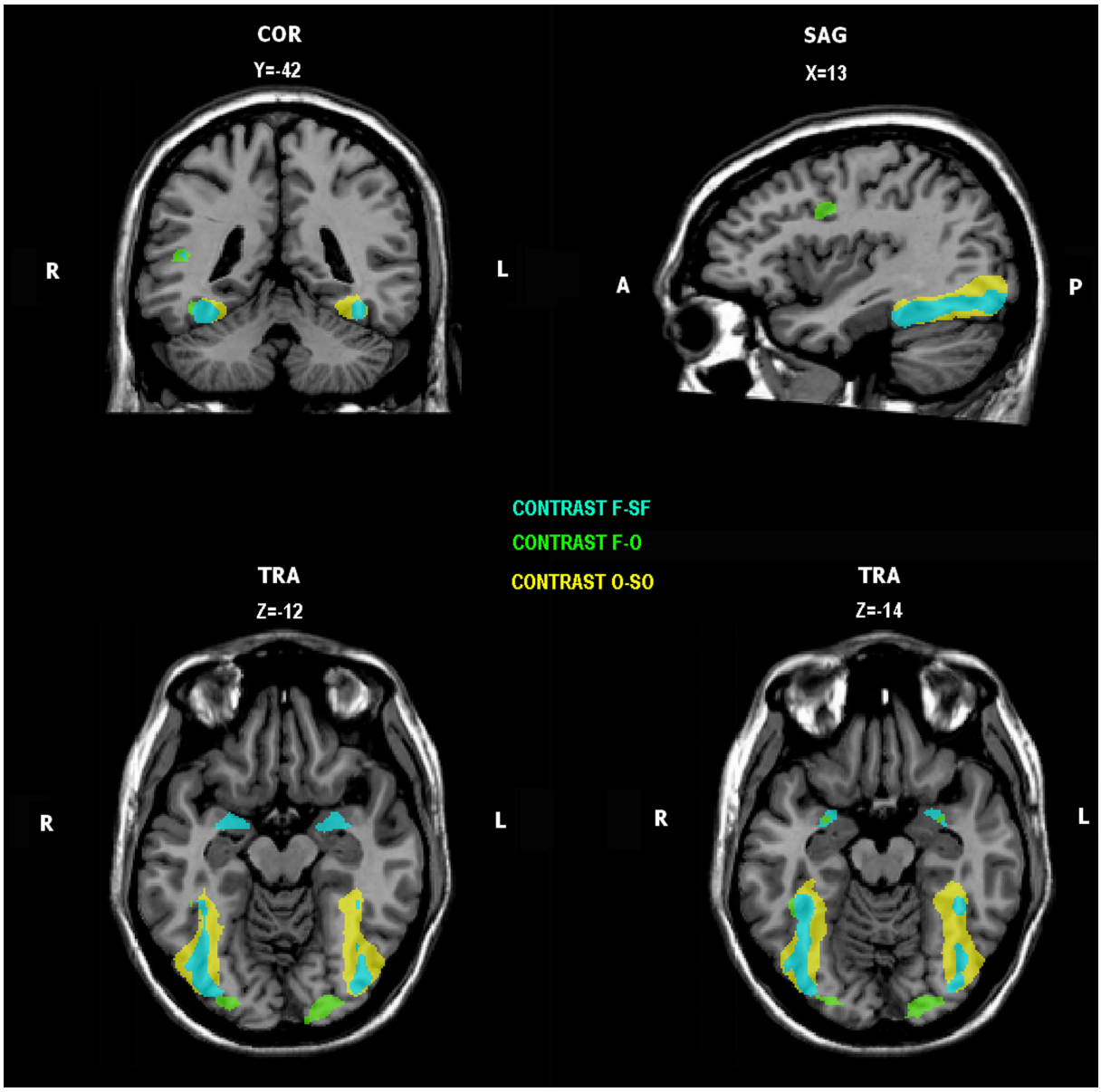


Supplementary Figure 1. A. Anova 2 (Category: Faces vs. Objects) x 2 (Shape: Scrambled vs. non-scrambled) on accuracy rates. There was no effect of category ($F_{1,35}$= 1.08; p=0.305), but a significant effect of shape ($F_{1,35}$= 35.21; p<0.0001). There was also a significant interaction between shape and category ($F_{1,35}$ =13.13; p<0.001). **B.** Anova 2 (Category: Faces vs. Objects) x 2 (Shape: Scrambled vs. non-scrambled) on response times. There was a main effect of

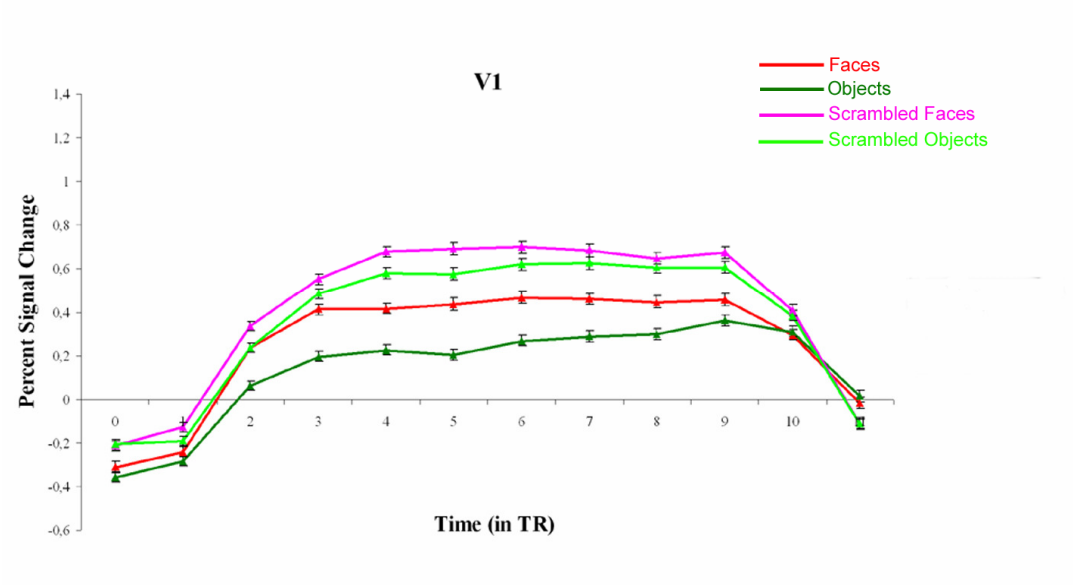
category ($F_{1,35}$=19.35; p<0.0001), and of shape ($F_{1,35}$=4.34; p=0.044). These main effects were qualified by a significant interaction between the two factors ($F_{1,35}$= 10.26; p<0.003).



Supplementary Figure 1. 2. Comparison of our behavioural results with one-back task in a face localizer with multiple objects. There was a highly significant difference between faces and objects both in accuracy (t_{14}=5.12, p<0.0002) and correct RTs (t_{14}=6.25, p<0.00002) in a typical group of the last 15 right-handed participants taken from our previous studies (Dricot et al., 2008). In the face localizer of the current study, a bootstrap analysis which takes 10.000 times 15 participants out of 36 randomly leads to an average t=1.28 (NS, p=0.220019; SD of t values = 0.71) for accuracy and t=3.90 (p<0.0016; SD of t values = 1.0578) for RTs.



Supplementary Figure 1. 3. Activation map at q(FDR)<0.001 (t=5.22) for O-SO and comparison with the activation maps at same q(FDR)<0.001 (t=5.22) for F-SF and F-O.



Supplementary Figure 1. 4. Signal percent change in the total region V1 anatomically defined: 1, -88, 2; 4750 voxels (Talairach coordinates).

Supplementary Table 1. 1. Talairach locations of all the regions found in the random analysis for the 40 right-handed subjects. Contrast: O-SO

at q(fdr)<0.001:	Talairach Coordinates:			Cluster size:
	x	y	z	mm^3
Right middle occipital gyrus gyrus (Broadman 19) = right dorsal posterior vertex of LO	49	-64	14	**64**
Large region encompassing right fusiform gyrus, parahippocampus gyrus and inferior occipital gyrus = right ventral posterior vertex of LO and ventral anterior vertex	37	-62	-11	**10781**
Large region encompassing left fusiform gyrus, parahippocampus gyrus and inferior occipital gyrus = left ventral posterior vertex of LO and ventral anterior vertex and left dorsal posterior vertex mixed	-38	-63	-11	**8792**

Supplementary Table 1. 2. Talairach locations of all the regions found in the random analysis for the 40 right-handed subjects. Contrast: INTERACTION: (F-SF)-(O-SO)

at q(fdr)<0.001:	Talairach Coordinates:			Cluster size:
	x	y	z	mm^3
Right amygdala	18	-6.2	-8	**200**
Right inferior occipital gyrus (BA 18) = right ‘‘OFA’’	26	-88	-10	**45**
Left amygdala	-20	-5.4	-10	**74**
Left cuneus (BA 17)	-2.6	-70	10	**40**

Supplementary Table 1. 3. Talairach locations of all the regions found in the random analysis for the 40 right-handed subjects. Contrast: CONJUNCTION: (O-F) and (O-SO)

at q(fdr)<0.001:	Talairach Coordinates:			Cluster size:
	x	y	z	mm^3
Right parahippocampus gyrus	27	-41	-16	**103**
Right inferior occipital gyrus (BA 18 or 19)	30	-67	-12	**25**
Left parahippocampus gyrus	-28	-38	-15	**228**

Supplementary Table 1. 4. Comparison between the four conditions and the baseline for the regions found when a right ''FFA'' of 500 mm^3 is considered and for the additional regions found when the threshold is minimum [random analysis for the 40 right-handed subjects, Contrast: CONJUNCTION: (F-O) and (F-SF)]*.

Regions found when a right ''FFA'' of 500 mm^3 is considered (in black) **Regions found when the threshold is minimum (in red)**	O vs baseline (t value)	F vs baseline (t value)	SO vs baseline (t value)	SF vs baseline (t value)	*SF-SO (t value)*	*O-SO (t value)*
Right fusiform gyrus (BA 37) = right ''FFA''	12.899	21.348	6.017	8.052	5.093	9.287
Right inferior occipital gyrus (BA 18) = right ''OFA''	8.458	11.476	7.293	7.351	0.826	0.171
Right superior temporal sulcus[32]	0.281	6.651	-2.23	-0.356	2.675	1.993
Right amygdala	-1.002	8.304	-2.465	-2.477	-0.407	2.068
Right perirhinal cortex and fusiform gyrus (BA 38)	1.56	7.532	-1.269	0.585	1.934	3.128
Right precentral gyrus (BA 6)[33]	3.501	6.205	3.177	3.908	1.916	0.648
Right hippocampus	4.959	8.76	3.834	3.074	-0.873	0.171
Right thalamus (pulvinar)	3.954	8.564	2.311	5.015	1.752	1.819
Left cuneus (BA 17)	-4.122	-2.079	-4.318	-4.564	-1.248	1.255
Left amygdala	-0.278	7.139	-2.297	-1.878	0.140	2.645
Left fusiform gyrus (BA 37) = left ''FFA''[2]	7.545	9.671	3.137	4.702	3.632	6.601
Left inferior occipital gyrus (BA 18) = left ''OFA''	6.667	10.608	5.303	5.732	2.764	2.478
Left superior temporal sulcus	1.56	4.372	0.285	0.761	0.999	2.842
Left perirhinal cortex and fusiform gyrus (BA 38)	1.212	4.521	0.285	0.906	0.908	1.036
Left precentral gyrus (BA 6)	5.1	6.763	3.927	4.368	0.565	1.196
Left hippocampus	5.508	9.174	4.737	5.626	1.013	1.100

* The two last columns show the results of the Table 1. 4. C. and 4. E.

[32] For the other more little STS we have the same behaviour except for SF-SO which is not significant (t=1.612, p<0.115060)
[33] Two clusters together.

3.1. Characterizing the face processing network in the human brain: a large-scale fMRI localizer study

Supplementary Table 1. 5. A. Number of subjects (on 36) per localization of face areas identified with the conjunction contrast [(F-FS) and (F-O)] when a ‘‘FFA’’ of 200 mm^3 is considered in the middle fusiform gyrus (BA 37). In green, all the regions which could be considered as right and left ‘‘OFA’’s (9 subjects on the right and 12 subjects on the left have no activations in all these regions).

Localisation	**Talairach Coordinates**			***Number of subjects (on 36) when a right ‘‘FFA’’ of 200 mm^3 is considered***		
	x	**y**	**z**	***1 region***	***2 regions***	***3or> regions***
Right middle fusiform gyrus (BA 37)	*36.9+/-3.4*	*-48.3+/-7.0*	*-15.4+/-4.1*	*30*	*6*	*0*
Right anterior fusiform gyrus (BA 20)	*37.8+/-4.0*	*-32.6+/-7.5*	*-17.2+/-4.0*	*15*	*0*	*0*
Right posterior fusiform gyrus (BA 19)	*36.2+/-4.2*	*-64.7+/-4.4*	*-13.0+/-6.1*	*8*	*0*	*0*
Right inferior occipital gyrus (BA 19)	*38.1+/-8.1*	*-72.2+/-8.5*	*-10.6+/-4.1*	*12*	*0*	*0*
Right inferior occipital gyrus (BA 18)	*32.2+/-7.1*	*-81.7+/-3.5*	*-10.2+/-6.0*	*20*	*0*	*0*
Right posterior STS	*48.7+/-6.0*	*-44.4+/-4*	*6.5+/-7.3*	*12*	*6*	*6*
Right anterior STS	*47.5+/-3.3*	*-12.3+/-11.9*	*-7.4+/-6.4*	*5*	*3*	*0*
Right precentral gyrus (BA 6)	*33.4+/-6.2*	*1.2+/-6.3*	*36+/-4.3*	*9*	*0*	*0*
Right anterior inferotemporal cortex	*31.8+/-3.3*	*-1.4+/-2.5*	*-25.3+/-2.7*	*8*	*0*	*0*
Right amygdala	*18*	*-7*	*-10*	*1*	*0*	*0*
Left middle fusiform gyrus (BA 37)	*-39.1+/-4.6*	*-46.9+/-9.0*	*-17.0+/-5.3*	*28*	*3*	*0*
Left anterior fusiform gyrus (BA 20)	*-35.7+/-3.1*	*-30.1+/-7.9*	*-17.3+/-5.5*	*14*	*0*	*0*
Left posterior fusiform gyrus (BA 19)	*-35.4+/-4.4*	*-67.5+/-6.2*	*-15.12+/-5.0*	*9*	*0*	*0*
Left inferior occipital gyrus (BA 19)	*-36.1+/-7.5*	*-72.2+/-5.9*	*-15.4+/-3.1*	*11*	*0*	*0*
Left inferior occipital gyrus (BA 18)	*-34.4+/-4.5*	*-81.2+/-2.9*	*-8.4+/-6.9*	*10*	*0*	*0*
Left posterior STS	*-50.1+/-5.3*	*-52.6+/-8.0*	*9.9+/-6.3*	*7*	*4*	*2*
Left anterior STS	*/*	*/*	*/*	*0*	*0*	*0*
Left precentral gyrus (BA 6)	*-42.7+/-6.3*	*9.3+/-2.3*	*23+/-1.7*	*2*	*0*	*0*
Left anterior inferotemporal cortex	*-31+/-2.8*	*-1.44+/-5.2*	*-25.8+/-5.4*	*4*	*0*	*0*
Left amygdala	*-18*	*-7*	*-7.5*	*1*	*0*	*0*

Supplementary Table 1. 5. B. Comparison of the right and left disparities in spatial localization between the right and left equivalent regions [right disparity is the mean of the distances for each right region from the centre of the right regions (centre is the mean Talairach coordinates) and left disparity is the mean of the distances for each of the equivalent left regions from the centre of the equivalent left regions (centre is the mean Talairach coordinates).

Localisation	***Difference in disparity ?***	***T VALUE***
Middle fusiform gyrus (BA 37)	***YES***	*1.67*
Anterior fusiform gyrus (BA 20)	***NO***	*0.31*
Posterior fusiform gyrus (BA 19)	***NO***	*0.99*
Inferior occipital gyrus (BA 19)	***NO***	*0.23*
Inferior occipital gyrus (BA 18)	***NO***	*0.7*
Posterior STS	***NO***	*-0.9*
Anterior STS	***/***	*/*
Precentral gyrus (BA 6)	***NO***	*-0.81*
Anterior inferotemporal cortex	***YES***	*3.51*
Amygdala	***/***	*/*

3.2. Cerebral lateralization of the face-cortical network in left-handers: only the FFA does not get it right[34]

3.2.1. Abstract

Face processing is a function that is highly lateralized in humans, as supported by original evidence from brain lesion studies (Hecaen and Anguerlergues, 1962), followed by studies using divided visual field presentations (Heller and Levy, 1981), neuroimaging (Sergent et al., 1992) and event-related potentials (Bentin et al., 1996). Studies in non-human primates (Perrett et al., 1988; Zangenehpour and Chaudhuri, 2005), or other mammals (Peirce and Kendrick, 2002) support the right lateralization of the function, which may be related to a dominance of the right hemisphere in global visual processing. However, in humans there is evidence that manual preference may shift or qualify the pattern of lateralization for faces in the visual cortex: face recognition impairments following unilateral left hemisphere brain damage have been found only in a few left-handers (e.g., Mattson et al., 2000; Barton, 2008). Here we measured the pattern of lateralization in the entire cortical face network in left-handers (11 subjects) with a well-balanced face-localizer block paradigm in fMRI (faces, cars, and their phase-scrambled versions) used in our precedent study of 40 right-handed subjects (Dricot et al., submitted). While the FFA was strongly right lateralized in right-handers, as described previously, it was not the case in left-handers. In contrast, other areas of the face-sensitive network (posterior superior temporal sulcus, pSTS; occipital face area, ‘‘OFA’’; anterior infero-temporal cortex, AiT; amygdala) remained identically right lateralized in both left- and right-handers. Accordingly, our results suggest that the face-sensitive network is equally lateralized for left- and right-handers, and thus the face processing is not influenced by handedness. However, the FFA is an important exception since it is right-lateralized for right-handers but its

34 Cette section est une version remise en page d’un article en préparation avec le même titre de Laurence Dricot and Henryk Bukowski, Bernard Hanseeuw et Bruno Rossion. Les données sur les sujets droitiers ont été supprimées car présentées au chapitre 1.

recruitment is more balanced between hemispheres for left-handers and it seems also that the fast way to the right "FFA" is lesser pronounced in the left-handers. These observations carry important theoretical and clinical implications for the etiology of brain lateralization depending on the left- or right-handedness.

3.2.2. Introduction

The right hemispheric dominance for face recognition is a well-established fact. It originates from the observation by Hécaen and colleagues (1957; Hécaen and Anguelergues, 1962) that patients suffering from prosopagnosia – the inability to recognize faces following brain damage – usually present clinical signs indicating a lesion in the right posterior hemisphere (i.e., left superior quadrant visual field defects). Rare autopsied cases of prosopagnosia also supported this early observation. The view that right unilateral lesions are sufficient to cause prosopagnosia was challenged only briefly by Damasio and colleagues (1982), but tens of cases with right unilateral damage have now been reported in the literature, supporting this view (e.g., Landis et al., 1986; Sergent and Signoret; 1992; de Renzi et al., 1986; 1991; Wada and Yamamoto, 2000; Busigny et al., 2010, in press …). Studies using tachistoscopic stimulation in split-brain patients or normal observers later confirmed the right hemispheric dominance for face recognition (Levy and Nagylaki, 1972; Heller et al., 1981; Parkin and Williamson, 1987), which is now firmly validated by neuroimaging studies of the healthy human brain (Sergent et al., 1992; Kanwisher et al., 1997), and electrophysiological recordings on the scalp (Bentin et al., 1996; Rossion et al., 2003a). What these latter studies also showed is that the right hemispheric dominance in the human brain is not only found in recognition tasks. Rather, it is observed following a simple visual presentation of stimuli: preferential brain responses to faces as compared to other visual object categories are generally larger in the right than in the left hemisphere. This asymmetry in face perception is not

exclusively human, but also occurs in other species such as monkey (Perrett et al., 1988; Zangenehpour et al., 2005) or sheep (Peirce et al., 2001).

The well known (since Broca, 1861) left hemispheric dominance for language depends on manual preference, 96% of right-handed people having language functions localized in the left hemisphere for only 73% of left-handed people (Corballis et al., 2009; Knecht et al., 2000). Thus, it is reasonable to test the hypothesis that lateralization of face perception would also depends on manual preference. However, since face perception is a much older brain function – evolutionary speaking - than language, the alternative view might also be correct and lateralization of face perception might be unrelated to manual preference. Interestingly, lesion studies rather support the former hypothesis, that is, a differential lateralization of face perception according to manual preference. Indeed, the very few cases of prosopagnosia following a left unilateral lesion were all, but one, left-handed persons (Eimer and McCarthy, 1999; Mattson et al., 2000; Barton, 2009; see also Tzavaras et al., 1973). The only right-handed patient with a left unilateral (fusiform) lesion developed prosopagnosia following a period of nonconvulsive epilepsy, and the authors suggested that functional damage was also present in the right hemisphere due to a spreading of epileptic seizures through interhemispheric connections (Wright et al., 2006).

More recently, two neuroimaging studies suggested a differential lateralization of face perception in left-handers than right-handers. Badzakova-Trajkov et al. (2010) reported a smaller proportion of left-handers (73%) than right-handers (94%) with a global right hemispheric dominance in BOLD signal across the whole brain for a simple face task (detection of repetition of video-clips). Willems et al. (2009) focused on a single area of the ventro-temporal cortex that is well known to respond more to faces than objects, the so-called ‘Fusiform face area’ (Kanwisher et al., 1997), to show that while the right ‘‘FFA’’ was larger in the right hemisphere in right-handers, it was bilateral in size in left-handers.

However, the extent and characterization of lateralization of face perception in left-handers compared to right-handers remain largely unclear. Indeed, it is now widely acknowledged that in each individual human brain there are multiple areas, of different sizes and distributed across the whole brain, that respond more to faces than nonface visual stimuli (e.g., Dricot et al., submitted; Fox et al., 2009; Haxby et al., 2000; Ishai, 2008; Tovée, 1998; Pinsk et al., 2009; Weiner and Grill-Spector, 2010). Specifically, these areas concern, in addition to the ‘‘FFA’’, the posterior part of the inferior occipital cortex (‘Occipital Face area’, ‘’OFA’’ e.g., Gauthier et al., 2000a), and of the superior temporal sulcus (pSTS, e.g., Puce et al., 1998), the anterior infero-temporal cortex or temporal pole (AiT) as reported mainly in PET studies (e.g., Sergent et al., 1992) but also more recently in fMRI studies (Rajimehr et al., 2009), the amygdala (e.g., Morris et al., 1996), and the prefrontal cortex. Recent studies have also shown that there are additional areas in the fusiform gyrus (posterior and anterior to the ‘‘FFA’’) and superior temporal sulcus that respond preferentially to faces (Dricot et al., submitted; Pinsk et al., 2009; Tsao et al., 2008; Weiner and Grill-Spector, 2010). Interestingly, fMRI studies carried out in the individual monkey brain also point to a network of areas responding more to faces than nonface visual stimuli, distributed in the occipital, temporal and prefrontal cortices (Tsao et al., 2006; 2008).

Although a number of authors in the neuroimaging community do not emphasize this fact (e.g., Haxby et al., 2000; Ishai, 2008), this set of face-sensitive areas is strongly right lateralized in right-handers. To be more precise, in a recent large-scale fMRI study of our group, we found that the proportion of voxels activated within this set of areas was of 79% in the RH and 21% in the LH (Dricot et al., submitted).

In the present study, we tested the exact same experiment in a group (n=11) of left-handers in order to assess the extent of lateralization of the set of areas in left-handers, as compared to right-handers. Compared to the two recent studies that reported data significant for this issue, the present study is interesting because it addresses the issue of lateralization of the neural basis of face

perception at what we believe to be the right level: beyond a single area of the whole set (Willems et al., 2009), but without considering the whole brain as a single entity for which a general degree of lateralization according to manual preference is derived (Badzakova-Trajkov et al., 2010). That is, we used a factorial face localizer paradigm that allows simultaneously controlling for the preference for faces over another highly familiar visual category, and assess how much of the preferential response to faces is due to low-level cues in the different areas of interest. Moreover, we made a number of interesting observations in our participants concerning these areas that might be dependent on manual preference, most notably the fact that the right ‘‘FFA’’ showed the lower degree of face-specificity and presented the earlier response to faces in right-handed.

3.2.3. Materials and Methods

3.2.3.1. Participants

51 subjects [age=25.20 +/- 5.17; 40 women; 11 left-handed according to the Edinburgh Inventory (Oldfield 1971)] were tested. None of them had a history of neurological or vascular disease, head injury or alcohol abuse, nor did they display cognitive complaints. The participants gave their informed written consent prior to the behavioral and fMRI experiments. The study was conformed to the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Department of the University of Louvain.

3.2.3.2. Experimental procedures

Stimuli, Paradigm and Imaging acquisition parameters are exactly the same than in chapter 3.1.3.2.[35]

[35] Left-handed subjects (as right handed subjects) pressed the button box with the right hand to answer.

3.2.3.3 Data analysis of the imaging experiments

Preprocessing

The fMRI signal in the different conditions was compared using BrainVoyager QX (Version 1.9.10, Brain Innovation, Maastricht, The Netherlands). Prior to analysis, the functional data sets were subjected to a series of preprocessing operations. Preprocessing consisted of a linear trend removal for excluding scanner-related signal, a temporal high-pass filtering applied to remove temporal frequencies lower than 3 cycles per run, and a correction for small interscan head movements by a rigid body algorithm rotating and translating each functional volume in 3D space. The data were corrected for the difference between the scan times of the different slices. Data was not smoothed in the spatial domain. In order to be able to compare the locations of activated brain region across subjects all anatomical as well as the functional volumes were spatially normalized (Talairach and Tournoux 1988) and the statistical maps computed were overlaid to the 3D T1-weighted scans in view to calculate Talairach coordinates for all relevant activation clusters. Subsequently, the functional data were analyzed using one multiple regression model (General Linear Model; GLM) consisting of predictors, which corresponded to the particular experimental conditions of each experiment. The predictor time courses used were computed on the basis of a linear model of the relation between neural activity and hemodynamic response, assuming a rectangular neural response during phases of visual stimulation (Boynton et al. 1996). All coregistrations were done manually and the corrections of the movement were optimized (sinc interpolation, only one run rejected out of 102, so that only one run was available for one subject).

Statistical analyses and contrasts of interest

Since our goal was to define the set of areas responding preferentially or exclusively to faces, but also to compare our observations between right-handers and left-handers, we performed the following conjunction [(F-FS) and (F-O)] in a group analysis (random analysis for each group) and for each individual participant. This contrast was aimed at isolating the areas responding more

to faces than nonface objects, and for which this difference could not be accounted for only by low-level visual parameters.

Statistical threshold for definition of areas

At the group level as in our previous right-handed's studies (Dricot et al., submitted), we fixed the size of the ''FFA'' at 500 mm^3 to define the peak of activation in this region (t) and other face-sensitive regions. In the individual participant analysis, we fixed the size of the ''FFA'' at 200 mm^3 to identify the other face-sensitive regions (see Fox et al., 2009 for a similar approach with 50 mm^3 cluster size of ''FFA'').

Bold latency mapping

Finally, to try to compare the time-course of activations across regions (Formisano and Goebel, 2003), we calculated for each of them the bold estimation of the onset time of the response to first face in each block of faces (432 trials in total for right-handers and 132 for left-handers) using a piece-wise linear trapezoidal model for the response without forcing a return to baseline (interpolation factor 2; Richter et al., 2000).

3.2.4. Results

3.2.4.1. Behavioural data during fMRI

Performance

The behavioural data of 5 participants in the one-back task was not recorded (1 left-handed). Overall, right-handed participants performed the task quite well in all condition (mean accuracy rates: 96.48% +/-1.84%; mean response times: 544.76ms +/-63.24ms) as well as left-handed subjects (mean accuracy rates: 96.93% +/-1.43%; mean response times: 510.22ms +/-41.50ms).

A 2 (Category: Faces vs. Objects) x 2 (Shape: Scrambled vs. non-scrambled) x 2 (Laterality: Left or Right-handers) ANOVA with 46 participants was performed on accuracy rates. There was no effect of laterality ($F_{1,44}$= 0.85; p=0.363) and of category ($F_{1,44}$= = 0.04; p=0.848), but a highly significant effect of shape ($F_{1,44}$= 29.23; p<0.000), due to a lower performance for scrambled stimuli. The was no interaction between laterality and category ($F_{1,44}$ =0.54; p=0.467), between laterality and shape ($F_{1,44}$ = 0.01; p=0.904) and between laterality, category and shape ($F_{1,44}$ = 0.19; p=0.668).

There was a significant interaction between shape and category ($F_{1,44}$ =9.86; p<0.003), due to the relatively low performance for scrambled objects (95.64%+/-1.76%). As we can see (Figure 2. 1.), the fact to be right or left-handed don't play any role at the performance level.

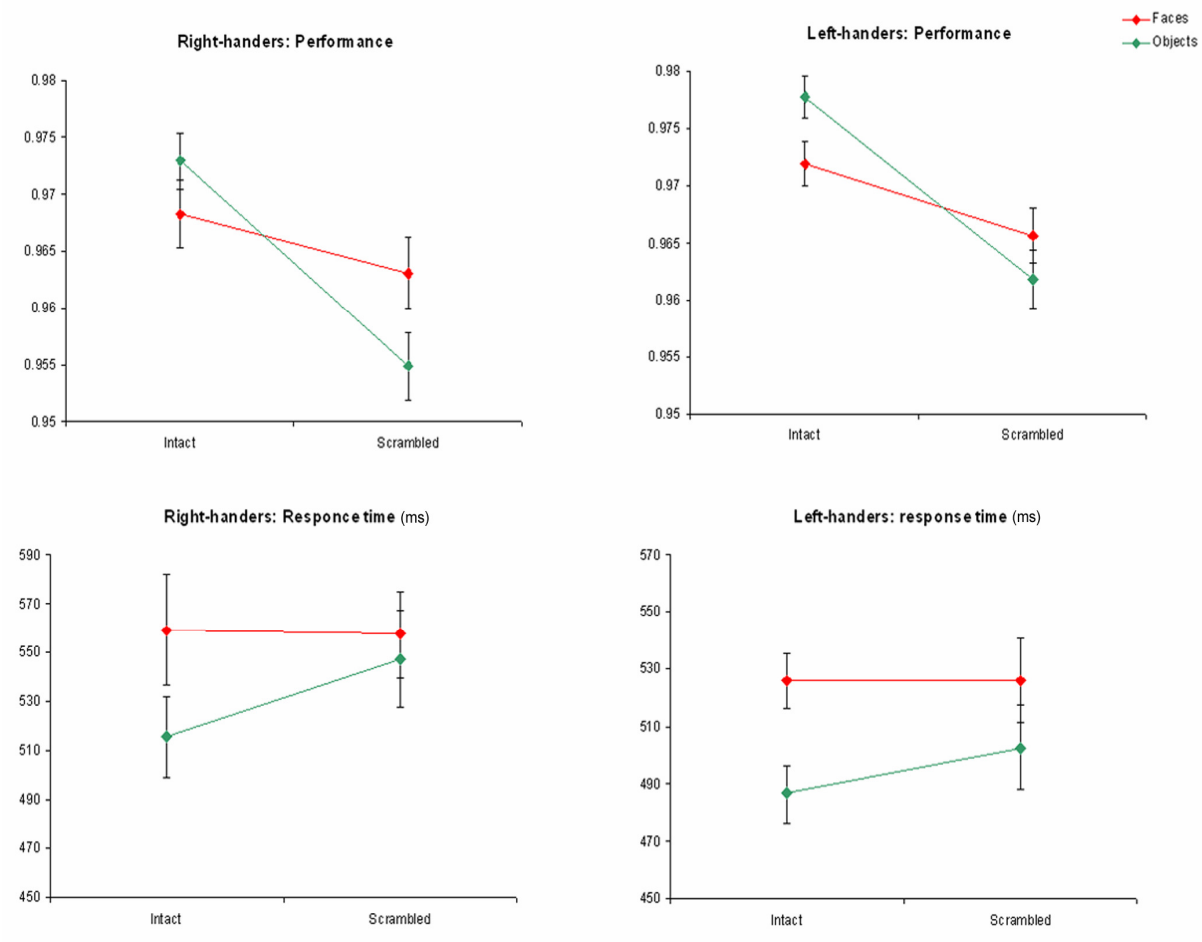


Figure 2. 1. Behavioural results (performance and response times) of the ANOVA with 46 subjects, 2 intra group factor: Category (Faces or Objects) and Integrity (Intact or Scrambled) and one inter group factor (Right or Left-

Handed). There was no effect of laterality ($F_{1,44}$= 0.85; p=0.363) for the performance. There was a quasi main effect of laterality ($F_{1,44}$=3.89; p<0.055) for the response time because the left-handed subjects are closed to be faster than our right-handed subjects.

Nevertheless, in parallel to the best way to do our neuroimaging analysis (see neuroimaging results) we have to consider only the two post-hoc following contrasts for the 36 right-handed subjects and for the 10 left-handed subjects:

the difference between Faces and Scrambled Faces which is not significant (t_{35}=1.87; p=0.070 for the 36 right-handed subjects and t_9=-0.25; p=0.809008 for the 10 left-handed subjects) and the difference between Faces and Object which is also not significant (t_{35}=-1.98; p=0.079 for the 36 right-handed subjects and t_9=1.32; p=0.220 for the 10 left-handed subjects).

Response time

With respect to response times (RT), there was a main effect of category ($F_{1,44}$=22.43; p<0.000), participants performing the task faster for objects than faces and a significant interaction between the category and the shape ($F_{1,44}$=5.68; p<0.022) because participants were the fastest for non-scrambled objects (509.13ms+/-50.00ms). There was a quasi main effect of laterality ($F_{1,44}$=3.89; p<0.055) because the left-handed subjects are close to be faster than our right-handed subjects (Figure 2. 1.). There was no main effect of shape ($F_{1,44}$=2.51; p=0.120). The was no interaction between laterality and category ($F_{1,44}$ =0.12; p=0.732), between laterality and shape ($F_{1,44}$ = 0.24; p=0.626) and between laterality, category and shape ($F_{1,44}$ = 0.79; p=0.380).

Nevertheless as we did for the performance, parallel to the best way to do our neuroimaging analysis (see neuroimaging results) we have to consider the two post-hoc following contrasts for the 36 right-handed subjects and for the 10 left-handed subjects: the difference between Faces and Scrambled Faces which is not significant [t_{35}=0.16; p=0.870 for the 36 right-handed subjects and t_9=-0.03; p=0.978 for the 10 left-handed subjects] and the difference between Faces and Object

which is unhappily significant [t_{35}=5.58; p<0.000 for the 36 right-handed subjects and t_9=4.34; p<0.002 for the 10 left-handed subjects].

3.2.4.2 Neuroimaging results

Random analysis

40 right-handed subjects (Dricot et al., submitted):

The results have been presented in chapter 3.1.4.2.

In summary, the right-handers group analysis revealed that

- Strong RH dominance. Very few regions in the left hemisphere for faces but at that stage we could not say if this observation was due to a smaller activation of the left hemisphere or to a greater disparity between subjects in the left hemisphere ➔ see also single subject study.
- ‘‘FFA’’ is the least face-selective region.
- There is an “OFA” (or part of it according to its definition) which respond very specifically to high-level properties of faces.

11 left-handed[36] subjects:

At size of right “FFA” equivalent [right “FFA”= 501 mm³; t=2.81], we find 17 clusters and we have the following results (Figure 2. 2.; Table 2. 1.):

[36] We have not the same number of subjects but we are working in random analysis !

3.2. Cerebral lateralization of the face-cortical network in left-handers: only the FFA does not get it right

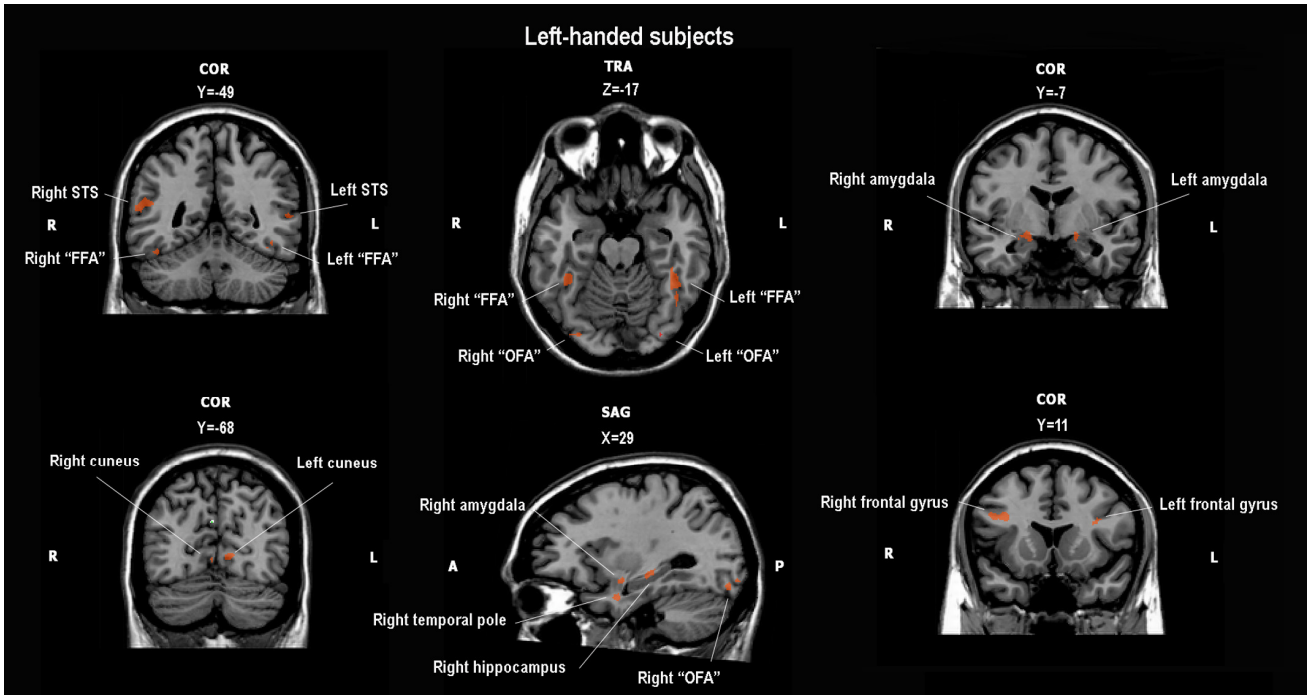


Figure 2. 2. Left-handers: Activation map at size of "FFA" = 501 mm³ (t=2.81) for the conjunction contrast: (F-SF) and (F-O).

Table 2. 1. Talairach locations of all the regions found in the random analysis for the 11 left-handed subjects. Contrast: CONJUNCTION: (F-SF) and (F-O)

when a right "FFA" of 500 mm^3 is considered:	**Talairach Coordinates:**			**Cluster size:**
	x	**y**	**z**	**mm^3**
Right fusiform gyrus (Broadman area 37) = right "FFA"	39	-43	-20	501
Right inferior occipital gyrus (Broadman area 18) = right "OFA"	27	-86	-11	208
Right occipital lobe, fusiform gyrus / inferior occipital gyrus (Broadman area 19 / 18)	42	-73	-9	24
Right superior temporal sulcus	52	-50	14	366
Right amygdala	22	-5	-9	503
Right perirhinal cortex and fusiform gyrus (Broadman area 38)	28	0	-23	128
Right precentral gyrus (Broadman area 6)	37	9	27	520
Right hippocampus	30	-24	-6	113
Right thalamus (pulvinar)	10	-30	1	28
Right cuneus (Broadman area 17)	8	-63	0	84
Right parieto-occipital junction	2	-70	26	65
Left fusiform gyrus (Broadman area 37) = left "FFA"	-40	-44	-15	566
Left inferior occipital gyrus (Broadman area 18) = left "OFA"	-27	-86	-16	28
Left superior temporal sulcus	-54	-49	7	33
Left amygdala	-23	-5	-9	181
Left precentral gyrus (Broadman area 6)	-33	12	24	48
Left cuneus (Broadman area 17)	-10	-68	0	147

1. We have a right hemispheric dominance (72%) slightly less important than the one with our right-handed subjects (79%). Except the left thalamus (and the cerebellum), all the regions found for the right-handed subjects (at size of right "FFA"= 500 mm³) are also found for the left-handed subjects but we find for the left-handed subjects 6 regions more:
    - 4 on the left: the left "FFA", the left "OFA", the left STS and one region in the left precentral gyrus
    - 2 on the right (the right parieto-occipital junction and the right cuneus)
2. It is particularly striking that among the 4 left regions only the left "FFA" is bigger than the right one: 566 voxels on the left for 501 on the right. The left "FFA" =113 % of the right "FFA"'s size contrary to the right-handed subject where it was =2.3% and then the fact to find this region is not depending of the threshold. For the others clusters and similarly to the right hemispheric dominance found in the right-handers, the size of the left "OFA" is about 13.5% of the right one (15.1% for the right-handers), the STS about 9.0% (0.4% for the right-handers) and the cluster in the left precentral gyrus about 9.2% (12.6% for the right-handers) (Table 2. 2.).

Table 2. 2. Percentage of the size of its right-sided homologue and Cluster sizes (mm3)

	Right-handers	Left-handers
Left "FFA"	2.3% 28 vs. 1212 mm³	113.0% 566 vs. 501 mm³
Left "OFA"	15.1% 100 vs. 662 mm³	13.5% 28 vs. 208 mm³
Left STS	0.4% 18 vs. 4730 mm³	9.0% 33 vs. 366 mm³
Left inferior frontal gyrus	12.6% 62 vs. 491 mm³	9.2% 48 vs. 520 mm³
Left Amygdale	80.9% 1580 vs. 1953 mm³	36.0% 1 . 503 mm³

3. Like in right-handers, the two "FFA"s (Figure 2. 3.; Table 2. 3.) are the lesser face-selective regions: t=7.120, p=0.000032 (right) and t=5.006, p=0.000533 (left) for the contrast O-SO. Nevertheless, the contrast SF-SO is not significant on the right (t=1.350, p=0.206744) and only almost significant on the left (t=1.883, p=0.089028).

3.2. Cerebral lateralization of the face-cortical network in left-handers: only the FFA does not get it right

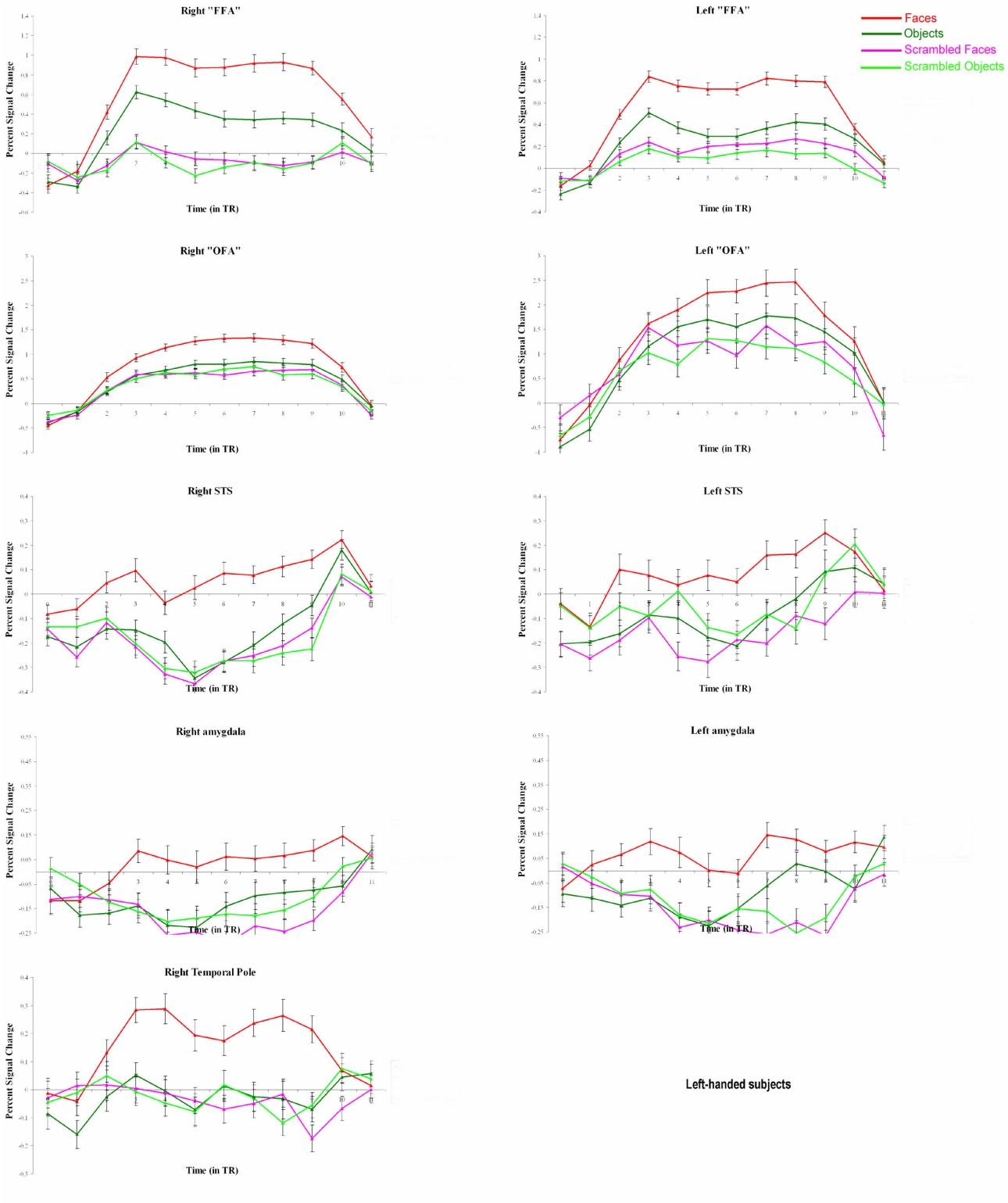


Figure 2. 3. Left-handers: Signals percent changes for the clusters of the core and extended system for the conjunction contrast (right "FFA" = 501 mm³; t=2.81). Note that the ''FFA''s respond highly to nonface objects. The left ''FFA'' responds almost (p=0.08) more to scrambled faces than scrambled objects. The "OFA"s respond above baseline for all conditions, but it is not more sensitive to low-level aspects of faces (scrambled faces) than objects, and

does not respond more to objects than scrambled objects either. Thus, paradoxically, the ''OFA'' appears to show a more selective response to faces than the ''FFA''.

Table 2. 3. Face's specificity for the regions found in the random analysis for the 11 left-handed subjects. Contrast: CONJUNCTION: (F-O) and (F-SF)

when a right "FFA" of 500 mm^3 is considered:	**SF-SO t**	**SF-SO p**	**O-SO t**	**O-SO p**
Right fusiform gyrus (Broadman area 37) = right "FFA"	1.350	*0.206744*	7.120	*0.000032*
Right inferior occipital gyrus (Broadman area 18) = right "OFA"	0.205	*0.841831*	1.501	*0.164344*
Right fusiform gyrus - inferior occipital gyrus (Broadman area 19 - 18)	3.736	*0.003872*	7.653	*0.000017*
Right superior temporal sulcus	-0.364	*0.723269*	0.664	*0.521711*
Right amygdala	-1.974	*0.076672*	0.711	*0.493099*
Right perirhinal cortex and fusiform gyrus (Broadman area 38)	-0.095	*0.926567*	0.454	*0.659450*
Right precentral gyrus (Broadman area 6)	-0.837	*0.421896*	-0.611	*0.554693*
Right hippocampus	-1.542	*0.154043*	-0.682	*0.510626*
Right thalamus (pulvinar)	0.711	*0.493310*	0.888	*0.395475*
Right cuneus (Broadman area 17)	-2.896	*0.015940*	-0.689	*0.405158*
Right parieto-occipital junction	-1.942	*0.080819*	2.945	*0.014654*
Left fusiform gyrus (Broadman area 37) = left "FFA"	1.883	*0.089028*	5.006	*0.000533*
Left inferior occipital gyrus (Broadman area 18) = left "OFA"	0.632	*0.541842*	1.985	*0.075283*
Left superior temporal sulcus	-3.161	*0.010134*	-0.099	*0.923264*
Left amygdala	-1.279	*0.229744*	1.361	*0.203333*
Left precentral gyrus (Broadman area 6)	-3.461	*0.006114*	-1.131	*0.284604*
Left cuneus (Broadman area 17)	-2.896	*0.015940*	-0.689	*0.405158*

4. The right[37] and left "OFA", the two STSs, the right temporal lobe and the two amygdales are selective and high-level (Table 2. 3. and Figure 2. 3.): SF not bigger than SO for the 7 regions and none of them are objects regions. We can nevertheless notify that the left "OFA" seems to be lesser face specific than the right "OFA" and O–SO shows a tendency to be significant (p=0.075283).

[37] Beside the right "OFA" of 208 mm³ we have one little region of 24 mm³ between the posterior fusiform and the inferior occipital gyrus which is not high-level face selective.

5. We find (Figure 2. 2., Table 2. 3., Figure 2. 4.) like in the right-handed subject the right hippocampus and the right thalamus (very high level face specific) and again like for the right-handers, the right junction between the precentral gyrus and the inferior frontal gyrus (operculum part) and in addition the same equivalent region on the left, also two face specific regions and not low-level face-specific. Finally, we find for the right parieto-occipital junction and the right cuneus (57% of the left cuneus size) a deactivation of the 4 conditions but lesser for the F than the 3 others.

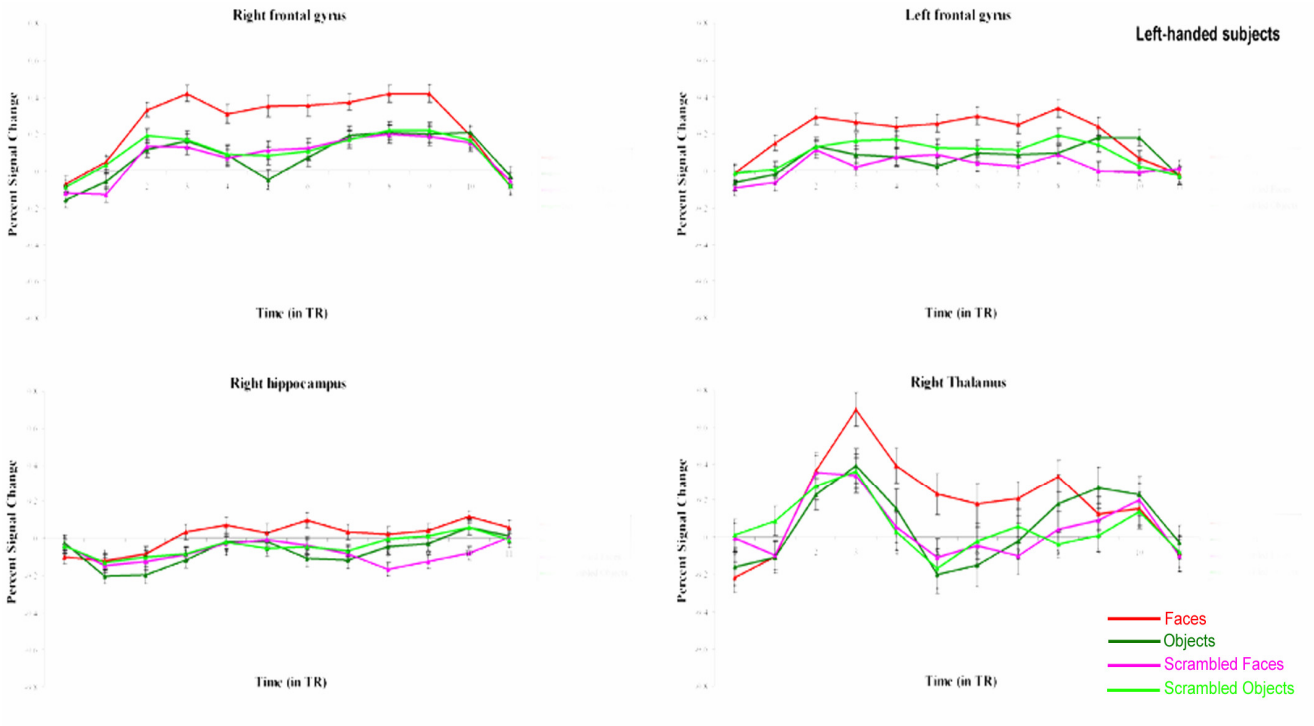


Figure 2. 4. Left-handers: Signals percent changes for the clusters belonging not to the core and extended system for the conjunction contrast (F-SF) and (F-O) ("FFA" = 501 mm³; t=2.81).

In summary, the left-handers group analysis revealed that

The left-handed subjects have a slightly more bilateral face network than the right-handed subjects due to the bigger bilaterality of the "FFA"s which are the lesser face specific regions of their face network.

Subject analysis

In the individual participant analysis, we used the conjunction contrast [(F-FS) and (F-O)] and fixed the size of the "FFA" (right middle fusiform gyrus, BA 37) at 200 mm^3 to identify the other face-sensitive regions (see Fox et al., 2009 for a similar approach with 50 mm^3 cluster size of "FFA"). At this threshold, 4 (right-handers) participants only out of 51 did not present a significant activation in the "FFA" ($t<1.97$) and were not taken into consideration. We made the following observations:

1. There is a huge amount of variability between individual participants in terms of the level of activation of their fusiform gyrus in response to faces. The average t value was at 4.33 with a standard deviation of 1.23 for right-handed subjects and at 3.93 with a standard deviation of 1.5 for the left-handed subjects[38]. The variation of t between the subjects is too important. Fixing a t could lead for some subjects to too big overlaps between their face regions and for others to the absence of avtivation in regions of interest.
2. The number of areas identified at that criterion (fixed "FFA" size), and their spatial distribution also vary a lot across participants. The correlation between the t value at the "FFA" fixed and the number of voxels activated in the whole brain ($\rho=-0.39$, $p<0.02$) explained only 15% of the variance between right-handed subjects. The rest, see below, must be explained by the individual variability of the face network. The correlation for the left-handers is not significant with 11 subjects ($\rho=-0.52$, $p=0.10$).

Concerning the "FFA"

Right-handers:

The results have been presented in chapter 3.1.4.2.

[38] There is no difference between left and right-handed subjects: $t_{14}=0.811$, $p=0.215$

Left-handers:

3. With respect to the right "FFA" found at 200 mm^3 in 11 individual participants, we observed for 5 of these 11 participants a second smaller area (t_4=4.29, p<0.0006 between the right "FFA" and this second area for the 5 subjects) activated in the anterior fusiform (BA 20) (different than AiT). This region contains 86.40 mm^3+/-67.55 mm^3 in the 5 subjects. For 2 of the 11 participants, we also found a second spatially distinct face-sensitive area in the middle fusiform gyrus (32.00 mm^3+/-29.70 mm^3 in the 2 subjects, t_1=5.84, p<0.054 between the right "FFA" and this second area in the middle fusiform gyrus for the 2 subjects). The total number of voxels which were face-sensitive in the right middle fusiform gyrus for the 11 participants was: 209.18 mm^3+/-13.56 mm^3.

4. For the right "FFA", the contrast O-SO is significant (t_{10}=8.976, p<0.000004, random effect in ROI analysis) contrary to the contrast SF-SO which is not significant (t_{10}=0.416, p=0.686, random effect in ROI analysis). The right anterior fusiform face-sensitive area[39] found in 5 participants has a higher degree of face-specificity than the right "FFA". The difference between the two regions is significant for the contrast O-SO (t_4=3.04, p<0.019). However, the difference between the two regions is not significant for the contrast SF-SO (t_4=0.156, p=0.440).

5. A left ''FFA'' (BA 37) is found in 11 participants (mean size: 326.90 mm^3+/-296.48 mm^3 in the 11 subjects). For 4 of these 11 participants, we also find a second area in the anterior fusiform (BA 20) (128,75mm^3+/-231.08 mm^3 in the 4 subjects, this region is quasi smaller in size than the left "FFA"; t_3=2.24, p<0.054 between the left "FFA" and this second area for the 4 subjects). In two of these 11 participants, there is also a second area in the middle fusiform gyrus (80.00mm^3+/-2.83 mm^3 in the 2 subjects; same size, t_1=2.06, p=0.14). The

[39] Due to the few number of subjects no random analysis were made.

total amount of voxels in the left middle fusiform gyrus calculated on the whole group of 11 participants is: 341.45 mm^3+/-286.52 mm^3.

6. For the left "FFA", the contrast O-SO is significant (t_{10}=8.197, p<0.000010, random effect in ROI analysis) contrary to the contrast SF-SO which is not significant (t_{10}=t=1.010, p=0.336, random effect in ROI analysis). The left anterior fusiform face-sensitive area[40] found in 4 participants has a higher degree of face-specificity than the left "FFA". The difference between the two regions is significant for the contrast O-SO (t_3=6.157, p<0.004) and for the contrast SF-SO (t_3=2.51, p<0.044).

If we compare the right and the left side:

7. Contrary to the right-handers (right "FFA" dominance), the left "FFA" is here NOT smaller in size than the right "FFA" (t_{10}=-1.67, p<0.067; almost left dominance). However, like the right-handers, there is no difference for the anterior fusiform (t_{10}=-0.169, p=0.434). The lateralization of the "FFA" (number of voxels in the right middle fusiform/ number of voxels in the left and right middle fusiform) is 48.04% +/-23.91, which is different than of mean value considering all areas of the network (63.29% +/- 18.29) (t_{10}=4.83, p=0.00034). The lateralization of the anterior region is 56.11% +/-48.53% on 6 subjects (5 subjects have no anterior regions), which is not significantly lesser than of mean value considering all areas of the network (t_5=0.237, p=0.411).

8. The left "FFA" found in 11 participants has NO higher degree of high-level face-sensitivity than the right "FFA". The difference between the two regions for the contrast SF-SO is not significant (t_{10}=0.55, p=0.296) as for the contrast O-SO (t_{10}=1.28, p=0.114). Only 3 subjects have the two anterior fusiform activated (right and left). There is no difference between the two sides for none of the contrast (SF-SO: t_2=0.160, p=0.444 and O-SO t_2=-0.998, p=0.212).

[40] Due to the few number of subjects no random analysis were made.

To resume the right side seems have the same behaviour than the left side and the anterior regions seem to have higher degree of high-level face-sensitivity than the "FFA"s.

9. Interestingly and contrary to the right-handers, the disparity in spatial localization is here the same in the left and in the right "FFA". We find no significant difference when we compare the distances for each right "FFA" from the centre of the all 11 right "FFA"s (centre is the mean Talairach coordinates) to the distances for each of the 11 left "FFA"s from the centre of the 11 left "FFA"s (t_{20}=0.171, p=0.433; Figure 2. 5.).

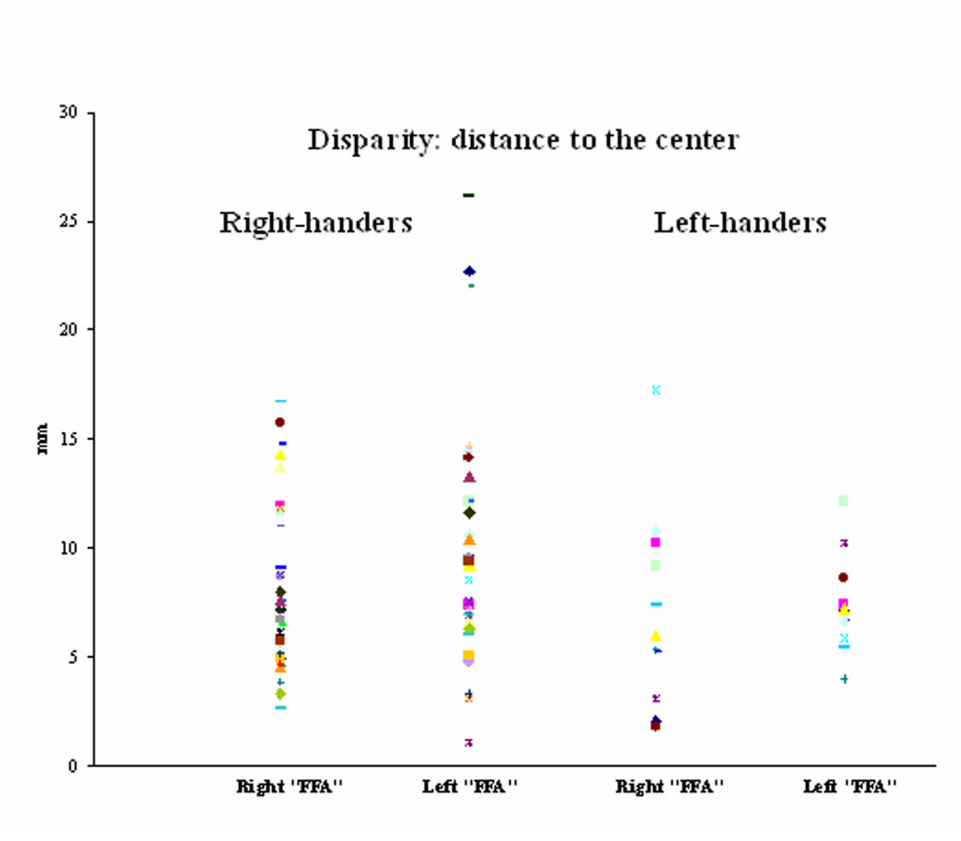


Figure 2. 5. Disparity (mm) in spatial localization for the right and left "FFA"s for the right and left-handed subjects. The left "FFA"s in right-handers has significant higher disparity in terms of localization. Right-handers: right ''FFA'' distance from the centre is significantly smaller than for left ''FFA'' (t_{65}=-1.67, p<0.050). Left-handers: right ''FFA'' distance from the centre is not different than for left ''FFA'' (t_{20}=0.171, p=0.433).

Concerning the "OFA"

Right-handers:

The results have been presented in chapter 3.1.4.2.

Left-handers:

10. At fixed (200 mm^3) size of right "FFA", and considering all the clusters found in the posterior part of the fusiform gyrus (in the occipital lobe, BA 19) and in the inferior occipital gyrus (BA 18 or 19), we found at least one right face-sensitive area for 9 participants and one left area for 8 participants. 7 participants have regions in both hemispheres and 1 in none of the sides. In the right hemisphere, 7 participants have two face-sensitive clusters in the occipital lobe, and 1 participants have 3 clusters. In the left hemisphere, 1 participant has 2 clusters and 2 have 3 clusters. All these spatially distinct regions could be considered as "OFA"s and 73.73% of the subjects could have more than one right "OFA" and 27.27% more than one left "OFA"s. The difference between the sum of all face-sensitive voxels in the right and left hemispheres is almost significant (right: 305.59 mm^3 +/-336.26 mm^3; left: 173.09 mm^3 +/-265.56 mm^3, t_{10}=1.53, p=0.079 if we consider all the 11 subjects and right: 450.14 mm^3 +/-269.71 mm^3; left: 340.48 mm^3 +/-295.89 mm^3, t_6=1.35, p=0.112 if we consider the 7 subjects having regions on both sides). Interestingly (see Table 2. 4. for the size of the regions), we found for 5 subjects one area activated in the right posterior part of the fusiform gyrus (5 on the left), for 5 subjects one area in the right inferior occipital gyrus, BA 19 (4 on the left), and for 8 subjects one area in the right inferior occipital gyrus, BA 18 (4 on the left). This spatial dominance of the right inferior occipital gyrus (like for the right-handers) explains why we found the bigger "OFA" cluster at that place in the random analysis (208 mm^3). However, if we compare the size of the areas activated in the 3 right regions (Anova 1*3) and in the 3 lefts regions we didn't

find a significant difference due to the high variance ($F_{2,15}$=1.42, p=0.27 and $F_{2,10}$=0.92, p=0.41). The lateralization of the "OFA" (number of voxels in the right / number of voxels in the left and right) is 67.83% +/-33.71% which is not different than of mean value considering all areas of the network (59.86% +/- 15.08%) (t_9=-0.65, p=0.265).

11. We can notify that the region found in the right BA 18 (8 participants) has not a so high degree of high-level face-sensitivity. The contrast SF-SO is almost significant (t_7=2.15, p=0.070, random effect in ROI analysis). The contrast O-SO is significant (t_7=3.05, p=0.0185, random effect in ROI analysis) but lesser than the right "FFA" of the 8 subjects (t_7=1.83, p<0.055). On the equivalent left region (4 subjects), the mean t is at 0.898 for the contrast SF-SO and not different than the left "FFA" (t_3=-0.92, p=0.212). The contrast O-SO is at 2.800 and is lesser than the left "FFA" of the 4 subjects (t_3=4.47, p<0.010).

Table 2. 4. At fixed (200 mm3) size of right ‘‘FFA’’, all the clusters found in the posterior part of the fusiform gyrus (in the occipital lobe, BA 19) and in the inferior occipital gyrus (BA 18 or 19) for the 11 left-handed subjects of the individual analysis.

	Right posterior fusiform gyrus	**Right inferior occipital gyrus, BA 19**	**Right inferior occipital gyrus, BA 18**	**Total in right**
Number of subjects	5	5	8	9
Mean size and standard-deviation (mm^3)	51,40 *+/-72,91*	305,60 *+/-323.89*	197,00 *+/-156,19*	373,44 *+/-316,66*
Mean size and standard-deviation on the 11 subjects (mm^3)	23,36 *+/-58,75*	138,91 *+/-279,15*	143,27 *+/-167,29*	305,55 *+/-336,26*

	Left posterior fusiform gyrus	**Left inferior occipital gyrus, BA 19**	**Left inferior occipital gyrus, BA 18**	**Total in left**
Number of subjects	5	4	4	8
Mean size and standard-deviation (mm^3)	150,80 *+/-166,38*	33,00 *+/-19,22*	254,50 *+/-259,52*	238,00 *+/-269.64*
Mean size and standard-deviation on the 11 subjects (mm^3)	68,55 *+/-141,58*	12,00 *+/-20.62*	92,55 *+/-208,39*	173,09 *+/-265,56*

Concerning the STS

Right-handers:

The results have been presented in chapter 3.1.4.2.

Left-handers:

12. We found activity in the right STS for 9 participants out of 11 and in the left STS for 5 subjects but we find often different clusters in the superior temporal sulcus per subject. 5 subjects have activity on the both side. All the subjects with left STS have also STS on the right activated. If we consider the global number we found a mean of 234.11 mm^3 +/-303.99 on the right for the 9 subjects and a mean of 253.40 mm^3 +/-310.21 on the left for the 5 subjects. The left STS is quasi smaller in size than the right STS (t_{10}=1.774 p<0.053 for the 11 subjects in total) but not if we consider only the 5 subjects having STS on both sides (t_5=-0.824, p=0.228, mean on the right: 305.20 mm^3 +/-384.55 slightly bigger than the mean of 253.40 mm^3 +/-310.21 on the left). The lateralization of the STS (number of voxels in the right / number of voxels in the left and right) is 78.72% +/-26.59 which is more than the mean considering all areas of the network (59.79% +/- 16.00%) (t_8=3.48, p=0.004) (2 subjects have none region). If we looked more in details we found that for our 9 participants having activities in the right STS, 3 subjects have two regions on the right posterior STS (Talairach coordinates y<-35). Like for the "OFA"s, it is not easy to choose which cluster to consider as the STS. More, 3 of the 9 have also activities in a more right anterior part (Talairach coordinates y>-35) of the STS. For our 5 subjects having activities in the left STS, 1 participants have 3 regions in the left posterior STS (Talairach coordinates y<-35) and 1 region in the anterior part (Talairach coordinates y>-35) of the left STS.
13. The right STS has a high degree of high-level face-sensitivity. The contrast SF-SO is not significant (t_8=0.498, p=0.6322, random effect in ROI analysis). The contrast O-SO is

significant (t_8=5.335, p=0.000550, random effect in ROI analysis) but lesser than the right "FFA" of the 9 subjects (t_8=4.18, p<0.0015). For the left STS, the contrast O-SO is lesser significant than for the left "FFA" of the 5 subjects (t_4=4.99, p<0.00016, mean t for the left STS at 2.12+/-2.43 and for the left "FFA" at 9.78+/-1.93). We did not find any difference between the two regions for the contrast SF-SO (t_4=1.44, p<0.111, mean t for the left STS at -0.28+/-1.81 and for the left "FFA" at 0.94+/-1.88). There was no difference between the right and left STS for the 5 subjects: (t_4=1.200, p=0.148 for the contrast O-SO and t_4=0.652, p=0.275 for the contrast SF-SO).

Concerning the other areas:

Right-handers:

The results have been presented in chapter 3.1.4.2.

Left-handers:

14. Like for the right-handers, there were very few clusters found at the individual participant level: amygdala was never found, right AiT was found in 2 out of 11 participants (122.00 mm^3 +/-162.63mm^3) and left AiT in 4 participants (mean of 60.75 mm^3 +/-74.33 mm^3). Two of these participants presented bilateral AiT activations. Face-sensitivity in the precentral gyrus (BA 6) was found for 1 participant in the hemisphere right (2 mm^3) and none of the 11 participants presented a cluster in the left homologous region. We noticed none activation in the right hippocampus and for 2 subjects activation in the left cuneus (BA 17, mean of 107.00 mm^3 +/-351.25 mm^3). What means that these regions are slightly but consistently activated in face processing.

Global comparison between right and left handed subjects

The principal difference is that we found **an important left "FFA" for our left-handed** subject contrary to our right-handed subjects. It is particularly striking if we consider the four

lateralization indices of the network, the "FFA", the "OFA" and the STS in a 2 (Laterality: Left or Right-handers) x 4 (Indices: Network, "FFA", "OFA", STS) ANOVA with our 47 participants (Figure 2. 6.). The main effect of laterality is not significant ($F_{1,45}$=0.425, p=0.519) contrary to the main effect of indices which is significant ($F_{3,135}$=3.834, p<0.012) and to the interaction which is almost also significant ($F_{3,135}$=2.163, p<0.097). Indeed, if we compare right-handers and left-handers for the four indices, we find only a difference for the "FFA" ($F_{1,45}$=6.909, p<0.013 and $F_{1,45}$=0.507, p=0.481, $F_{1,45}$=0.043, p=0.837, $F_{1,45}$=0.240, p=0.627 respectively for the network, the STS and the "OFA").

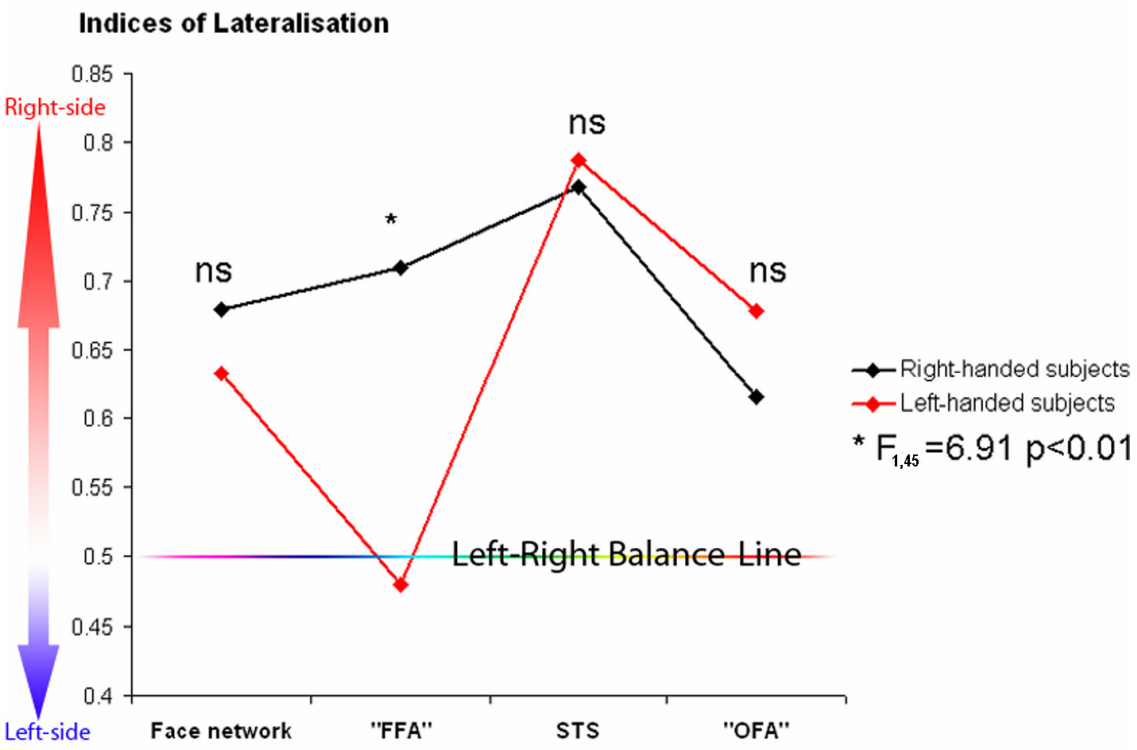


Figure 2. 6. If we compare right-handers and left-handers for four indices [number of voxels in the right region (all the right cortex, "FFA", "OFA" and STS)/ number of voxels in the left and right region (all the cortex, "FFA"s, "OFA"s and STSs)/], we find only a difference for the "FFA" ($F_{1,45}$=6.909, p<0.013 and $F_{1,45}$=0.507, p=0.481, $F_{1,45}$=0.043, p=0.837, $F_{1,45}$=0.240, p=0.627 respectively for the network, the STS and the "OFA").

Moreover, at the individual level, **the right STS in right- and left-handers are significantly more right-lateralized** than the whole face network (t_{26}=1.90, p=0.034; t_9=3.48, p=0.004) and appears to be the most right-lateralized of the face network.

More, inside the right-handers, only 19.44 % of them have an "FFA" index lower than 0.5 against 36.36 % of the left-handers with an index more than 0.5 (χ^2corrected=5,881, p<0.015); **left-handers** being probably **more variable** than right-handers. **For the network index**, both groups have exactly the **same behaviour** (χ^2corrected=0.038, p=0.955).

We can also notify that the **correlations** between the "FFA" index and "OFA" and STS indices are **not significant** in right and left-handers (respectively: p=0.170, p=0.160, p=0.165 and p=0.512).

Finally, if we compare in the **right-handers** the **index of the network to the 3 others** indices, **none of them are significant**: t_{35}=0.343, p=0.562 ("FFA"), t_{35}=1.392, p=0.247 ("OFA"[41]) and t_{35}=3.177, p=0.084 (STS almost significant). If we do the same with **left-handers**, **the index of "FFA" is significantly different** than the one of the network (t_{10}=8.839, p<0.006) contrary to the two others indices for which we find exactly the same than in the right-handers: "OFA" not significant (t_{10}=0.159, p=0.693) and STS almost significant (t_{10}=3.382, p=0.075). To summarize, the face network is rightly dominant for right and left-handers except for the "FFA" which is quasi left-dominant in left-handers. The STS is probably the most right dominant region for both of our groups.

We can also notify that the difference between right and left-handers is not only the left "FFA"'s size but also the disparity (Figure 2. 5.) of the Talairach coordinates of the left "FFA" clusters: The right-handers have a good overlap of their right "FFA"s but not of their left "FFA"s (significant difference between the left and right disparity: t_{65}=-1.671, p<0.050) contrary to the left-handed subjects (same disparity: t_{20}=0.171, p=0.433). More, on the right side, right and left-handers have the same disparity: t_{45}=-0.652, p=0.260 but non on the left side: t_{40}=-1.781, p<0.045.

[41] The right inferior occipital gyrus, BA 18 is the most consistent region for right and left-handers (higher number of subject).

Concerning the specificity and the sensitivity of the regions activated, we have seen that the "FFA"s were the lesser high level face-specific regions of the network for right as for left-handers. If we compare the contrast SF-SO and O-SO between the right and left-handers for all the regions, we find **only a difference in the right "FFA"** for the contrast SF-SO (t_{45}=1.755, p<0.047 with left-handers of higher level; but O-SO is not significant: t_{45}=0.583, p=0.282) **and in the left anterior fusiform** for the contrast O-SO (t_{16}=2.143, p<0.024 with left-handers higher specific; SF-SO is not significant: t_{16}=0.782, p=0.226). We did **not** find **any difference** for **the right STS** (t_{31}=0.408, p=0.344 for SF-SO, t_{31}=-0.988, p=0.169 for O-SO), **the left STS** (t_{16}=-0.403, p=0.349 for SF-SO, t_{16}=-0.800, p=0.227 for O-SO), **the right "OFA" BA18** (t_{26}=-0.799, p=0.219 for SF-SO, t_{26}=-0.120, p=0.453 for O-SO), **the left "OFA" BA18** (t_{12}=-0.866 p=0.206 for SF-SO, t_{12}=0.295, p=0.389 for O-SO), **the left "FFA"** (t_{40}=0.7810, p=0.213 for SF-SO, t_{40}=-0.679, p=0.253 for O-SO) **and the right anterior fusiform** (t_{18}=0.958, p=0.182 for SF-SO, t_{18}=0.597, p=0.280 for O-SO).

Bold latency mapping (Figure 2. 7.)

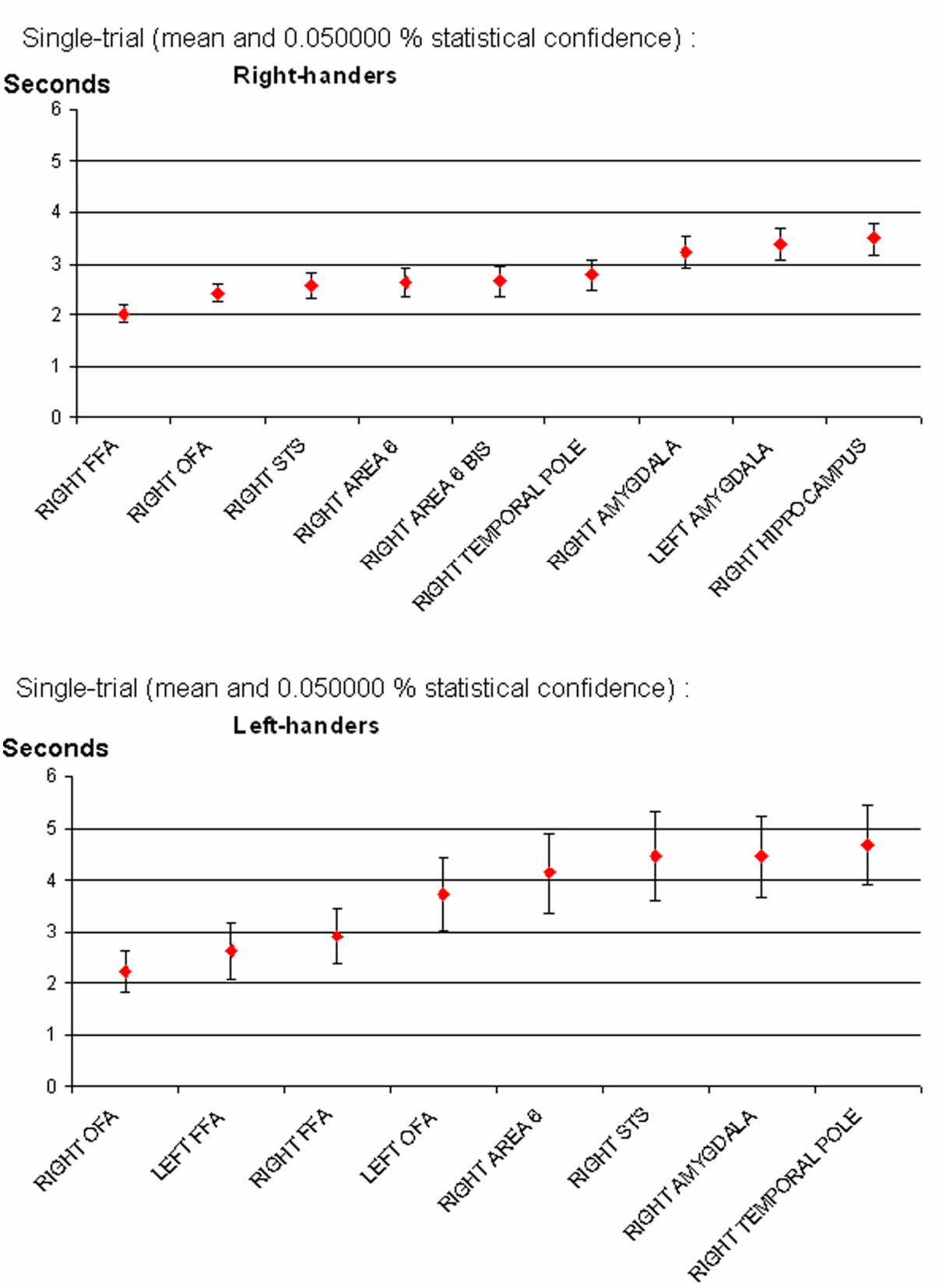


Figure 2. 7. Onset time of the response to first face in each block for right and left-handers across the regions of the core and extended face network (conjunction contrast, size of ''FFA'' = at 500 mm³). The right "FFA" is the fastest

region of the face network before the "OFA" (t_{35}=8.14, p<0.000) for right-handers contrary to the left-handers where the ''FFA'' is activated after the right "OFA" (t_{10}=3.26, p<0.004).

For the right-handers, when the onset time of the response to first face in each block is compared across the regions of the core and extended face network (conjunction contrast, size of ''FFA'' = at 500 mm³), the right "FFA" is the fastest region of the face network before the "OFA" (t_{35}=8.14, p<0.000). It seems not be the case for the left-handed subjects (conjunction contrast, size of ''FFA'' = at 500 mm³): the right (and left) "FFA" is activated after the right "OFA" (t_{10}=3.26, p<0.004)[42]. Noteworthy, if we compare the results of the bold latency mapping for the right "FFA" and the right "OFA" and the high-level face specificity of these regions (contrast SF-SO) between right and left-handed subjects (Figure 2. 8.), we find the following result: when the right "FFA" is activated before the right "OFA" like in right-handers, it seems that the right "FFA" has a lesser level of face specificity than the "OFA" contrary to the left-handers where the right "FFA" is activated after the right "OFA" but has a higher level than this last region. Indeed, at the individual level, we find significant interaction between the laterality (right or left-handers) and the t values of the contrast SF-SO[43]: F(1, 45)=4.98, p<0.0306.

[42] The left "FFA" is also activated after the right "OFA" (t_{10}=1.8, p<0.05).

[43] We dont find a similar significant interaction for the contrast O-SO.

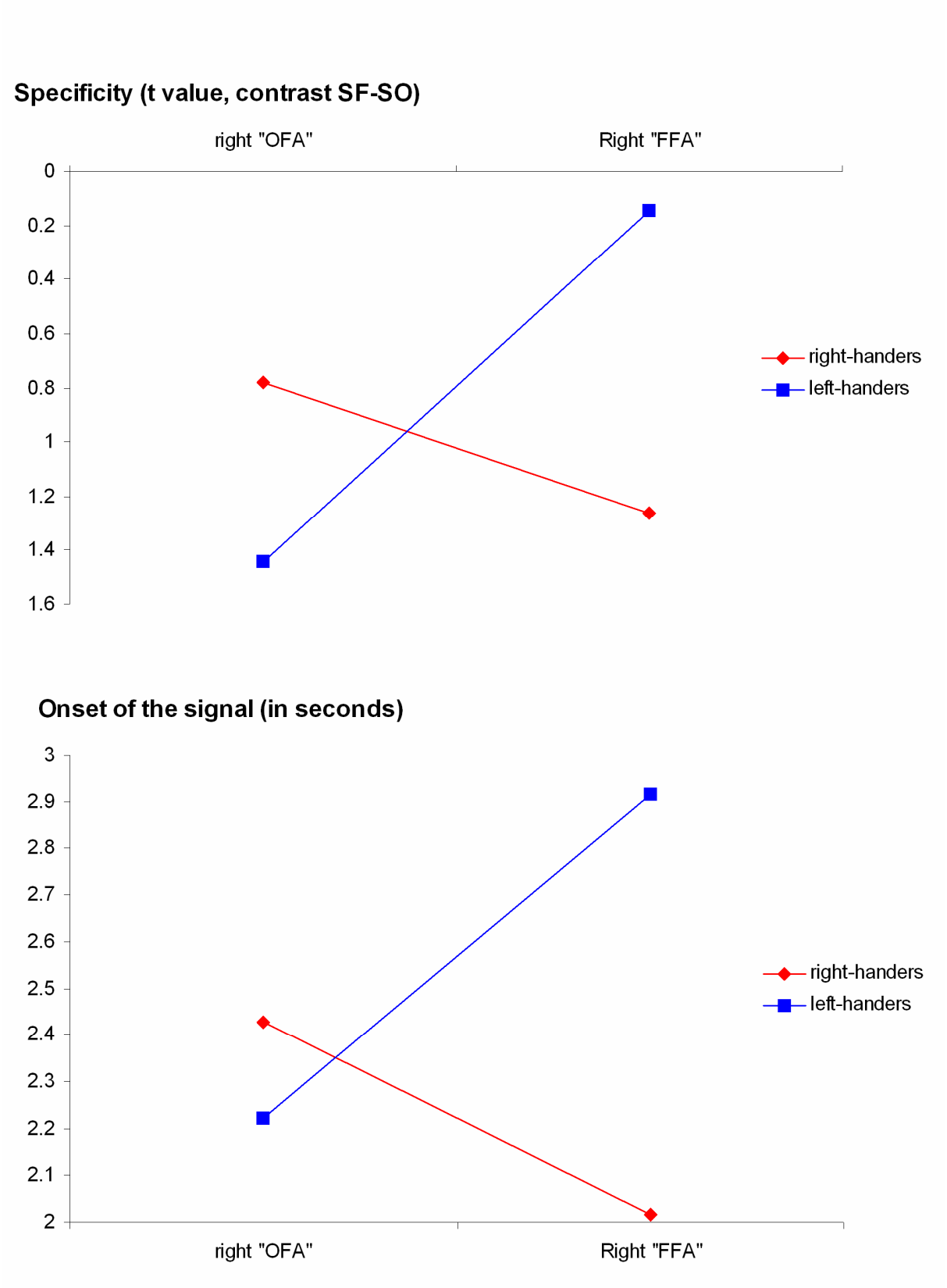


Figure 2. 8. Comparison of the results of the bold latency mapping for the right "FFA" and the right "OFA" and the high-level face specificity of these regions (contrast SF-SO) between right and left-handed subjects. At the individual

level, we find significant interaction between the laterality (right or left-handers) and the t values of the contrast SF-SO: $F(1, 45)=4.98$, $p<0.0306$. When the right "FFA" is activated before the right "OFA" like in right-handers, it seems that the right "FFA" has a lesser level of face specificity than the "OFA" contrary to the left-handers where the right "FFA" is activated after the right "OFA" but has a higher level than this last region.

3.2.5 Discussion générale

Dans cette étude, nous avons comparé les bases neuronales de la reconnaissance des visages entre sujets gauchers et droitiers grâce à un localizer robuste et puissant (Dricot et al., submitted) permettant un contrôle simultané (par la conjonction des contrastes F-O et F-SF) des caractéristiques de haut et de bas niveau des stimuli. Ce localizer permet également une comparaison en seconde analyse des régions trouvées au niveau de leur spécificité (de haut ou de bas niveau) aux visages (contrastes SF-SO et O-SO). Combiné aux paramètres de scanning utilisés, le localizer permet d'avoir par condition et par run 48 fois l'entièreté du cerveau. Au niveau individuel, sur deux runs, cela nous a permis de faire la conjonction des 4 contrastes suivants : F-SF run1 ∩ F-SF run2 ∩ F-O run1 ∩ F-O run2 qui a éliminé beaucoup de bruit et de voxels inconsistants entre les runs relevés par Duncan et al. (2009). Les analyses effectuées tant au niveau individuel qu'au niveau des groupes (droitiers, gauchers) nous ont donc amené à des observations solides que nous pensons importantes tant théoriquement que cliniquement, que ce soit au niveau de l'étiologie de la latéralisation cérébrale en fonction de la latéralité manuelle ou au niveau de la compréhension des patients prosopagnosiques.

- De manière générale, il y a une dominance droite du réseau neuronal de la reconnaissance des visages chez les droitiers ET chez les gauchers (79% et 72%

respectivement). Au niveau individuel 78% de nos droitiers et 73% de nos gauchers présentent clairement une plus grande activité dans l'hémisphère droit que gauche[44].

- Cependant, il y a une exception au niveau du gyrus fusiforme moyen dans cette dominance droite: la ''FFA'' est latéralisée différemment chez les gauchers que chez les droitiers. Au niveau de notre groupe de gauchers, les ''FFA'' sont bilatérales avec probablement une hétérogénéité plus importante entre les individus gauchers que droitiers. En effet, au niveau individuel, seuls 64% des gauchers ont une ''FFA'' gauche plus importante que leur ''FFA'' droite là où 81% des droitiers ont une nette dominance droite.

- Les ''FFA''s droites des gauchers tendent à se comporter différemment que celles des droitiers au niveau de leur rapidité d'activation et de leur sélectivité de plus haut niveau aux visages. De fait la FFA droite des gauchers tend à être plus lente mais plus spécifique aux visages que son homologue chez les droitiers.

3.2.5.1. Droitiers et Gauchers : dominance droite du réseau neuronal.

Les études chez l'homme de lésions cérébrales (Hecaen et al., 1962), en champs visuels divisés (Heller et al., 1981), de neuroimagerie (Sergent et al., 1992) et de potentiel évoqués (Bentin et al., 1996 ; Rossion et al., 2003b) et des études chez le primate (Perrett et al., 1988 ; Zangenehpour and Chaudhuri, 2005) ou chez d'autres mammifères (Peirce and Kendrick, 2002) attestent depuis longtemps de la supériorité de l'hémisphère droit dans la reconnaissance des visages. A notre connaissance, les études comparant gauchers et droitiers sains sont assez rares dans le champ pourtant large de la reconnaissance des visages (mais voir cependant : Willems et al.,

[44] La proportion d'homme est équivalente dans nos deux groupes (respectivement 19% et 18% pour les droitiers et gauchers).

2009). Les études portant sur la compréhension de l'évolution et de la génétique de la latéralité cérébrale et manuelle sont par contre plus fréquentes. Depuis Broca, le langage a été rapporté comme dominant dans l'hémisphère gauche (Knecht et al., 2000, Gaillard et al., 2004) et le traitement spatial (par exemple : Fink et al., 2000) comme dominant dans l'hémisphère droit. Dans une étude fMRI discutant les asymétries cérébrales (Badzakova-Trajkov et al., 2010) au niveau du langage, de la reconnaissance des visages et des traitements spatiaux comparant sujets droitiers et gauchers, les auteurs rapportent des proportions similaires aux nôtres: seulement 27% des gauchers ont une dominance hémisphérique gauche de la reconnaissance des visages. Il est à ce niveau intéressant de remarquer la similitude entre cette proportion et la proportion des gauchers ayant une dominance droite pour leur langage (20 à 30% selon Badzakova-Trajkov et al., 2010 ou 10% pour Llaurens et al., 2010 mais 30% dans cette étude présentent une dominance bilatérale).

Notre étude ne nous a pas permis de faire des distinctions au niveau comportemental (ou en corrélant le comportemental aux résultats fMRI) entre les deux groupes de sujets[45], la tâche n'étant pas vraiment appropriée (et les sujets y plafonnent), il est donc difficile de tirer des conclusions sur les avantages et les désavantages d'être gaucher (pour une revue voir Corballis et al., 2009 et Llaurens et al., 2010). Soulignons cependant que les prosopagnosies acquises et pures sur lésions gauches sont très rares (pour une revue de cas voir Barton, 2008). Les 4 cas recensés à ce jour sont signalés, pour trois d'entre eux, chez des sujets gauchers (Eimer and McCarthy, 1999 ; Mattson et al., 2000 ; Barton et al., 2008) et pour le quatrième, chez un patient épileptique (Wright et al., 2006) dont on peut penser que les crises d'épilepsie récurrentes avant l'ablation du centre épileptogène situé dans le gyrus fusiforme gauche ont engendré des lésions miroirs à droite.

[45] Le groupe de gaucher a une légère tendance à être plus rapide mais est également plus jeune ($p<0.056$).

De la littérature, tout comme de nos résultats, il ressort donc que l'ensemble du réseau visage est latéralisé à droite et ce aussi bien au niveau des sujets droitiers que des sujets gauchers.

3.2.5.2. Droitiers et Gauchers : la différence c'est la ''FFA''

Quant on s'intéresse de plus près aux différentes régions du réseau, à part pour la ''FFA'', on retrouve les mêmes régions et pour toutes, au niveau de l'analyse random, des proportions semblables entre les régions droites et gauches chez les droitiers et chez les gauchers. La taille de l' ''OFA'' gauche correspond respectivement à 15.0% et 13.5% de l' ''OFA'' droite des droitiers et des gauchers par exemple. Seules les ''FFA''s sont différentes: dans notre étude en random chez les droitiers, la taille de la ''FFA''gauche est à 2.3% de la taille de la ''FFA'' droite alors que chez les gauchers la FFA gauche représente 113% de la droite. Au niveau individuel, le même résultat est retrouvé, seules les ''FFA''s diffèrent en terme d'indice de latéralisation. Cette différence peut paraitre moins importante qu'en random. Dans l'analyse random cependant, la disparité spatiale plus grande entre les ''FFA'' gauches des sujets droitiers qu'entre les ''FFA''s gauches des sujets gauchers a certainement amplifié le phénomène. Toutefois même au niveau individuel, la différence de latéralisation des ''FFA'' est très importante: tous les sujets gauchers (100%) dominant globalement à gauche (27% des gauchers) et 50% des gauchers dominants droit (73% des gauchers) ont une ''FFA'' gauche plus grande qu'à droite contre respectivement 62% (chez les 22% des droitiers dominant globalement à gauche) et 7% (chez les 78% de droitiers dominant globalement à droite) chez les droitiers. Dans une étude mesurant l'impact de la latéralité manuelle sur 4 aires fonctionnelles connues (la ''FFA'', l'extrastriate body area ou ''EBA'', la fusiform body area ou ''FBA'' et la human motion area ou ''hMT''), Willems (Willems et al., 2009) rapporte que la latéralisation de la''FFA'' et de l'''EBA'' dépend de la latéralité manuelle (bilatéralisation de la ''FFA'' chez les gauchers) mais ne soulève pas comme nous la possibilité d'une population gauchère plus hétérogène. Dans notre étude, à première vue aussi l'on pourrait conclure à la même hypothèse de bilatéralité de la ''FFA''mais seulement 27% des gauchers ont un index de

latéralisation de leur ''FFA'' compris entre 0.45 et 0.55 (o=latéralisation gauche et 1=latéralisation droite), il faut donc être prudent quand on parle de bilatéralisation même si chez les droitiers la proportion tombe à 11%. Willems n'étend malheureusement pas non plus son analyse à l'entièreté du réseau visage et ne se concentre que sur 3 régions. Il ressort de nos résultats que seule la ''FFA'' semble différer entre droitiers et gauchers. Par ailleurs, Yovel (Yovel et al., 2008) a démontré récemment chez des sujets droitiers l'existence d'une corrélation positive entre le nombre de voxels activées dans la ''FFA'' droite par rapport à la ''FFA'' gauche et un biais comportemental. Ce biais consiste en une facilitation de traitement des parties présentées dans le champ hémisphérique gauche de visages chimériques. Elle a également démontré la non significativité de cette même corrélation dans LO et dans une région visage définie comme ''OFA'' dans le lobe occipital droit par le contraste: Visages moins différents types d'Objets. La dominance de la ''FFA'', plutôt que la dominance générale, semblerait donc un témoin clé de la réelle influence de la latéralisation manuelle sur la reconnaissance des visages. Il est cependant possible que cette corrélation (ou cette absence de corrélation) soit fonction de la tâche. Il se peut aussi, comme le décrit Hirnstein (Hirnstein et al., 2010), que la relation entre les asymétries hémisphériques et le gain comportemental ne soit pas linéairement positive mais de type courbe U inversée. Il serait donc important, à notre avis, dans les études chez les gauchers (sains et prosopagnosiques) de distinguer parmi eux 4 groupes : ceux à dominance générale et ''FFA'' droites, ceux à dominance générale et ''FFA'' gauches et les deux groupes combinant des latéralités différentes encore que dans notre étude il n'y ait aucun gauchers à dominance générale gauche et ''FFA'' droite (voir un cinquième groupe de vrais bilatéraux). Malheureusement nous ne pouvons pas le faire dans notre étude car trop peu de sujets se retrouvent dans le premier groupe entre autres et nous sommes peut-être passé à côté de différences comportementales ou de signal intéressantes, les visages étant traités à travers les hémisphères de façon différente et la dominance droite corrélant avec l'engagement de mécanismes holistiques (globaux) chez les droitiers (Rossion et al., 2000 ; Schiltz et al., 2006).

Yovel (Yovel et al., 2008) souligne également la très grande stabilité à travers les expériences et le temps de l'indice de latéralisation de la FFA contrairement d'ailleurs à celui de l' ''OFA'' (définie uniquement avec le contraste F-O ce qui ne permet pas d'éliminer les voxels dus à une différence de bas niveau entre les deux types de stimuli). L' ''OFA'' semble en effet être plus dépendante de la tâche voire peut-être du feed-back de la ''FFA'' (Rossion, 2009).

Remarquons finalement qu'au niveau des régions du réseau visage, c'est le STS qui est le plus latéralisé droit (chez les gauchers et chez les droitiers), ce qui tendrait à montrer une certaine indépendance possible entre l'identification (plus fonction de la latéralité manuelle) et le suivi du mouvement des yeux (voir Puce et al., 1998) moins fonction de la latéralité manuelle à l'image de la moindre dépendance entre le traitement spatial et la latéralité manuelle (Badzakova-Trajkov et al., 2010). Nos visages étant tous d'expressions neutres, nous ne pouvons pas juger, par contre, de l'influence de la latéralité sur le traitement des émotions.

3.2.5.3. Comportement des ''FFA''s droites, comparaison gauchers et droitiers

De manière générale, chez les droitiers, les ''FFA'', droites et gauches, ont le plus bas niveau de spécificité aux visages de tout le réseau visage. Chez les droitiers, au niveau de l'analyse random, nous trouvons une ''OFA'' droite hautement spécifique aux visages. De même, au niveau individuel, le contraste SF-SO est PLUS élevé dans la ''FFA'' droite, qui est donc moins spécifique que l' ''OFA'' droite. Chez les gauchers, en revanche, on observe la situation inverse: l' ''OFA'' droite n'est pas de haut niveau et est de plus bas niveau que la ''FFA'' droite qui a un contraste SF-SO MOINS significatif[46].

De plus, s'il est difficile, vu le faible nombre de sujets, d'établir des liens entre les niveaux de spécificités et la latéralité des sujets, une analyse comparative entre les deux groupes basée sur

[46] A gauche, le contraste SF-SO n'est pas différent entre la ''FFA'' et l'''OFA'' aussi bien pour les droitiers que pour les gauchers.

les valeurs individuelles de significativité des contrastes SF-SO et O-SO montre que la seule région significativement différente en terme de spécificité aux visages entre droitiers et gauchers est la ‘’FFA’’ droite. Celle-ci est de plus haut niveau chez les gauchers (différence significative entre les deux groupes pour le contraste SF-SO).

Rossion (voir Figure 2 dans Rossion, 2009) a émis l'hypothèse, chez des sujets droitiers, d'une voie directe des aires visuelles primaires vers la ‘’FFA’’ droite (comportant donc très peu de processing préalable) qui permettrait de détecter rapidement un template global. Il postule également une voie de retour vers des régions (‘’OFA’’) de haut niveau spécifiques aux visages. Les informations basses fréquences arriveraient plus vite à la ‘’FFA’’ et génèreraient une représentation initiale grossière des visages guidant le processing plus détaillé des informations convoyées par les voies hautes fréquences qui s'effectuerait dans l' ‘’OFA’’ ainsi que dans la ‘’FFA’’ mais plus tardivement. Cette théorie semble en accord avec la ‘’coarse to fine’’ hypothèse. (Sergent (1986) ; Ramon and Rossion., 2010). Il est intéressant de remarquer dans ce cadre la différence d'onset de la ‘’FFA’’ droite entre les droitiers et les gauchers. Chez les droitiers, la ‘’FFA’’ droite est la première région à démarrer, significativement plus rapidement que l' ‘’OFA’’ droite et le résultat opposé est trouvé chez les gauchers[47] : leur ‘’OFA’’ démarre avant la ‘’FFA’’ soulignant la possibilité d'une importance atténuée de la voie directe chez les gauchers. Ceci peut être mis en relation avec les différences hémisphériques local versus global et basses versus hautes fréquences en fonction de la latéralité manuelle (Ivry et al., 1998). Plus généralement, étudier les différents types de gauchers pourraient aider à la compréhension du réseau visage droitier.

[47] Il est évidemment dommage que le nombre de sujet et de runs par sujets n'ait pas permis de faire du bold latency mapping sujet par sujet ou par type de gaucher.

3.2.6 Conclusion

In summary, the face network is rightly dominant for right- and left-handers except for the "FFA" which is strongly right lateralized in right-handers but more balanced between hemispheres for left-handers. The left "FFA" scarcely appears in right-handers (in random analysis) probably because of its smaller size and its higher disparity in terms of localization and the STS is probably the more right dominant region for both of our groups. Finally, it seems that the fast way to the right "FFA" is depending on the lateralization of the ''FFA''.

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3.3. Global face categorization in higher-level cortical visual areas of the normal and prosopagnosic brain: towards a non-hierarchical view of face perception[48]

3.3.1. Abstract

How a visual stimulus is initially categorized as a face in a network of human brain areas remains largely unclear. Traditional hierarchical neuro-computational models of face perception assume that the visual stimulus is decomposed in local facial parts in lower-level visual face-sensitive areas. These parts would then be combined into a global representation in higher-order face-sensitive areas of the occipito-temporal cortex. Here we tested this view with visual stimuli that are categorized as faces based on their global configuration rather than their local parts (2-tones Mooney figures and Arcimboldo's facelike paintings). Compared to the same inverted visual stimuli that are not categorized as faces, they activated high-level visual areas in the right middle fusiform gyrus ("FFA") and posterior superior temporal sulcus (pSTS), with no significant activation in the inferior occipital cortex, including a functionally localized face-sensitive area ("OFA"). This observation is strengthened by behavioral and neural evidence for normal face categorization of these stimuli in a brain-damaged prosopagnosic patient (PS) whose intact right middle fusiform gyrus is devoid of potential face-sensitive inputs from the lesioned right inferior occipital cortex. Together, these results indicate that face-preferential activation may emerge in high-level visual areas of the right hemisphere without any face-sensitive inputs from lower-level visual areas. They provide evidence for a non-hierarchical view of face perception, according to which high-level visual areas support the initial perception of a face as a whole configuration.

48 Cette section est une version remise en page d'un article in Frontiers in Human Neuroscience (in revision) avec le même titre de Laurence Dricot, Thomas Busigny, Rainer Goebel et Bruno Rossion.

3.3.2. Introduction

The human brain can detect a face in a visual scene in a fraction of a second [e.g. (Crouzet, Kirchner and Thorpe, 2010; Lewis and Edmonds, 2003; Rousselet et al., 2003; Fei-Fei et al., 2007)], yet the neural mechanisms subtending the initial categorization of a visual stimulus as a face remain largely unclear. Neuroimaging studies of the healthy human brain have identified a set of areas of the visual cortex that respond significantly more to pictures of faces than to other object shapes (Sergent et al., 1992) thus potentially playing an important role in the fast and accurate categorization of a visual stimulus as a face. These areas, as identified in functional magnetic resonance imaging (fMRI), are of few mm^2 and are located outside of well-defined retinotopic visual cortex (Halgren et al., 1999), in the lateral part of the inferior occipital lobe ["Occipital Face Area", "OFA" e.g. (Gauthier et al., 2000a)], more anteriorly in the middle fusiform gyrus [the "Fusiform Face Area", "FFA", e.g. (Kanwisher et al., 1997)] and in the posterior part of the superior temporal sulcus [pSTS, e.g. (Puce et al., 1998)]. These areas are bilateral but with a much stronger face-sensitive response in the right than in the left hemisphere (e.g., Kanwisher et al., 1997; Sergent et al., 1992). These 3 areas are considered to form the core section of an extensive network of cortical areas which are particularly sensitive to faces (Haxby et al., 2000; Ishai, 2008; Fox et al., 2009; Weiner and Grill-Spector, 2010), and which can also be identified in the nonhuman primate brain (Tsao et al., 2008).

An important question to clarify is how the processes carried out within this set of face-sensitive areas lead to the initial perception of a visual stimulus as a face.

According to one view, face stimuli are processed through hierarchical stages in the visual system, starting with the extraction of simple facial parts (eyes, mouth, nose, …) in lower-level visual areas of the occipital cortex. These parts would then be combined to form a global face representation in higher-order face-sensitive areas of the occipito-temporal pathway. This "local to global" view is inspired by the hierarchical view of the visual system (Hubel and Wiesel, 1968;

Felleman and Van Essen, 1991), and influential computational models of object recognition (Marr and Vaina, 1982; Biederman, 1987; Riesenhuber and Poggio, 1999; Ullman, 2007) postulating an initial decomposition of the (segmented) visual stimulus into parts and the subsequent combination of these parts through several stages of increasing complexity. A similar "local-to-global" view has been endorsed by computational and theoretical accounts of face perception in the human brain (Burton, 1994; Jiang et al., 2006). More specifically, neurofunctional models of face perception derived from neuroimaging studies postulate that face-sensitive processes are initiated in the inferior occipital cortex (OFA), feed information forward to the anteriorly located middle fusiform gyrus (FFA) and pSTS, and then to the anterior section of the temporal and prefrontal cortices (Haxby et al., 2000; Fairhall and Ishai, 2007; Ishai, 2008; see also Lerner et al., 2001; Pitcher et al., 2007).

However, according to an alternative view of the microgenesis of face processing in the human brain, a face stimulus could be first perceived as a global – coarse - representation (i.e., a whole face), which would then be progressively refined into a detailed face percept allowing finer-grained categorizations (Sergent, 1986). At the neural level, it has been postulated that initial coarse categorization of the face stimulus may take place in a high-level visual area such as the FFA, particularly in the dominant right hemisphere for faces (Rossion, 2008). Perceptual computations and representations that involve high resolution details, fine geometry and spatial precision may then involve lower visual areas such as the right OFA through reentrant connections (Rossion, 2008).

This latter "global-to-local" and/or "coarse-to-fine" view is largely inspired from theoretical and experimental work carried out on object recognition, and more generally on how low-level visual response properties in early visual areas are shaped by neural activity in higher visual areas [(Mumford, 1992; Hupé et al., 1998; Lee et al., 1998; Lamme and Roelfsema, 2000; Bullier et al., 2001; Galuske et al., 2002; Hochstein and Ahissar, 2002; Murray et al., 2002; see also (Bar, 2003)].

With respect to face processing, and the areas mentioned above in particular, this view has received recent support from a fMRI study with spatially filtered faces presented during brief or longer durations (Goffaux et al., 2010). More generally, this view is supported by at least two observations about the categorization of a stimulus as a face by the human brain. First, a visual stimulus can be readily categorized as a face even if it does *not* contain clear elementary facial parts, its faceness being defined solely or primarily by the global organization of the elements. A classical example is provided by two-tone (thresholded, black and white) images of faces introduced in the 1950s (Mooney, 1956, 1957) to test the ability of children to form a coherent percept of shape on the basis of very little detail. These "Mooney" faces (Figure 3. 1A) have been of great interest to psychologists and neuroscientists throughout the past half a century [e.g. (Mooney, 1956, 1957; Perrett et al., 1984; Parkin and Williamson, 1987; Jeffreys, 1989; Dolan et al., 1997; George et al., 1997; Kanwisher et al., 1998; McKone, 2004; Moore and Cavanagh, 1998; Ramachandran et al., 1998; Rodriguez et al., 1999; Jemel et al., 2003; McKeeff and Tong, 2007)] because of their ambiguous nature, specificity [two-tone faces seem more readily identifiable than other objects; (Moore and Cavanagh, 1998)] and their sudden interpretability.

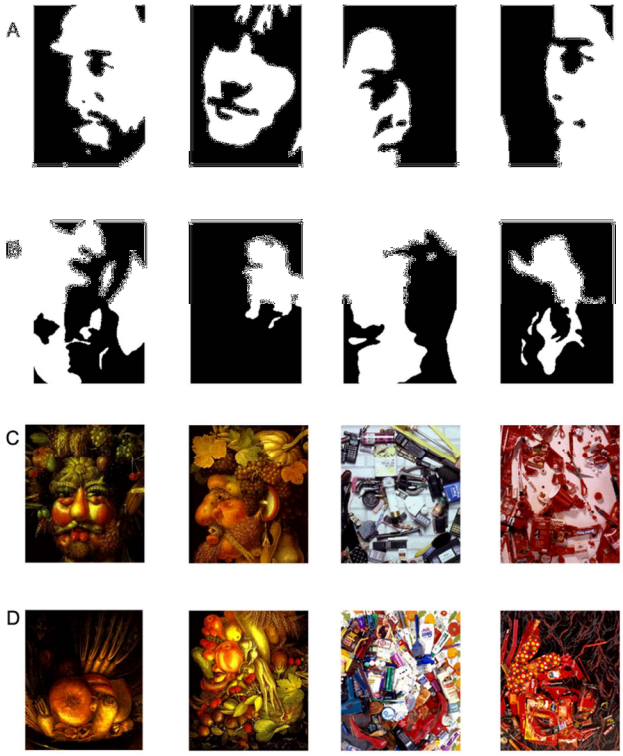


Figure 3. 1. Above. Examples of stimuli used in the experiment 1, Mooney faces (http://www.princeton.edu/artofscience/gallery): A. Upright stimuli (response = face) and B. Inverted stimuli (response = nonface). Below. Examples of stimuli used in the experiment 2 Arcimboldo faces (http://www.princeton.edu/artofscience/gallery), C. Upright stimuli (response = face) and D. Inverted stimuli (response = nonface).

In a Mooney image, the local parts are too ambiguous to be recognized as facelike individually, as illustrated on Figure 3. 1A. Rather, these local parts must be disambiguated based on their context within a global configuration. Consequently, Mooney faces require holistic/configural processing for successful perception (e.g., Newcombe, 1974; Parkin and Williamson, 1987; McKone, 2004): the stimulus needs to be processed as an integrated whole rather than as a collection of independent parts. Moreover, since two-tone images of novel objects do not lend themselves to volumetric interpretations, the correct perception of a Mooney stimulus appears to depend on previously stored representations in memory, or a top-down application of a 2D global face template (Cavanagh, 1991; Moore and Cavanagh, 1998; Hegdé et al. 2007; Kemelmacher-Shlizerman, et al. 2008). Indeed, when a Mooney picture is presented upside-down, the face is usually not perceived (e.g., Figure 3. 1 B), presumably because the visual input cannot be disambiguated with the help of internal 2D global representations (i.e., top-down processes).

Although two-tone "Mooney" images of nonface objects can be adequately interpreted, the stimulus is perceived particularly easily when it is a face (Moore and Cavanagh, 1998).

Yet another example of face perception based on global configuration rather than local parts is illustrated by the famous paintings of Giuseppe Arcimboldo [16th century; (Hulten, 1987)], in which a face is constituted of nonface (usually organic) elements such as fruits and vegetables, animals, flowers, etc ... (Figure 3. 1C). Here, the parts can be identified relatively easily, but they correspond to nonface objects, not to elementary facial parts. Like Mooney stimuli, an Arcimboldo's painting can be categorized as a face due to the global face configuration formed by these non-face elements rather than through the identification of the elements themselves. As a matter fact, a visual agnosic patient who cannot identify the constituent object parts may still perceive the face in these Arcimboldo's paintings (Moscovitch et al., 1997), indicating that the face is perceived independently of the nature of the parts *per se*. Again, the face is usually not perceived when the painting is presented upside-down, an aspect that was used by the artist Arcimboldo to make his paintings reversible [Figure 3. 1D; (Hulten, 1987)].

If a face stimulus can be readily perceived despite the absence or the reduced saliency of local facial parts in Mooney and "Arcimboldo" stimuli, this poses an important challenge to hierarchical neurofunctional and computational models of face perception. Indeed, it indicates that under certain circumstances at least, a whole face configuration can be seen without identifying the parts as being facelike.

A second observation casting doubts on a strict hierarchical scheme of face perception in the human brain is that face-sensitivity can be observed in high-level visual areas of the right middle fusiform gyrus (right FFA) and pSTS despite a structural damage to the territory of the posteriorly located and lower-level right OFA. This was first observed on the patient PS (Rossion et al., 2003a) who presents with a severe inability to recognize and discriminate individual faces [acquired prosopagnosia; Bodamer, 1947; Quaglino and Borelli, 1867], but can nevertheless categorize a

stimulus as a face (Schiltz et al. 2006). This observation of an FFA without OFA has been replicated in several fMRI studies of the same patient [e.g. (Schiltz et al., 2006; Dricot et al., 2008)], also disclosing face preferential activation in her right pSTS (Sorger et al., 2007). A preferential activation to faces of the FFA despite a bilateral lesion of the territory of the OFA in another (prosop)agnosic patient has strengthened this finding (Steeves et al., 2006). Thus, higher-order visual areas such as the FFA may show a preference for faces despite the absence of any face-sensitive response in the structurally damaged posterior regions. These observations suggest that, in the normal brain, a preferential activation to faces in a high-level visual areas such as the FFA may arise independently of putative face-sensitive inputs from the inferior occipital cortex (OFA), perhaps through direct connections from early (non face-sensitive) visual areas (Rossion, 2008).

After taking both of these observations discussed above into consideration, it was proposed that putative direct connections from early visual cortices to the right hemisphere FFA could support the initial perception of a global ("holistic") face configuration [Figure 3. 1 in (Rossion, 2008)]. That is, the stimulus would not need to go through a detailed analysis of local facial parts in the OFA, before reaching the right FFA.

In the present study, we aimed at testing further this latter view of the microgenesis of face perception by combining the two sets of evidence reviewed above. That is, we recorded the behavioral and neural response(s) of normal observers and of the brain-damaged prosopagnosic patient PS to the presentation of Mooney and Arcimboldo face stimuli, in order to test three predictions drawn from this hypothesis. (1) First, the response to Mooney and Arcimboldo stimuli that are perceived as faces by means of holistic processing exclusively should be much larger in the right FFA than the OFA (compared to the response of these two areas in a classical face localizer). This would be particularly true if the stimuli do not have to be analyzed at a finer-grain level for individualization, but merely categorized as faces or nonfaces. (2) Second, providing that low-level vision is well preserved, cases of prosopagnosia who have a right FFA such as the patient PS

described above, should still be able to categorize readily a Mooney or an Arcimboldo stimulus as a face. Previous neuropsychological investigations have not clarified this issue, and it is often claimed that many prosopagnosics (if not all) have particular trouble perceiving a face in binary-tone (Mooney) images (e.g., Levine and Calvanio, 1989; Laeng and Caviness, 2001) or in Arcimboldo paintings (Harris and Aguirre, 2007). In truth, only a few exemplars of Mooney faces have been presented to acquired prosopagnosics as part of neuropsychological examinations, with various recognition success rates [e.g. (Sergent and Villemure, 1989; Davidoff and Landis, 1990; Young et al., 1990; Sergent and Signoret, 1992; Steeves et al., 2006; Rivest et al., 2009)], and only recently a prosopagnosic patient was tested and succeeded at detecting a face in a few Arcimboldo paintings (Rivest et al., 2009). Hence, this issue is still largely open, and deserve to be tested more formally with a prosopagnosic patient who has well preserved low-level vision, does not present general visual integrative agnosia, and shows face-sensitive responses in high-level visual areas. The interest of testing the patient PS' ability to perceive faces in such stimuli requiring holistic processing is also increased by recent evidence showing that this patient cannot rely on holistic processes to *individualize* (recognize or match/discriminate) faces (Busigny and Rossion, 2010; Ramon et al., 2010; Van Belle et al., 2010). While impairment in holistic processing for individualizing faces has also been shown in other cases of acquired prosopagnosia (e.g., Levine and Calvanio, 1989; Sergent and Villemure, 1989; Boutsen and Humphreys, 2002), dissociation between holistic processing for face categorization (intact) and face individualization (impaired) has never been reported to our knowledge. (3) Third, provided that the patient PS is able to detect a face stimulus in a substantial amount of Mooney/Arcimboldo stimuli, we tested the hypothesis that she recruits primarily, as normal observers would, her right FFA to perform this function. This last finding would show that holistic face perception can be initiated in high level visual areas, independently of the perception of facial elements in lower visual areas responding preferentially to faces, providing further evidence for a non-hierarchical view of face perception in the human brain.

In order to test these hypotheses, we first recorded PS and a group of normal controls' performance in a behavioral face categorization task with Mooney and Arcimboldo stimuli. Then, we presented these stimuli to PS and healthy controls in event-related fMRI experiments in order to assess the strength of brain activations to these stimuli. The neural response to upright and inverted Mooney/Arcimboldo stimuli was analyzed in each area identified in an independent face localizer, as well as in a whole-brain analysis.

3.3.3. Materials and methods

3.3.3.1. Participants

Patient PS

The prosopagnosic patient PS' behavioral and neural profiles have been described in detail in several previous studies (Rossion et al., 2003a; Caldara et al., 2005; Sorger et al., 2007). Briefly, PS was born in 1950 and sustained a closed head injury in 1992 that left her with extensive lesions of the left mid-ventral (mainly fusiform gyrus) and the right inferior occipital cortex. Minor damages to the left posterior cerebellum and the right middle temporal gyrus were also detected [see (Sorger et al., 2007)] for all information about the patient's lesions). PS' only continuing complaint is a profound difficulty in recognizing familiar faces, including those of her family when they are presented out of context [see Table 1 in (Rossion et al., 2003a) for the neuropsychological profile of the patient]. This impairment in face recognition and individual face discrimination has been formally established in several behavioral studies with classical neuropsychological tests [(Benton and Van Allen, 1972); Warrington Recognition Memory Test, (Warrington, 1984)] as well as individual face matching and recognition computer tasks [see (Busigny and Rossion, 2010; Rossion et al., 2003a; Caldara et al., 2005; Schiltz et al., 2006; Orban de Xivry, 2008)]. Importantly, PS does not present any difficulty in recognizing and discriminating nonface objects, even at the

subordinate level and when response times are considered (Busigny et al., 2010; Rossion et al., 2003a; Schiltz et al., 2006). Her visual field is almost full [small left paracentral scotoma, see (Sorger et al., 2007)] and her visual acuity is below normal but good (0.8 for both eyes as tested in August 2003).

Behavioral study

Ten healthy control participants took part in the behavioral study. They were matched to PS for gender, age (PS: 56 at time of testing; controls' mean: 53.4, SD: 3.6), and education. None of them had a history of neurological or vascular disease, head injury or alcohol abuse, nor did they display cognitive complaints. Two experiments (Mooney faces experiment 1 and Arcimboldo faces experiment 2) were conducted with all the participants.

fMRI study

Beside PS, a group of seven (S1 to S7, age range 20 to 26, 7 females) healthy controls performed the face localizer and the Mooney faces experiment 1. Three of these participants (S1, S4 and S5) and 3 additional participants (S8 to S10, age range 20 to 26, 5 females) performed the Arcimboldo faces experiment 2. None of them had a history of neurological or vascular disease, head injury or alcohol abuse, nor did they display cognitive complaints. In addition, one age-matched participant (AM, 53 years, female) performed the face localizers and the experiments 1 and 2. We tested only one age-matched control to PS because the profile of activation in the right "FFA" has been shown to remain stable across decades (Brodtmann et al., 2003) as also confirmed by our previous studies (Schiltz et al., 2006; Sorger et al., 2007). The participant AM's data did not differ from the young control participants in this study. Both PS and the control participants gave their informed written consent prior to the behavioral and fMRI experiments. The study was conformed to the Declaration of Helsinki and was approved by the Ethics Committee of the

Medical Department of the University of Louvain. All participants and PS proved to be strongly right-handed according to the Edinburgh Inventory (Oldfield, 1971).

3.3.3.2. Stimuli

a. The stimuli used in the behavioral and fMRI Mooney faces experiments were taken from the dataset originally created by Aaron Schurger and colleagues (Art of Science Competition, Princeton University, http://www.princeton.edu/ artofscience/gallery). These types of stimuli were created following the same procedure that the one used by Craig Mooney (Mooney, 1957) in his study to explore the perceptual closure ability – that is the ability to form a global and coherent perceptual representation *on the basis of few details*. To create our experiment, we selected 80 Mooney faces among the Schurger's set (Figure 3. 1A).

b. The stimuli used in the behavioral and fMRI Arcimboldo experiments are inspired by the paintings of the 16th Century artist, Giuseppe Arcimboldo (see Hulten, 1987; or for example http://www.artyst.net/A/Arcimboldo16/ Arcimboldo.htm) and by the creations of the contemporary mosaic portrait artist, Jason Mecier (http://www.jasonmecier.com). Both created works of art consisting of faces composed by non facial elements (vegetables, fruits, animals, candies, stationeries, pebbles, …). The pictures were downloaded from the websites and were cropped so that only the area of the face was present. Next, the pictures were homogenized to have roughly the same size and resolution. In total, 40 Arcimboldo face stimuli were created (Figure 3. 1C).

c. Four categories of stimuli were used in the fMRI localizer experiment: Faces, Cars, and their phase-scrambled versions: Scrambled Faces and Scrambled Cars. The Face condition consisted of 43 pictures of faces (22 females) cropped so that no external parts (hair, etc.) were revealed. All the faces were shown in frontal view. There were inserted in a gray rectangle to form a rectangular image (Figure 3. 2).

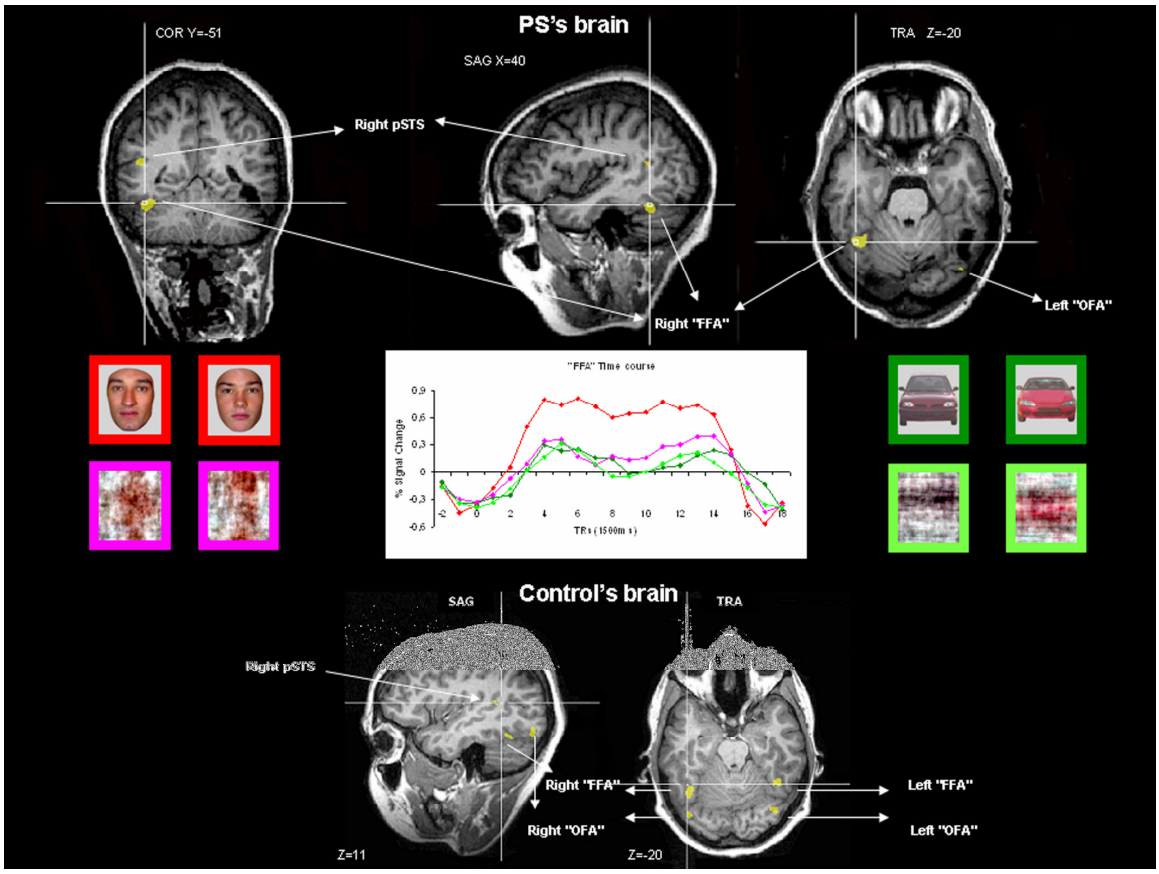


Figure 3. 2. Functional brain areas disclosed in the face localizer experiment with faces, scrambled faces, pictures of cars and scrambled cars. The different areas (bilateral FFA, OFA and right pSTS) are displayed below for a normal participant, and the intact part of this network is illustrated for the patient PS on top (right 'FFA, left OFA, right pSTS). Note the asymmetrical lesions, damaging the cortical territory of the right OFA and left FFA [for a full description, see (Sorger et al., 2007)].

Similarly, the Car condition consisted of 43 pictures of different cars in a full-front view also embedded in a gray rectangle. Faces and cars were presented in color and equalized in luminance. The scrambled stimuli were made using a Fourier phase randomization procedure [see e.g. Sadr and Sinha, 2004] that yields images preserving the global low-level properties of the original image (i.e. luminance, contrast, spectral energy…), while completely degrading any category-related information (Figure 3. 2). Pictures of faces/cars and the phase scrambled face/car pictures subtended equal shape, size and contrast against background.

3.3.3.3. Procedure

Behavioral Mooney and Arcimboldo faces experiment

The stimuli were presented using E-prime 1.1 (Schneider et al. 2002) on a 15 in. laptop display and subtended approximately 5.4° in height and 3.8° in width. Participants indicated a response by pressing designated keys on a keyboard. The back color of the screen was in gray (128, 128, 128). Percentages of correct responses and response times on correct trials were calculated.

The 80 selected items were presented upright (Figure 3. 1A) and upside-down (Figure 3. 1B) and were displayed in random order in two blocks of 80 trials. Each picture appeared on the screen sequentially, and the observers had to decide whether they could see a face in the stimulus or not. The instructions were the following: *"You will see black and white pictures displayed one by one sequentially. In these pictures, sometimes one can see a face, sometimes not. For each picture, you have to decide if you see a face or not. If you see a face, press on key "l". The face has to be in upright position, but it can be full front or presented from different viewpoints. If you cannot see a face, press on "s". Try to be as accurate and fast as possible."* Each stimulus was presented on the screen until the participant responsed, and was followed by a central cross (300 ms) and a gray screen (300 ms).

For statistical analysis, the modified T-test of (Crawford and Howell, 1998) was used. The principle of this method is to treat the control sample statistics as statistics rather than as parameters (in contrast with z-scores). This procedure decreases the type 1 error as it tests whether a patient's score is significantly below controls by providing a point estimate of the abnormality of the score (a *p* value). Here we used a <0.05 *p* value within the framework of a unilateral hypothesis. Analysis was performed with a computerized version of Crawford and Howell 's method: *SINGLIMS.EXE: Point estimate and confidence limits on the abnormality of a test score* (Crawford and Garthwaite, 2002) .

fMRI localizer experiment

PS and normal controls performed one block-design localizer fMRI experiment aimed at defining the areas responding preferentially to faces. PS and controls viewed 24 blocks per run (18 s per block, two runs of 11 min) of alternating pictures of faces, scrambled faces, cars and scrambled cars (6 blocks/condition), with 9 s fixation cross epochs between the blocks. They performed a one-back identity task (two or 3 positives per block). During a block, 18 stimuli were presented for 750 ms followed by a 250 ms black screen during each block. All images sustained a size of roughly 5.4° in height and 3.8° in width of visual angle and varied slightly in location in X (10%) and in Y (13%) on each trial.

fMRI Mooney faces experiment

PS and control participants viewed three runs (10 min 13 s per run; run 3 was the same as run 1) of 40 Mooneys faces upright and 40 Mooneys faces upside-down displayed in random order. Each picture sustained a size of roughly 5.2° in height and 3.6° in width of visual angle and varied in location in X (10%) and in Y (13%) on a gray screen (128 128 128). The stimuli appeared on the screen during 1750 ms followed by a cross of 4250, 5500 or 6750 ms and a gray screen of 250 ms. This timing ensured that the onset of distinct events were separated by at least 6-8 repetition times (TRs) to avoid the overlapping and saturation of the hemodynamic responses. Full randomization of trial order and of ISI duration further reduced any potential top-down effects of anticipation of the stimuli.

Participants were asked to press the right response key when they saw a face and the left response key (with the same hand) when they could not see a face in the stimulus. The stimuli were displayed with a PC running E-prime 1.1 (PST Inc.) through a projector surface located over the head of the subject and viewed with an angled mirror.

fMRI Arcimboldo faces experiment

The exact same procedure as the fMRI Mooney faces experiment was used with the 40 Arcimboldo faces (3 identical runs of 10 min 13s). Each picture sustained a size of roughly 6.6° in height and 5.4° in width of visual angle.

3.3.3.4. Imaging parameters

MR images of brain activity were collected from PS and normal controls using a 3T head scanner (Siemens Allegra, Siemens AG, Erlangen, Germany), with repeated single-shot echo-planar imaging: echo time (TE) = 50 ms, flip angle (FA) = 90°, matrix size = 64x64, field of view (FOV) = 224x224 mm², slice order descending and interleaved, slice thickness = 3.5 mm. The other scan parameters varied over the different experiments: repetition time (TR) = 2250 ms, 36 slices for the face localizer [or (TR) = 1500 ms, 24 slices for 4 control participants)]; TR = 1250 ms, 20 slices for the event-related Mooneys and Arcimboldo faces experiments (all participants). A three-dimensional (3D) T1-weighted data set encompassing the whole brain was acquired to provide detailed anatomy (1 mm^3) thanks to aADNI sequence (TR = 2250 ms, TE = 2.6 ms, FA =9°, matrix size = 256 × 256, FOV = 256 × 256 mm^2, 192 slices, slice thickness = 1 mm, no gap, total scan time = 8 min 5 s).

3.3.3.5. Data analysis of the imaging experiments

The fMRI signal in the different conditions was compared using BrainVoyager QX (Version 1.9.10, Brain Innovation, Maastricht, The Netherlands). Prior to analysis, the functional data sets were subjected to a series of preprocessing operations. Preprocessing consisted of a linear trend removal for excluding scanner-related signal, a temporal high-pass filtering applied to remove temporal frequencies lower than 3 cycles per run, and a correction for small interscan head movements by a rigid body algorithm rotating and translating each functional volume in 3D space. The data were corrected for the difference between the scan times of the different slices. Data was

not smoothed in the spatial domain for any of the experiments. In order to be able to compare the locations of activated brain region across participants all anatomical as well as the functional volumes were spatially normalized (Talairach and Tournoux, 1988) and the statistical maps computed were overlaid to the 3D T1-weighted scans in view to calculate Talairach coordinates for all relevant activation clusters. Subsequently, the functional data were analyzed using one multiple regression model (General Linear Model; GLM) consisting of predictors, which corresponded to the particular experimental conditions of each experiment. The predictor time courses used were computed on the basis of a linear model of the relation between neural activity and hemodynamic response, assuming a rectangular neural response during phases of visual stimulation (Boynton et al., 1996).

Statistical analyses were carried out in several steps, in line with the goals of the experiments.

First, the areas responding preferentially to faces were defined independently for PS and each individual participant using the face localizer experiment. The conjunction of the contrast [(Faces - Scrambled faces) ∩ (Faces - Objects)] between the two face localizer runs was computed. This conservative procedure ensured that the larger activations to faces than objects identified were those consistent across the two runs, and the voxels identified were not responding preferentially to faces because of low-level parameters. All contiguous voxels in the right and left middle fusiform gyrus (FFA) and in the bilateral inferior occipital cortex (OFA), as well as in the pSTS significant at [q(False Discovery Rate) < 0.05] were considered for further analysis. If foci of activations were not found for some participants, the statistical threshold was adjusted to a less conservative value in order to be able to test all the areas in all participants (see Dricot et al., 2008). All information about the regions of interest and statistical thresholds for each individual participant is provided in Table 3. S1. The above-defined regions of interest (ROIs) were tested in PS and AM 's brain with the contrast: [upright Mooney (or Arcimboldo) faces – inverted Mooney (or Arcimboldo) faces], and

for every participant with the same contrast in a random effect analysis (multi-subject GLM with predictors separated for each included control participant).

Second, in order to directly compare PS and the normal participants, fMRI signals averaged over PS' ROIs were also extracted and percent signal change was computed using the baseline epochs as reference for each condition. An index of the strength of the response was computed by means of the beta weights of the GLM analysis as follow: [(upright Mooney/Arcimboldo faces – inverted Mooney/"Arcimboldo" faces) divided by /(Mooney/Arcimboldo faces + Mooney/Arcimboldo faces upside-down/]. The exact same analysis was also done with the "correct trials" only ("face" response for upright stimuli; "nonface" response for inverted stimuli).

Finally, a whole brain analysis for PS versus control participants considered altogether was conducted in order to determine, without a priori functional localization, the regions which were primarily involved in the categorization of the stimulus as a face.

3.3.4. Results

3.3.4.1. Experiment 1. Mooney faces

Behavioral Mooney faces experiment

The acquired prosopagnosic patient PS was asked to classify upright and inverted Mooney stimuli as depicting a face or not, respectively. She detected 73.8% of the upright stimuli as faces, a normal range performance [control mean = 83.1%; SD = 17.9; t (Crawford and Garthwaite, 2002) = –0.495; p = 0.316]. She made very few false alarms (3.8%) comparable to the normal controls (6%; SD = 9.4; t = 0.223; p = 0.414) (Figure 3. 3A). PS was also as fast as the normal controls, independently of the presence of a face in the picture or not (respectively t = –0.451; p = 0.331 and t= –0,474; p = 0.324) (supplementary material S1A).

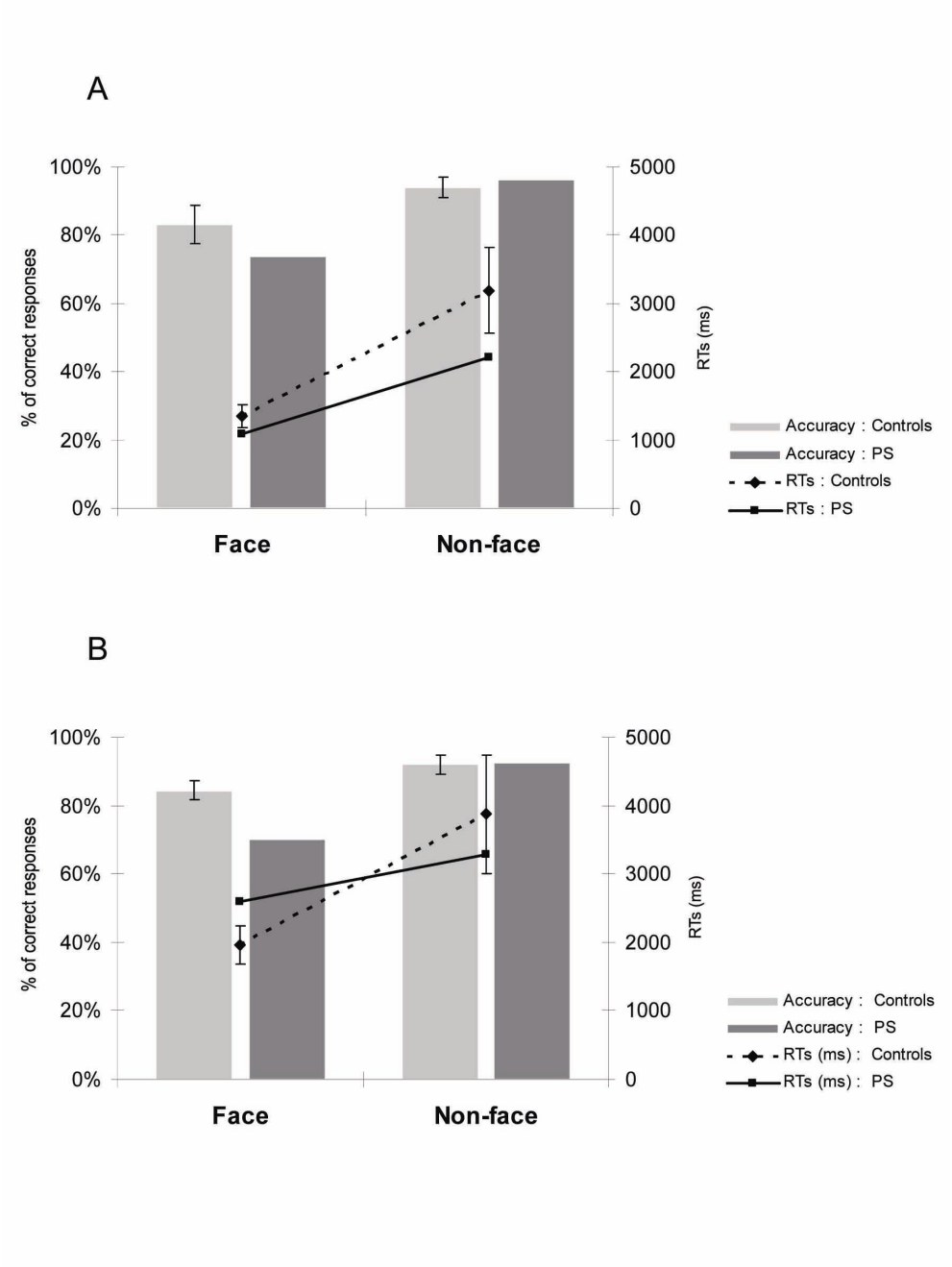


Figure 3. 3. A. Behavioral Results of the prosopagnosic patient PS and the control participants in the experiment 1 (detecting Mooney faces). **B**. Results of experiment 2 (Arcimboldo faces). For both experiments, the average response times are calculated on correct trials, separately for "Face" and "Nonface" stimuli. PS' accuracy rates are in the normal average, both for the "Face" as for the "Nonface" items. Regarding response times, PS is even faster than control participants. Bars in the graph represent the standard errors.

Thus, the acquired prosopagnosic patient PS was able to detect efficiently and readily a Mooney face stimulus, a visual categorization task that is assumed to rely on the global organization of the facial elements rather than a detailed analysis of these elements. Although many other cases

of acquired prosopagnosia have been tested with Mooney face stimuli, most of these tests were part of a clinical neuropsychological preliminary report (a test of visual closure) rather than a systematic experiment. Patients have been reported to either be impaired at processing Mooney face stimuli [e.g. (Young et al., 1990); one case in (Davidoff and Landis, 1990); (Steeves et al., 2006); Laeng and Caviness, 2001] or to perform in the normal range [2 cases in (Davidoff and Landis, 1990); (Sergent and Villemure, 1989; Sergent and Signoret, 1992a); Rivest et al., 2009]. However, these investigations were never systematic. Specifically, the patient data was never compared to appropriate control data, the patients suffered from general visual impairments, they were tested in variants of the face/non face decision task (e.g. categorizing the Mooney faces according to gender), and response times were never considered. To the best of our knowledge, the present study thus provides the first solid evidence of the preserved ability to perceive a face stimulus in ambiguous Mooney stimuli in acquired prosopagnosia.

fMRI experiment: Mooney face perception

The patient PS, one age-matched control (AM) and 7 young normal control participants were tested in the same face/nonface decision task on Mooney stimuli while scanning brain activity across the whole brain.

Functional localizer approach (Table 3. 1)

First, to isolate face-specific responses and remove any potential low-level visual difference between faces and nonface control stimuli, we contrasted faces *vs.* nonface objects in conjunction with the contrast faces *vs.* phase-scrambled pictures of faces (see methods and Figure 3. 2). Normal participants showed activation (see Table 3. S1 in supplementary material for details) in the right and left FFA (mean Talairach coordinates: 36.7, -46.7, -19.1 for the right FFA and -40.9, -46.3, -19.6 for the left FFA), in the right and left OFA (38, -78.4, -11.8 for the right OFA and -34.6, -73.6,

-15.6, for the left OFA) and in the right pSTS (43.1, -44.6, 9.2)[49]. Consistent with previous observations, there were significant activations at [q(False Discovery Rate) < 0.05] to faces in the FFA and pSTS of the right hemisphere for PS (36 -51 -21 for the FFA, and 45 -56 10 for the pSTS). These areas were normal in size and anatomical location as previously reported for normal observers (e.g., Kanwisher et al., 1997; Gauthier et al., 2000a) and for PS (Rossion et al., 2003a; Sorger et al., 2007; Dricot et al., 2008). There was also a small significant activation in the left inferior occipital cortex for PS [left OFA, at p(uncorrected)<0.05, -40 -73 -19], as found in some previous studies of the patient (Sorger et al., 2007). In summary, the missing components of the network of face preferential activation in PS' brain (left FFA and right OFA) were areas located in structurally damaged tissue (Figure 3. 2).

During the fMRI experiment with Mooney faces, PS again presented a similar response profile to the control participants, both for accuracy (72.8%; control group average was 69.1%, SD = 8.5%; *t* (Crawford and Garthwaite, 2002) = 0.41; *p*= 0.35; AM: 83%) and response times on correct trial (1384 ms, controls' average = 1216 ms, SD = 335 ms; *t* = 0.89; *p*= 0.21; AM: 1000 ms).

In each area showing preferential activation for faces in PS' brain, we tested the contrast (Mooney faces upright - Mooney faces inverted) in the group of normal controls (random effect analysis). We found significant effects in the two right hemisphere high-level "face areas" (FFA, pSTS), but not in the left OFA (FFA, t=3.33, p<0.016; pSTS, t=3.59, p<0.012; left OFA, t=1.15, p=0.30) (Table 3. 1; Figure 3. 4, 5A and supplementary material S2A).

[49] There were other areas activated by the conjunction contrast in some participants, but unlike the FFA, OFA and pSTS they were not consistent across participants, and were not the focus of the present study.

3.3. Global face categorization in higher-level cortical visual areas of the normal and prosopagnosic brain: towards a non-hierarchical view of face perception

Table 3. 1. Summary of the statistical significance (t-values; all ps<0.05 in yellow) in the regions of interest defined in the functional localizer experiment for the patient PS and the control participants (random analysis).

	Right FFA	Right OFA	Left FFA	Left OFA	Right pSTS
PS: Mooneys faces Up minus Mooneys faces Down	3.87	*lesioned*	*lesioned*	-1.20	2.75
Control Participants: Mooneys faces Up minus Mooneys faces Down	3.33	-0.28	3.17	1.15	3.59
PS: Mooneys faces Up Recognised minus Mooneys faces Down Not recognised	5.07	*lesioned*	*lesioned*	-1.56	3.37
Control Participants: Mooneys faces Up Recognised minus Mooneys faces Down Not recognised	2.94	-1.47	1.86	1.07	3.39

Arcimboldo faces experiment 2 : T values of the contrast	Right FFA	Right OFA	Left FFA	Left OFA	Right pSTS
PS: Arcimboldo faces Up minus Arcimboldo faces Down	5.06	*lesioned*	*lesioned*	1.31	6.02
Control Participants: Arcimboldo faces Up minus Arcimboldo faces Down	4.18	1.70	3.15	0.986	2.60
PS: Arcimboldo faces Up Recognised minus Arcimboldo faces Down Not recognised	5.02	*lesioned*	*lesioned*	1.03	4.92
Control Participants: Arcimboldo faces Up Recognised minus Arcimboldo faces Down Not recognised	2.99	1.82	2.24	1.03	3.37

3.3. Global face categorization in higher-level cortical visual areas of the normal and prosopagnosic brain: towards a non-hierarchical view of face perception

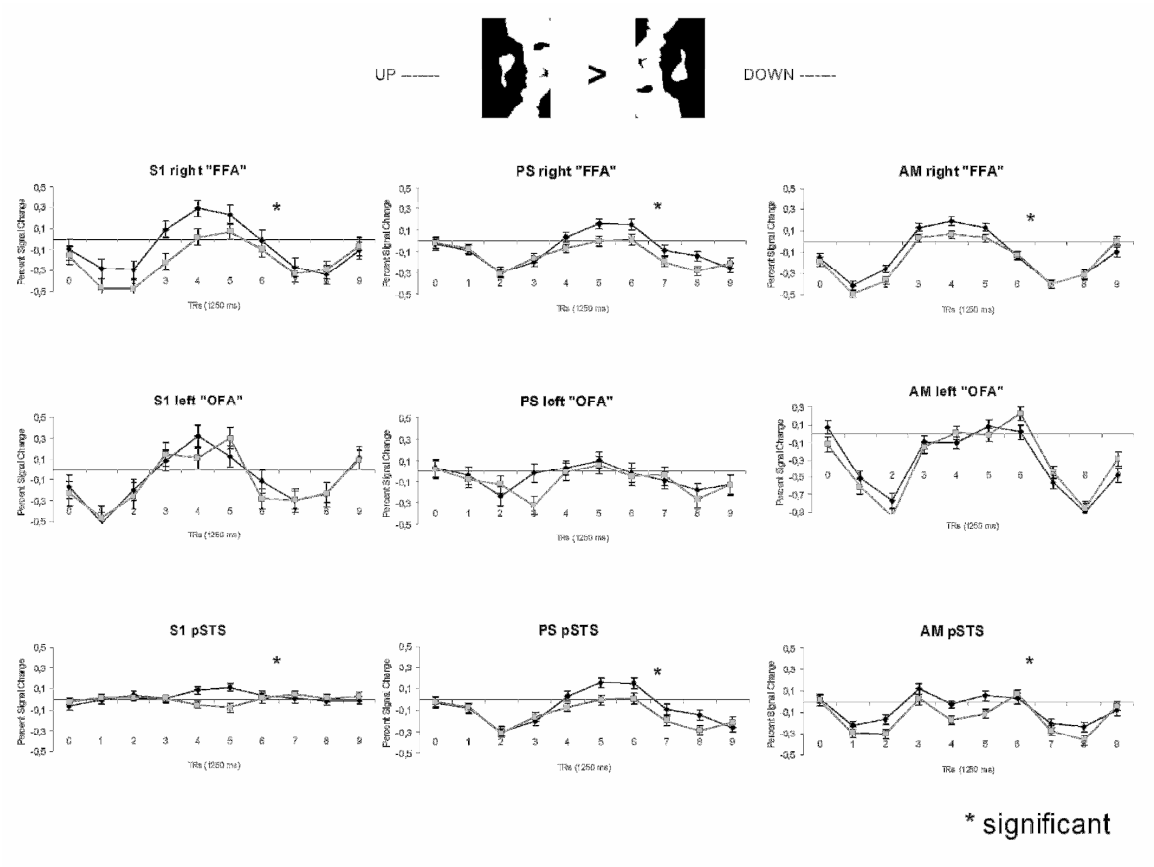


Figure 3. 4. Among the face-sensitive areas that are intact in the prosopagnosic patient's brain, only the right FFA, and the pSTS to a lesser extent, show a larger response to Mooney stimuli perceived as faces as compared to the same pictures presented upside-down ("nonfaces"). Similar findings are made control participants (S1 illustrated), PS and the age-matched control (AM). The left OFA does not show any enhanced response to the Mooney face stimuli.

The exact same results were found in PS' brain: FFA ($t=3.873$, $p<0.0001$), pSTS ($t=2.751$, $p<0.0060$), left OFA ($t=-1.201$, $p=0.23$) and for the age-matched participant (AM: FFA, $t=2.73$, $p<0.0064$; pSTS, $t=3.69$, $p<0.0002$; left OFA, $t=-1.93$, $p=0.05$) (Figure 3. 4).

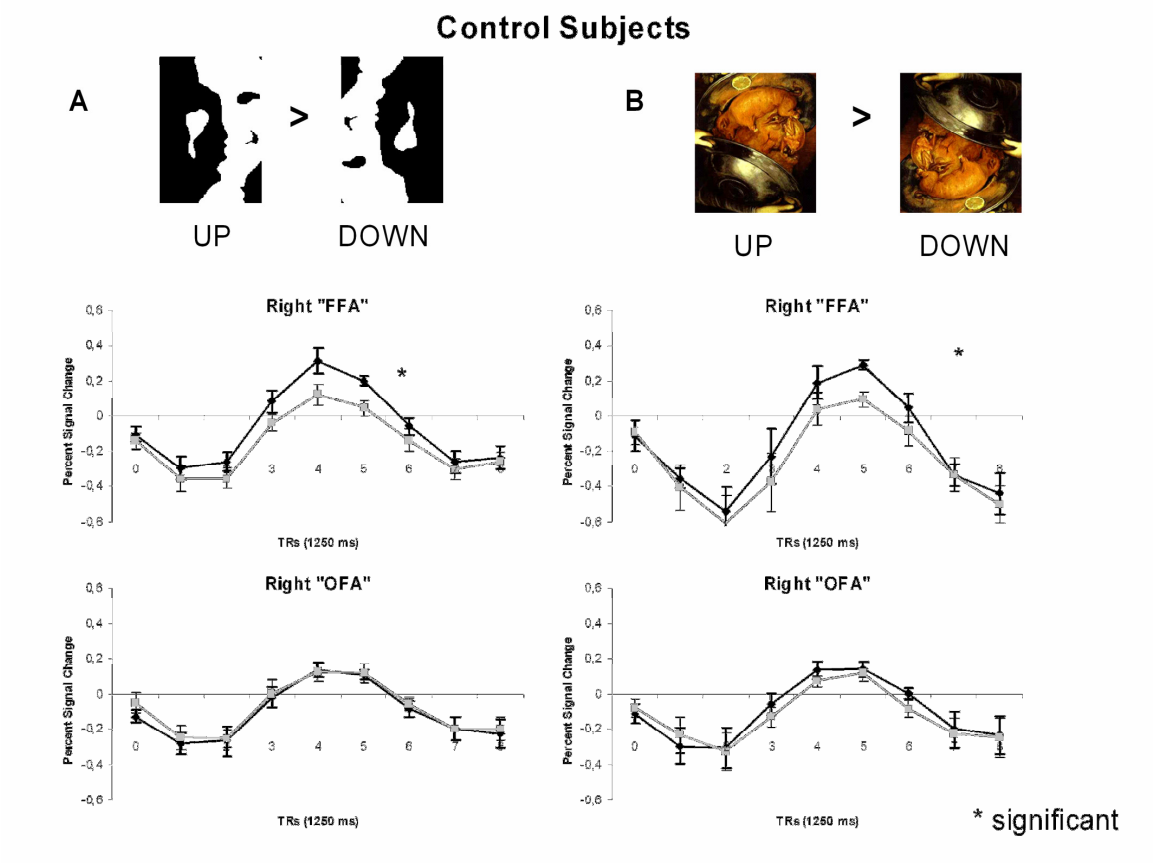


Figure 3. 5. A. Response to upright ("face") and inverted ("nonface") Mooney stimuli in the right FFA and OFA for the group of normal participants in the experiment. Note that while the right FFA showed a significantly larger response to Mooney faces, as shown previously [e.g. (Kanwisher et al., 1998)], there was no such effect in the right OFA. B. The same observations were made for Arcimboldo stimuli, even though there was a non-significant trend in the right OFA with such stimuli.

In the right OFA, located in a region of cortex structurally damaged in PS' brain, control participants showed no difference between the two conditions (random effect analysis: t=-0.28, p=0.79; AM: t=-2.21, p=0.03) (Figure 3. 5A). However, the contrast was also significant in the left FFA (also lesioned in PS' brain) in the group of normal participants (t=3.17, p<0.019) (supplementary material S2A), but it was not significant for the AM participant (t=-1.17, p=0.24).

PS and Controls: upright Mooney faces recognized compared with upside-down Mooney faces not recognized

The same analysis as above was performed only on trials with correct responses [contrast: (upright Mooney faces recognized – inverted Mooney faces not recognized)] (supplementary material S3 and S4). Identical results were found, except in the left FFA of the control group and

the age-matched participant, in which these areas no longer reached the significance level (left FFA: t=1.86, p=0.11; AM: t=0.85, p=0.40). Note that this observation cannot be accounted for by the reduced number of trials in this analysis, since the response to faces is even stronger in PS' and AM' right FFA in the same analysis (FFA in PS, t=5.07, p<0.000001; FFA in AM, t=4.39, p<0.00001).

Direct comparison of PS and normal participants: upright vs. inverted Mooney faces

In order to statistically compare PS' level of activation to these stimuli in face-sensitive areas to the normal population, we calculated an index of activation for upright Mooney faces for each participant [(Upright Mooney faces – Inverted Mooney faces/ Upright Mooney faces + Inverted Mooney faces].

In the right FFA, the larger activation for upright Mooney faces was identical for PS and normal participants, including AM, whether the activation index was computed on all trials (PS: 0.107) or only on correct trials (PS: 0.152) only [all trials: mean = 0.069, SD = 0.023; t (Crawford and Garthwaite, 2002)= 1.54, p= 0.17; correct trials: mean = 0.145, SD = 0.066; t = 0.10, p= 0.92] (AM's indexes: 0.049 and 0.095 respectively) (Figure 3. 6A). Similarly, in the right pSTS, there was no difference between PS (all trials: 0.134 and correct trials: 0.227) and the controls: (all trials: mean = 1.021, SD = 2.703; t= -0.31, p= 0.38; correct trials: mean = 0.286, SD = 0.758; t = -0.08, p= 0.47) (AM's indexes: 1.35; 1.92).

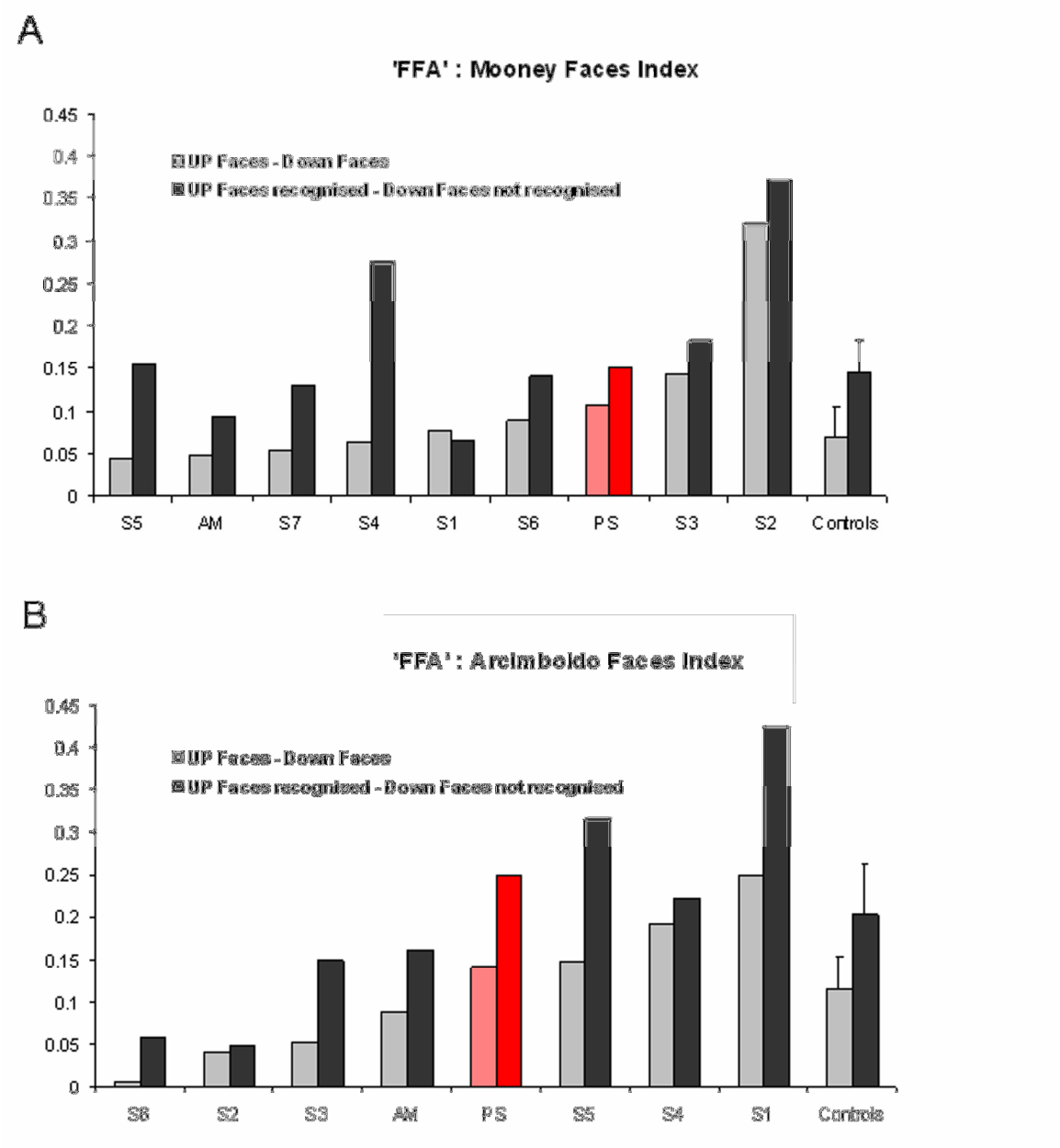


Figure 3. 6. A. Indexes of the level of differential activation (see methods) in the right FFA for face and nonface stimuli in experiment 1 (Mooney stimuli), reported for the group of controls (right) and for each individual participant, including PS and the age-matched control. Note that the difference was larger when only the trials that were correctly categorized as faces or nonfaces were considered in the analysis. B. Indexes of the level of differential activation for face and nonface stimuli in the experiment 2 with Arcimboldo stimuli.

In summary (Table 3. 1), independently of whether the analysis was computed on correct trials or on all trials, we found significant activations to the perception of Mooney faces primarily in the right FFA and right pSTS in the normal population. Strikingly, identical observations were made for the prosopagnosic patient PS. In the left inferior occipital cortex, structurally intact in PS'

brain and where a face-sensitive response (left OFA) was found in the localizer, there was no evidence for sensitivity to faces presented as Mooney stimuli, neither for the normal controls nor for PS. Finally, in the 2 regions that are structurally damaged in PS' brain, there was little (left FFA) or no (right OFA) evidence for sensitivity to the categorization of a Mooney stimulus as a face in the normal population.

Whole brain analysis

To strengthen our results, a whole brain analysis was performed on PS' data with the conjunction of the 3 contrasts (one per fMRI run): (upright Mooney faces - inverted Mooney faces). Two clusters were found at p(uncorrected)<0.05 in PS' brain (Figure 3. 7).

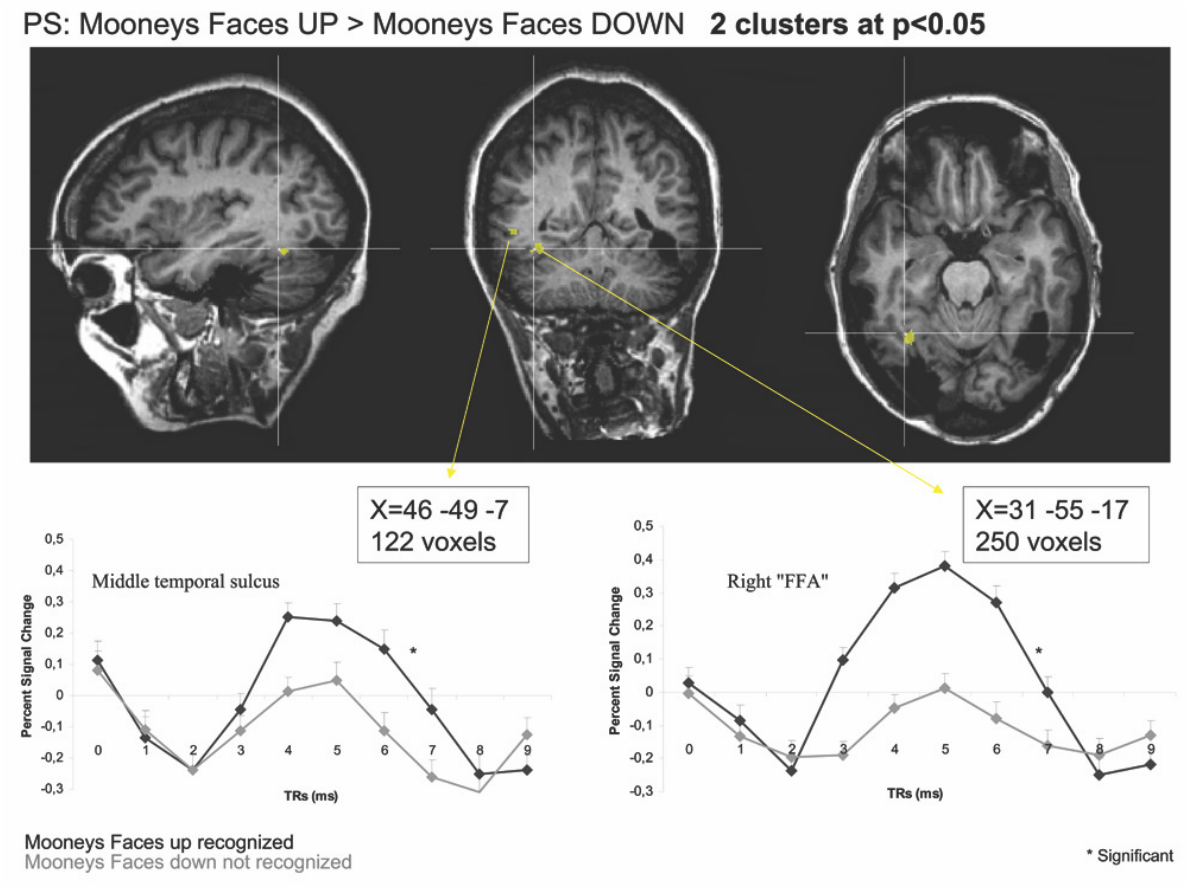


Figure 3. 7. Whole-brain analysis performed on the patient PS in the Mooney face categorization experiment. Two areas were found at significant, one corresponding roughly to the patient's right FFA, presenting face preferential response to faces in the localizer experiment, and the other one in the middle temporal sulcus, which did not show a preferential response to faces in the localizer experiment.

The first one corresponds quite well to the FFA (31, -55, -17, 250 voxels). It showed a preferential response to faces over cars and scrambled faces in PS's face localizer (F-O: t=8.34, p<0.000001, F-SF: t=8.36, p<0.000001). The other one was located near the middle temporal sulcus (46, -49, -7, 122 voxels), and did not show a preferential response to faces in the localizer (larger for both objects and scrambled faces than faces: F-O: t=-1.45, p<0.15 and F-SF: t=-2.11, p=0.04). The same analysis was performed with AM (Figure 3. 8), for which we also found two clusters: 34, -52, -13 (67 voxels; face sensitivity: F-O: t=15.25, p<0.000001, F-SF: t=26.31, p<0.000001) corresponding exactly to her right FFA, and 52 -50 -5 (60 voxels) in the middle temporal sulcus (face sensitivity: F-O: t=10.27, p<0.000001, F-SF: t=11.35, p<0.000001; note the proximity with the pSTS).

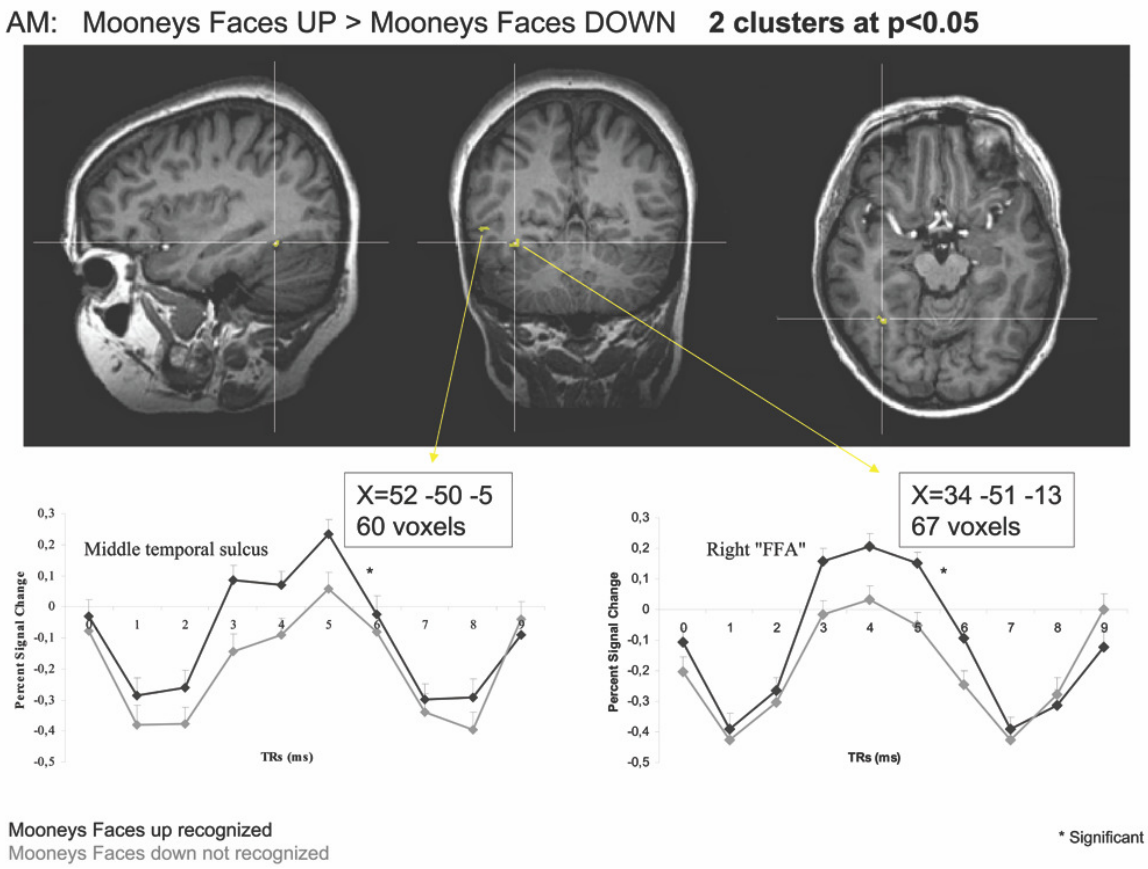


Figure 3. 8. Whole-brain analysis performed on the age-matched control (AM) in the Mooney face categorization experiment. As for the patient PS, two areas were found to be significant, one corresponding roughly to the right FFA, presenting face preferential response to faces in the localizer experiment, and the other one in the middle temporal sulcus, which did not show a preferential response to faces in the localizer experiment.

With our 7 participants considered as a group, we found only one significant cluster at p(uncorrected)<0.05, corresponding to the Talairach coordinates of the right FFA (33, -42, -19, 344 voxels). This region showed a preferential response to faces as identified in the face localizer with the 7 participants (F-O: t=5.44, p<0.000001, F-SF: t=30.11, p<0.000001). There was no significant activation in the right inferior occipital cortex, or the left hemisphere in this whole brain analysis.

Note that the whole brain analysis of the face localizer in the same 7 participants at the same statistical threshold [p(uncorrected)<0.05] gave rise to a rFFA of 1124 voxels, with a rOFA of 359 voxels. The rOFA' size was thus of 32% of the rFFA' size in the face localizer experiment. Considering this proportion, one could have expected a rOFA of about 110 voxels in the Mooney experiment. Instead, we found a significant rFFA at 344 voxels, with no voxel in the right inferior occipital cortex above statistical threshold. The same reasoning can be drawn for the left FFA (494 voxels at p<0.05; 151 voxels expected, 0 found) and the left OFA (268 voxels at p<0.05; 82 voxels expected, 0 found.

In summary, both the functional localizer approach and the whole-brain analysis indicate that the categorization of the stimulus as a face based on the Mooney stimuli takes place primarily in face-sensitive populations of neurons in the middle fusiform gyrus (FFA) of the right hemisphere, and to a lesser extent in the right posterior part of the STS. These areas are structurally intact in PS' brain and they show the exact same response profile in fMRI in this task as for normal observers. Overall, these observations indicate that the categorization of the visual Mooney stimulus as a face does not rely on lower-level visual areas that are sensitive to segmented face photographs in the localizer, but is supported almost exclusively by high-level areas in the right hemisphere.

3.3.4.2. Experiment 2. Arcimboldo stimuli

The goal of this second experiment was to test whether the prosopagnosic patient PS is able to readily categorize an Arcimboldo stimulus as being a face. More precisely, she was required to

classify upright and inverted Arcimboldo stimuli as depicting a face or not, respectively (see Figure 3. 1C).

Behavioral Arcimboldo faces experiment

Here PS obtained an accuracy rate 70% on the stimuli in which a face is detectable (Figure 3. 2B). In comparison to control participants (mean = 84.5%; SD = 8.3), this score is slightly, but not significantly, below average [t (Crawford and Garthwaite, 2002) = –1.662; p = 0.07]. Even though the patient cannot be considered as impaired based on these results (supplementary material S1B), one might argue that this indicates abnormal perception of these stimuli as compared to normal controls. However, a qualitative analysis of the errors, comparing the items failed by PS and the normal controls indicate that the nature of the responses for PS and controls is similar: each of the stimuli that she classified incorrectly was also classified incorrectly by at least one, and often several control participants (supplementary material S1C). In fact, if we consider only the 17 items that were always detected as faces by the controls, PS obtained a score of 100% correct responses. This implies that PS does not process these stimuli qualitatively differently than the control participants. Moreover, when considering her performance for non-face items, she is as accurate as the controls (92.5%; average= 92%; SD = 8.8%) (t = 0.05; p = 0.48). As for response times on correct trials, PS was again comparable to the control participants, for both face and non-face items (respectively t = 0.69; p = 0.25 and t = –0.21; p = 0.42). Thus, overall, PS (irrespective of the presence of a face) presents a profile of response that is similar to the control participants (supplementary material S1).

To our knowledge, this is the first demonstration of accurate and fast perception of faces made of non-face elements such as the paintings of Arcimboldo by a patient suffering from acquired prosopagnosia. It contradicts the view that such patients are unable to see a face in an Arcimboldo's painting (Harris and Aguirre, 2007). However, this is perfectly in agreement with the ability of acquired prosopagnosic patients to categorize a stimulus as a face, as opposed to their

impairment in individualizing faces. Moreover, the patient PS does not present object perception impairments and her low-level vision is well preserved, contrary to most cases of acquired prosopagnosia with extensive lesions [e.g. (Barton et al. 2004)], or cases of aperceptive agnosia like DF who may indeed be unable to see the face in a painting of Arcimboldo [e.g. (Steeves et al., 2006)].

fMRI Arcimboldo faces experiment

Performing the same task in the scanner, PS was as accurate as the controls [60.4%, mean = 62%, SD = 8.3%; *t* (Crawford and Garthwaite, 2002)= -0.19; *p*= 0.43; AM: 63%]. For response times on correct trials, PS (1384 ms) was also within the normal range (controls' mean = 1271 ms, SD = 319 ms; $t = 0.33$; $p = 0.37$; AM: 1028 ms).

Functional localizer analysis (Table 3. 1)

PS' data for face-sensitive areas were the same as used for the Mooney face experiment: significant activation of the right FFA and pSTS, as well as the left OFA. Mean Talairach coordinates of the ROIs for the control participants of the second experiment (S1, S4, S5, S8, S9, S10) are: 37.5, -46.0, -19.5 for the right FFA, -39.7, -45.3, -17.8 for the left FFA, 30.8, -79.7, -7.7 for the right OFA, -36.7, -70.2, -14.3 for the left OFA and -44, -50.3, 9.8 for the right pSTS (see Table 3. S1 for details about individual coordinates).

PS and Control Participants: upright Arcimboldo faces compared with inverted Arcimboldo faces

In each of the areas showing preferential activation for faces in PS' brain, we tested the contrast (upright Arcimboldo faces – inverted Arcimboldo faces) for normal participants, including AM. We found significant effects in the two high-level "face areas" (right FFA, random effect analysis: $t=4.18$, $p<0.0087$; right pSTS: $t=2.60$, $p<0.0484$; AM: FFA: $t=4.25$, $p<0.00002$; pSTS: $t=3.84$, $p<0.0001$) but it was not significant in the left OFA: $t=0.99$, $p=0.37$ (AM: $t=0.51$, $p=0.61$) (Figure 3. 9, 5B and supplementary material S2B). Identical results were found for PS, with

significant effects in the right FFA (t=5.60, p<0.000001), in the pSTS (t=6.02, p<0.000001) but not in the left OFA (t=1.31, p=0.19) (Figure 3. 9).

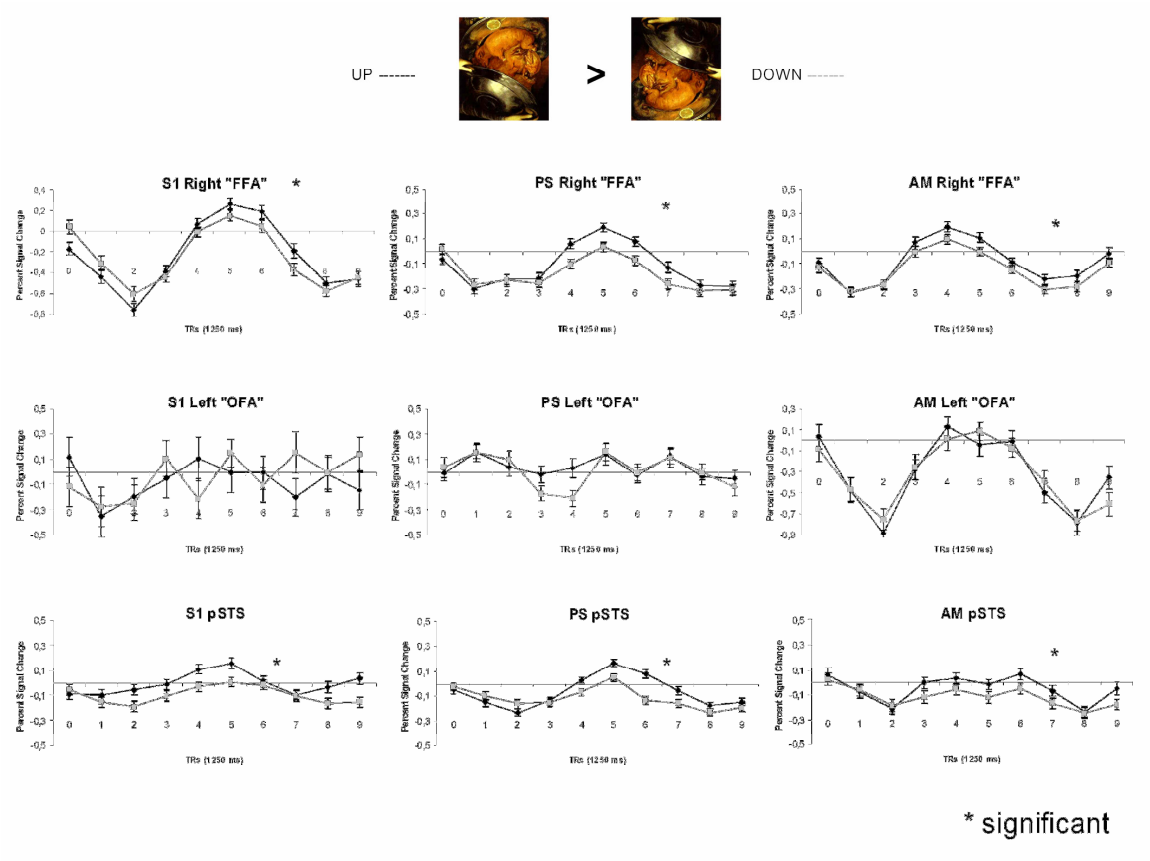


Figure 3. 9. Among the face-sensitive areas that are intact in the prosopagnosic patient's brain, the right FFA, as well as the pSTS showed a larger response to Arcimboldo stimuli perceived as faces as compared to the same pictures presented upside-down ("nonfaces"). Similar findings are made for control participants (here S1 illustrated), PS and the age-matched control (AM).

In regions structurally damaged in PS' brain, the group of control participants showed a difference between the two conditions in the left FFA (smaller than the right FFA) but not in the right OFA (left FFA: t=3.15, p<0.025, Right OFA: t=1.70, p=0.15; for AM: left FFA: t=2.45, p=0.014; right OFA: t=0.36, p=0.72) (Figure 3. 5B and supplementary material S2B).

PS and Control Participants: upright Arcimboldo faces recognized compared with inverted Arcimboldo faces not recognized

For correct trials only, the results were the same for PS [significant in the FFA (t=5.02, p<0.000001), in the pSTS (t=4.92, p<0.00001) but not in the left OFA (t=1.03, p=0.30)] and for the

group of control participants [right FFA, t=2.99, p<0.030; pSTS, t=3.37, p<0.020; left FFA, t=2.24, p<0.076; right OFA, t=1.82, p=0.13, left OFA, t=1.03, p=0.35]. For AM, the right and left OFA also reached significance in this comparison (AM: right FFA, t=5.54, p<0.000001; pSTS, t=3.09, p<0.002061, left FFA, t=5.568, p<0.00001, right OFA, t=2.77, p<0.0057, left OFA, t=2.83, p=0.0046], although the BOLD signal rather showed a deactivation for the condition inverted Arcimboldo faces not recognized in the OFA, (supplementary material S5 and S6).

In summary (Table 3. 1), we found significant activations to the perception of Arcimboldo faces primarily in the right FFA and right pSTS in the normal population and PS. In the left OFA, structurally intact in PS' brain, there was no evidence for sensitivity to faces presented as Arcimboldo stimuli, neither for the normal controls nor for PS. Finally, in the 2 regions that are structurally damaged in PS' brain, there was little (left FFA) or no (right OFA) evidence for sensitivity to the categorization of an Arcimboldo stimulus as a face in the normal population.

Direct comparison of PS and normal participants: upright vs. inverted Arcimboldo faces indexes

In the right FFA, the larger activation for upright Arcimboldo faces was identical for PS and normal participants, whether the index (see methods) was computed for all trials or only for correct trials [PS: 0.114 and 0.250, respectively; controls: all trials, mean = 0.114, SD = 0.097; t (Crawford and Garthwaite, 2002)= 0.26, p= 0.81; correct trials, mean = 0.203, SD = 0.149; t = 0.29, p= 0.78; AM: 0.088 and 0.162] (Figure 3. 6B). The same findings were made for the right pSTS (PS: all trials: 0.167 and correct trials: 0.378; controls: all trials: mean = 0.150, SD = 0.368; t= 0.04, p= 0.48; correct trials: mean = 0.101, SD = 0.246; t = 1.04, p= 0.17; AM: 0.78, 0.80).

Thus, the direct comparison between PS and normal observers did not reveal any significant difference in the level of activation in the right FFA or other face-sensitive area for Arcimboldo stimuli perceived as faces.

Whole brain analysis

As for the Mooney faces experiment, a whole brain analysis was performed on PS' brain with the conjunction of the 3 contrasts (one per run): (Arcimboldo faces upright minus Arcimboldo faces upside-down). Four clusters were found in PS at p(uncorrected)<0.05 (supplementary material S7): one corresponding to the Talairach coordinates of the right FFA (34, -56, -18, 507 voxels) (significant in PS' face localizer: F-O: t=7.71, p<0.000001 and F-SF: t=9.63, p<0.000001); two in the right dorsolateral prefrontal cortex (41, 31, 29, 136 voxels and 41, 18, 29, 161 voxels), not responding preferentially to faces: F-O not significant: t=0.51, p=0.61 and t=0.90, p=0.37 respectively). Finally, there was also one cluster in the left lingual gyrus (-20, -62, -15, 192 voxels), close to the V4/V8 region found previously [-23, -70, -15, (Sorger et al., 2007)] and responding more to Faces and Scrambled faces than Object and Scrambled Objects (t=5.20, p<0.000001 and F-SF not significant: t=-0.34, p<0.73) in PS' face localizer. The same analysis was performed with AM (supplementary material S8) in which we also found 4 clusters: one large cluster, corresponding to the Talairach coordinates of the right FFA (34, -50, -15, 276 voxels, significant in AM' face localizer: F-O: t=11.53, p<0.000001 and F-SF: t=22.61, p<0.000001), one small cluster located closely to the left FFA (-41, -44, -13, 76 voxels, face-sensitivity in the localizer: F-O: t=6.36, p<0.000001 and F-SF: t=10.88, p<0.000001), and one probably in the lateral occipital complex but overlapping the right OFA [LO, e.g. (Malach et al., 1995); 35, -77, -6, 53 voxels, object-sensitivity: t=15.04, p<0.000001 and face-sensitivity: F-O, t=4.12, p<0.00004)]. There was also significant activation in the postcentral gyrus (-55, -25, 38, 69 voxels, no face-sensitivity: F-O: t=0.87, p=0.38). When considering our 6 control participants as a group, we found only 3 significant clusters, one corresponding to the Talairach coordinates of the right FFA (32, -58, -14, 120 voxels) (6 participants' face localizer, F-O: t=2.38, p<0.017230, F-SF: t=15.717, p<0.000001) and two belonging most probably to the lateral occipital complex [LO, e.g. (Malach et al., 1995): -30, -78, -16, with 65 voxels, corresponding to the left ventral posterior part of LO (6 participants'

face localizer, F-O: t=1.60, p=0.11, O-SO: t=7.43, p<0.000001) and one 28, -41, -18 (52 voxels) to the right ventral anterior part of LO (6 participants' face localizer, F-O: t=1.07, p=0.28, O-SO: t=17.09, p<0.000001)].

To summarize, the whole brain analysis confirmed the dominant role of the right FFA in categorizing the Arcimboldo stimuli as faces. This region was the most significant in all comparisons, independently of whether all trials or only correct trials only were considered, both for the normal control participants and for the patient PS. It was also the only face-sensitive region that responded to Arcimboldo faces for all participants. Other areas, such as the right pSTS were involved, to a lesser extent. This observation is strengthened by the comparison of the whole brain analysis of the face localizer in the same 6 participants at the same statistical threshold [p(uncorrected)<0.05] gave rise to a rFFA of 373 voxels, with a rOFA of 28 voxels. The rOFA' size was thus only of 8% of the rFFA' size in the face localizer experiment with these participants. Considering that the size of the rFFA was even larger in the Arcimboldo experiment at this threshold (507 voxels), one could have expected to disclose a rOFA of at least 38 voxels. Instead, we found a significant rFFA at 507 voxels, with no voxel in the right inferior occipital cortex above statistical threshold. The same reasoning can be drawn for the left FFA (115 voxels in the localizer at p<0.05, 156 voxels expected, 0 found) and the left OFA (in the localizer at p<0.05, 35 voxels expected, 0 found).

Considering experiments 1 and 2 altogether, it appears that holistic face detection is subtended first and foremost by high-level face-sensitive areas of the right hemisphere, in particular the right FFA, rather than by face-sensitive lower-level visual areas such as the rOFA, both in the normal brain and for the patient PS. To fully support this claim, we also tested directly for the interaction between the two main areas of interest identified in all normal brains (rFFA, rOFA) and the conditions (upright, inverted Mooney or Arcimboldo faces), taking the individual beta weights of the GLM analysis in an 2 x 2 ANOVA model for repeated measures. For Mooney faces, we

found a significant interaction ($F_{1,6}$=10.80, p=0.017) between the two factors, reflecting the significant difference in the FFA (post-hoc t-test: p=0.016) but not in the OFA (p=0.8). For Arcimboldo faces, there was also a significant interaction ($F_{1,5}$=10.99, p=0.021) between the two factors, reflecting the significant difference in the FFA (post-hoc t-test: p=0.008) which failed to reach significance in the OFA (p=0.16) (Figure 3. 10).

Finally, across all face-sensitive regions, we also observed a lateralization index (see methods) of 58% of the significant face-sensitive voxels in the right hemisphere in the functional face localizer, which increased up to 100 % for the Mooney face stimuli (experiment 1) and 73% for the Arcimboldo face stimuli (experiment 2).

3.3.5. Discussion

Three observations were made in this study.

First, the fMRI study in normal participants revealed the areas that are involved in perceiving a stimulus as a face when this perception is based on the global configuration of the stimulus (Mooney and Arcimboldo faces) rather than on local parts. Compared to the functional localizer, where full photographs of faces were shown, there was a substantial increase in right hemisphere lateralization for Mooney and Arcimboldo face stimuli. Morover, and most importantly, face-preferential responses were found only in high-level visual cortex for Mooney and arcimboldo stimuli (FFA and to a lesser extent the pSTS), while there was no evidence of face-preferential response in the inferior occipital cortex (i.e., no OFA).

Second, the behavioral study shows that holistic perception of faces is not all or none : a brain-damaged prosopagnosic patient who is impaired at holistic perception of individual faces (Busigny et al., 2010 ; Ramon et al., 2010 ; Van Belle et al., 2010) may be unimpaired at seeing a face as a face, even when it requires holistic processing.

Finally, it was found that the prosopagnosic patient – like normal observers - recruits primarily her intact right FFA to categorize these stimuli based on their overall configuration. Thus, the prosopagnosic patient presents a normal profile of response both at the behavioral and neural level.

Altogether, the present observations support the view that there would be a direct functional pathway from early visual areas to a high-level visual area in the right middle fusiform gyrus. This pathway would lead to face-preferential responses in the middle fusiform gyrus (i.e., an FFA), and support the perception of a global ("holistic") face configuration [Figure 1 in (Rossion, 2008)]. That is, the visual stimulus would not necessarily need to go through a stage of processing in the inferior occipital cortex where local facial parts would be analyzed (and face-preferential responses elicited, i.e. an OFA), before reaching higher-level visual areas. Thus, these data support a view of face perception at the neural level that would not be strictly hierarchical: face preferential responses – which are related to the phenomenological perception of a face (e.g., Tong et al., 1998; Jiang and He, 2006) - may emerge first in a high visual area of the right hemisphere.

3.3.5.1. Global to local face perception in the normal brain

Several neuroimaging studies of the normal brain have shown that the middle fusiform gyrus, in particular the pre-localized right FFA, respond more to two-tone Mooney stimuli when they are perceived as faces (Dolan et al., 1997; Kanwisher et al., 1998; Andrews and Schluppeck, 2004; McKeeff and Tong, 2007). This observation has generally been taken as evidence for a role of the FFA in perceptual awareness, or perceptual decision, about the faceness of the stimulus. However, to our knowledge, the present study is the first to investigate the response to such ambiguous stimuli in the entire network of areas subtending face perception, both using a functional localizer approach and a whole brain analysis. In particular, the profile of response in the functionally localized face-sensitive area in the inferior occipital cortex (OFA) had not been investigated and compared to the FFA response.

Across the two experiments, our observations indicate that the primary locus for the perception of a stimulus categorized as a face through its global configuration is the FFA of the right hemisphere. With perceived Mooney faces, this area showed the highest level of activation. There was also a contribution of the right pSTS and to a much lesser extent of the left FFA. However, remarkably, there was no significant face-sensitivity observed in the lower-level inferior occipital cortex (i.e., no OFA in the whole-brain analysis, and no difference between face *vs.* no face perception found in this region of interested as defined in the localizer). Importantly, our analyses show that the dominance of the right FFA in normal observers in this experiment is not a mere replication of what is generally observed when presenting full pictures of faces and nonface visual shapes, as in a face localizer experiment: both the right lateralization and the relative contribution of the FFA (as compared to the OFA) is significantly increased by presenting visual stimuli whose faceness is defined primarily by their global configuration, not their local parts.

The results were largely confirmed in the second fMRI experiment performed with Arcimboldo face stimuli, used for the first time to our knowledge in neuroimaging. Even though they may require less ground segregation and internal contour definition than two-tone Mooney faces (Cavanagh, 1991; Peterson and Gibson, 1991), they share with Mooney faces the fact that their facelike appearance emerges from the global configuration of the elements rather than the elements themselves, which are not face-like. Presented with these stimuli, the right FFA again showed the strongest response. Overall, the right hemispheric dominance, and the particular sensitivity of high-level face areas versus lower-level face sensitive areas were again clearly outlined in these results, which largely support the view that face-sensitivity can arise in high-level visual areas independently of putative face-related inputs from the OFA.

These observations are difficult to reconcile with the conventional view that the processing of face stimuli must go through hierarchical stages, with the extraction of simple facial parts in the OFA, leading to the subsequent perception of whole faces in the FFA (Haxby et al., 2000; Jiang et

al., 2006; Fairhall and Ishai, 2007; Ishai, 2008; see also Lerner et al., 2001 and Pitcher et al., 2007[50]). Rather, it indicates that face-sensitivity can arise in high-level visual areas, leading to an FFA, independently of putative face-related inputs from the OFA, perhaps through direct visual connections from retinotopic visual areas. This view 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 have been reported (Kim et al., 2006), suggesting that early visual areas can send non-category-related visual information that may be interpreted as facelike in high-level visual areas.

What would then be the function(s) of the OFA(s) when dealing with normal faces? One hypothesis is that it contributes to face perception following – rather than preceding - the initial categorization of the stimulus as a face in higher visual areas (right FFA and pSTS) (Rossion et al., 2003a; Rossion, 2008). According to this view, neurons in the OFA, presenting a smaller receptive field, may be useful to extract finer-grained information from the visual stimulus, for instance to identify the particular face components (e.g. eyes, nose, mouth, ...). An interesting prediction of this view is that the contribution of the OFA in the present face/nonface categorization task with Mooney or Arcimboldo stimuli may be enhanced if the stimuli are presented long enough and observers are requested to extract details about the faces for finer-grained categorization judgments [i.e. male/female faces, estimating the age of the face, ...see (Mooney, 1957; McKone, 2004)].

[50] In that latter study, transcranial magnetic stimulation (TMS) applied over an average coordinate of the right OFA at a very early stage in time (60-100 ms following visual stimulation) disrupted individualization of faces differing by facial parts (Pitcher et al., 2007). This finding has been taken as evidence that the OFA is the first face-sensitive relay in the human brain, coding for facial parts. However, while Pitcher et al. (2007)'s findings may indeed be taken in favor of an early role of the OFA in face processing, they concern the specific case of face individualization. In order to contradict the present findings and their interpretation, one would rather have to show that TMS applied to the (right) OFA leads to impairment in holistic face detection, and to a reduced or abolished response to faces in the FFA if TMS is combined with fMRI.

The view of a neural microgenesis of face perception, starting with a coarse categorization of the stimulus in high visual areas (here the FFA) followed by a refinement of the face representation through reentrant interactions with lower visual areas (here the OFA) is highly plausible, for a number of reasons.

First, it makes sense that an initial global representation of the stimulus would depend on neurons that are sensitive to the entire face stimulus, i.e. neurons located quite high in the visual hierarchy and with a large receptive field (Desimone et al., 1984; Tsunoda et al., 2001). Previous neuroimaging studies have shown that the FFA (also called mFUs or pFus in some studies) is more sensitive to progressive image scrambling than the OFA (also referred to as the face-sensitive responses in the LOC), suggesting that the FFA represents faces at a more global level than the OFA (Lerner et al., 2001; see also Grill-Spector et al., 1998). Moreover, the FFA shows a small degree of larger overlap for central as opposed to peripheral visual stimuli, while the central *vs.* periphery advantage is much larger in the OFA (Levy et al., 2001).

Second, according to a number of authors, processing in the visual system is though to follow a coarse-to-fine sequence, with the coarse structure of the stimulus, carried by low spatial frequency (LSF) channels, being processed before the fine local details transmitted by high SF (e.g., Flavell and Draguns, 1957; Ginsburg, 1978; Hugues, Nozawa, and Ketterle, 1996; Loftus and Harley, 2004; Parker and Costen, 1999; Schyns and Oliva, 1994; Watt, 1987). Because of the initial availability of LSF, the early visual representation would be that of the global structure of the face stimulus, this coarse frame being refined over time with the slower accumulation of higher spatial frequencies (Sergent, 1986). A recent fMRI study supports this view, showing that the rFFA, and to a lesser extent the right pSTS, respond preferentially to LSF faces in early stages of face processing (i.e., until 75 ms of exposure duration) as compared to higher SFs (Goffaux et al., 2010). Moreover, in that study, the response to finer-grained face information, i.e. high SF, became more significant over time in the bilateral FFAs and in the right OFA, supporting the view advocated here.

Third, many authors have suggested that rather than initiating the process of object/face categorization, lower visual areas (such as the OFA) may rather be contacted through feedback from high-level visual areas (such as the FFA) to perform perceptual computations and representations that involve high-resolution details, fine geometry and spatial precision (Mumford, 1992; Hupé et al., 1998; Lee et al., 1998; Lamme and Roelfsema, 2000; Bullier et al., 2001; Galuske et al., 2002; Bar, 2003). This view is consistent 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, 1978, 1993). It is entirely in line with an influential theoretical framework of visual perception, the reverse hierarchy theory [RHT; (Hochstein and Ahissar, 2002)], according to which explicit perception begins at high-level visual cortex, representing "the gist of the scene", or an object at the basic level. 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 (Hochstein and Ahissar, 2002; Ahissar and Hochstein, 2004). The initial categorization of a face based on the global organization of its elements rather than the local details, as in a Mooney or Arcimboldo stimulus, would certainly fall into this category, insofar as this process depend on internal knowledge of the face structure (Moore and Cavanagh, 1998; Hegdé et al., 2007; Kemelmacher-Shlizerman et al., 2008), which would be stored in high-level rather than low-level visual areas (O'Craven and Kanwisher, 2000; Peelen, Fei-Fei, and Kastner, 2009).

Finally, we note that the inferences made here about the neuro-functional organization of face categorization are based on the magnitude of signal in the areas of interest and the whole brain. That is, we found both the FFA and OFA (bilaterally) in the face-localizer in our normal observers'

brains, while only the right FFA was present for Mooney and Arcimboldo stimuli. However, one cannot exclude that face-sensitivity in the inferior occipital cortex is present at a level of spatial resolution below the level of these regions of interest, when presenting such stimuli. More precisely, the pattern of response across voxels in the inferior occipital cortex, rather than the absolute magnitude of signal, may differ between perceived and non-perceived Mooney faces (see Hsieh et al., 2010). This hypothesis could be explored in future studies by multivariate pattern analysis methods (e.g., Haxby et al., 2001; O'Toole et al., 2007; Peelen et al., 2009)[51]. Nevertheless, our data indicate that the OFA, as defined as an area showing a larger response to faces than objects (and scrambled faces) in the inferior occipital cortex here and in previous studies, is not found for face stimuli requiring holistic perception, suggesting that it is not a necessary stage of face perception in general.

3.3.5.2. A neural locus for the right hemisphere dominance in holistic face perception

The right hemispheric dominance for unfamiliar face perception is now a well established fact. Acquired prosopagnosia follow either bilateral or right unilateral occipito-temporal lesions (Hécaen and Anguelergues, 1962; Landis et al., 1988; Bouvier and Engel, 2006; Sorger et al., 2007), and multiple sources of evidence ranging from divided visual field studies (Parkin and Williamson, 1987; Hillger and Koenig, 1991), neuroimaging [e.g. (Sergent et al., 1992; Kanwisher et al., 1997; McCarthy et al., 1997)], event-related potentials [ERPs, e.g. N170 (Bentin et al., 1996)] or single-cell recordings in the nonhuman primate brain (Perrett et al., 1988) have supported the dominant role of the right posterior visual areas in processing face stimuli [see also (Zangenehpour and Chaudhuri, 2005)]. Here we observed enhanced right lateralization when perceiving faces

51 Note that such observations are unlikely, for two reasons at least. First, the whole-brain analysis performed at the voxel level, with unsmoothed fMRI data, did not reveal any face-preferential response in the inferior-occipital cortex in the Mooney/Arcimboldo experiments. Hence, if consistent face-preferential responses were present, they would have to be fully distributed (i.e., peppered) at the voxel level so that no contiguous voxels would show a larger response to faces over nonface stimuli. Second, the patient PS has a lesion in the right inferior occipital cortex, ruling out any form of face-preferential response in this part of the brain. Nevertheless, she shows rFFA activation to Mooney/acrimboldo stimuli.

defined on the basis of their global configuration. This observation provides further evidence – and a neural locus – to classical evidence of a right hemispheric advantage at perceiving Mooney face stimuli from lesion studies (Lansdell, 1970; Newcombe, 1974) and divided visual field experiments (Parkin and Williamson, 1987). More generally, it offers strong support to the long-standing view that the right hemisphere dominance in processing faces is directly related to global/holistic perception (Ellis, 1983; Sergent and Villemure, 1989; de Schonen and Mathivet, 1989; Hillger and Koenig, 1991).

3.3.5.3. Normal holistic perception of a generic face in acquired prosopagnosia

We found that acquired prosopagnosia does not necessarily prevent the perception of a face based on the general configuration of the elements such as in two-tone Mooney faces, and Arcimboldo's famous paintings. The patient PS was not only able to see the faces adequately in these stimuli, but her pattern of responses looks perfectly normal, even when considering response speed.

To the best of our knowledge, the present study provides the first solid evidence of the preserved ability to perceive a face stimulus in ambiguous Mooney and Arcimboldo figures following acquired prosopagnosia. We believe that this observation is particularly interesting because there is now wide evidence that the patient PS is impaired at holistic processing of individual faces. For instance, she does not show any advantage at matching upright over inverted faces (Busigny and Rossion, 2010), and when she has to match specific parts of individual faces, her performance is not influenced by the identity of the other face parts (lack of whole-part advantage and composite face effect, Ramon et al., 2010). Eye gaze fixation and performance during gaze-contingency also demonstrate a lack of holistic perception when the patient has to individualize faces (Orban de Xivry et al., 2008; Van Belle et al., 2010). Considered together with the present evidence for normal holistic (generic) face perception, these data indicate that there may be two forms of holistic face perception that should be clearly distinguished: one that allows

categorizing a face stimulus at the basic-level ("it's a face"), a necessary stage of processing that is preserved for PS, but which is not sufficient for the extraction of a more fined-grained representation of the whole individual face, a process that is damaged for PS.

At first glance, considering that the patient PS has an intact right FFA and pSTS (Rossion et al., 2003a; Sorger et al., 2007), that the FFA lights up for Mooney faces in normal observers (Dolan et al., 1997; Kanwisher et al., 1998; Andrews and Schluppeck, 2004; McKeeff and Tong, 2007), and that the patient perceives these stimuli as well as normal observers (the present behavioral results), the normal pattern of activation to Mooney and Arcimboldo face stimuli in PS' brain is not a surprising observation. Yet, the patient might have shown normal behavior at these tasks while recruiting distinct areas as normal observers. For instance, although being impaired at face individualization, PS performs well above chance level at such tasks, yet recruits object areas (LOC) rather than her intact FFA to do so (Dricot et al., 2008). However, here we found normal level activation to Mooney/Arcimboldo faces in the exact same brain areas, the right FFA primarily, for PS and normal observers. This observation reinforces the view that the patient perceives a generic face holistically, just as normal viewers. Moreover, the fact that she performed as well as normal viewers without her right OFA reinforces the finding that this area is not critically involved in holistic (generic) face perception.

We note that this last observation can be related to a previous study in which normal FFA response was found in a case of prosopagnosia during perception of a face in a biased vase/face illusion (Hasson et al., 2003). However, the patient tested by Hasson et al. (2003) had no brain damage, so that his OFA was intact. Second, the FFA and OFA were activated by a single stimulus (modified vase-face illusion) that is fundamentally different than the many Mooney faces used here. The vase/face stimulus can be defined as two profile faces just based on the contour (a line) defining the (2) face(s). It is segmented, with all the parts being well separated from the background by a different texture/colour and identified as forming the face stimulus precisely because they

share the same surface properties. In contrast, Mooney face stimuli are two-tone images for which some blobs making the face are in black and others are in white, counfounded by two-tone background blobs. The visual system thus has to rely on an internal 2D face template to segment the stimulus and see it as a face (Cavanagh, 1991 ; Moore and Cavanagh, 1998).

Because the right FFA was the strongest, and most consistently activated region in the Mooney/Arcimboldo experiments, it suggests that this area is necessary for the initial categorization of a visual stimulus as a face based on global configuration. This claim may appear at odds with pattern-based classification studies of fMRI data indicating that even without the contribution of the (bilateral) FFA, faces can be reliably distinguished from other object categories, suggesting rather a distributed representation of categories in the ventral temporal cortex (Haxby et al., 2001; O'Toole et al., 2005). Similarly, prosopagnosia can arise from different bilateral and right hemispheric lesion sites, including the right FFA (Barton et al., 2002), yet these patients are generally still able to categorize a face as opposed to a non-face object, supporting a distribution of resources to perform the simple categorization of the stimulus as a face. However, face classification in prosopagnosic patients, or pattern-based classification in fMRI studies of the normal brain, are generally performed with well-segmented visual stimuli, which can be distinguished (i.e. categorized unambiguously) based on multiple local and global cues. In the present study, we used stimuli that had to be perceived holistically in order to be categorized as faces. Hence, the present data suggests that insofar as a holistic representation of the stimulus is *required* for face perception, the right FFA may be a fundamental region. Although a role of the right pSTS cannot be excluded, the present observations lead to the prediction that a lesion, or a functional depression, of the right FFA should significantly reduce the ability to perceive a face as a face if holistic perception is necessary. In contrast, while the left middle fusiform showed face-related activation for Mooney and Arcimboldo faces in the ROI analysis, the fact that this region is damaged in PS' brain suggests that it is not strictly necessary to perform holistic face perception.

Finally, we note that a critical role of the right FFA in holistic generic face perception does not confine this area to this basic, yet important, function. There is wide evidence that representations of individual faces are coded in a network of visual areas, including the right FFA and OFA [e.g. (Gauthier et al., 2000a; Grill-Spector and Malach, 2001; Yovel and Kanwisher, 2005; Gilaie-Dotan and Malach, 2007)]. Interestingly, the right FFA is also the area which shows the strongest sensitivity to holistic perception of the (finer-grained) individual face, as demonstrated by the composite face effect (Schiltz and Rossion, 2006; Schiltz et al., 2010; see also Harris and Aguirre, 2008; Andrews et al., 2010). That is, face detection and individualization appear to be subtended by overlapping neural circuits in the human brain, and the right FFA seems to play a dominant role in coding faces holistically, both at coarse and fine-grained representational levels. According to a reverse hierarchical scheme as suggested here and previously (Rossion, 2008), the first face representation emerging in the rFFA following feedforward processing would be holistic and coarse (Goffaux et al., 2010; see also Sugase et al., 1999, Sripati and Olson, 2009 for electrophysiological evidence in the monkey infero-temporal cortex). This holistic representation could then be refined by a second wave of inputs and/or reentrant functional interactions with lower visual areas such as the OFA.

3.3.6. Summary and Conclusions

We provided evidence from neuroimaging in normal viewers that when holistic perception is required to categorize a visual stimulus as a face, it can activate the rFFA without a contribution of the rOFA. This finding is strengthened by normal behavioral and neural responses during holistic perception of faces in a prosopagnosic patient with brain damage to the cortical territory of the rOFA. Altogether, these observations suggest that even during the presentation of full face pictures, face-preferential responses may emerge independently in high-level visual cortex (FFA) and perhaps before any similar responses in inferior occipital cortex (OFA). Thus, they challenge

conventional hierarchical models of face perception and provide neural support to the view that a face can be initially perceived through a match between the incoming visual input and a holistic representation in high level visual areas of the right hemisphere.

Acknowledgements

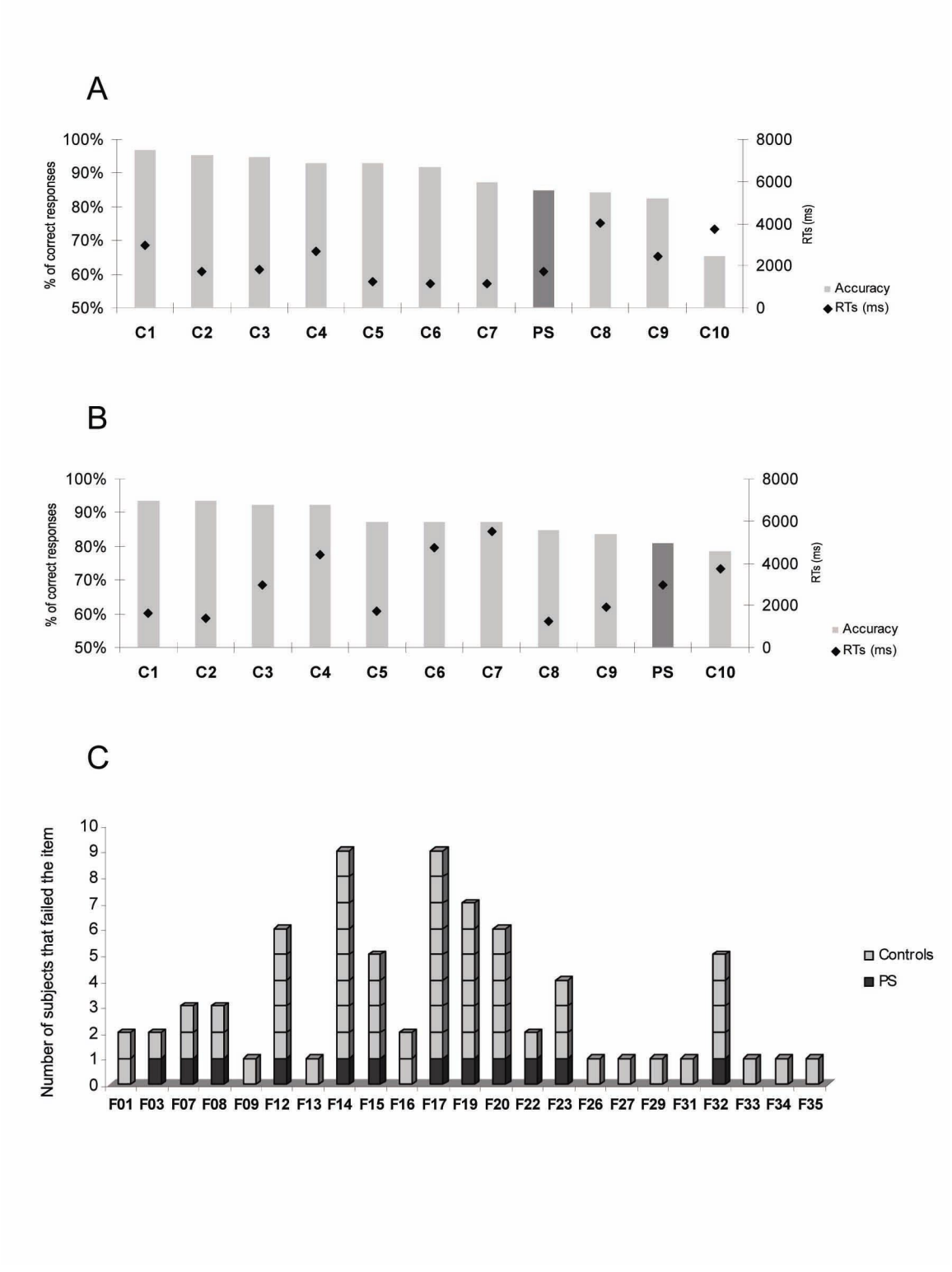
We are grateful to PS for her patience during the experiments and to all our control participants. We also thank Aaron Schurger for providing us with the Mooney face stimuli, and Dana Kuefner for her helpful comments on a previous version of this manuscript. This research was supported by a grant ARC 07/12-007, and a Mandat d'impulsion scientifique (FNRS) 2008-2011 to BR. BR and TB are supported by the Belgian National Fund for Scientific Research (FNRS).

Supplementary Table 3. 1. Talairach locations, t-values and cluster sizes of the functionally defined regions of interests (right and left-sided FFA, OFA and right pSTS) in the localizer experiments for the patient PS and the control participants.

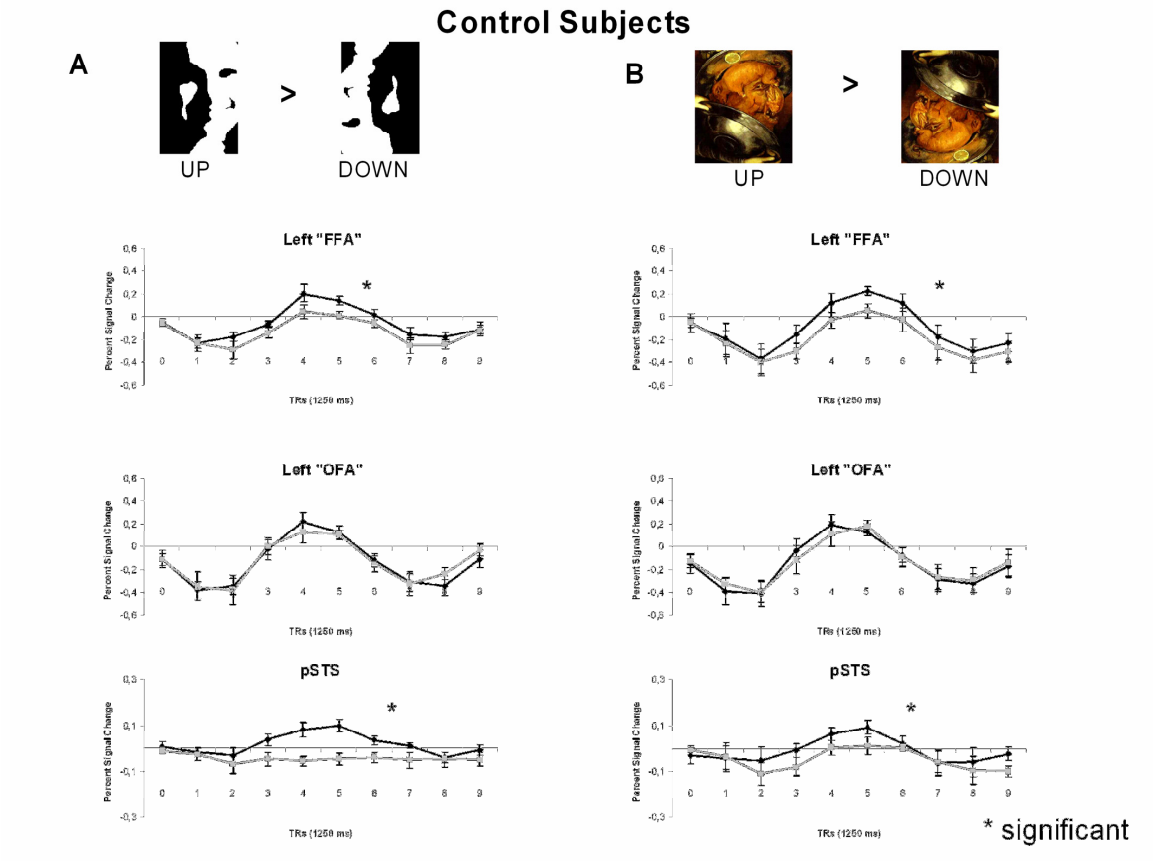
	SUBJECTS	Talairach Coordinates:			Cluster size:	
		x	Y	z	(mm^3)	
PS	RFFA	36	-51	-21	579	
	ROFA	Lesioned				
	LFFA	Lesioned				
	LOFA	-40	-73	-19	34	*
	STS	45	-56	10	479	
S1	RFFA	39	-47	-20	362	
	ROFA	38	-67	-16	284	
	LFFA	-40	-46	-18	155	
	LOFA	-46	-61	-18	45	
	STS	48	-55	3.8	1020	
S2	RFFA	31	-37	-13	101	
	ROFA	11	-89	-14	288	*
	LFFA	-39	-58	-11	141	*
	LOFA	-31	-87	-8.6	72	**
	STS	42	-39	2.7	363	**
S3	RFFA	31	-44	-22	742	
	ROFA	45	-68	-10	271	
	LFFA	-41	-40	-15	1396	
	LOFA	-41	-74	-13	162	
	STS	46	-67	26	71	
S4	RFFA	37	-49	-22	172	
	ROFA	20	-83	-3.5	16	**
	LFFA	-40	-47	-17	24	
	LOFA	-17	-77	-18	15	*
	STS	38	-40	13	49	

S5	RFFA	39	-47	-24	152	
	ROFA	35	-76	-12	11	**
	LFFA	-39	-32	-24	256	
	LOFA	-43	-57	-21	214	
	STS	41	-55	4.6	72	*
S6	RFFA	43	-58	-19	55	
	ROFA	17	-89	-15	19	
	LFFA	-46	-49	-22	352	
	LOFA	-31	-87	-8.6	72	*
	STS	50	-44	2.9	55	
S7	RFFA	34	-45	-16	932	
	ROFA	38	-69	-5.9	101	
	LFFA	-40	-44	-17	8	**
	LOFA	-36	-75	-18	153	
	STS	41	-48	3.8	317	
S8	RFFA	34	-44	-20	1790	
	ROFA	37	-76	-16	321	
	LFFA	-42	-48	-21	682	
	LOFA	-38	-71	-17	1201	*
	STS	42	-31	-1.6	56	
S9	RFFA	41	-46	-17	306	
	ROFA	25	-89	3.2	182	
	LFFA	-40	-59	-12	156	
	LOFA	-36	-87	2.1	55	*
	STS	46	-62	15	23	
S10	RFFA	35	-43	-14	1285	
	ROFA	30	-87	-2	301	
	LFFA	-37	-40	-15	325	
	LOFA	-40	-68	-14	98	*
	STS	52	-59	24	374	
AM	RFFA	33	-52	-14	352	
	ROFA	29	-79	-9	34	
	LFFA	-38	-48	-12	316	
	LOFA	-34	-77	-18	46	
	STS	52	-52	-5	420	

Remarks: *p(uncorrected)<0.05; otherwise: clusters defined at q(False Discovery Rate)<0.05
**p(uncorrected)<0.005; otherwise: clusters defined at q(False Discovery Rate)<0.05

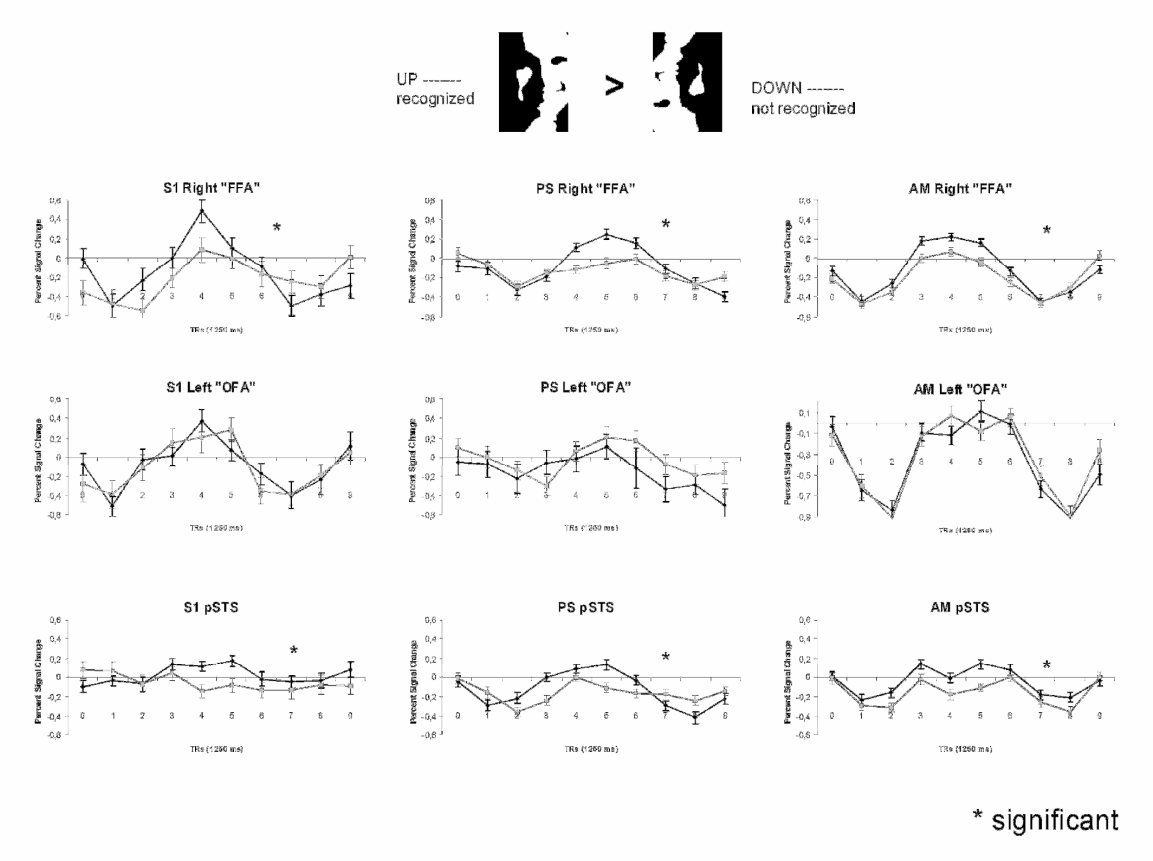


Supplementary Figure 3. 1. Detailed behavioral results of the patient PS and each normal age-matched controls in the behavioral experiments **A**. Accuracy and error rates for the face/nonface decision on Mooney stimuli **B**. Accuracy and error rates for the face/nonface decision on Arcimboldo stimuli **C**. PS' errors in the face decision task with Arcimboldo stimuli compared to control participants: all errors of PS took place on items that were missed at least by one control participant as well, showing that her behavior, qualitatively, does not differ from controls.



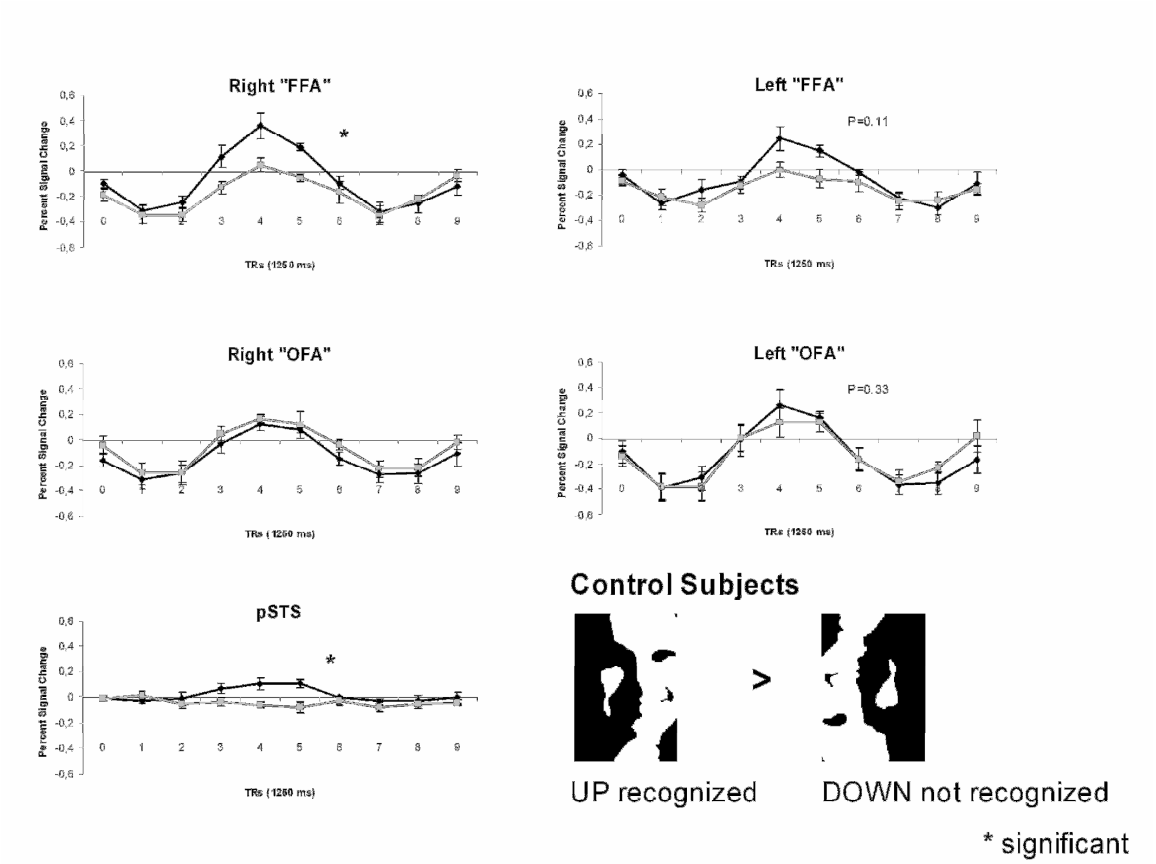
Supplementary Figure 3. 2. A. Time-course of activation in complementary face-sensitive regions for the group of normal participants in the Mooney face detection task. Note that in addition to the right pSTS, the left 'FFA' showed a larger response to Mooney faces, which was not found in the left 'OFA', as in the right hemisphere (Figure 3. 5A). **B**. Same results observed in the Arcimboldo face detection task.

3.3. Global face categorization in higher-level cortical visual areas of the normal and prosopagnosic brain: towards a non-hierarchical view of face perception



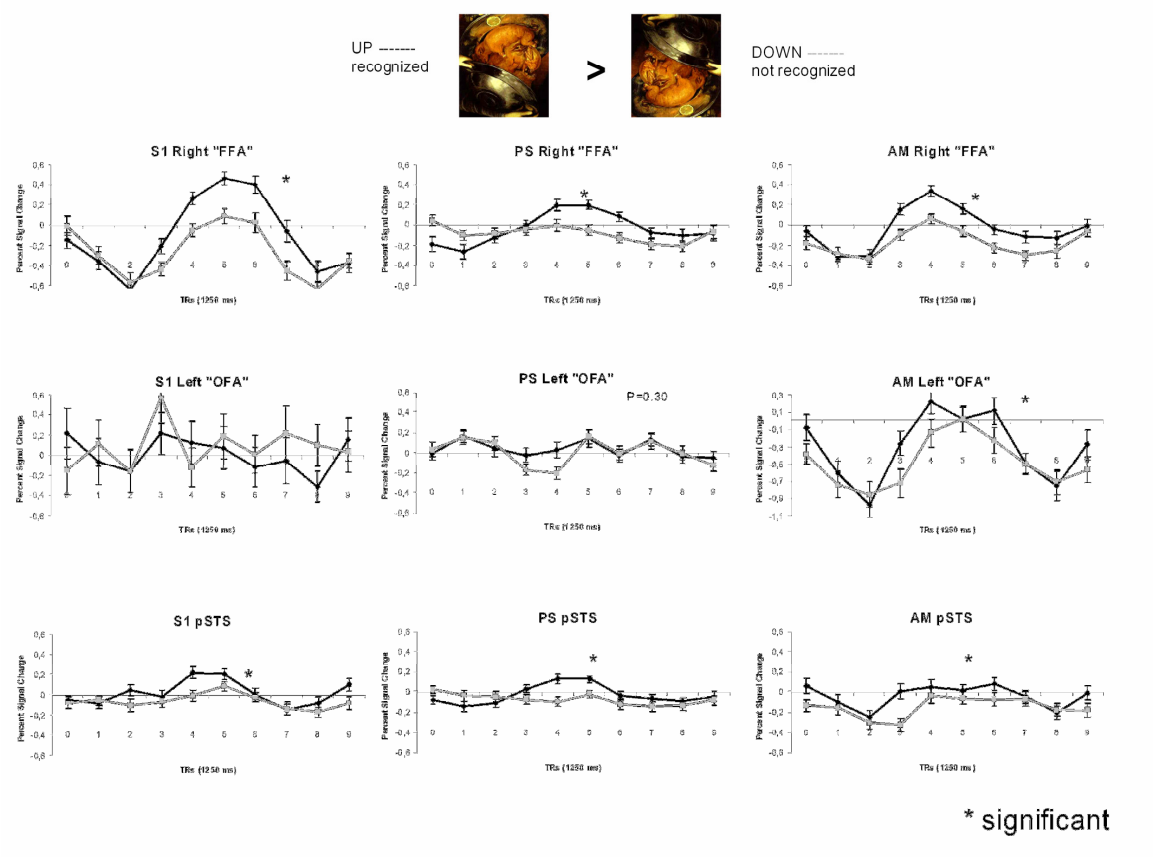
Supplementary Figure 3. 3. Same data as in Figure 3. 4, but for correct trials only. Among the face-sensitive areas that are intact in the prosopagnosic patient's brain, only the right 'FFA' and pSTS to a lesser extent showed a larger response to Mooney stimuli perceived as faces as compared to the same pictures presented upside-down ("nonfaces"). Similar findings are made for one control participant (S1) of the group, PS, and the age-matched control (AM). The left 'OFA' does not show an enhanced response to the Mooney face stimuli.

3.3. Global face categorization in higher-level cortical visual areas of the normal and prosopagnosic brain: towards a non-hierarchical view of face perception



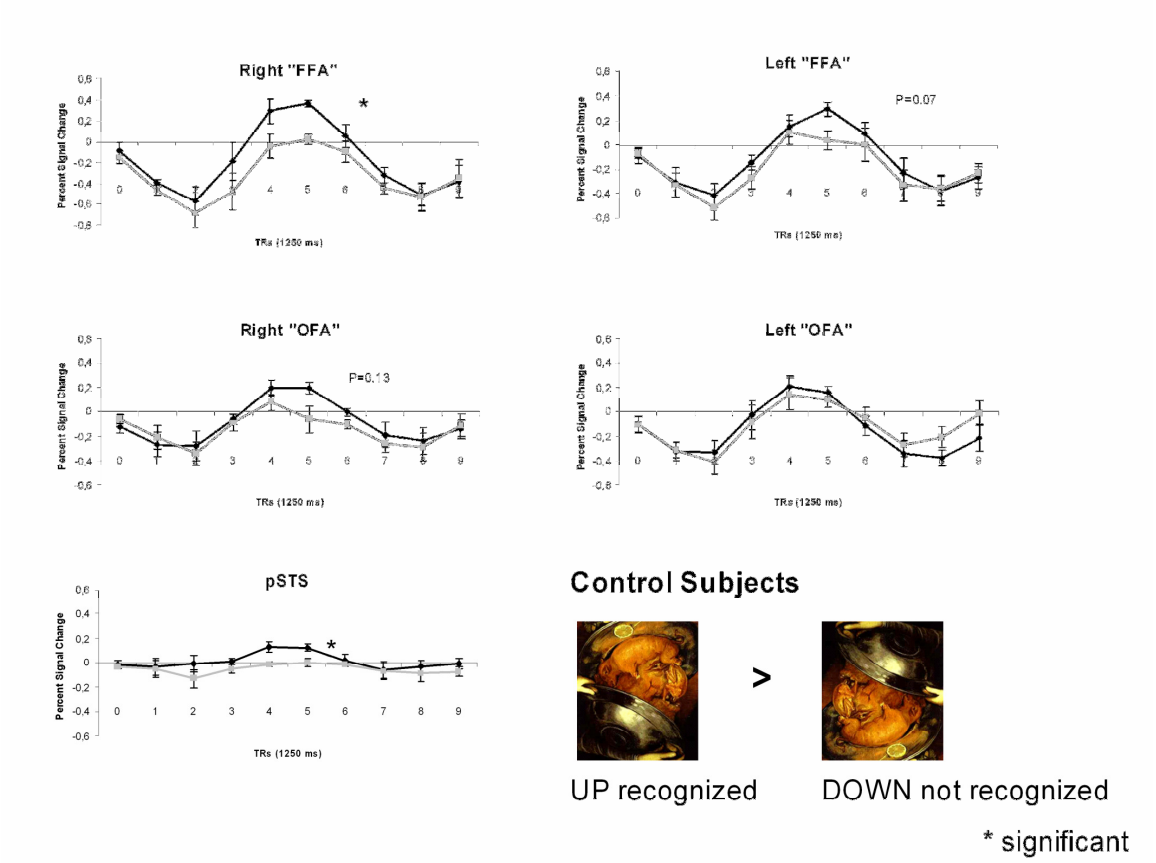
Supplementary Figure 3. 4. Time-course of activation in face-sensitive regions for the group of normal participants in the Mooney face detection task, for correct trials only. Only the right 'FFA' and the right STS to a lesser extent showed a larger response to stimuli correctly detected as faces.

3.3. Global face categorization in higher-level cortical visual areas of the normal and prosopagnosic brain: towards a non-hierarchical view of face perception



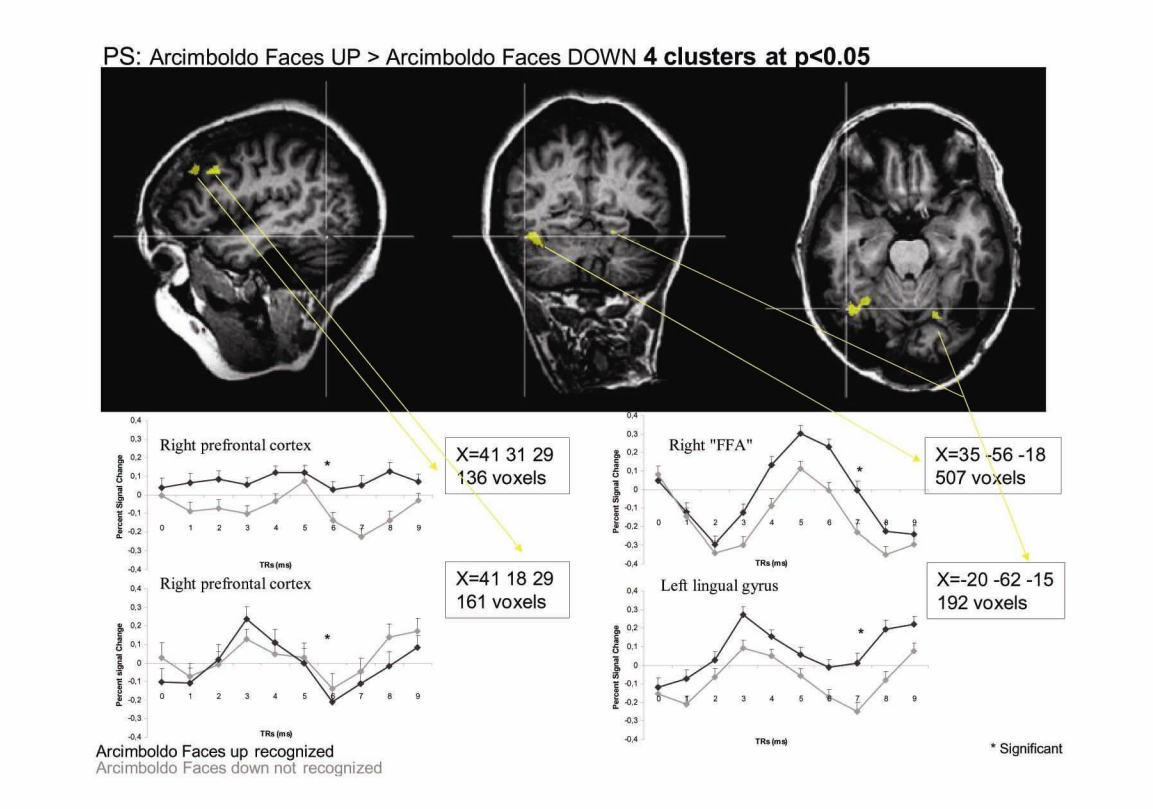
Supplementary Figure 3. 5. Same data as in Figure 3. 9, but for correct trials only. As for the Mooneys faces, among the face-sensitive areas that are intact in the prosopagnosic patient's brain, only the right 'FFA' and pSTS to a lesser extent showed a larger response to Arcimboldo stimuli perceived as faces as compared to the same pictures presented upside-down ("nonfaces"). Similar findings are made for the control group (e.g. S1), although the AM's left 'OFA' attained significance (but with a t corresponding to 50% of the t of his own 'FFA').

3.3. Global face categorization in higher-level cortical visual areas of the normal and prosopagnosic brain: towards a non-hierarchical view of face perception



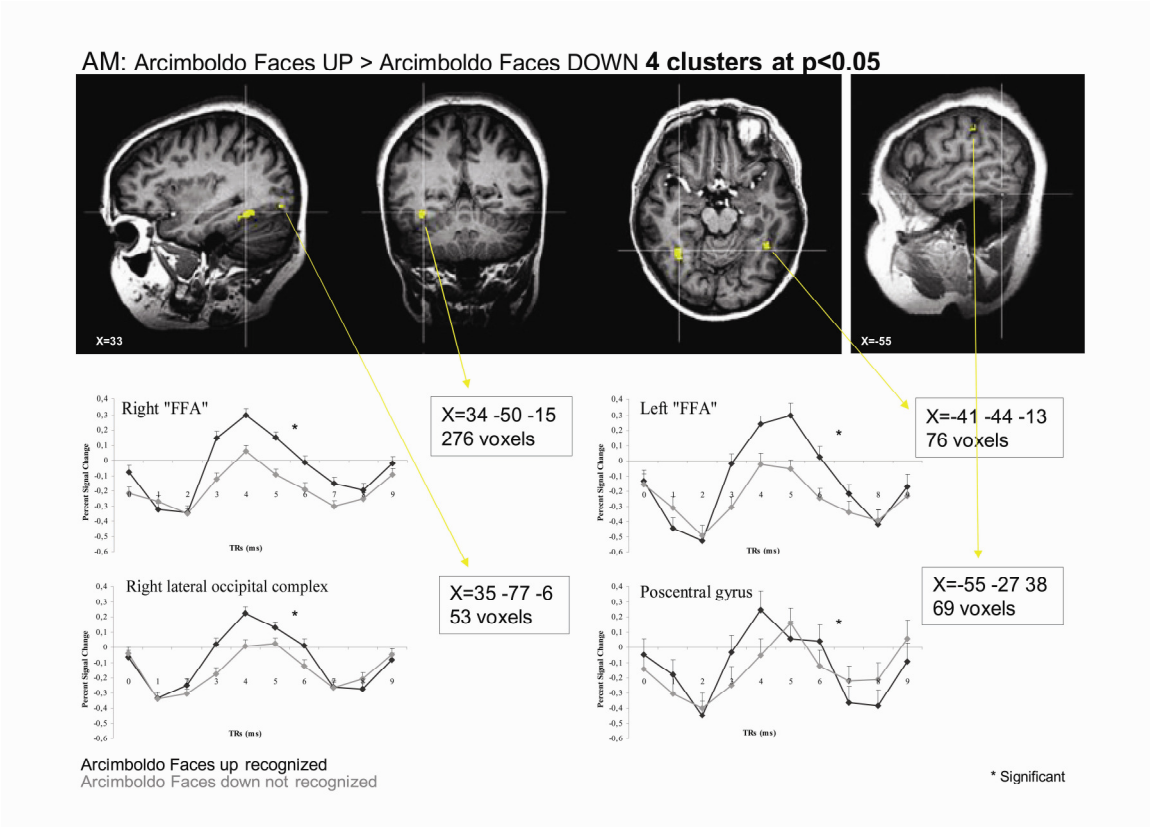
Supplementary Figure 3. 6. Time-course of activation in face-sensitive regions for the group of normal participants in the Arcimboldo face detection task, for correct trials only. Only the right 'FFA' and the right STS showed a larger response to stimuli correctly detected as faces (but the left 'FFA' is close to be significant).

3.3. Global face categorization in higher-level cortical visual areas of the normal and prosopagnosic brain: towards a non-hierarchical view of face perception



Supplementary Figure 3. 7. Whole-brain analysis performed on the patient PS in the Arcimboldo face categorization experiment. Four areas were found at significant, one corresponding roughly to the patient's right 'FFA', presenting face preferential response to faces in the localizer experiment, and three other regions, in the right preferontal cortex and left lingual gyrus, without any involvement of the right posterior occipital cortex.

3.3. Global face categorization in higher-level cortical visual areas of the normal and prosopagnosic brain: towards a non-hierarchical view of face perception



Supplementary Figure 3. 8. Whole-brain analysis performed on the age-matched control (AM) in the Arcimboldo face categorization experiment. Four areas were found at significant, one corresponding roughly to the right 'FFA' and one to the left 'FFA', two regions presenting face preferential response to faces in the localizer experiment ($p<0.000007$), one close to the right 'OFA' or to the right ventral posterior part of LO [35, -77, -6, 53 voxels, object-sensitivity: $t=15.04$, $p<0.000001$ presenting a little face preferential response ($p<0.01$)] and one other nonface region, in the postcentral gyrus.

3.4. The roles of "face" and "non-face" areas during individual face perception: evidence by fMRI adaptation in a brain-damaged prosopagnosic patient[52]

Préambule

Les expériences décrites dans le chapitre 3.4 et 3.5 n'utilisent pas le localizer décrit dans le chapitre 3.1 développé après ces expériences pour comprendre les différents résultats de la littérature visage concernant l' ''OFA''. Néanmoins, le propos principal de ces deux chapitres étant la comparaison de l'adaptation visage et objets dans la ''FFA'' chez deux patientes prosopagnosiques dont les lésions englobent l' ''OFA'', les résultats n'en sont pas invalidés. La ''FFA'' est en effet, quant à elle, beaucoup plus stable à travers les différents choix de stimuli (voir Berman et al., 2010).

3.4.1. Abstract

Two regions in the human occipito-temporal cortex respond preferentially to faces: 'the fusiform face area' ('FFA') and the 'occipital face area' ('OFA'). Whether these areas have a dominant or exclusive role in face perception, or if sub-maximal responses in other visual areas such as the lateral occipital complex (LOC) are also involved, is currently debated. To shed light on this issue, we tested normal participants and PS, a well known brain-damaged patient presenting a face-specific perception deficit (prosopagnosia) (Rossion et al., 2003a), with functional magnetic resonance imaging (fMRI). Of particular interest, the right hemisphere lesion of the patient PS encompasses the 'OFA' but preserves the 'FFA' and LOC (Sorger et al., 2007). Using fMRI-adaptation, we found a dissociation between the coding of individual exemplars in the structurally intact 'FFA', which was impaired for faces but preserved for objects in the patient PS's brain. Most importantly, a larger response to different faces than repeated faces was found in the ventral part of the LOC both for normals and the patient, next to the right hemisphere lesion. Thus, following prosopagnosia, areas that do not respond preferentially to faces such as the ventral part of the LOC

52 Cette section est une version remise en page d'un article paru dans neuroimage avec le même titre de Laurence Dricot, Bettina Sorger, Christine Schiltz, Rainer Goebel et Bruno Rossion.

(vLOC) may still be recruited for compensatory or residual individual face perception. Overall, these observations indicate that several high-level visual areas in the human brain contribute to individual face perception. However, a subset of these areas, those responding preferentially to faces (‘FFA’ and ‘OFA’), appear critical for this function.

3.4.2. Introduction

Functional neuroimaging studies of the human visual cortex have identified several areas that play an important role in object perception and recognition (Grill-Spector and Malach, 2004). These regions respond more strongly when viewing pictures of object shapes than control stimuli preserving low-level visual information such as textures, visual noise, or scrambled objects. Among these areas, the lateral occipital cortex [LOC; e.g. (Grill-Spector et al., 2001; Malach et al., 1995)] shows greater fMRI response to objects (including faces) than such control stimuli, but this area does not show systematic larger responses to some object categories than others. It is located anterior to retinotopic visual areas, extending both ventrally (vLOC) on the lateral bank of the fusiform gyrus and dorsally (dLOC) in two anatomically segregated subregions. Anterior to the vLOC, a region of the lateral fusiform gyrus, the ‘fusiform face area’, or ‘FFA’ [e.g. (Kanwisher et al., 1997; Sergent et al., 1992) also responds more strongly to objects than control stimuli, but shows a preferential response for faces above all other object categories. Larger responses to faces than objects are also consistently observed in the inferior occipital gyrus, the so-called ‘occipital face area’ [‘OFA’; (Gauthier et al., 2000a)] generally posterior to, and partially overlapping with the vLOC.

FMRI-adaptation (Grill-Spector et al., 2006a; Grill-Spector and Malach, 2001) or repetition-suppression (Henson and Rugg, 2003) studies show a larger response in the LOC to novel objects than to repeated objects (Avidan et al., 2002; Grill-Spector et al., 1999; Sayres and Grill-Spector, 2006) and a correlation of that response with recognition performance (Avidan et al., 2002; Bar et al., 2001; Grill-Spector et al., 2000; James et al., 2000). Similar effects have been observed in both

the 'FFA' and 'OFA' for faces [e.g. (Eger et al., 2004b; Gauthier et al., 2000b; Gilaie-Dotan and Malach, 2007; Grill-Spector et al., 2004; Loffler et al., 2005; Rotshtein et al., 2005; Schiltz and Rossion, 2006)]. These observations indicate that the LOC and both of the 'face areas' are directly involved in the perception of individual exemplars of objects and faces respectively.

An unresolved issue is whether a high-level visual area that does *not* respond preferentially to one category, i.e. the LOC for faces, nevertheless plays a role in discriminating individual members of that category. According to a strict localizationist view, the answer to this question is negative. This view suggests a dominant or exclusive role of areas responding preferentially to faces, such as the 'FFA', for face perception (Kanwisher et al., 1997; Kleinschmidt and Cohen, 2006; Spiridon and Kanwisher, 2002). In contrast, according to a more distributed view, a large part of the ventral stream, including the 'FFA', contributes to face perception (Haxby et al., 2001; Tovee, 1998). That is, visual areas that do not respond preferentially to faces, such as the LOC, would also play a role in face perception. Moreover, areas responding preferentially to faces, such as the 'FFA', would also contribute to object perception.

Here we aimed to shed light on this issue by recording fMRI-adaptation in a well described brain-damaged patient, PS, who is no longer able to perceive and recognize individual faces, i.e. acquired prosopagnosia (Quaglino and Borelli, 1867; Bodamer, 1947; e.g. Sergent and Signoret, 1992). Contrary to most cases of prosopagnosia, the patient's ability to recognize nonface objects is remarkably preserved (Rossion et al., 2003a; Schiltz et al., 2006). Her prosopagnosia follows a dominant right hemispheric lesion in the inferior occipital cortex, which damaged the territory of the right 'OFA', where no face preferential activation can be observed. Despite this lesion, the patient has a right 'FFA' as significant and large in size as in normal controls (Rossion et al., 2003a; Sorger et al., 2007), a finding that has been also reported in another recent brain-damaged case study with bilateral inferior occipital lesions encompassing the 'OFA' (Steeves et al., 2006). However, there is a lack of release from identity adaptation to individual faces in the patient PS'

right ‘FFA’, in agreement with her behavioral impairment at discriminating individual faces (Schiltz et al., 2006). Most recently, we have mapped the low- and high-level visual areas of the patient PS with respect to her lesions, and observed a right vLOC area of equal size and level of activation than normals, next to the dominant lesion causing prosopagnosia (Sorger et al., 2007).

In the present study, we took advantage of this pattern of structurally damaged (right ‘OFA’) and intact (right ‘FFA’ and LOC) tissue in this patient’s brain to test two hypotheses.

First, we asked whether the patient’s ‘FFA’, which does not show release from adaptation to face identity (Schiltz et al., 2006), may nevertheless play a role in her preserved ability to discriminate object exemplars. To do that, we used an experiment in which all normal participants showed release from identity adaptation to both objects and faces in the ‘FFA’, and tested it in the same area in the patient’s brain. We found for the first time that release from adaptation was significant for objects in both normal viewers and the patient’s ‘FFA’, still in the absence of any effect for faces for the patient.

Second, a whole-brain analysis of the patient’s data in the same experiment revealed a significant release from adaptation to individual exemplars in the right vLOC only, an area that does not respond stronger to faces than objects. More specifically, both objects and faces showed release from adaptation effects in all normal participants, and in the patient’s brain, in the right vLOC. These results suggest that following brain damage, the prosopagnosic patient is unable to recruit her dominant face perception system in the ‘FFA’ to discriminate individual faces, but rather relies on an area that does not respond preferentially to faces. This is in line with her performances during individual face discrimination tasks, which are seriously deficient, but yet largely above chance level.

These observations were tested further in two fMRI experiments using an event-related paradigm. In experiment 2, pictures of faces and objects were used by pairs and showed the same

results as in the block design used in experiment 1. In the third experiment, an active discrimination of facial identity was performed.

3.4.3. Materials and methods

3.4.3.1. Subjects

The prosopagnosic patient PS has already been described in detail in previous studies (Caldara et al., 2005; Rossion et al., 2003a; Schiltz et al., 2006; Sorger et al., 2007). Briefly, PS was born in 1950 and sustained a closed head injury in 1992 that left her with extensive lesions of the left mid-ventral (mainly fusiform gyrus) and the right inferior occipital cortex. Minor damages to the left posterior cerebellum and the right middle temporal gyrus were also detected (see Sorger et al., 2007 and Figure 4. 1 for all information about the patient’s lesions).

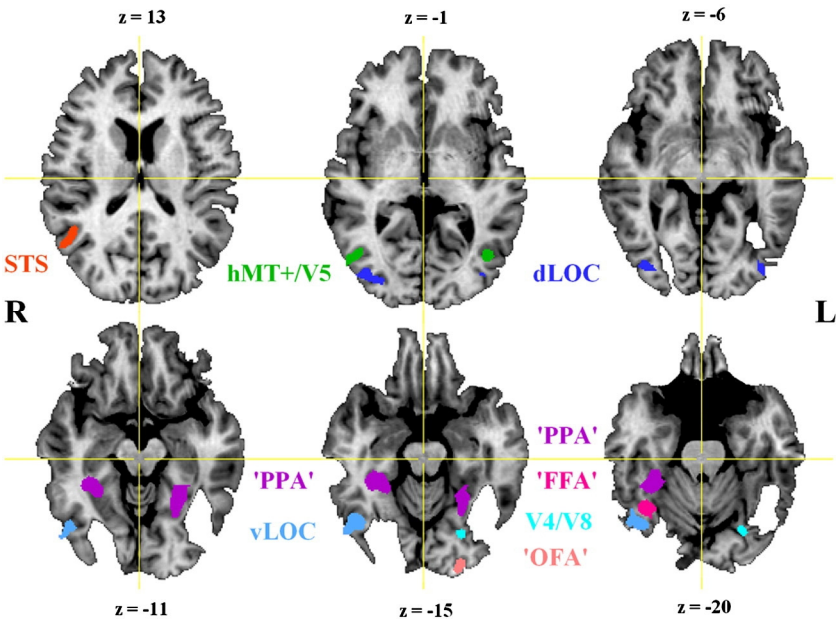


Figure 4. 1. Functional areas of the patient PS on segmented brain slices.

‘FFA’: ‘fusiform face area’, area responding more to faces than objects in the right fusiform gyrus; ‘OFA’: ‘occipital face area’, area responding more to faces than objects in the left inferior occipital gyrus; dLOC and vLOC: dorsal and ventral part of the lateral occipital complex, area responding more to objects than scrambled objects; STS: area of the superior temporal sulcus responding more to faces than objects; hMT+/V5: motion area; ‘PPA’, ‘Parahippocampal Place Area’, area responding more to pictures of scenes than faces and objects; V4/V8: colour area; [for functional localization methods, see (Sorger et al., 2007)].

After medical treatment and neuropsychological rehabilitation, PS recovered extremely well from her cognitive deficits following the accident. Her only continuing complaint remains a profound difficulty in recognizing familiar faces, including those of her family when they are presented out of context. To determine a person’s identity, she relies on external (non-face-inherent) cues such as haircut, moustache or glasses, but also on the person’s voice, posture, gait, etc. She may also use sub-optimal facial cues such as the mouth or the external contour of the face to recognize faces, and is particularly impaired at extracting diagnostic information from the eyes of the face (Caldara et al., 2005). Effectively, PS is like normal subjects (100%, fast) to discriminate faces from other objects but is impaired and slowed down to recognize faces at the individual level (Schiltz et al., 2006). The Benton Face Recognition Test (BFRT) (Benton and Van Allen, 1972) ranks her as highly impaired, and her score at the Warrington Recognition Memory Test (WRMT) (Warrington, 1984) for faces characterizes her as significantly less accurate as controls [see Table 1 in (Rossion et al., 2003a)]. PS does not present any difficulty in recognizing objects, even at the subordinate level (Rossion et al., 2003a; Schiltz et al., 2006). Her visual field is almost full (small left paracentral scotoma) and her visual acuity is good (0.8 for both eyes as tested in August 2003). As indicated in the introduction section, in our previous neuroimaging studies of the patient PS, we found that she had a right ‘FFA’ as significant and large in size as normal controls (Rossion et al., 2003a; Schiltz et al., 2006) in the absence of a right ‘OFA’ or left ‘FFA’ (damaged, see Sorger et al., 2007). However, there was a lack of release from face adaptation to faces in the patient’s right ‘FFA’ (Schiltz et al., 2006). Our more recent investigations have identified a right vLOC area of equal size and level of activation than normals (see Sorger et al., 2007).

In the present study, besides PS, a group of five control subjects (S2 to S6, age range 25 to 35, 3 females), 3 subjects (S5, S8, S11; age range 25 to 35, 3 females), and six subjects (S5 to S10, age range 25 to 35, 3 females) performed the same localizers, and respectively the block design experiment 1, the event-related experiments 2 and 3 of the present study. In addition, one age-

matched (S1, 54 years, female) performed the localizers and the experiments 1 and 2. We tested only one age-matched control to PS because the profile of activation in the right middle fusiform gyrus remains stable across decades (Brodtmann et al., 2003) and our previous studies have shown identical face and object differential responses, as well as adaptation effects to faces in the ‘FFA’ for 3 age-matched controls and younger controls (Schiltz et al., 2006; Sorger et al., 2007). Similarly, the profile of neural response in the present fMRI experiments was not different for the age-matched control and the young controls in the areas of interest.

PS and the control subjects gave their informed written consent prior to the fMRI experiments. The study was conformed to the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Department of the University of Louvain. All subjects and PS proved to be strongly right-handed according to the Edinburgh Inventory (Oldfield, 1971).

3.4.3.2. Stimuli and procedures

Localizers

PS and normal controls performed two block-design localizer fMRI experiments aimed at defining the areas responding preferentially to faces (‘FFA’ and ‘OFA’), and to objects (vLOC and dLOC). In the ‘FFA’ localizer experiment, PS and controls viewed 8 blocks per run (36 s per block, two runs of 6 min 42 s) of alternating pictures of faces and objects, with 12 s fixation cross epochs between the blocks. They performed a one-back identity task (two positives per block). 36 stimuli were presented for 800 ms followed by a 200 ms blank screen during each block. All images (pictures of faces and objects) were presented in color and sustained a size of roughly 4° of visual angle. They were matched for mean luminosity and varied location in X (10%) and in Y (13%) on each trial. Faces (half male) were cropped so that no external features (hair, etc…) were present. PS and normal controls were also scanned during an independent LOC localizer (Sorger et al., 2007). In the LOC localizer experiment, participants viewed 6 blocks per run (30 s per block, two runs of 5

min 20 s) of alternating pictures of common objects from different object categories and objects scrambled, with 20 s fixation cross epochs between the blocks. 44 black and white photographs per block (252 x 252 pixel gray-scale images) were foveally presented during 666 ms per object or scrambled objects. The scrambling was realized by tessellating the objects photos into squares of 10x10 pixels. Participants simply had to fixate attentively the visual stimulation.

Experiment 1: block design adaptation with faces and objects

In the first experimental runs, an fMRI-adaptation paradigm (block design) was used in a 2 x 2 factorial design: repetition (identical or different pictures in a block) x category (faces or butterflies) (Figure 4. 2).

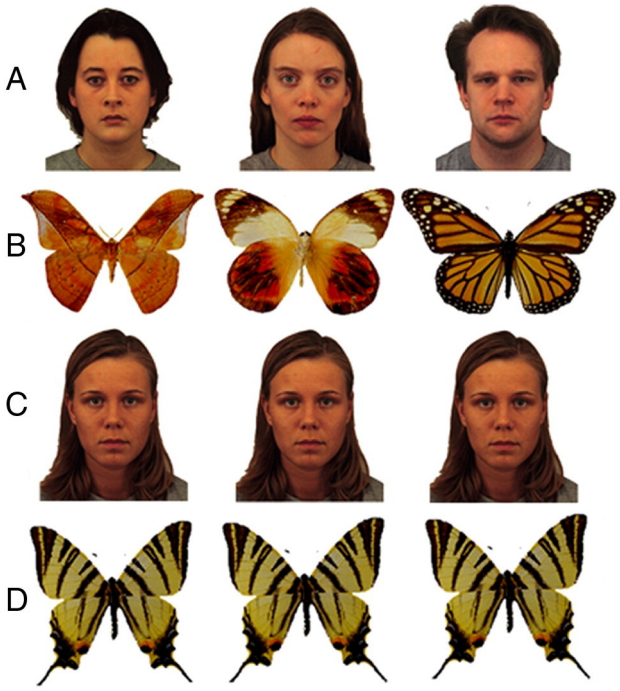


Figure 4. 2. Examples of pictures of faces and butterflies used in the block design fMRI experiment 1. Four conditions were presented to PS and control subjects: blocks with A different faces; B. different butterflies; C. identical faces; D. identical butterflies. All images were presented in colour and sustained a size of roughly 4° of visual angle.

We used pictures of butterflies as our object category because they showed robust ‘FFA’ activation in pilot experiments and strong adaptation effects in all our normal participants in this area. In our previous study using a 1.5T scanner, we found significant release from adaptation for

pictures of cars in the ‘FFA’ in a group analysis, but it was not significant in every single control subjects, and in the patient PS [who did not differ significantly from controls, (Schiltz et al., 2006)]. In the event-related experiment with pictures of chairs, there was no significant release from adaptation, neither for controls and the patient (Schiltz et al., 2006). Here, besides using a more sensitive methodology, we selected an object category for which exemplars were highly different in shape, texture and color (Figure 4. 1), in order to maximize our chances to observe significant release from adaptation in the ‘FFA’ of every single normal participant. Similarly, face stimuli were presented in color, with external features (hairstyle …), unlike the cropped grayscale faces used in our previous study (Schiltz et al., 2006), both to test the robustness of our previous results and to ensure significant effects in every normal participant, even in areas which do not respond preferentially to faces. Note that the degree of similarity between two members of the object category and the face category was not meant to be equal. In fact, when color is not considered, the mean inter-pixel correlation computed for faces and butterflies separately was slightly higher for pictures of butterflies than faces (0.5 vs 0.57; $p<0.001$). Note that if color is considered, pictures of butterflies may appear more dissimilar than pictures of individual faces (Figure 4. 1), but our goal here was to compare differential adaptation effects between the patient and the normals for the two categories, not to compare directly the adaptation for the two types of stimuli (see discussion of this issue in Discussion section).

The subject’s task was to indicate the rare occurrence of a face or a butterfly picture that appeared colorized in red, in a block of normally colorized stimuli (color detection task). We used a task that is orthogonal to the variable manipulated (repetition), as done previously (Gauthier et al., 2000b; Rotshtein et al., 2005; Schiltz et al., 2006; Winston et al., 2004), to ensure that subjects were paying attention during the whole experiment, while performing at the same level for all conditions. It is also a task that the patient PS can perform easily, so that any activation difference between PS and the controls cannot be attributed to task difficulty (Price and Friston, 1999).

We presented 8 alternating blocks per run (36 s per block, 4 runs of 6 min 42 s) of pictures of faces and butterflies: two blocks with 36 identical faces or butterflies and two blocks with 36 different faces or butterflies. 36 stimuli were presented for 800 ms followed by a 200 ms blank screen during each block. Stimuli were displayed in pseudo-random order. All images (pictures of faces and butterflies, Figure 4. 1) were presented in color, and sustained a size of roughly 4° of visual angle.

Experiment 2: event-related paradigm with faces and objects

Participants viewed three runs of 80 pairs of stimuli. The stimuli were pictures of faces and butterflies as shown in Figure 4. 1. Thirty-eight face images and 42 butterfly pictures were used in an event-related design. There were 4 conditions of interest: two different face identities, two identical face identities, two different butterflies, two identical butterflies in the pair. A fifth condition of a butterfly followed by a face image (or the opposite order for half of the trials) was used. Participants were asked to press the response key only for this latter condition - that is, to detect face-object pair trials. This basic-level discrimination task ensured that the participants were paying attention to the stimuli, and it was again a task that PS could perform well. Further, the factors of interest of the study (category effect: faces *vs.* butterflies; adaptation effect: same *vs.* different identities) would not be contaminated by any decisional and/or motor processes since the behavioural task was completely orthogonal to these factors. Hence, any difference between patients and PS could not be attributed to general processing difficulties on the trials of interest. There were 16 trials/condition/run, for a total of 80 trials in each run, and 48 trials/condition over three runs. The order of conditions was fully randomized within a run. Within a trial, the first stimulus of a pair was presented for 1000 ms following by a blank of 500 ms and thereafter by the second stimulus of the pair, which was presented for 1000 ms. The pairs were separated by a fixation cross with a duration 5000, 6250 or 7500 ms (4-6 TRs), and these ISI durations were also fully randomized. This timing ensured that the onset of distinct events were separated by at least 6-8

TRs (7500-10000 ms) to avoid the overlapping of hemodynamic responses. Randomization of trial order and of ISI duration further reduced any potential top-down effets of anticipation of the stimuli.

Experiment 3: event-related paradigm during face discrimination

To test further the patient’s residual individual face discrimination abilities while monitoring brain activation, we tested PS and normal participants in an event-related paradigm during an active individual face discrimination task. In this experiment, PS and control subjects viewed three runs (8 min 57 s 500 ms per run) of 60 pairs of faces. The first face of the pair was presented during 1000 ms following by a blank of 500 ms and thereafter by the second face of the pair. The pairs were separated by a fixation cross during 5000, 6250 or 7500 ms. The subject had to determine whether the 2 faces were the same person (identical image) or not. All the faces (half male) were shown on frontal view and were cropped so that no external features (hair, etc.) were revealed (Figure 4. 8 A.). All the faces were in color.

For all 3 experiments, the stimuli were jittered in location by 40 pixels in X (5%, 1.2° visual angle) and 40 pixels in Y (7%, 1.2°) from trial-to-trial to avoid that the same pixels would be repeated at the same position in the conditions of adaptation. Stimuli (and blocks) were displayed with a PC running E-prime 1.1 (PST Inc.) through a projector surface located over the head of the subject and viewed with an angled mirror.

3.4.3.3. Imaging parameters

MR images of brain activity were collected from PS and normal controls using a 3T head scanner (Siemens Allegra, Siemens AG, Erlangen, Germany), with repeated single-shot echo-planar imaging: echo time (TE) = 50 ms, flip angle (FA) = 90°, matrix size = 64x64, field of view (FOV) = 224x224 mm², slice order descending and interleaved, slice thickness = 3.5 mm. The other scan parameters varied over the different experiments: repetition time (TR) = 1500 ms, 24 slices,

run time = 6 min 42 s for the ‘FFA’ localizer and the block experiment 1; TR = 2000 ms, 24 slices, run time = 5 min 20 s for the vLOC localizer; and TR = 1250 ms, 21 slices, for the event-related experiments (2: run time = 11’ min 46 sec 250 ms, and 3: run time = 8 min 57 s 500 ms). A three-dimensional (3D) T1-weighted data set encompassing the whole brain was acquired to provide detailed anatomy (1 mm^3) thanks to a ″Modified Driven Equilibrium Fourier Transform” (MDEFT) sequence (scan parameters: TR = 7.92 ms, TE = 2.4 ms, FA =15°, matrix size = 256 × 256, FOV = 256 × 256 mm^2, 176 slices, slice thickness = 1 mm, no gap, total scan time = 13 min and 43 s).

3.4.3.4. Data analysis of the imaging experiments

The fMRI signal in the different conditions was compared using BrainVoyager QX (Version 1.4, Brain Innovation, Maastricht, The Netherlands). Prior to analysis, the functional data sets were subjected to a series of preprocessing operations. Preprocessing consisted of a linear trend removal for excluding scanner-related signal, a temporal high-pass filtering applied to remove temporal frequencies lower than 3 cycles per run, and a correction for small interscan head movements by a rigid body algorithm rotating and translating each functional volume in 3D space. In addition, the data from the event-related experiment were also corrected for the difference between the scan times of the 21 slices. Data was not smoothed in the spatial domain for any of the experiments. In order to be able to compare the locations of activated brain region across subjects all anatomical as well as the functional volumes were spatially normalized [Talairach-transformation; (Talairach and Tournoux, 1988)] and the statistical maps computed were overlaid to the 3D T1-weighted scans in view to calculate Talairach coordinates for all relevant activation clusters. Subsequently, the functional data were analyzed using multiple regression models (General Linear Model; GLM) consisting of predictors, which corresponded to the particular experimental conditions of each experiment. The predictor time courses used were computed on the basis of a linear model of the

relation between neural activity and hemodynamic response, assuming a rectangular neural response during phases of visual stimulation (Boynton et al., 1996).

The areas responding preferentially to faces were first defined independently for PS and each individual subject using the localizer experiment. In order to localize the 'FFA' and the 'OFA', the conjunction of the contrast (faces *vs.* objects) between the two runs was computed. This procedure ensured that larger activations to faces than objects identified were those consistent across the two runs. A similar procedure was applied to disclose LOC voxels with the contrast (objects *vs.* objects scrambled) in the LOC localizer. All contiguous voxels in the right 'FFA' and the right 'OFA' significant at $t > 5.59$ [one-tailed, p(Bonferroni corrected for multiple comparison) < 0.002] were considered for further analysis. When foci of activations were too large so that fusiform and inferior occipital activation foci overlapped, the statistical threshold was raised to a more conservative value [one-tailed, p(Bonf) < 0.000] to separate the two functional regions spatially (see Table 4. 1).

Table 4. 1. Talairach locations, t-values and cluster sizes of the functionally defined regions of interests (right-sided 'FFA', 'OFA' and vLOC) defined in the localizer experiments for PS and the control subjects. Note that the use of different statistical thresholds was done only to define our regions of interest in the different subjects, not to test our hypotheses. For these localizers, the same definition of statistical threshold for all subjects and areas was not the best procedure because of the variability in the differential fMRI response between subjects: the clear separation of the 3 regions of interest requested a more conservative threshold for a subset of subjects. Here, we report all information about the thresholds and size of regions for all individual subjects so that one can compare the patient PS with the controls. It is clear that at the same threshold, PS's 'FFA' is in the normal range of activation (as described previously, see Rossion et al., 2003a; Sorger et al., 2007). For the majority of control participants, the statistical thresholds were the same as for the patient PS. Note also that if we use different thresholds within subject, the differential size of the ROI clusters have little if any effect on the adaptation effects observed for PS and our control subjects. *Remarks: q(False Discovery Rate)<0.05, otherwise: clusters defined at p<0.002 (Bonferroni corrected for multiple comparisons).

subject	region	Talairach coordinates			t	cluster size ($mm^{3)}$
		x	y	z		
PS	'FFA'	35	-53	-20	5.59	479
	'OFA'	lesioned				
	vLOC	43	-64	-12	6	632
S1	'FFA'	31	-56	-12	5.59	479
	'OFA'	36	-85	-8	5.59	1116
	vLOC	35	-65	-7	6	798
S2	'FFA'	43	-57	-13	5.59	772
	'OFA'	31	-73	-18	5.59	492
	vLOC	46	-66	-14	4.6	44*

S3	‘FFA’	34	-48	-11	7.6	281
	‘OFA’	37	-66	-15	7.6	1996
	vLOC	46	-70	-9	6	493
S4	‘FFA’	32	-40	-19	5.59	608
	‘OFA’	34	-61	-14	5.59	573
	vLOC	41	-72	-8	6	538
S5	‘FFA’	37	-41	-16	5.59	1410
	‘OFA’	36	-68	-16	5.59	2545
	vLOC	38	-73	-9	7	245
S6	‘FFA’	39	-44	-16	8	526
	‘OFA’	39	-70	-19	8	253
	vLOC	37	-69	-15	8.25	278
S7	‘FFA’	31	-58	-9	5.59	464
	‘OFA’	24	-73	-10	5.59	171
	vLOC	34	-63	-14	8.35	61
S8	‘FFA’	39	-49	-20	10	654
	‘OFA’	35	-67	-18	10	64
	vLOC	43	-68	-9	8.25	233
S9	‘FFA’	34	-41	-15	5.59	1795
	‘OFA’	28	-79	-7	5.59	153
	vLOC	41	-71	-6	6	567
S10	‘FFA’	39	-47	-18	9.6	91
	‘OFA’	38	-72	-11	9.6	43
	vLOC	38	-41	-18	3.6	263*
S11	‘FFA’	39	-50	-20	5.59	809
	‘OFA’	38	-71	-16	5.59	916
	vLOC	48	-58	-12	8.25	255
S1-S10	‘FFA’	36±4	-48±6	-15±4	-	717±491
S1-S10	‘OFA’	34±5	-71±6	-14±4	-	756±833
S2-S10	vLOC	41±5	-65±9	-11±4	-	385±228

Remarks: *q (False Discovery Rate) < 0.05, otherwise: clusters defined at p < 0.002 (Bonferroni corrected for multiple comparisons).

For the ventral part of the LOC, all contiguous voxels significant at t > 5.6 [one-tailed, p(Bonf) < 0.002] or a more conservative threshold when necessary (i.e. if there was an overlap between vLOC and dLOC) were considered for further analysis. For two subjects, a threshold of t > 3.6 or 4.6 [q(False Discovery Rate) < 0.05] was used due to the smaller size of their vLOC. All information about the regions of interest and thresholds for each individual subject is provided in Table 4. 1.

Second, the above-defined regions of interest (ROIs) were tested for fMRI-adaptation to identity in the block design with repeated-measures ANOVA using the contrast (different *vs.* same) for each category. The interaction between the fMRI-adaptation to butterfly and to faces was computed by the contrast: [(faces different - faces repeated)-(butterflies different - butterflies repeated)]. A random effect analysis to test these effects across subjects was also performed by running a multi-subject GLM with predictors separated for each included control subject. FMRI signals averaged over each subject’s ROIs were also extracted and percent signal change was computed using the baseline epochs as reference for each condition. An adaptation index [(different-same)/(different+same)] allowing a comparison between PS and the control group was computed for each category using the beta weights of the GLM analysis.

For the event-related experiment 2, an identical analysis was performed to test the fMRI-adaptation to individual faces and objects in the ROIs. In experiment 3, we used a GLM analysis with the contrast (different faces *vs.* same faces). Correct trials only were included in the analyses. We also extracted the averaged fMRI signals and computed a Faces Index adaptation as in the other experiments.

3.4.4. Results

In the face localizer, there was a significantly larger response to faces compared to objects in the right middle fusiform gyrus (‘FFA’) for all control subjects (Talairach coordinates: 36±4, -48±6, -15±4; mean cluster size: 717 voxels±491) and for PS (35, -53, -20; 479 voxels) (Table 4. 1).

In the object localizer, there was a significantly larger response to objects compared to scrambled objects with an activation corresponding to the ventral part of the occipital complex (vLOC) for both controls (Talairach coordinates: 41±5, -65±9, -11±4; mean cluster size: 385 voxels±228) and PS (43, -64, -12; 632 voxels) (Table 4. 1). In addition, the ‘OFA’ for each control

was defined: (Talairach coordinates: 34±5, -71±6, -14±4; mean cluster size: 756 voxels±833) (Table 4. 1).

3.4.4.1. FMRI-adaptation to faces and objects (block-design experiment)

PS and control subjects performed the color detection task at ceiling in all conditions (mean = 99.5%±0.4%), without any significant difference in RTs across conditions (same butterflies: 467 ms; different butterflies: 471 ms; same faces: 481 ms; different faces: 476 ms) or between control subjects and PS [$t = 0.269$, $p = 0.407$; modified t-test (Crawford and Garthwaite, 2002)].

The 'FFA' and vLOC were tested for fMRI-adaptation to identity using the contrast (different *vs.* same) for each category. Below, we always report the results for the group (random) analysis (p-value), as well as the highest individual p-value ($p_s<$) in the group of normal participants. Indeed, in line with our previous behavioral and neuroimaging work on the single case PS (Rossion et al., 2003a; Caldara et al., 2005; Schiltz et al., 2006), we define her results as abnormal when they present a different profile than every single control tested in the study.

An adaptation index allowing a comparison between PS and the control group was computed for each category using the beta weights of the general linear model (GLM) analysis [Faces Index = (different faces-same faces)/(different faces+same faces)] (Methods). For each control subject the neural activity was significantly larger when viewing pictures of faces than butterflies (all individual p-values: $p_s < 0.000042$) in the right 'FFA'. More interestingly, the response was significantly larger during a block for different faces than identical faces (random effect analysis: $p < 0.0009$; individual p-values: $p_s < 0.000004$; Faces adaptation index = 0.177±0.072) and when viewing different butterflies than identical butterflies (random effect analysis: $p < 0.00002$; $p_s < 0.000008$; Objects Index = 0.253±0.054) (Figure 4. 3). There was no interaction between *repetition* and *category* (random effect analysis: $p < 0.37$; p_s ranging from

0.1 to 0.93). For PS, there was a larger response to faces than butterflies ($p < 0.0082$), but the difference between different and same faces was not significant (Index = -0.060; $p = 0.507$), replicating previous observations (Schiltz et al., 2006). However, there was a significantly larger response for different pictures of butterflies than same pictures (Objects Index = 0.287, contrast $p<0.035$) in PS's 'FFA'. When comparing PS's indices directly to controls, they were significantly different in the 'FFA' for Faces [$t = -3.035$, $p<0.014$; modified t-test (Crawford and Garthwaite, 2002)], but not for objects ($t = 0.583$, $p=0.293$). As a result, she was the only participant presenting a significant interaction between the factors category and repetition ($p <0.049$) (Figure 4. 3).

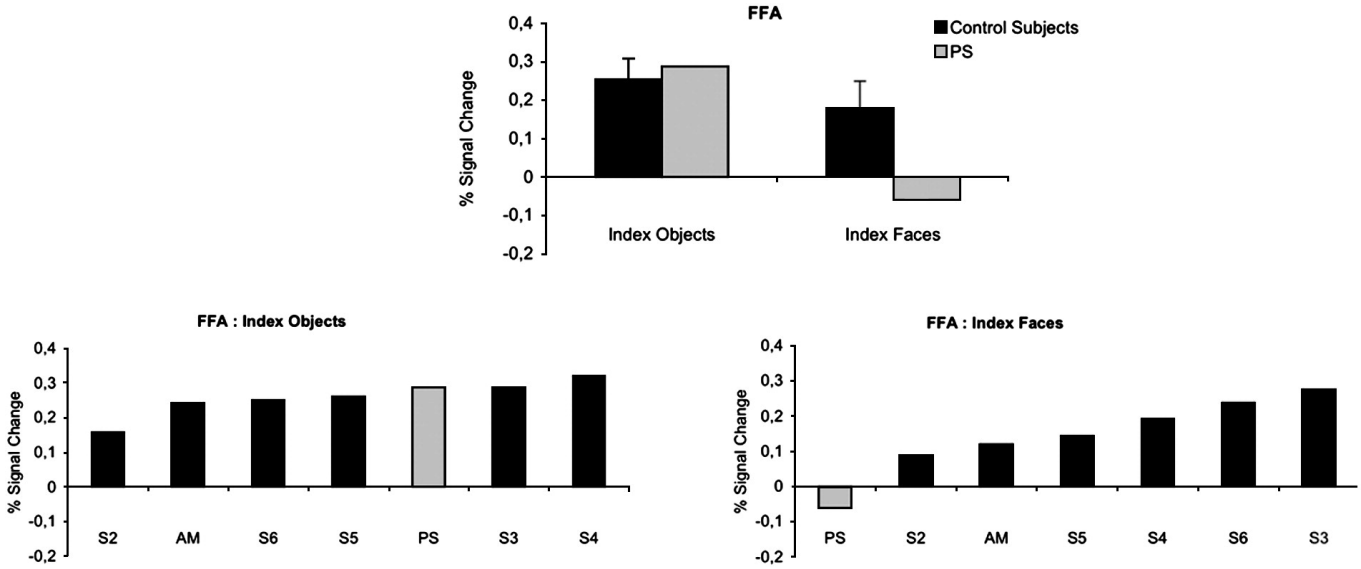


Figure 4. 3. Comparison between PS and the control subjects in the fMRI- adaptation block experiment 1 ('FFA').

Above: An adaptation index [(different-same)/(different+same)] was computed for each category in PS' and each subject's 'FFA' using the beta weights of the GLM analysis. The Faces Index was significant for all subjects but PS, replicating previous observations (Schiltz et al., 2006). The adaptation index for objects was significant for PS, and of identical magnitude to the controls' index in the 'FFA'.

Below: individual subject's indexes, showing that the deficit of release from adaptation in the 'FFA' of PS was found only for faces, not for objects.

In the right 'OFA', located in a region structurally damaged in PS's brain [see Figure 4. 1; (Rossion et al., 2003a)], all control subjects also showed a strong release from adaptation for both faces (random effect analysis: $p<0.005$; $p_s < 0.05$; Index = 0.142±0.05) and butterflies (random

effect analysis: $p < 0.001$; $p_s < 0.015$ Index = 0.160±0.03) without any interaction (random effect analysis: $p>0.9$; p_s ranging from 0.26 to 0.94), i.e. the same response pattern as in the 'FFA'.

In the right vLOC of control subjects (Figure 4. 4), we found release from adaptation both to faces (random effect analysis: $p < 0.002$; $p_s < 0.000004$; Faces Index = 0.194±0.06) and butterflies (random effect analysis: $p < 0.0006$; $p_s < 0.000008$; Objects Index = 0.187±0.03) without interaction (random effect analysis $p>0.65$; p_s: 0.12 to 0.83). For PS, there was also a significant difference for butterflies (Objects Index = 0.161, contrast $p<0.0000001$). Most importantly, in contrast to the absence of effect in the 'FFA', there was a significant release from adaptation for faces (Faces Index = 0.127, contrast $p<0.0003$) in PS's vLOC (Figure 4. 4). When comparing PS's indices directly to controls, there was not significant difference in the vLOC for the Faces Index [$t = -1.034$, $p = 0.174$; modified t-test (Crawford and Garthwaite, 2002)], and for the Objects Index ($t = -0.688$, $p = 0.261$). There was no interaction between repetition and category ($p = 0.16$) either.

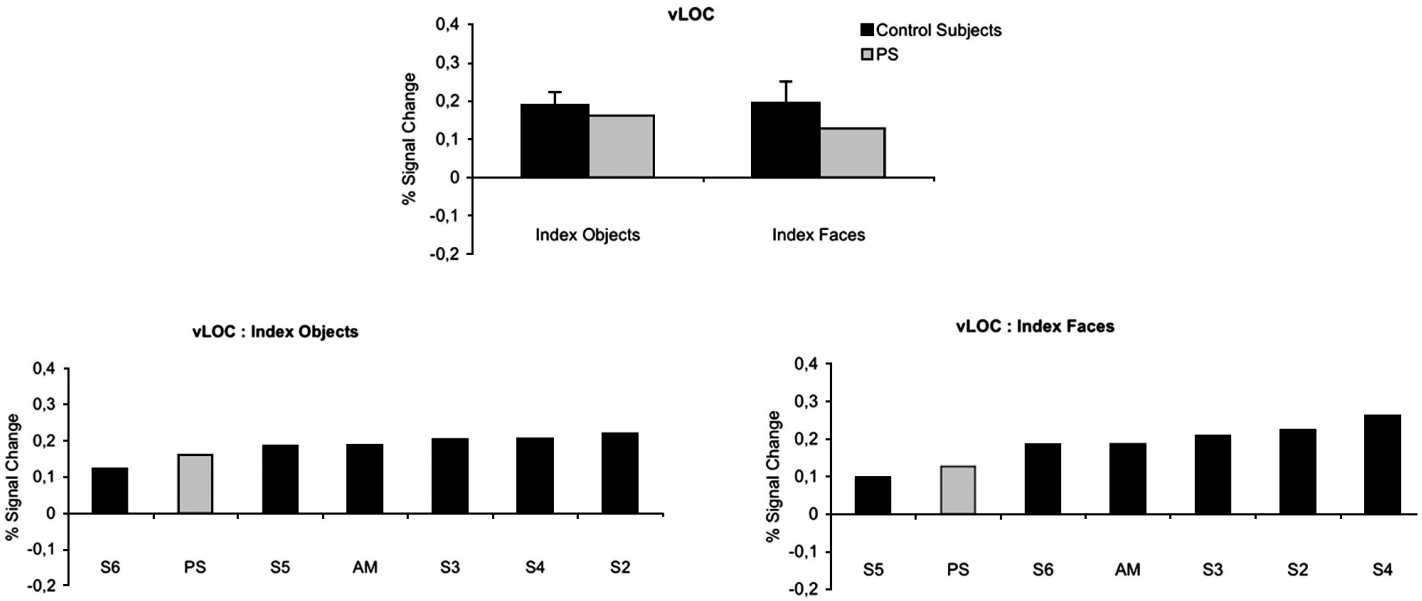


Figure 4. 4. Comparison between PS and the control subjects in the fMRI- adaptation block experiment 1 (vLOC).

Above: An adaptation index [(different-same)/(different+same)] was computed for each category in PS' and each subject's vLOC using the beta weights of the GLM analysis. The adaptation index was significant and of identical magnitude for all subjects and PS.

Below: individual subject's indexes, showing that PS had normal adaptation indexes for both faces and objects in this experiment.

To complement these observations, we ran a conjunction analysis using the contrasts (butterflies: different *vs.* same) and (faces: different *vs.* same) in the whole of the patient PS, without a priori localization. Strikingly, the coordinates of the *only* region significantly activated in the whole brain of the patient was in the vLOC [43, -62, -17, q([False Discovery Rate) < 0.05, 11 voxels] (Figure 4. 5). When we did the same whole brain conjunction with the control group, we found 4 regions at p(bonf)< 0.001: 35 -42 -17, 801 voxels [‘FFA’ (see Table 4. 1); face sensitive region: (Faces – Butterflies contrast) p<0.0001], 36 -73 -13, 105 voxels [‘OFA’ (see Table 4. 1); face sensitive region: p<0.0003], 37 -61 -15, 448 voxels [vLOC (see Table 4. 1), not a face sensitive region p<0.2], -36 -44 -17, 523 voxels [left ‘FFA’; face sensitive region: p<0.0001]. Finally, running the conjunction analysis separately for faces and objects, we observed for the patient PS an effect in the vLOC only for faces [44, -62, -16, q(FDR)<0.05, 122 voxels], whereas several areas light up in the different *vs.* same contrast for objects: the vLOC [42, -64, -15, q([FDR) < 0.05, 692 voxels], an area in the parahippocampal gyrus responding highly to objects [‘PPA’; 31, -32, -20, q([FDR) < 0.05, 103 voxels], a region of the precuneus [15, -81, -40, q(FDR) < 0.05, 69 voxels] and the ‘FFA’ at a lower threshold [32 -53 -17, p(uncorrected)<0.04, 107 voxels].

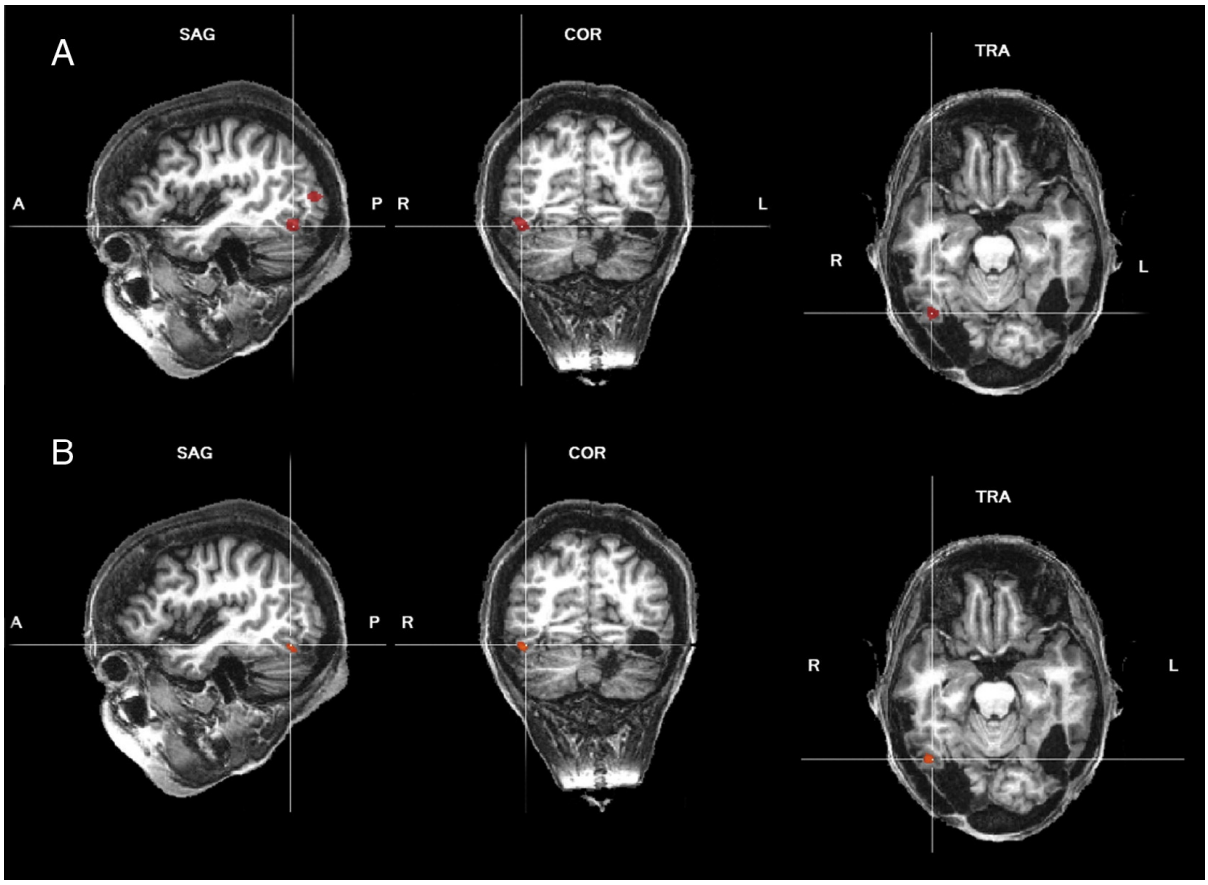


Figure 4. 5. Single subject analysis of patient PS in the the fMRI- adaptation block experiment 1. Localization of the LOC: $t > 6$, p (Bonf) < 0.000, vLOC: 43, -64, -12 (632 voxels) and dLOC: 39, -77, 3 (485 voxels). Results of the conjunction analysis using the contrasts (butterflies: different vs. same) and (faces: different vs. same). The coordinates of the *only* region significantly activated [$t > 3.66$, $p < 0.00025$ (uncorr.), 176 voxels (illustrated) and q (False Discovery Rate) < 0.05, 11 voxels] was in the vLOC (center: 43, -62, -17).

In summary, these data show that the absence of release from adaptation in the ‘FFA’ of the brain damaged patient is restricted to face stimuli: there were large effects for nonface objects, as in the normal brain. Moreover, discrimination of individual faces in the patient’s brain takes place only in an area that does not respond preferentially to faces: the vLOC. Normal participants also show release from adaptation in this area, suggesting that the patient’s findings are not due to cortical reorganization of function. However, normal participants also showed large release from adaptation effects in the ‘FFA’ and ‘OFA’ of the right hemisphere, functionally and structurally damaged in the patient’s brain respectively.

3.4.4.2. Event-related fMRI of faces and objects

All participants performed the behavioural task of indicating across-category trials at ceiling (control means: 94%+/-3,5% correct detection, no false alarm), PS (96% correct detection, no false alarm). They were all quite fast and PS showed comparable response latencies to control subjects [controls: 599+/-147 ms, PS: 576 ms; $t = -0.703$, $p = 0.266$; modified t-test (Crawford and Garthwaite, 2002)].

Again, PS’s and subjects’ ‘FFA’ and vLOC were tested for fMRI-adaptation to identity using the contrast (different *vs.* same) for each category and an adaptation index was computed using the beta weights of the general linear model (GLM) analysis (Methods). For each control subject, the neural activity was significantly larger when viewing pictures of faces than butterflies (individual p-values ranging from 0.000001 to 0.05) in the right ‘FFA’. Although only 4 subjects, a random analysis was created and analyzed. As in the block experiment 1, the response was significantly larger for different faces than identical faces (random effect analysis: $p < 0.0285$; individual p-values: $p_s < 0.015$; Faces adaptation index = 0.235±0.16) and when viewing different butterflies than identical butterflies [random effect analysis: $p < 0.010$; $p_s < 0.001$ except for S11 ($p<0.1$); Objects Index = 0.228±0.12] (Figure 4. 6). There was no interaction between *repetition* and *category* [random effect analysis: $p < 0.23$; p_s ranging from 0.06 to 0.89 except for S11 ($p<0.04$) who had a poor butterfly effect]. For PS, there was a larger response to faces than butterflies ($p < 0.001$), but the difference between different and same faces was not significant (Index = 0.070; $p<0.214$), replicating our block experiment. There was also a significantly larger response for different pictures of butterflies than same pictures (Objects Index = 0.330, contrast $p<0.042$) in PS’s ‘FFA’. PS had the lowest adaptation index for faces of all subjects (i.e. 0.07 for PS vs. 0.235 for controls on average) even though it was not significantly different than the controls due to the large inter-subject variance in the ‘FFA’ for faces [$t=0.984$, $p<0.199$] (Fig. 6). Her adaptation index for butterflies was undistinguishable from the index of the controls ($t=0.688$, $p=0.270$). Notably, she

was the only participant presenting an adaptation index significantly larger for butterflies than faces [significant interaction between the factors category and repetition ($p<0.042$), all other $p_s > 0.1$] (Fig. 6).

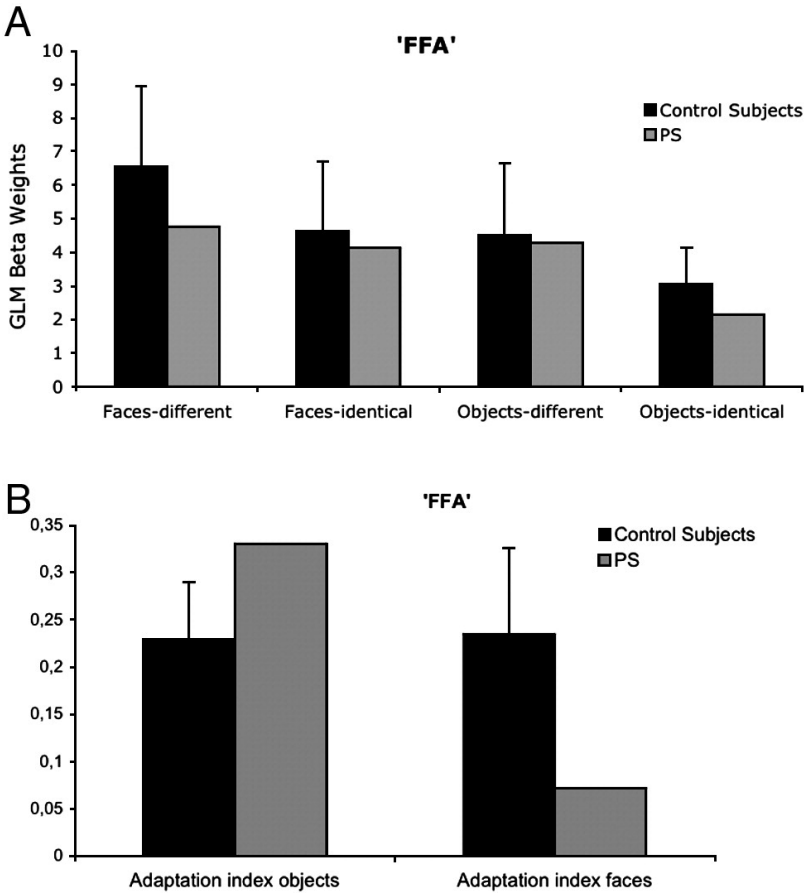


Figure 4. 6. PS and normal control data for the ‘FFA’ (beta weights of the general linear model analysis) in the fMRI-adaptation experiment 2. PS was the only participant who did not show a significant release from adaptation to face identity while showing a significant effect for pictures of objects. (B) Adaptation indices for PS and normal controls in experiment 2 (‘FFA’).

In the right vLOC of control subjects (Figure 4. 7), we found release from adaptation both to faces [random effect analysis: $p < 0.046$; $p_s < 0.003$ except for S1 ($p<0.36$); Faces Index = 0.133±0.11] and butterflies [random effect analysis: $p < 0.0147$; $p_s < 0.031$ except for S1 ($p<0.22$); Objects Index = 0.112±0.05] without interaction (random effect analysis $p>0.456$; p_s: 0.19 to 0.99). For PS, there was also a significant difference for butterflies (Objects Index = 0.140, contrast $p<0.000001$). Most importantly, in contrast to the absence of effect in the ‘FFA’, there was

a significant release from adaptation for faces (Faces Index = 0.063, contrast $p<0.046$) in PS's vLOC (Figure 4. 7). When comparing PS's indices directly to controls, there was not significant difference in the vLOC for the Faces Index [$t = -0.537$, $p = 0.314$; modified t-test (Crawford and Garthwaite, 2002)], and for the Objects Index ($t = 0.501$, $p = 0.325$).

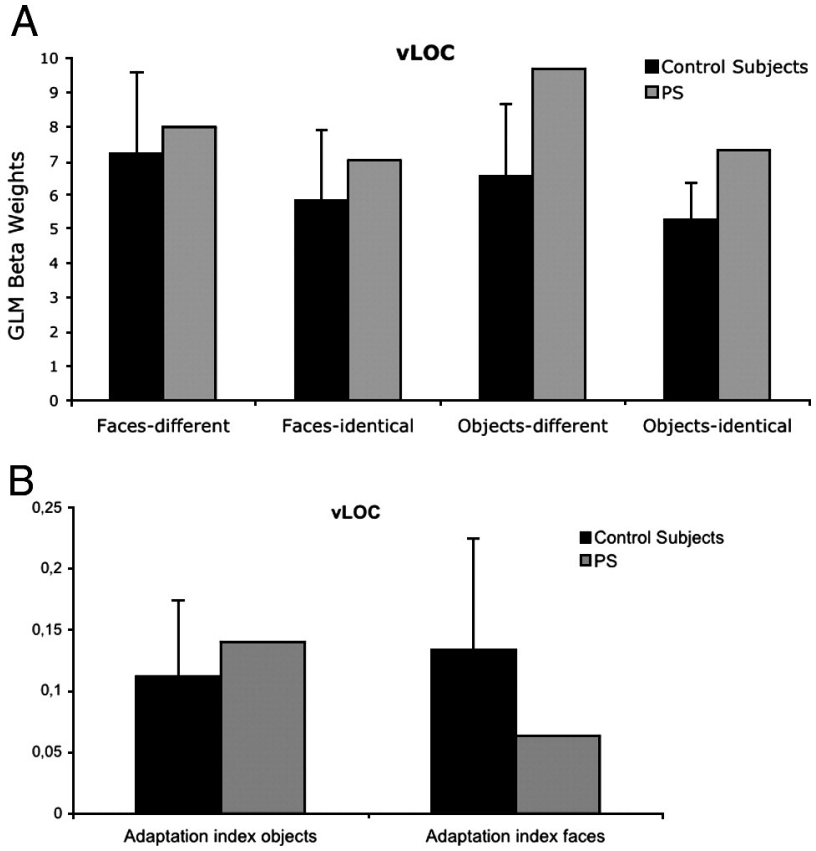


Figure 4. 7. (A) PS and normal control data for the vLOC (beta weights of the general linear model analysis) in the fMRI-adaptation experiment 2. All participants, including PS, showed a significant release from adaptation both to face and object identity. (B) Adaptation indices for PS and normal controls in experiment 2 (vLOC).

3.4.4.3. Event-related fMRI during face discrimination

Despite her prosopagnosia, PS succeeds in individual face discrimination above chance level, especially when the viewpoint between the face stimuli remains constant and she is given prolonged time to answer (Rossion et al., 2003a; Schiltz et al., 2006). To test further whether the right vLOC could subtend the patient's residual individual face discrimination abilities, we tested PS and normal participants in an event-related paradigm during an active individual face

discrimination task (Figure 4. 8A). Normal participants performed the discrimination task at ceiling during their three runs (mean = 99.1%±0.74%) whereas PS's accuracy was at 86.2 % (12.2% of different faces considered as identical, and 15.5% of identical considered as different). PS (1379 ms across conditions) was also much slower [$t = 6.169$, $p < 0.000$, modified t-test (Crawford and Garthwaite, 2002)] than the control subjects (659 ms ± 113 ms).

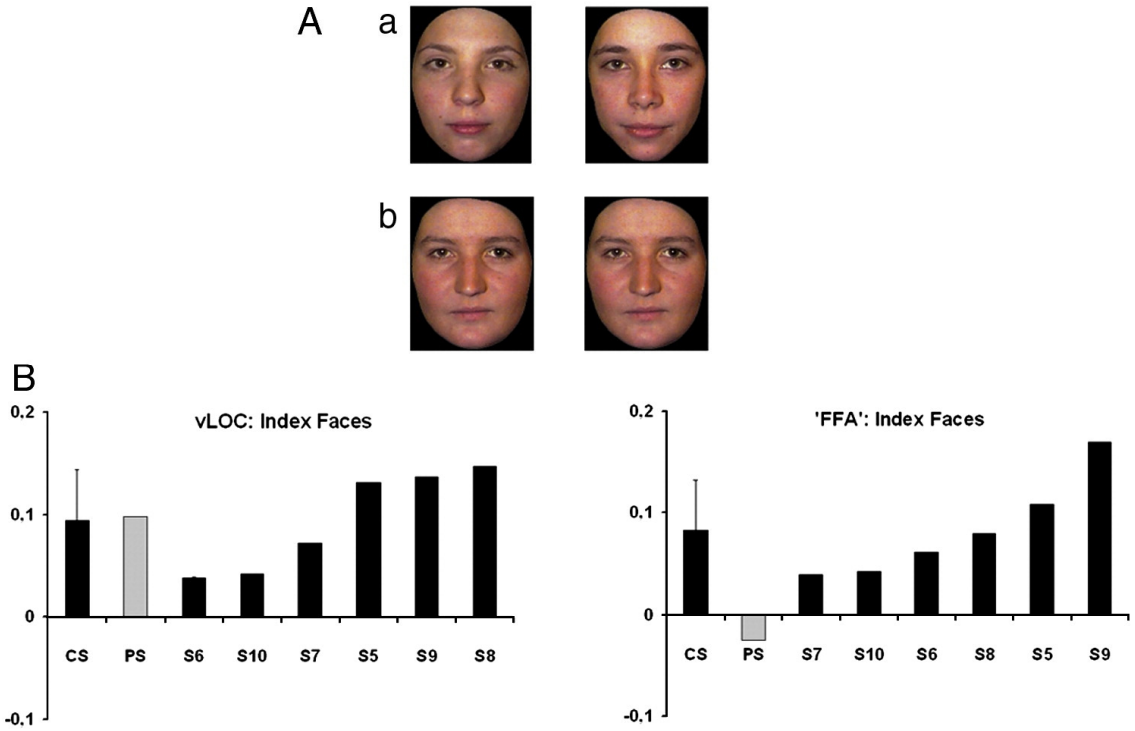


Figure 4. 8. Comparison between PS and the control subjects in the event-related fMRI-face discrimination experiment 3. **A**. Two conditions were presented to PS and control subjects: second face different than the first (a) and second face identical to the first (b). All the faces were shown on frontal view presented in colour and sustained a size of roughly 4° of visual angle. The faces were cropped. **B.** Comparison between PS and the control subjects (CS): an Faces Index [(different-same)/(different+same)] was computed for PS's and each subject's vLOC and 'FFA' using the beta weights of the GLM analysis. The Faces Index in the 'FFA' was significant for all subjects but PS, contrary to her adaptation index in the vLOC, which is significant and of identical magnitude to the control's index.

In this experiment (Figures 4. 8-10), there were strong releases from adaptation in both the 'FFA' (random effect analysis: $p < 0.001$; individual $p_s < 0.048$; Faces Index = 0.083±0.049) and the vLOC (random effect analysis: $p < 0.012$; $p_s < 0.016$; Faces Index = 0.094±0.049) of the normal participants. In contrast, PS did not show release from adaptation to individual faces in the 'FFA' (Index = -0.025; $p = 0.46$) but a significant effect in the vLOC (Index = 0.098; $p < 0.00368$) only.

3.4. The roles of “face” and “non-face” areas during individual face perception: evidence by fMRI adaptation in a brain-damaged prosopagnosic patient

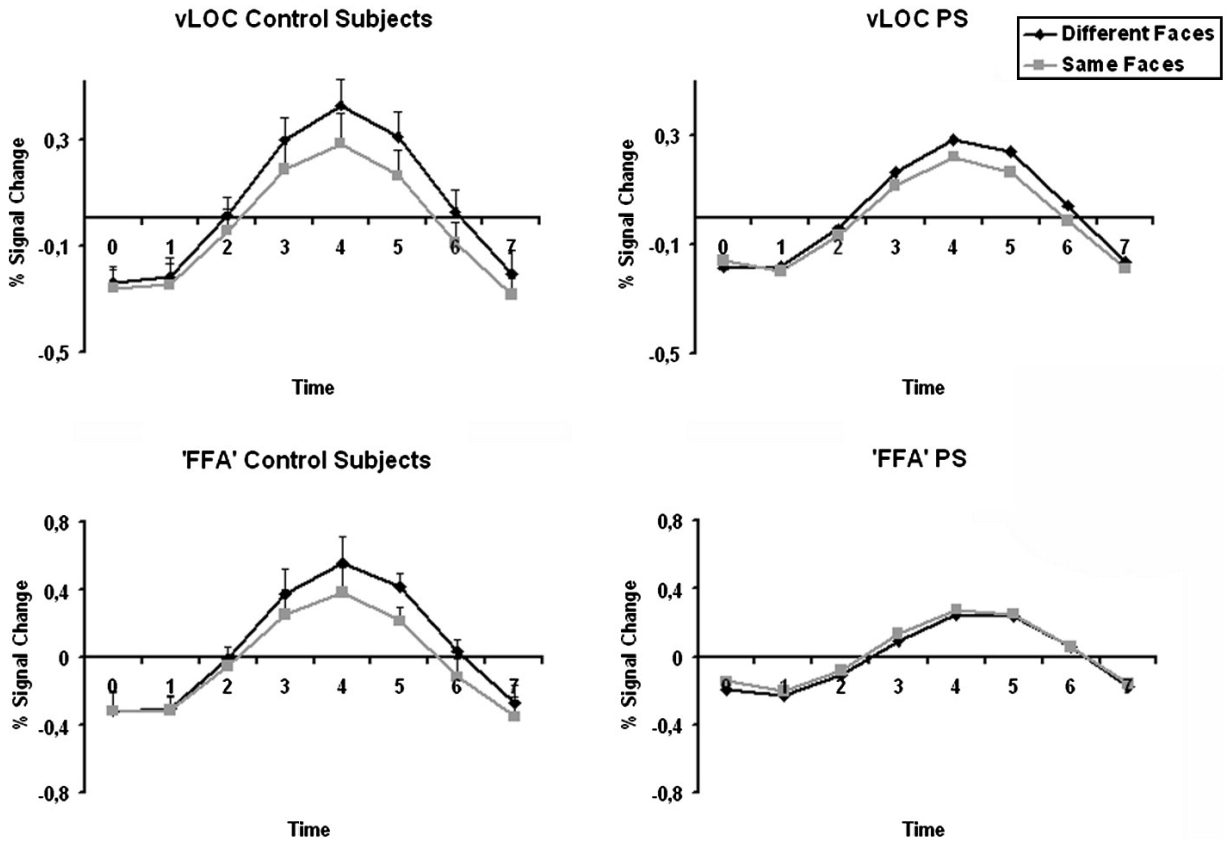


Figure 4. 9. PS’s and control subjects’ time-courses in the right-hemispheric vLOC and ‘FFA’ in the event-related fMRI- face discrimination experiment 3. PS did not show any evidence of a release from adaptation in the ‘FFA’, but normal effects in the vLOC.

3.4. The roles of “face” and “non-face” areas during individual face perception: evidence by fMRI adaptation in a brain-damaged prosopagnosic patient

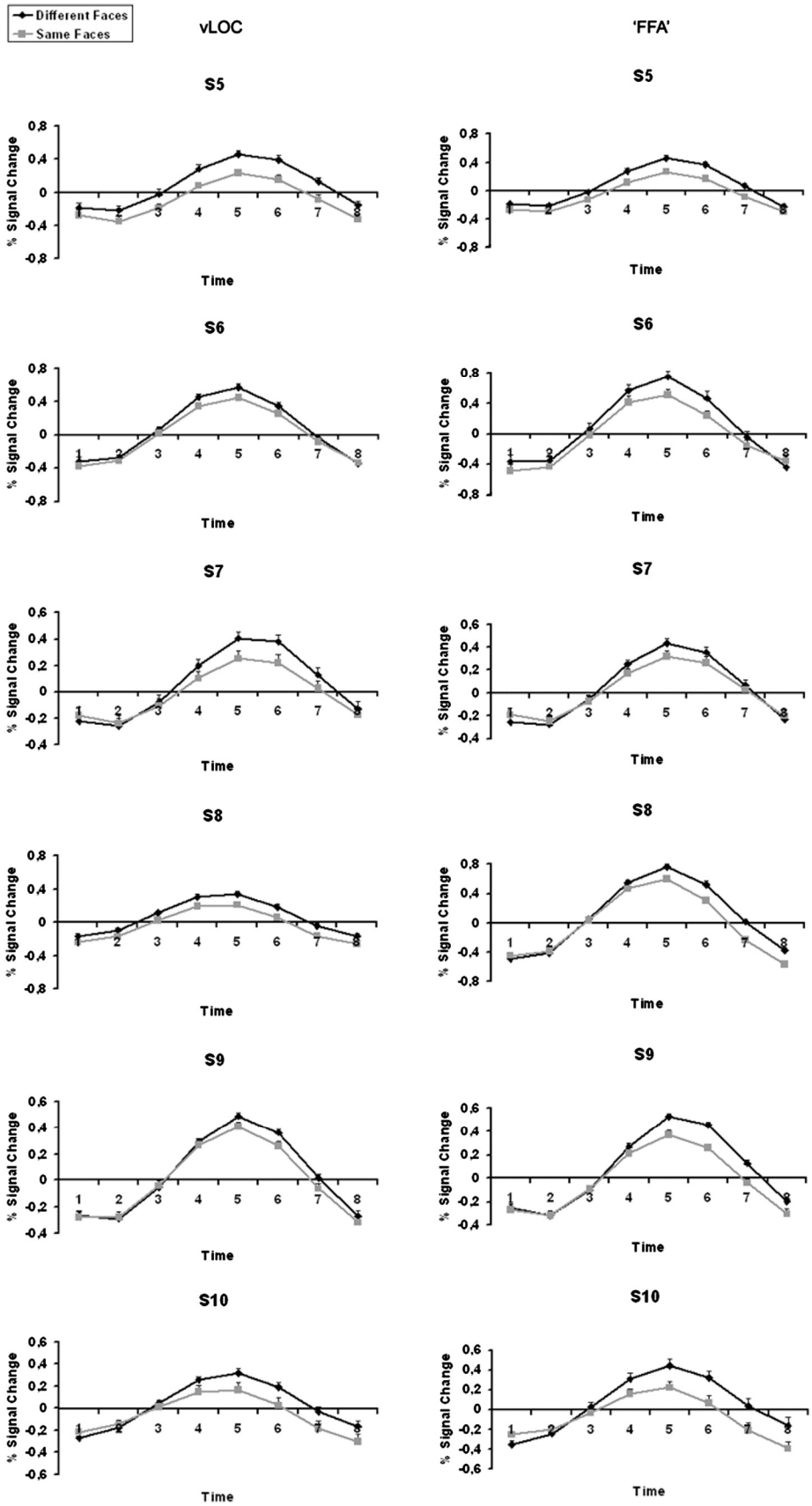


Figure 4. 10. Individual time-courses in the right-hemispheric vLOC and ‘FFA’ in the event-related fMRI- face discrimination experiment 3.

In the right ‘OFA’, all but one (S10) control subjects also showed a release from adaptation for faces (random effect analysis: $p< 0.0047$ (or $p< 0.03$ including the subject without significant release), individual $p_s< 0.043$; Index = 0.100±0.07,) i.e. the same response pattern as in the ‘FFA’.

When comparing PS’s indices directly to those of the controls, there was a significant difference in the ‘FFA’ [$t = -2.041$, $p< 0.048$; modified t-test (Crawford and Garthwaite, 2002)], but not in the vLOC ($t= 0.057$, $p= 0.478$), indicating that the magnitude of the effect was as large for PS and normal controls.

In the area where the different faces response is larger than the same faces response [i.e. corresponding to the vLOC area (43, -63, -17)] of the patient PS, we found using the data of the face localizer 1.538 and 1.736 for the faces and objects beta weights respectively ($p<0.015$). Hence, PS is indeed using primarily a region that does not respond preferentially to faces to discriminate individual exemplars of that category. For normal controls, when we considered the regions showing the largest different>same faces response in a random analysis, we found two areas at p(uncorrected)<0.01 : 37 –35 –16, 108 voxels and –30 –45 –12 334 voxels, which correspond to two face sensitive regions in all our subjects (highest individual p-value $p_s<0.0001$ and 0.0007 respectively).

To sum up, the results of this third event-related fMRI experiment confirms that the active discrimination of individual faces in the patient’s brain still take place in the vLOC, despite the absence of any such effect in the area responding preferentially to faces, the ‘FFA’.

3.4.5. Discussion

Our three fMRI-adaptation experiments carried out with normal participants and the brain-damaged prosopagnosic patient PS show two novel observations.

In the same high-level visual area, i.e. the ‘FFA’, the processes allowing for the discrimination of individual members of a visual category can be preserved for non-face objects but

is impaired for faces. This suggests that faces and nonface objects responses in this area are functionally independent.

High-level visual areas that do *not* respond preferentially to faces, such as the vLOC, subtend complementary visual processes to discriminate individual faces. The data strongly suggest that these processes are both *independent* from processes taking place in areas responding maximally to faces (‘FFA’ and ‘OFA’) and *insufficient* to carry normal face perception.

3.4.5.1 Selective preservation of individual object perception in the ‘FFA’

In rare cases of prosopagnosia, object perception is intact and impairments are restricted to faces [e.g. (De Renzi and di Pellegrino, 1998; Henke et al., 1998; Sergent and Signoret, 1992)] even when RTs are considered during fine visual discrimination within the same object category (Rossion et al., 2003a; Schiltz et al., 2006). What is the neural basis of this preserved object perception ability in prosopagnosia? We showed previously that the acquired prosopagnosic patient PS presents a right hemisphere lesion encompassing the ‘OFA’ (Rossion et al., 2003a) but leaving the entire LOC intact (Sorger et al., 2007). The data collected here further indicate that neurons in the patient’s right vLOC carry out discrimination of individual exemplars of objects, as in normal subjects. More interestingly, while we replicated the absence of such identity adaptation effects for faces (Schiltz et al., 2006) in three experiments, we observed for the first time fMRI-adaptation effects for objects in the ‘FFA’ of PS. Thus, within-category object discrimination can takes place in both the vLOC and the ‘FFA’ in the patient’s visual cortex, in line with her normal behavioral performance at such tasks (Rossion et al., 2003a; Schiltz et al., 2006).

Why do we observe a preserved release from adaptation to individual object exemplars in the patient’s ‘FFA’ while there is no such effect for faces? Obviously, this cannot be due to a lower sensitivity of this area to faces, because its response is higher to faces for both normal controls and the patient PS. Moreover, this dissociation observed in PS’s ‘FFA’ is unlikely to be due to

attentional confounds (Eger et al., 2004a; Kanwisher and Wojciulik, 2000; Schiltz et al., 2006). First, one would have to posit that attention was increased only when different objects were shown during a block in experiment 1, not during the presentation of different faces, and this only for the patient. Second, the results were also found in an event-related paradigm (experiment 2), when the order of conditions was unpredictable, limiting the possibility of attentional confounds. Finally, we used an identical orthogonal task for both categories, for which the patient performs at the same level in all conditions and as well as the controls.

One may argue that the individual pictures of objects used (butterflies) were more dissimilar than the individual faces (Fig. 2, see Materials and methods), a factor that could potentially explain why significant release from identity adaptation is found in PS’s ‘FFA’ for objects but not for faces. As we indicated earlier, testing our hypothesis required to maximize our chances to observe significant releases from adaptation to objects in the ‘FFA’ of *every* single participant of the study, hence using individual exemplars of an object category differing substantially in shape, color and texture. However, as far as shape and texture are concerned, individual exemplars of the 2 categories were roughly equally distinct, or even more similar for butterflies (see Materials and methods). Moreover, in the present study we also used exemplars of faces that differed substantially in shape (internal and external features including hairstyle, etc.) and surface properties, including color. This point is worth to note because it strengthens our previous observations of a lack of release from face identity adaptation with the patient PS using pictures of faces without external features (Schiltz et al., 2006). In addition to this point, identity adaptation effects in the present study were equally large for individual exemplars of objects and faces in the vLOC of the control participants (Fig. 4). Thus, it is unlikely that the absence of significant release from identity adaptation restricted to faces in PS’s ‘FFA’ may be due to a simple factor such a higher physical similarity of face exemplars over object exemplars.

More generally, even though we used the exact same images, the effects of adaptation that we observed in these areas for objects and faces are unlikely to be due to simple image-based cues. First, these were minimized by jittering the stimuli in position, a factor that decreases substantially pixel-similarity indexes (Grill-Spector and Malach, 2001; Rossion and Jacques, 2008) and yet leads to substantial release from adaptation as in previous studies [e.g. Schiltz et al., 2006; Fang et al., 2007]. Second, in the whole brain analysis of the patient PS, we found significant release from adaptation in high-level visual areas only: the vLOC for faces, the ‘FFA’, vLOC and ‘PPA’ for objects. Finally, and more generally, it is likely that identity adaptation effects found for faces and objects in the ‘FFA’ in the present and previous studies are not only driven by high-level visual cues, but also by low-level cues which are naturally used to discriminate individual exemplars (e.g. eye color, hairstyle, contour ...). This information is part of what defines an individual object or face representation for our visual system (e.g. see Lee and Perrett, 1997 for the role of color in individual face perception). Neuroimaging experiments performed in normal viewers will have to clarify the nature of the face cues that leads to identity adaptation effects in the ‘FFA’ (and other ‘face areas’), something that is currently unknown. While a substantial part of these effects may be driven by high-level cues (e.g. symmetry, Chen et al., 2007; holistic integration of facial features, (Schiltz and Rossion, 2006), low-level information on local cues (e.g. eye color, mouth shape ...) certainly contributes to these effects. It is particularly interesting that prosopagnosic patients such as PS, despite being able to use such “low-level” cues to discriminate individual faces at least to some extent (see Caldara et al., 2005), does not recruit her structurally intact ‘FFA’ for this process.

The dissociation between the adaptation effects for objects and faces in the ‘FFA’ is particularly interesting because the *same* high-level visual area, defined on the basis of a functional criterion, shows abnormal discriminative responses to items of one category - faces - while presenting normal responses to another category (here, pictures of butterflies). Thus, non-face individual discrimination in the ‘FFA’ is preserved for PS, and these lower responses may well play

a role in her preserved object discrimination abilities, in line with earlier proposals (Avidan et al., 2002; Haxby et al., 2001).

There is recent evidence suggesting that these lower responses to objects in the 'FFA' do not originate from the same populations than the responses to faces. Using high-resolution fMRI, Grill-Spector et al. (2006b; 2007) found that the 'FFA' is not an unitary region, but rather contains clusters of highly specific neurons responding preferentially to faces intermixed with fewer clusters that are non-specific for faces (Grill-Spector et al., 2006b, 2007)[53]. This concur with earlier single-cell recording data in the monkey brain, showing that the areas of the infero-temporal (IT) cortex, such as the lower bank of the superior temporal sulcus (STS), contains between 10 and 20% of face-specific neurons (Baylis et al., 1985) intermixed with neurons coding for non-face moderately complex features (Logothetis and Sheinberg, 1996; Tanaka et al., 1991). More recently, Tsao et al. (2006) recorded from localized fMRI 'face areas' in the monkey brain and found that almost all cells (about 97%) within these areas responded specifically to faces. However, the authors made a few recordings, most likely from the same highly face-specific clusters of cells in these areas. Hence, these observations are not in disagreement with the finding that the area as whole contains clusters of cells that are non-specific for faces, as found by Grill-Spector et al. (2006b; 2007), and which may explain the release from adaptation to objects in the 'FFA' observed here and in previous studies.

Given these observations, one plausible intepretation of our findings is that the clusters of face-cells in the anatomically preserved 'FFA' of PS do not show enough specificity in their response to distinct facial identities (Schiltz et al., 2006). This lack of sensitivity to facial identity in the 'FFA' may be due to a lack of inputs from the lesioned right 'OFA', a region where release from adaptation effects were observed here in normal subjects, as in previous studies (see Schiltz et

[53] Note that the original contribution of Grill-Spector and colleagues (2006b) reported clusters in the 'FFA' that were highly selective for non-face object categories, but these conclusions were dimissed and these clusters rather appear as non-category selective (see Baker et al., 2007; Simmons et al., 2007). However, the conclusion that the 'FFA' is a heterogenous region in humans remains valid (Grill-Spector et al., 2007).

al., 2006). However, non face object clusters in the same area may still code for distinct objects, perhaps based on moderately complex features, leading to the release from adaptation to objects that we observed here. Future experiments combinig high-resolution fMRI with object and face adaptation paradigms should be able to test this hypothesis.

3.4.5.2. Residual perception of individual faces subserved by vLOC neurons

Despite her massive prosopagnosia, PS’s performance in individual face discrimination tasks remains well above chance level, especially when there is no change in viewpoint between the faces to compare, and she is given unlimited time to answer (Rossion et al., 2003a; Schiltz et al., 2006). Here, in the active face discrimination task during the ER adaptation experiment, she was at 86.2% and was slowed down relative to controls, who performed at ceiling. Such residual abilities are commonly observed in prosopagnosic patients, who may obtain relatively good scores at the Benton face matching tests (Benton and Van Allen, 1968) with unlimited time presentation (Bukach et al., 2006; Davidoff and Landis, 1990; Delvenne et al., 2004; Levine and Calvanio, 1989; Sergent and Signoret, 1992). There is now strong evidence that these residual individual face discrimination abilities are not subtended by the ‘FFA’ of the patient, since this region does not show release from adaptation effects to identity, no matter the different procedures and stimuli used [(Schiltz et al., 2006); the present experiments].

In contrast to the absence of adaptation effects in the ‘FFA’ for faces, the whole brain analysis in the first experiment, testing for adaptation effects to face identity, revealed a significant effect in the right vLOC, next to the patient’s posterior lesion. The second experiment confirmed that this area was sensitive to different facial identities during an active face discrimination task in an ER paradigm. We believe that this is an interesting observation, for three reasons.

First, to our knowledge, release from adaptation to facial identity has not been described, or emphasized before in normal subjects in areas that do not respond preferentially to faces. Normal

subjects appear to rely on several visual areas to discriminate individual faces, some responding preferentially to this category ['FFA', 'OFA'; the STS also, see (Winston et al., 2004)], while others do not (e.g. vLOC). Thus, responses in areas that do not process faces preferentially, such as the vLOC, may play a role in face categorization (Avidan et al., 2002; Haxby et al., 2001). This view is strengthened here by the observation that, in the patient's brain, the only remaining area subtending individual face discrimination was the vLOC. Since normal controls also show face adaptation effects in this area, the residual ability to discriminate individual faces in the patient's vLOC cannot be attributed to a functional reorganization, but rather to a residual, compensatory process. Similarly to our discussion of the origin of the effect for objects in the 'FFA', the face adaptation effect in the vLOC may originate from sub-populations of neurons tuned specifically to faces. However, to our knowledge, there is no reliable evidence for the presence of such face-specific population responses in LO. More generally, our conclusions that faces are processed by non-face specific mechanisms for the patient PS hold true for the level of organization corresponding to brain areas at current (low) fMRI resolution.

Second, individual face discrimination in vLOC may be *independent* of the processes carried out in the 'FFA' (or 'OFA'). PS's data strongly support this view because there was no evidence of individual face discrimination in the latter regions: the 'OFA' is structurally damaged and the 'FFA' does not show release from adaptation to face identity. These observations suggest that there are multiple processes, with a certain degree of independence, which allow the extraction of individual face representations in the normal brain. When the most efficient processes, calling on the 'FFA' and 'OFA', are unavailable, one may still rely on alternative processes in areas that do not respond mainly to faces (e.g. vLOC).

Third, the discriminative responses of facial identities observed in the vLOC of the patient and in the normal brain are *insufficient* to carry efficient face discrimination behaviour. Whereas the role of the 'OFA', and most probably the 'FFA' is critical for efficient discrimination of individual

faces and recognition (Barton et al., 2002; Bouvier and Engel, 2006; Rossion et al., 2003a; Schiltz et al., 2006) the vLOC appears to carry different and complementary functions that may or may not be necessary for face processing. To clarify whether this region is necessary, one would need to test patients with lesions specifically disrupting vLOC while leaving the two areas responding preferentially to faces intact. To our knowledge, such cases have not been reported, and are very unlikely to be found given the proximal location of these areas. Indeed, most cases of prosopagnosia following occipito-temporal right hemisphere lesions, usually following a posterior cerebral artery infarct (Goldsmith and Liu, 2001), present deficit at both face and object recognition (Barton et al., 2002; Bouvier and Engel, 2006; Clarke et al., 1997; Damasio et al., 1982; Farah, 1990; Gauthier et al., 1999; Rossion et al., 2003a; Schiltz et al., 2006). Future investigations will have to clarify the nature of complementary processes allowing a certain level of individual face discrimination that can be performed by the vLOC, for both the patient and the control. One hypothesis is that the prosopagnosic patient’s over reliance on non-diagnostic facial features to discriminate faces such as the mouth at the expense of the eyes (Caldara et al., 2005), or her feature-by-feature analysis due to an individual holistic face perception defect (Ramon and Rossion, 2007) may be subtended by non-face areas such as the vLOC.

3.4.6. Conclusions

Our results show that the right fusiform gyrus (‘FFA’) in the patient’s brain is selectively impaired for discriminating individual items of its preferential category, faces, in line with the behaviour of the patient. Thus, the same brain area can be functional for one category and disrupted for another. Second, we observed a larger signal to different faces than same faces in the ventral part of the lateral occipital complex (vLOC), next to the lesioned area. These results indicate that faces are processed through a network of visual areas in the human brain, in line with a distributed view of face perception. However the subset of areas responding preferentially to faces (‘FFA’ and

‘OFA’) is critical for efficient individual face processing. Following damage to these areas, other areas that do not respond preferentially to faces such as the vLOC may still subtend residual individual face processes.

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3.5. Abnormal face identity coding in the middle fusiform gyrus of two brain-damaged prosopagnosic patients[54]

3.5.1. Préambule

Nous reprenons ici la partie expérimentale que nous avons écrite d'une étude pour laquelle nous ne sommes pas premier auteur mais pour laquelle nous avons scanné nous même la patiente exactement dans les mêmes conditions que la patiente PS et avec nos paradigmes (event-related) de l'étude du point 3.4. ainsi qu'analysé et décrit entièrement les résultats. Nous avions pour but de reproduire chez une autre patiente prosopagnosique (même si la patiente DF décrite ici est beaucoup plus déficiente que PS et souffre également d'agnosie visuelle) l'activation dans le gyrus fusiforme droit d'une région sensible aux visages (''FFA'') malgré des lésions importantes dans le cortex occipital droit et gauche (absence d' ''OFA''s dans un paradigme en block design, Steeves et al., 2006) et l'absence par contre d'effet d'adaptation aux visages dans cette région. Cette activation normale en catégorisation de visage mais déficiente en individualisation de visage retrouvée également chez cette nouvelle patiente est très importante car elle confirme la possibilité d'activation de la ''FFA'' par des voies directes venant d'aires visuelles précoces et le rôle indispensable de l'''OFA'' droite pour discriminer les visages.

3.5.2. Introduction

L'objectif de cette étude était donc triple :

1. Reproduire avec un paradigme non sensible aux effets attentionnels une activation aux visages (''FFA'') dans le gyrus fusiforme droit de la patiente DF [Steeves et al. (2006) la montrait dans un paradigme en block).

[54] Cette section est basée sur une version remise en page de la partie expérimentale d'un article de Neuropsychologia avec le même titre de Jennifer Steeves, Laurence Dricot, Herbert C. Goltz, Bettina Sorger, Judith Peters, A. David Milner, Melvyn A. Goodale, Rainer Goebel and Bruno Rossion.
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2. Une absence de sensibilité aux différences individuelles des visages dans cette même région comme chez la patiente PS mais contrairement aux sujets contrôles.
3. Une absence de sensibilité aux différences individuelles d'exemplaires choisis parmi une autre classe d'objets. En effet, la patiente DF est, contrairement à PS, profondément lésée dans sa capacité à discriminer non seulement les visages mais aussi les objets, en particulier quand elle doit distinguer des exemplaires individuels (Humphrey et al., 1994).

Partie expérimentale

3.5.3. Materials and methods

3.5.3.1. Subjects

Patient DF is a female, 51 years of age at the time of testing, whose neuropsychological profile has been described in detail previously (e.g., Humphrey et al., 1994, James et al., 2003, Milner et al., 1991 and Servos et al., 1993). Her primary neurological symptoms are profound visual form agnosia and prosopagnosia. She shows relatively normal static perimetry in the central visual field up to 30° eccentricity but with some upper right quadrant loss (see Milner et al., 1991). Neuroimaging studies of patient DF's brain have been reported in James et al., 2003 and Steeves et al., 2004 and Steeves et al., 2006. An extensive description of DF's behavioural and neural response to face images is found in Steeves et al. (2006). In brief, however, she is unable to recognize face identity, gender or emotional expression but she can generally categorize faces and discriminate faces from objects that she cannot recognize. Patient DF also shows robust activation for face images within the "FFA", which is normal in terms of amplitude and spatial extent, bilaterally, with a block design face/scene localizer but she does not show face sensitive responses in the inferior occipital cortex (i.e., no "OFA").

Patient PS is a female, 56 years of age at the time of testing, whose neuropsychological profile and brain damage has been described in detail previously (Caldara et al., 2005, Rossion et al., 2003a, Schiltz et al., 2006 and Sorger et al., 2007. Her presenting neurological symptom is prosopagnosia and unlike patient DF, she does not present object recognition difficulties. Patient PS has normal visual fields, with the exception of a small left paracentral scotoma. The data collected on PS have been recently reported as a subset of a larger study (Dricot et al., 2008) that tested identity adaptation to faces with an independent localizer. This independent localizer was unavailable for patient DF due to limited scanning time and as a result the present data include a re-analysis of the Dricot et al. (2008) data so that the analysis for patient DF and PS is exactly the same.

In addition to the two patients, four neurologically intact participants (age: 25–35 years, two female) as well as one age-matched control participant (S5, 56 years of age, female) were tested. While it has been shown that the profile of activation in the right middle fusiform gyrus remains stable across decades (Brodtmann, et al., 2003) and therefore perhaps not necessary to ensure exact age-matching of participants, we also include the data from the age-matched control.

The patients and the control subjects gave informed written consent prior to the fMRI experiments. The study conformed to the Declaration of Helsinki and was approved by the Ethics Committees of the Department of Medicine at the University of Louvain and the York University Office of Research Ethics. Control subjects and PS were strongly right-handed according to the Edinburgh Inventory (Oldfield, 1971) and patient DF is also right handed.

3.5.3.2. Stimuli and procedures

Participants viewed three runs of 80 pairs of stimuli during fMRI recordings. The stimuli were pictures of faces and butterflies as shown in Figure 5. 1. Thirty-two face and 32 butterfly images were used in an event-related design. There were four conditions of interest:

two different face identities, two identical face identities, two different butterflies, and two identical butterflies in each pair. Finally, a fifth condition of a butterfly followed by a face image (or the opposite order for half of the trials) was used and participants were asked to respond to these face–object pair trials by pressing a response key. This task was well suited to the goals of the experiment because it ensured that the participants were attending to the stimuli, and it was a task that both patients could perform well. DF has been shown previously to be able to categorize faces even though she cannot recognize them (Steeves et al., 2006). Further, this task ensured that the factors of interest of the study (category effect: faces versus butterflies; adaptation effect: same versus different identities) would not be contaminated by any decisional and/or motor processes since the behavioural task was completely orthogonal to the test factors in the study, and any difference between patients and the controls could not be attributed to general processing difficulties on the trials of interest.

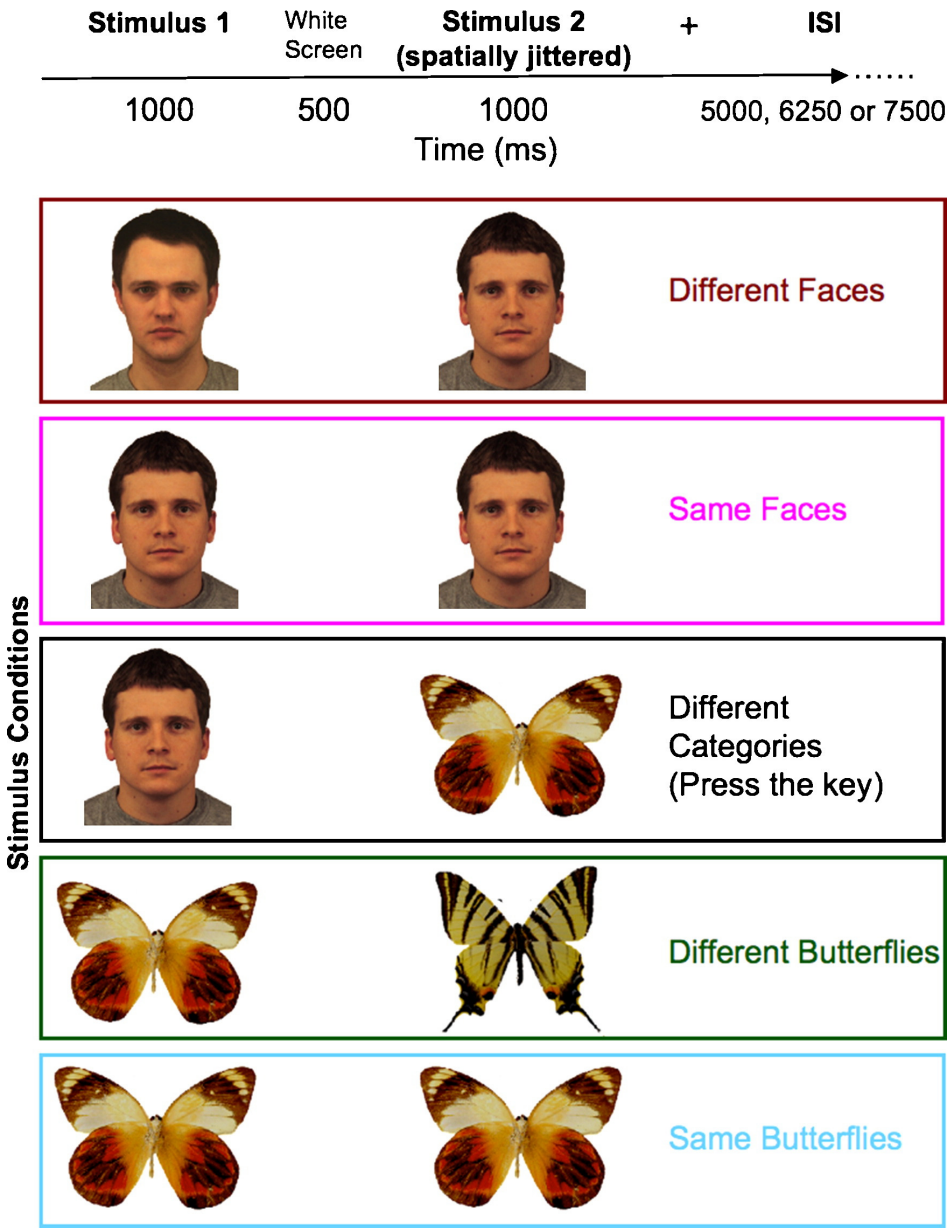


Figure 5. 1. Stimuli and task used in the experiment, with the time line of the presentation of events shown across the top.

There were 16 trials per condition per run and the order of conditions was fully randomized within a run. Within a trial, the first stimulus of a pair was presented for 1000 ms followed by a blank screen for 500 ms and thereafter by the second stimulus of the pair, which was also presented for 1000 ms (Figure 5. 1). The pairs were separated by a fixation cross with a duration of 5000, 6250 or 7500 ms (4–6 functional volumes), and these interstimulus interval (ISI) durations were also fully randomized. This timing ensured that the onset of distinct events was separated by at least

6–8 functional volumes (7500–10,000 ms). Randomization of trial order and of ISI duration further reduced any potential top-down effects of anticipation of the stimuli.

All images (pictures of faces and butterflies) were presented in the central visual field in colour and subtended approximately 4° of visual angle. Stimuli were spatially jittered by 40 pixels in *X* (5%) and 40 pixels in *Y* (7%) dimensions. The pairs were displayed in random order with a PC using E-prime 1.1 (PST Inc.) and projected onto a screen located above the head of the subject and viewed through an angled mirror.

3.5.3.3. Imaging experiments

MR images of brain activity were acquired on all participants using a 3T head scanner (Siemens Allegra, Siemens AG, Erlangen, Germany), with repeated single-shot echo-planar imaging: echo time (TE) = 50 ms, flip angle (FA) = 90°, matrix size = 64 × 64, field of view (FOV) = 224 mm × 224 mm, slice order descending and interleaved. Scan parameters were: repetition time (TR) = 1250 ms, 21 slices, slice thickness = 3.5 mm, no gap between slices, run time length = 11 min, 46 s, 250 ms. A three-dimensional (3D) T1-weighted data set encompassing the whole brain was acquired for each subject to provide detailed anatomy (1 mm^3) using a "modified driven equilibrium Fourier transform" (MDEFT) sequence (scan parameters: TR = 7.92 ms, TE = 2.4 ms, FA = 15°, matrix size = 256 × 256, FOV = 256 mm × 256 mm, 176 slices, slice thickness = 1 mm, no gap, total scan time = 13 min and 43 s).

3.5.3.4. Data analysis of the imaging experiments

The fMRI signal in the different conditions was compared using BrainVoyager QX (Version 1.4, Brain Innovation, Maastricht, The Netherlands) applying a General Linear Model analysis. Prior to analysis, the functional data sets were subjected to a series of preprocessing operations. This preprocessing consisted of linear trend removal to exclude scanner-related signal drift, temporal high-pass filtering in order to remove temporal frequencies lower than 3 cycles per run,

and a correction for small interscan head movements using a rigid body algorithm rotating and translating each functional volume in 3D space (Friston et al., 1995a,b). In addition to preprocessing, the data from the event-related experiment were also corrected for the difference between the scan times of the slices. Data were not smoothed in the spatial domain but were filtered in the temporal domain (FWHM = 2.8 cycles per second). In order to compare activated brain regions across subjects, all anatomical images and functional volumes were spatially normalized (Talairach-transformation; Talairach and Tournoux, 1988). Computed statistical maps were overlaid on the 3D T1-weighted scans to determine Talairach coordinates for all relevant activation clusters.

Subsequently, the functional data were analyzed using multiple regression models consisting of predictors, which corresponded to the particular experimental conditions of the experiment. The predictor time courses used were computed on the basis of a general linear model (GLM) of the relationship between neural activity and hemodynamic response, assuming a square wave neural response during phases of visual stimulation (Boynton et al., 1996). For our two patients and the control subjects, we computed a main effect to localize the face-preferential areas (faces versus butterflies), and tested the interaction and simple adaptation effects for each stimulus condition in these areas. Statistical thresholds were chosen with [q(false discovery rate) < 0.01] with a minimum of 50 voxel clustering.

3.5.4. Results

3.5.4.1. Behavioural data during fMRI

All participants performed the behavioural task of indicating across-category trials at ceiling (control means: 95 ± 0.03%), PS (96%) and DF (100% correct detection but one false alarm). Patients showed comparable response latencies to each other and to controls (controls:

595 ± 128 ms; PS: 576 ms; DF: 747 ms) with $t = -0.100$, $p = 0.463$ for PS and $t = 1.084$, $p = 0.17$ for DF [modified *t*-test (Crawford and Garthwaite, 2002)].

3.5.4.2. Neuroimaging results

Whole brain analysis

Main effect of category: faces versus objects

The comparison of face and butterfly images, independent of adaptation effects, led to significant activation in several high-level visual areas for the control participants as well as for both patients (Figure 5. 2). Our group of normal controls (including the age-matched control) showed significant activation at [p(Bonferroni-corrected) < 0.001] in the right and left 'FFA' (mean Talairach coordinates, right 'FFA': 39, −45, −19; 559 voxels and left 'FFA': −39, −43, −19; 777 voxels), and [at q(FDR) < 0.001] in the right 'pSTS' (mean Talairach coordinates, 49, −44, 12; 77 voxels) and in the right and left 'OFA' (mean Talairach coordinates, right 'OFA': 40, −69, −13; 188 voxels and left 'OFA': −40, −66, −16; 101 voxels).

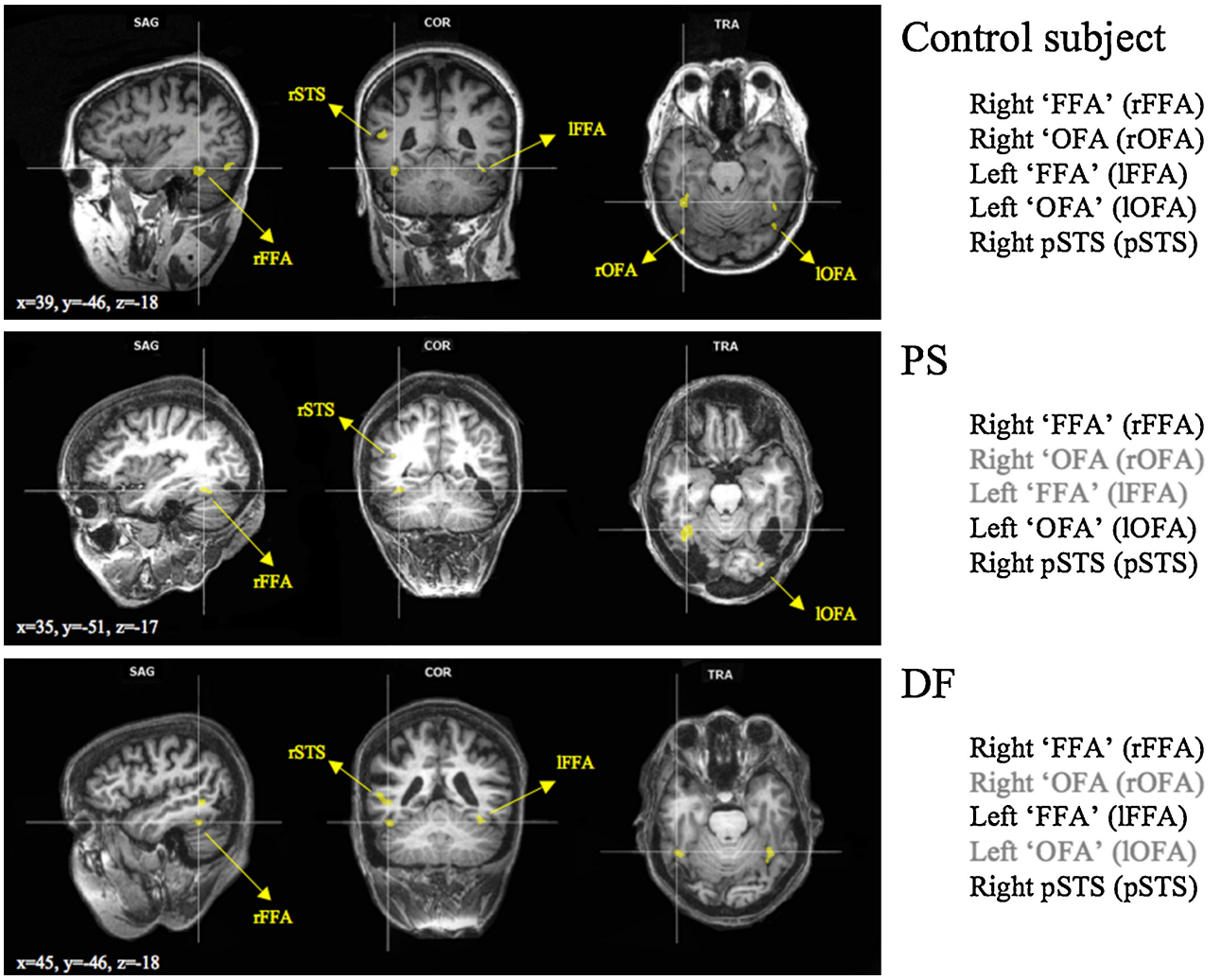


Figure 5. 2. Face-preferential activation in sagittal, coronal and axial slices for each of patients PS, DF and control S1 for the contrast of faces minus butterflies. Right hemisphere 'FFA' and left hemisphere 'OFA' activation are observed in patient PS while bilateral 'FFA' and right 'pSTS' activation are seen in patient DF. Control S1 shows bilateral 'FFA', 'OFA' and right hemisphere 'pSTS' activation. Talairach coordinates and cluster sizes are listed in Table 5. 1.

Consistent with previous observations, there was significant activation [at q(FDR) < 0.001] for faces in the 'FFA' and 'pSTS' of the right hemisphere for both patient PS and DF (Talairach coordinates, patient PS: 'FFA': 37, –54, –18; 591 voxels and 'pSTS': 41, –49, 14; 37 voxels and patient DF: 'FFA': 44, –47, –21; 178 voxels and 'pSTS': 48, –47, –1; 525 voxels) (Figure 5. 2). These activations were within the normal range for size and anatomical location as previously reported (PS: Rossion et al., 2003a and Sorger et al., 2007; DF: Steeves et al., 2006). Also consistent with previous work, there was significant activation in the left 'FFA' for patient DF

(Talairach coordinates: −36, −48, −19; 434 voxels) and in the left 'OFA' for patient PS [but at p(uncorrected) < 0.045, −31, −81, −17; 30 voxels]. In summary, the missing components of the network of face-preferential activation in both patients were areas that would have been located in structurally damaged tissue (Figure 5. 2). The common lesion site in the two patients is the right hemisphere 'OFA'.

ROI-based analysis

Adaptation effects for faces

In each of the areas showing preferential activation for faces, we tested for interactions between adaptation and category, as well as separately for effects of adaptation for each of the image categories (faces and butterflies). Adaptation indices were computed using the beta weights of the general linear model (GLM) analysis [faces index = (different faces versus same faces)/(different faces + same faces)]. Consistent with previous findings (Dricot et al., 2008) and (Schiltz et al., 2006), PS did not show any evidence of release from adaptation to face identity in the right 'FFA' (t = 1.499; p = 0.1339; Figure 5. 3), unlike normal participants (t = 3.732; p < 0.0002; Figure 5. 3). Hence, her middle fusiform gyrus responds preferentially to a picture of a face, but does not distinguish between different face identities. Strikingly, this absence of release from adaptation to face identity was also observed for the first time in the right 'FFA' of patient DF (Figure 5. 3) for which there was, in fact, a trend toward a pattern of activation opposite that which was expected (slightly higher signal for pairs of identical faces than different faces) (t = −1.698, p = 0.09). Thus, the right 'FFAs' of the two acquired prosopagnosia patients do not show release from adaptation to identity, in contrast to the healthy control participants.

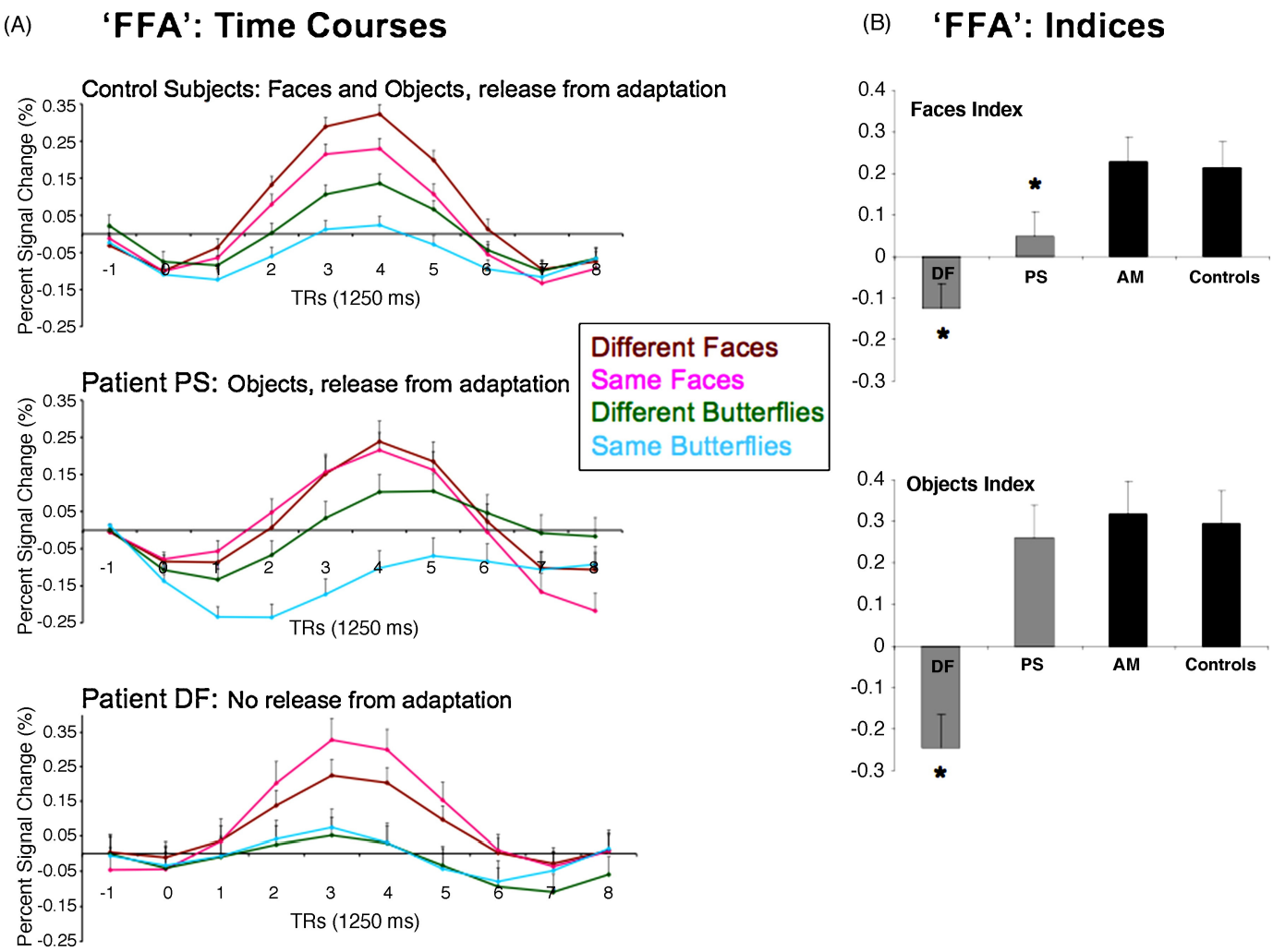


Figure 5. 3. (A) Event-related average time courses within the right 'FFA' for patients PS, DF and controls for the four experimental conditions of the study. (B) Histograms with adaptation indices computed using the beta weights of the general linear model (GLM) analysis [faces index = (different faces versus same faces)/(different faces + same faces)]. AM refers to the age-matched control. The * indicates a significantly different repetition index from controls.

Release from adaptation to identity was observed, however, in other face-preferential areas of the control participants (right 'OFA': $t = 2.449$, $p < 0.0143$ and left 'FFA': $t = 2.414$, $p < 0.0158$) but not in the left 'OFA' ($t = 0.594$, $p = 0.5527$) and right pSTS ($t = 0.644$, $p = 0.5194$). In contrast, none of these regions that were intact in either patient showed such effects. There was no release from adaptation to face identity for patient PS in the left 'OFA' ($t = 0.242$, $p = 0.8089$) or right 'pSTS' ($t = 0.043$, $p = 0.9656$) nor for patient DF in the left 'FFA' ($t = -0.967$, $p = 0.3339$) or the right 'pSTS' ($t = -1.442$, $p = 0.1494$) (Supplementary Figure 5. 1).

When comparing patient indices directly to those of controls, there was a significant difference in the 'FFA' for patient DF ($t = -5.07$, $p = 0.004$) and for patient PS ($t = -2.48$, $p = 0.034$).

Adaptation effects for objects

This absence of release from adaptation to identity, in particular in the right 'FFA' cannot be attributed to a lower signal overall for the patients, because this area responds robustly to faces in both patients (Figure 5. 3). Moreover, this area (right FFA) shows an identity adaptation effect when contrasting different and identical pictures of butterflies in not only our control participants ($t = 5.281$, $p < 0.00001$; Figure 5. 3), but also in patient PS ($t = 4.725$, $p < 0.00001$; Figure 5. 3; see also Dricot et al., 2008). There was no such effect for patient DF ($t = -0.882$, $p = 0.3778$; Figure 5. 3).

Release from adaptation to identity for butterflies was observed in other face-preferential areas of the normal participants including the right 'OFA' ($t = 3.040$, $p < 0.0024$), left 'OFA' ($t = 3.416$, $p < 0.0006$) and left 'FFA' ($t = 5.499$, $p < 0.00001$) but not the right pSTS ($t = 0.376$, $p = 0.7063$). For patient PS, release from adaptation was found in the pSTS ($t = 2.787$, $p < 0.0053$) but not in the left 'OFA' ($t = -0.181$, $p = 0.8569$) and there was no release from adaptation at all for patient DF in any of the regions of interest responding preferentially to faces (left 'FFA': $t = 1.331$, $p = 0.1833$; right 'pSTS': $t = -2.075$,$p = 0.0381$) (Supplementary Figure 5. 1).

When comparing patient indices directly to those of controls, there was a significant difference in the 'FFA' for patient DF ($t = -6.26$, $p = 0.002$) and but not for patient PS ($t = -0.387$, $p = 0.36$).

Interaction between adaptation and category

In summary, identity adaptation effects for both faces and objects were observed in normal participants in the right 'FFA' and in other face-preferential areas (Table 5. 1). For patient PS, identity adaptation effects were only observed for objects, while for patient DF there were no adaptation effects for objects or faces. When testing the interaction between category and adaptation, normal participants showed equally large identity adaptation in the 'FFA' for faces and objects (interaction: $t = -1.091$, $p = 0.2755$), while PS showed a larger effect for objects ($t = -2.293$, $p < 0.0219$) than for faces in the right 'FFA', and DF did not show identity adaptation for either image category in any of these areas ($t = -0.573$, $p = 5665$).

Table 5. 1. Talairach coordinates and cluster size in face-preferential areas for controls and patients PS and DF.

		Controls	PS	DF
Right "FFA"	Talairach coordinates	39, –45, –19	37, –54, –18	44, –47, –21
	Size [mm^2; q(FDR) < 0.001]	559*	591	178
	Face adaptation	Yes	No	No
	Object adaptation	Yes	Yes	No

		Controls	PS	DF
Left “FFA”	Talairach coordinates	−39, −43, −19	Lesioned	−36, −48, −19
	Size [mm^2; q(FDR) < 0.001]	111*		434
	Face adaptation	Yes		No
	Object adaptation	Yes		No
Right “OFA”	Talairach coordinates	40, −69, −13	Lesioned	Lesioned
	Size [mm^2; q(FDR) < 0.001]	188		
	Face adaptation	Yes		
	Object adaptation	Yes		
Left “OFA”	Talairach coordinates	−40, −66, −16	−31,−81,−17	Lesioned
	Size [mm^2; q(FDR) < 0.001]	101	30**	
	Face adaptation	No	No	
	Object adaptation	Yes	No	

		Controls	PS	DF
Right pSTS	Talairach coordinates	49, –44, 12	41, –49, 14	48, –47, –1
	Size [mm^2; q(FDR) < 0.001]	77*	37	525
	Face adaptation	No	No	No
	Object adaptation	No	Yes	No

* Bonferroni corrected.

** p(uncorrected) < 0.045.

Whole brain conjunction analysis

To strengthen our results, a whole brain analysis was performed on the control participants with the conjunction of three contrasts: [((different faces + same faces) versus (different butterflies + same butterflies)) and (different faces – same faces) and (different butterflies – same butterflies)]. This was done using a fixed effects analysis with our five subjects, for which we found only one significant cluster, corresponding to the Talairach coordinates of the 'FFA' (Figure 5. 4): 37, –43, –22; 31 voxels, q(FDR) < 0.05. The same analysis did not reveal any activation for either patient, which is consistent with their absence of adaptation effects for faces in the faces' ROI analyses. In addition, we performed a whole brain analysis searching for identity adaptation effects for pictures of faces and butterflies in patient PS and DF's brain. Consistent with our most recent findings (Dricot et al., 2008), we found a significant release from face and object identity adaptation for PS in an area adjacent to her right inferior

occipital lesion, corresponding to the ventral part of the lateral occipital complex (vLOC, see Dricot et al., 2008) [Talairach coordinates: 50, −64, −10; 506 voxels at p(uncorrected) < 0.045, t = 3.705, p < 0.0002 for face adaptation and$t$ = 3.206, p < 0.0014 for object adaptation without an interaction between category and adaptation (t = 0.344, p = 0.7306); Figure 5. 5].

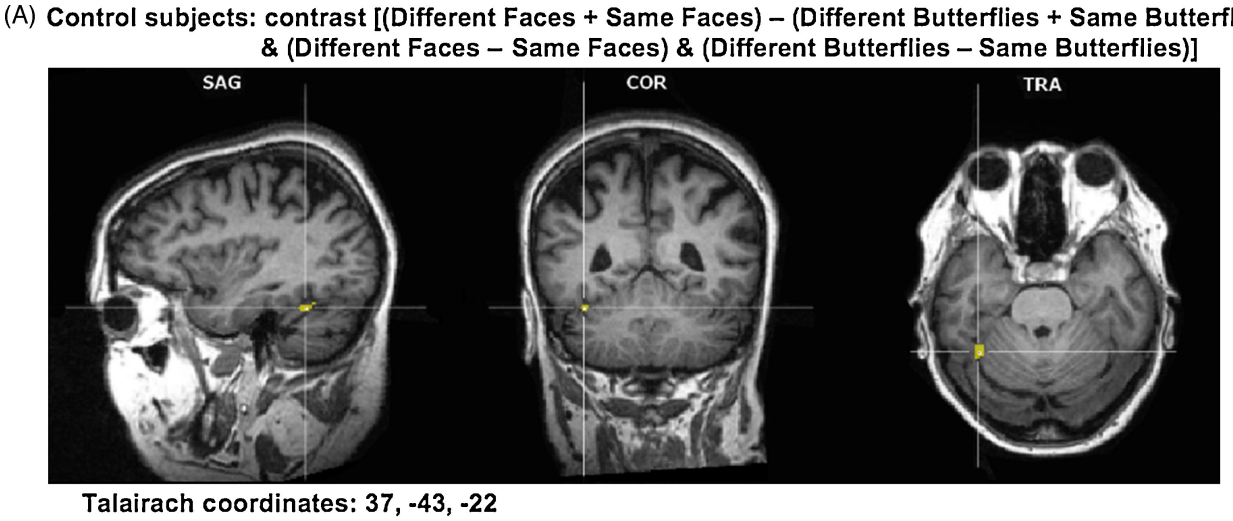


Figure 5. 4. (A) Whole brain fixed effects analysis on the control subjects with the conjunction of three contrasts: [(different faces + same faces) versus (differentbutterflies + same butterflies) and (different faces versus same faces) and (different butterflies versus same butterflies)]. This revealed only one significant cluster corresponding to the Talairach coordinates of the 'FFA': 37, −43, −22; 31 voxels, q(FDR) < 0.05 [represented at p(uncorrected < 0.001, 105 voxels]. The same analysis did not reveal any activation in either patient PS or DF. (B) Event-related average time courses for the four experimental conditions in the study.

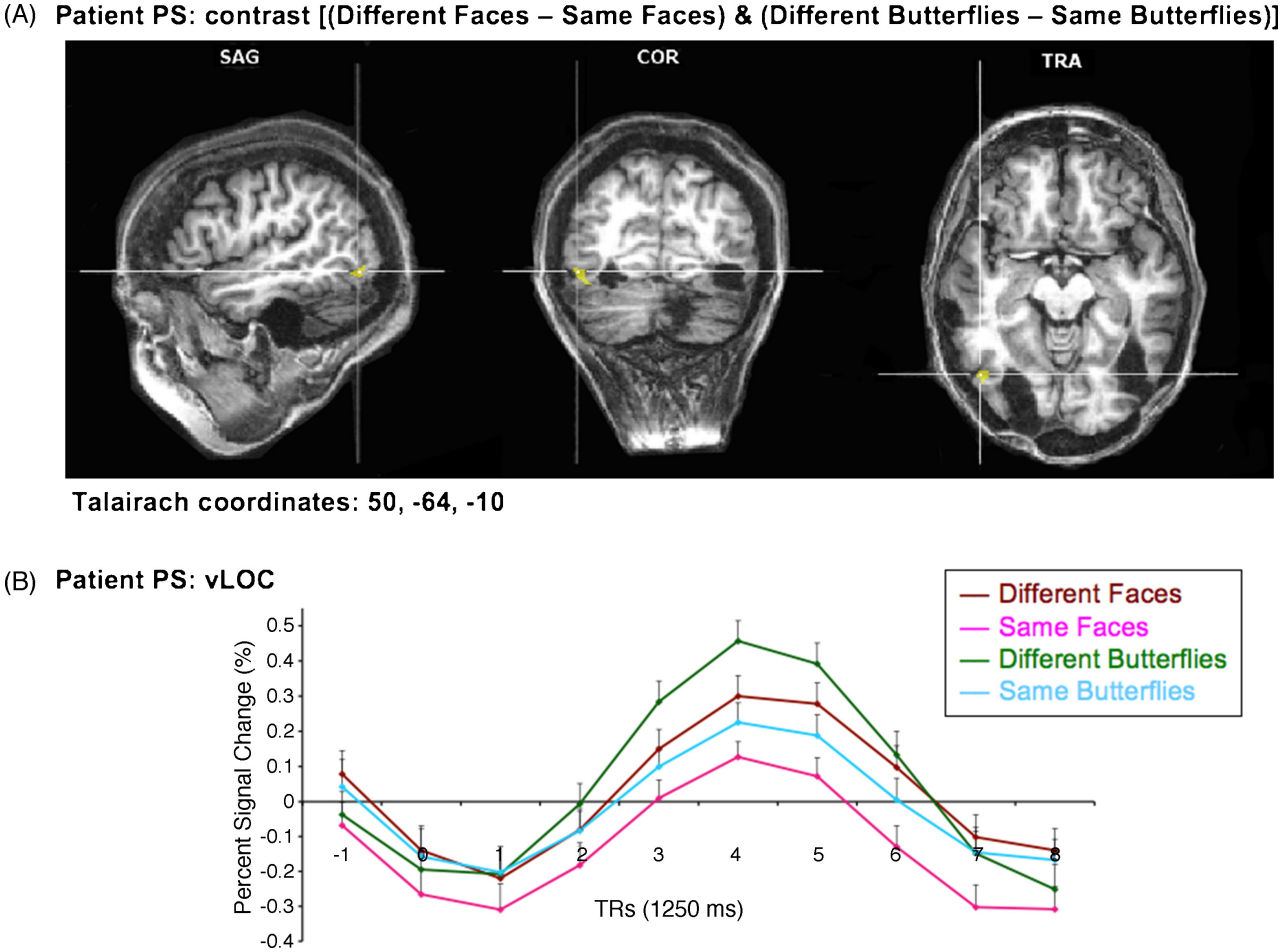


Figure 5. 5. Event-related average time courses for the four experimental conditions in the study in a whole brain analysis for patient PS with the conjunction of two contrasts: [(different faces versus same faces) and (different butterflies versus same butterflies)]. Significant release from face identity adaptation was found in patient PS in an area adjacent to her right inferior occipital lesion, corresponding to the ventral part of the lateral occipital complex [Talairach coordinates: 50, −64, −10; 506 voxels at p(uncorrected) < 0.045]. The same analysis did not reveal any activation in patient DF.

This cluster is not specific to faces and responds even more to objects than to faces [contrast ([different butterflies + same butterflies] versus [different faces + same faces]), $t = 2.758$, $p < 0.0059$]. This indicates that patient PS recruits an area that does not respond preferentially to faces, the vLOC, to differentiate face identities. Importantly, this effect is not specific to patient PS—when the vLOC is localized independently in normal observers, this region also shows a larger response to different exemplars than same exemplars, irrespective of the category. This has been observed in several studies with normal observers (Avidan et al., 2002, Grill-Spector et al., 1999 and Sayres and Grill-Spector, 2006), as well as for both faces and

objects in individual normal subjects tested with the paradigm used in the present study, in which the vLOC was localized independently (Dricot et al., 2008). Hence, the sensitivity to different individual faces in the vLOC of patient PS appears to reflect a residual rather than a compensatory mode of processing the individual face.

In contrast, there was no evidence for any identity adaptation effects in patient DF's brain for faces or butterflies, consistent with her general visual form agnosia.

3.5.5. Conclusions

Within the network of occipitotemporal areas that respond preferentially to faces, our two acquired prosopagnosia patients present a common lesion site encompassing the right 'OFA'. Each of the other components of the network was intact either in one of the patients (left 'OFA' for PS; left 'FFA' for DF), or in both patients' brain (right pSTS and 'FFA'). The preferential activation for faces in the two patients was in the normal range in terms of amplitude and spatial extent, even though the large variability in patterns of activation in the healthy control participants may mask minor abnormalities at this level. That is, one can never rule out the possibility that without the lesions to other face-sensitive regions (e.g., the right 'OFA'), the level of activation in response to faces in the other components of the network might have been higher in these patients. Nevertheless, these findings strongly support the notion that, in addition to the right middle fusiform gyrus (Barton, Press, Keenan, and O'Connor, 2002), a critical site implicated in prosopagnosia is located in the inferior occipital cortex in the right hemisphere, in the vicinity of the right 'OFA' (Bouvier and Engel, 2006). Moreover, these data indicate that the 'OFA', whether it is located in the right or left hemisphere, does not constitute a stage of processing that necessarily has to precede and send input to the rest of the face cortical network in order for those higher areas to be activated.

This observation casts doubts on a hierarchical view of face processing, advocated in several papers (Haxby et al., 2000 and Ishai, 2008; see also Jiang et al., 2006 and Pitcher et al., 2008). Rather, these data support the view that there must be direct connections from early visual areas that do not show preferential sensitivity to faces, to the middle fusiform gyrus and possibly the pSTS, leading to face-preferential responses in those areas (Rossion, 2008).

This hypothesis is not novel, but is reinforced by the present data and by previous observations made by two groups of independent researchers with these patients. The key observation of the present study, however, is the lack of release from adaptation to face identity in the 'FFA' of both patients DF and PS. This is consistent with previous findings observed in patient PS (Dricot et al., 2008 and Schiltz et al., 2006). Behaviourally, both patients present strong impairments at individualizing faces, and they do not show the release from adaptation to face identity that is observed in the healthy control participants both in the present experiment and in numerous other studies (e.g., Gauthier et al., 2000b and Grill-Spector and Malach, 2001). Taken together, this strengthens the notion that the right 'OFA' – the two patients' common missing region within the cortical face network – is an integral component of the network for processing face identity (Gauthier et al., 2000a), and is necessary for this function. Its role within this network may not be to precede the preferential activation for faces at the level of the FFA but rather its role in face identity processing, in particular in the right hemisphere, may be to contribute to the refinement of the face representation, following the initial categorization of a face in the "higher-order" right 'FFA' (Rossion, 2008). This reverse hierarchical view (Hochstein and Ahissar, 2002) of face perception is consistent with the presence of massive cortical bi-directional connections (Felleman and Van Essen, 1991) and the hypothesis of reentrant phasic signaling between areas of visual cortex ([Edelman, 1978] and [Edelman, 1993]). In a similar vein, a number of authors have suggested that higher level perceptual computations and representations that require high resolution details, fine geometry and spatial precision may involve lower visual areas through

feedback connections (Bullier et al., 2001, Galuske et al., 2002, Mumford, 1992 and Lee et al., 1998). For the recognition of face identity, refinement in the initial coarse face representation would require the high resolution details both at the level of the face features and of its configuration (Sergent, 1986).

Despite presenting a common lesion in the right inferior occipital cortex that is most likely critical in causing their face processing impairment (Bouvier and Engel, 2006), patients PS and DF do not present the same neuropsychological profile. While patient DF has a visual form agnosia, and is unable to recognize common objects (Milner et al., 1991), patient PS does not present any difficulty in recognizing objects, whether they have to be identified or discriminated at the basic-level or at more fine-grained categorization levels (Rossion et al., 2003a and Schiltz et al., 2006). Consistent with these behavioural differences, patient DF has bilateral damage to the lateral occipital area (LO, James et al., 2003), while this region is both structurally and functionally intact for patient PS (bilateral dorsal LO and right ventral LO, Sorger et al., 2007). Moreover, patient PS' area LO shows a larger response to normal shapes compared to scrambled shapes (Sorger et al., 2007), and it also shows release from adaptation to the repetition of the same object shape (Dricot et al., 2008; the present study).

In addition, we note that while patient PS showed a significant release from adaptation in the right 'FFA' to object shapes, patient DF did not. This is an interesting observation because patient DF is able to discriminate some non-face stimuli, particularly natural objects such as fruits and vegetable based on surface properties such as colour (Humphrey et al., 1994), yet her right 'FFA' did not show release from adaptation in this condition. This suggests that the positive adaptation effect observed for patient PS in the 'FFA' for objects (Dricot et al., 2008) may not be attributable to a simple release from adaptation driven by colour alone.

Further to these differences in object recognition, the two patients are not equally strongly impaired with respect to face processing. Patient DF is severely impaired in individual face

discrimination, scoring generally at chance levels (Steeves et al., 2006). Patient PS, however, is impaired relative to controls but nonetheless performs well above chance levels in individual face discrimination tasks ([Rossion et al., 2003a] and [Schiltz et al., 2006]). Previous studies have shown that patient PS relies on suboptimal cues to discriminate and recognize individual faces (e.g., the mouth and lower external contour; Caldara et al., 2005), and appears to analyze each facial feature consecutively, in detail, rather than resorting to an efficient holistic processing of the individual face, as do normal observers (Orban de Xivry, et al., 2008). The imaging data for patient PS collected previously (Dricot et al., 2008) and that in the present study suggest that this sub-efficient, analytical mode of processing the individual face does not rely on areas responding preferentially to faces, but may involve more general processes in the ventral part of the lateral occipital complex.

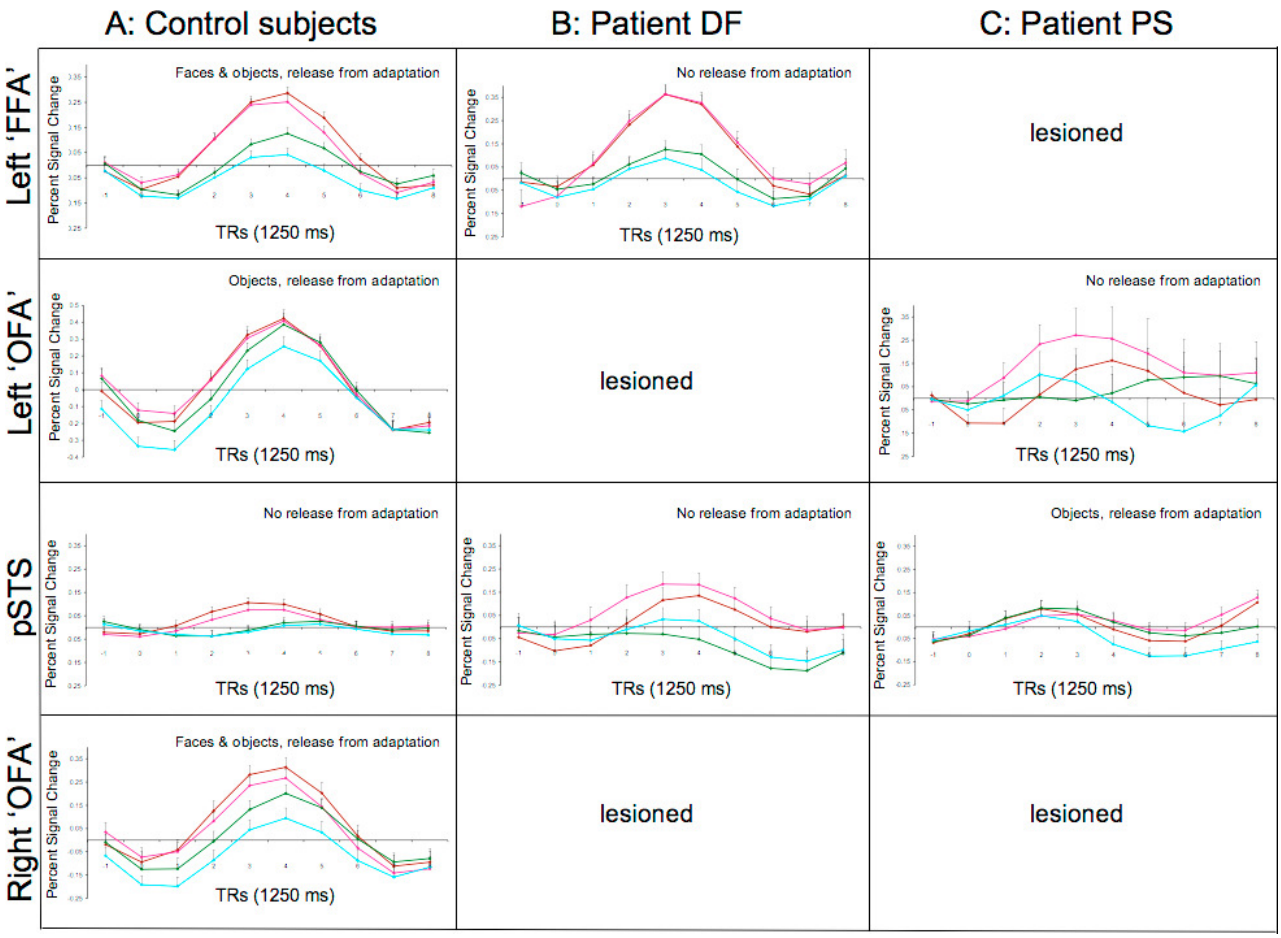
Another original aspect of the present experiment lies in the fact that while patient DF's face-preferential regions in the middle fusiform gyrus ('FFA') were reported previously in a block design face localizer experiment (Steeves et al., 2006), this is the first time that this face specific-activation is reported in an ER design, limiting the putative role of top-down influences on the activation of the 'FFA'. This is an important observation, since it is known that the 'FFA' can be modulated and activated through top-down processes, for instance through visual imagery of faces (O'Craven and Kanwisher, 2000) or recognizing the voices of familiar people (von Kriegstein et al., 2005). In the kind of paradigm used here, the participant does not know in advance which stimulus category will be presented (pair of faces or objects) and thus anticipatory top-down processes cannot account for the differential activity observed in these areas. A further novel aspect of the present study is that we used a different category for the contrast compared to the previous study with patient DF (Steeves et al., 2006). Here we define these areas by contrasting faces with objects while the previous study contrasted faces with scenes.

In summary, the present study compared functional brain activation in two unique brain-damaged patients who both suffer from acquired prosopagnosia. The findings strengthen the critical role of the right inferior occipital cortex, in the vicinity of the right 'occipital face area', in acquired prosopagnosia (Bouvier and Engel, 2006 and Sorger et al., 2007). Damage to this region does not prevent overall face sensitivity within the right middle fusiform gyrus ('FFA'), thus arguing against a strict hierarchical view of face processing in the human brain. However, right 'OFA' damage does appear to prevent the differential sensitivity of the 'FFA' to different face identity, suggesting a reentrant role of the right 'OFA' in extracting fine-grained individual representations of faces in the normal brain.

Acknowledgements

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Supplementary materials



Supplementary Figure 5. 1. Event-related average time courses within other face sensitive regions for patients PS, DF and controls for the four experimental conditions of the study (red : difference faces, purple : same faces, green : different butterflies, blue: same butterflies.

3.6. Granger causality mapping in a brain-damaged prosopagnosic patient incompatible with a feedforward hierarchical model of the face recognition[55]

3.6.1. Introduction

Pictures of faces activate preferentially three high-level visual areas of the human brain: in the lateral part of the middle fusiform gyrus (the so-called 'fusiform face area', 'FFA'), the inferior occipital gyrus ('occipital face area', 'OFA') and the posterior part of the superior temporal sulcus (pSTS) [for reviews, see (Haxby et al., 2000)]. A number of neuroimaging, mostly functional magnetic resonance imaging (fMRI) studies have been investigating the nature of face representations and processes in these areas over the past ten years. However, the functional relationships between these areas during face processing remain unclear. Haxby (Haxby et al., 2000) originally proposed the most posterior region, the 'OFA', as being the front-end of the neuro-functional architecture of face processing, feeding forward to both the 'FFA' and pSTS (Figure 6. 1).

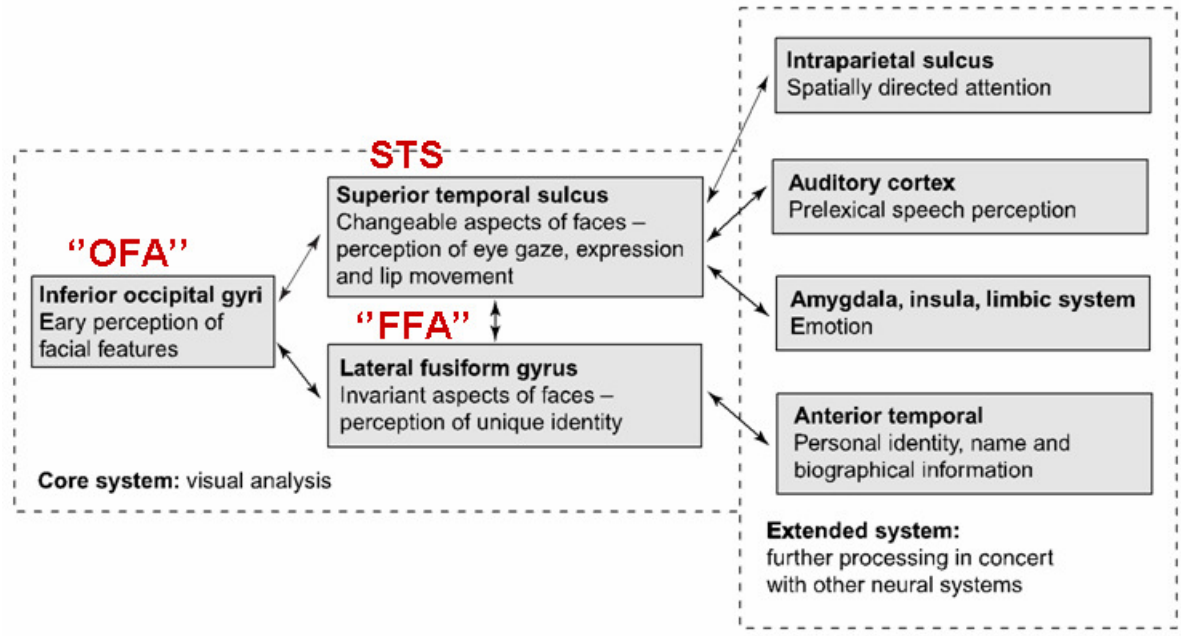


Figure 6. 1. (from Haxby et al., 2000). Hierarchical feedforward view of face processing in the ventral visual stream.

55 Cette section est un article en préparation avec le même titre de Laurence Dricot, Rainer Goebel et Bruno Rossion.

Supporting evidence come from the modelization of effective connectivity by means of dynamic causal modelling (DCM ; Friston et al., 2000) revealing exclusive feedfoward outputs from the 'OFA' to the 'FFA' and pSTS within the core aspect of the face perception model (Fairhall and Ishai, 2007). TMS to the 'OFA' also impairs processing of facial parts in faces if it is applied early on (dual pulses, 60-100 ms, Pitcher et al., 2007). However, the interpretation of these findings is problematic, in particular because of the 'OFA' definition in these studies. For instance, Fairhall and Ishai (2007) as well as Eger et al. (2004b) defined the 'OFA' as a large area of the occipital cortex responding more to faces than scrambled faces (F-SF). The domain-preference or specificity of this area is unknown in these studies, and according to our observations, it should not have been labeled an 'OFA' because it encompasses the whole LOC (LOC, Grill-Spector and Malach, 2004; Malach et al., 1995) at least. Thus, it is not surprising that other fMRI studies using DCM have found opposite results than Fairhall and Ishai (2007) with stronger outputs from 'FFA' to 'OFA' than the opposite ('OFA' to 'FFA') during face processing (Rotshtein et al., 2007 who had defined the 'OFA' in contrasting high and low spatial-frequency components in faces). Similarly, Pitcher et al. (2007) defined the 'OFA' based on an average coordinate of previous studies, ignoring the large amount of interindividual variance in terms of 'OFA' localization. More recent TMS evidence collected after individual definition of the 'OFA's rather suggests that the early contribution of the 'OFA' to face perception is general, with a later response carrying specific information about faces (Pitcher et al., 2009).

The hierarchical feedforward view of face processing in the ventral visual stream has also been challenged by the case report of a brain-damaged patient, PS, who presents a preferential activation for faces in the right hemisphere 'FFA', despite a lesion encompassing completely the territory of the right 'OFA'. These observations, which have been replicated several times with the patient PS (Schiltz et al., 2006; Sorger et al., 2007; Dricot et al., 2008) and in another brain-damaged case (Steeves et al., 2006, Steeves et al., 2010) are incompatible with a feedforward

hierarchical view in normal subjects during face processing. Rather, they suggest either that the 'FFA' and 'OFA' can respond referentially to faces independently (e.g. following inputs from early visual areas) in the normal brain, or that the 'FFA' may be the first activated area that respond preferentially to faces, feeding back the posterior visual cortex to elicit face-preferential activation at this level [the 'OFA', see (Rossion et al., 2003a)].

In a recent detailed investigation of the functional neuroanatomy of the patient PS using multiple face localizer scans with a 3T scanner, we observed multiple preferential activations for faces in her visual cortex, besides the right 'FFA' (Sorger et al., 2007). More specifically, face-activation was found in the right pSTS, and in a posterior area of the left hemisphere which may correspond to the left 'OFA'. This observation raises the intriguing possibility that the face-related activation found in the right hemisphere of the patient ('FFA' and pSTS) may originate from posterior areas of the other hemisphere, such as the left 'OFA', through callosal connections. Here we tested this idea with a non a-priori effective connectivity and exploratory approach of mapping influences between a region of interest (the 'FFA') and the rest of the brain based on Granger causality (Roebroeck et al., 2005). This method could be help to decide if the 'FFA' could respond following inputs from early ipsi lateral visual areas independently of a feedforward 'OFA'-'FFA' way.

3.6.2. Materials and methods

3.6.2.1. Subjects

The prosopagnosic patient PS has been already described in detail in Rossion et al., 2003a [see also (Caldara et al., 2005; Schiltz et al., 2006; Sorger et al., 2007)]. Briefly, PS was born in 1950 and sustained a closed head injury in 1992 that left her with extensive lesions of the left mid-

ventral (mainly fusiform gyrus) and the right inferior occipital cortex. Minor damages to the left posterior cerebellum and the right middle temporal gyrus were also detected.

At the level of the white matter, PS did not seem however to present any lesion within the inferior longitudinal fasciculus (ILF). By combining the data from DTI (Figure 6. 2 and 6.3.) and fMRI to localize in particular the ‘FFA’ (see supplementary methods), we expose the ILF is a possible anatomical pathway from the early visual areas to the 'FFA' (Figure 6. 4). Indeed, this region is normaly activated despite of the absence of the ‘OFA’ in the inferior occipital gyrus and also the interruption of the hierachal stream consisted in a lack of short associative fibers.

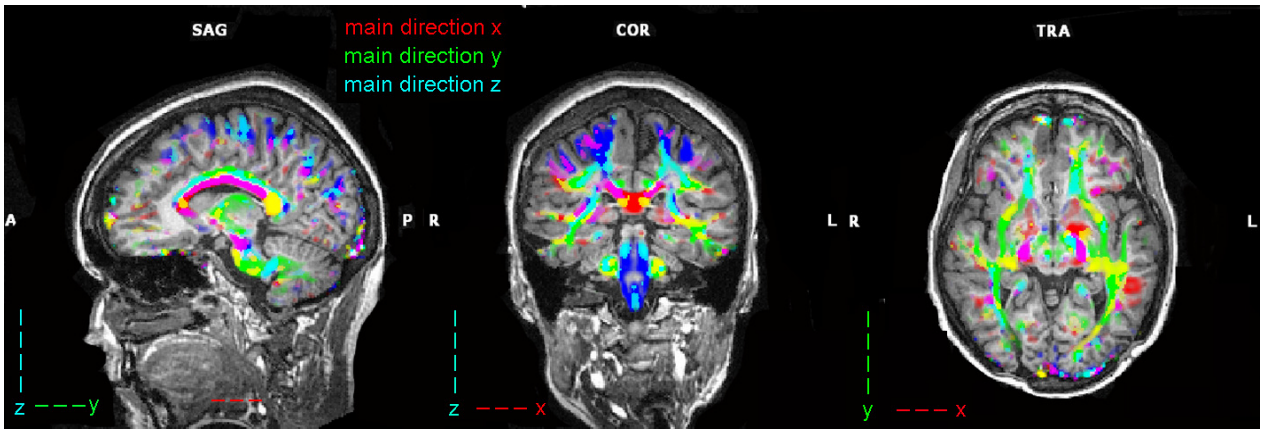


Figure 6. 2. Fractional Anisotropy (FA) maps in PS’s brain. Only directions with a FA more than 0.20 are represented.

3.6. Granger causality mapping in a brain-damaged prosopagnosic patient incompatible with a feedforward hierarchical model of the face recognition

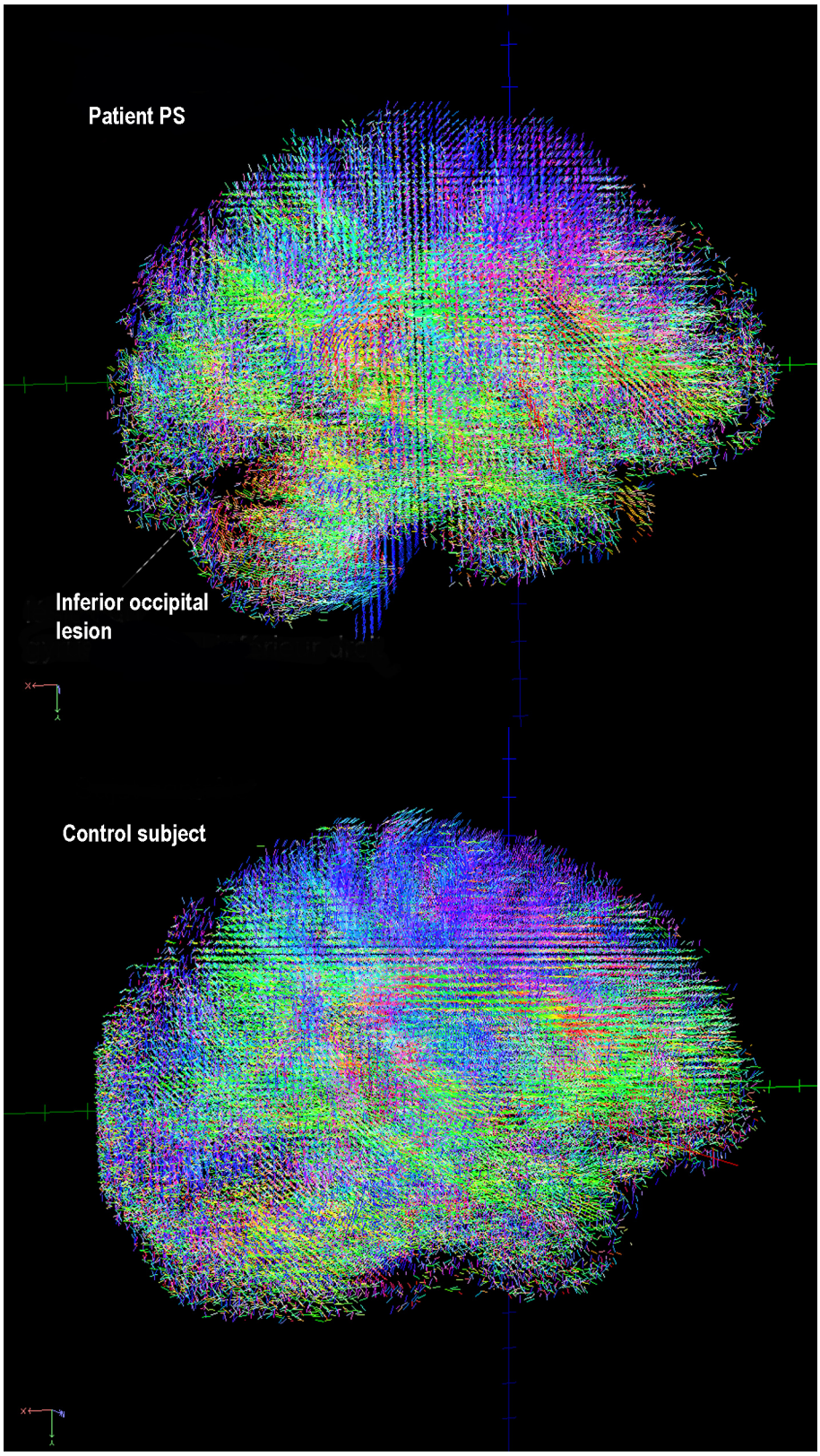


Figure 6. 3. Tridensional representation of FA values of the patient PS and a control woman of 24 years. PS's lesions in the inferior occipital gyrus is well illustrated by the absence of FA (i.e water molecules are moving freely in a unordered fashion) that is colored in black (the lesion in the right temporal gyrus is also slightly visible). It must be noted that we could not properly compare FA and MD values between the subjects because of their sensitivity to age difference (Thomas and al., 2008).

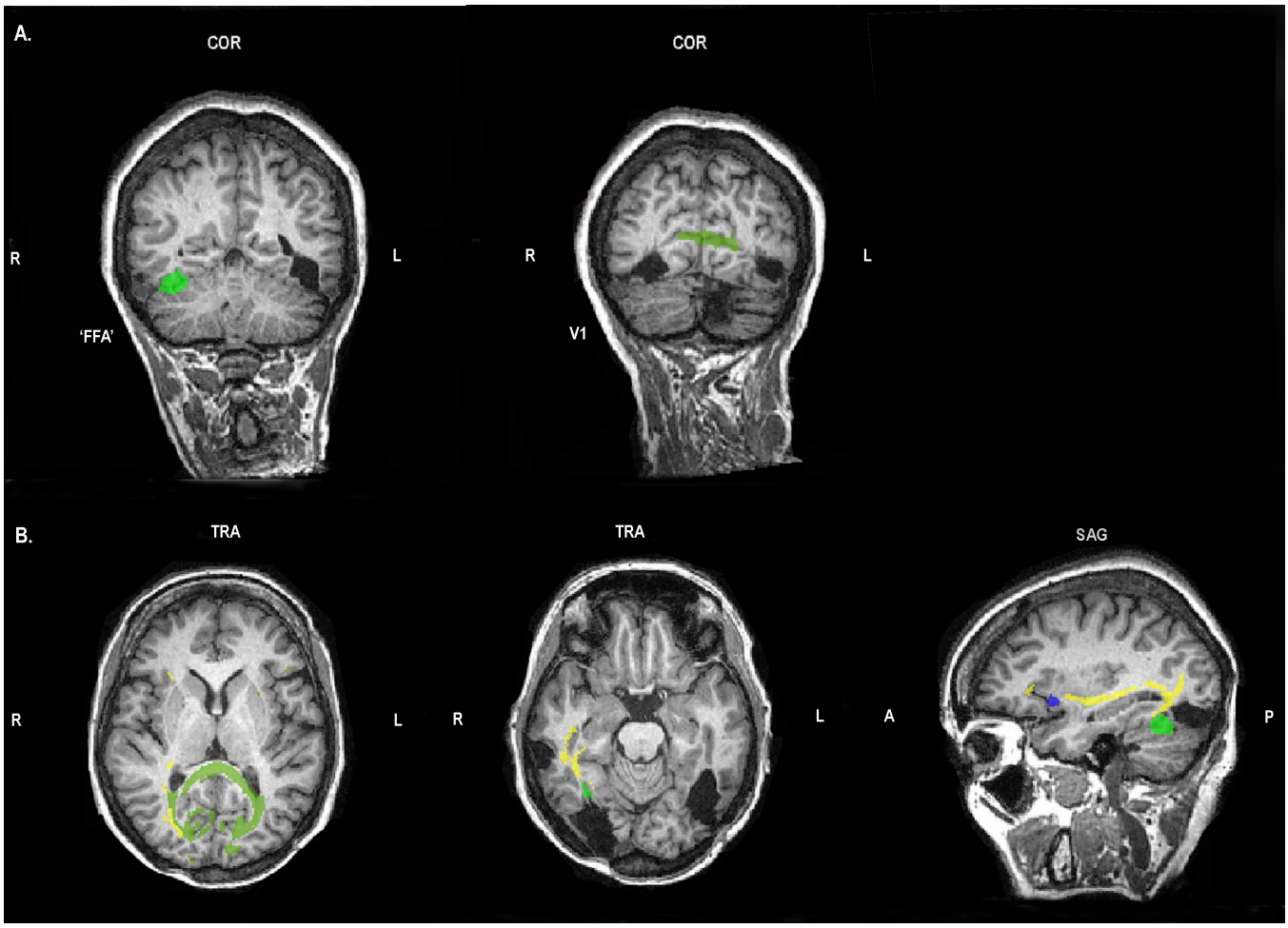


Figure 6. 4. A. Regions of interest (in green) from which the anatomical pathway was tracked. The 'FFA' (left coronal view) was functionally defined by the conjunction of the contrasts Faces minus Scrambled faces and Faces minus Objets (F-SF : $p<0.000001$ et F-O : $p< 0.00001$). The early visual areas zone (right coronal view) was defined anatomically around V1 (F-O $p = 0.67$) and V2. **B.** The early visual areas join the 'FFA' through the ILF (left transversal view, yellow beam; in green, tracking since V1 of the corpus callusum), as described by Catani and al. (2003). The ILF extends up to the anterior temporal lobe (right transversal view). The inferior occipito-frontal beam (yellow beam, sagital view) connects with the early visual areas and extends up to a face cluster of the lower frontal lobe (blue region, F-SF : $p < 0.000001$ and F-O : $p < 0.000006$).

After medical treatment and neuropsychological rehabilitation, PS recovered extremely well from her cognitive deficits following the accident. Her only continuing complaint remains a profound difficulty in recognizing familiar faces, including those of her family when they are presented out of context. To determine a person's identity, she relies on external (non-face-inherent) cues such as haircut, moustache or glasses, but also on the person's voice, posture, gait, etc. She may also use sub-optimal facial cues such as the mouth or the external contour of the face to recognize faces, and is particularly impaired at extracting diagnostic information from the eyes of the face (Caldara et al., 2005). Effectively, PS is like normal subjects (100%, fast) to discriminate faces from other objects but is impaired and slowed down to recognize faces at the individual level

(Schiltz et al., 2006). The Benton Face Recognition Test (BFRT) (Benton and Van Allen, 1972) ranks her as highly impaired, and in addition her score at the Warrington Recognition Memory Test (WRMT) (Warrington, 1984) for faces characterizes her as significantly less accurate as controls [see Table 1 in (Rossion et al., 2003a)].

On the other hand, PS does not present any difficulty in recognizing objects, even at the subordinate level (Rossion et al., 2003a; Schiltz et al., 2006). Her visual field is almost full (small left paracentral scotoma) and her visual acuity is good (0.8 for both eyes as tested in August 2003).

Beside PS, 8 right-handed participants [age=23.83 +/- 2.80; 2 women; Edinburgh Inventory (Oldfield 1971)] were also tested. None of them had a history of neurological or vascular disease, head injury or alcohol abuse, nor did they display cognitive complaints. The participants gave their informed written consent prior to the fMRI experiments.

The study was conformed to the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Department of the University of Louvain. Control subject and PS proved to be strongly right-handed according to the Edinburgh Inventory (Oldfield, 1971).

3.6.2.2. Stimuli and procedures

Granger Causality Mapping

Granger Causality Mapping (Roebroeck et al., 2005) has been proposed as an approach to explore directed influences between neuronal populations (effective connectivity) in fMRI data. This approach uses vector autoregressive modeling of fMRI time series in the context of Granger Causality (Granger, 1969). Ordinarily, regressions reflect “mere” correlations, but Granger argued that there is an interpretation of a set of tests as revealing something about causality. A time-series X[t] is said to Granger cause a time-serie Y[t] if it can be shown, usually through a series of F-Tests on lagged values of X (and with lagged values of Y also known), that those X values provide statistically significant information on future values of Y or to say easier if the past of X improves

the prediction of the current value of Y, given that all other sources of influence (as the Y's own past) have been taken into account. The test works by first doing a regression of ΔY on lagged values of ΔY. Once the appropriate lag interval for Y is proved significant subsequent regressions for lagged levels of ΔX are performed and added to the regression provided they are 1) significant in off themselves and 2) add explanatory power to the model. More than 1 lag level (auto regression order) can be included in the final regression but at the more realistic sample rates for whole-brain fMRI (1000 to 1250 ms; 3T tesla scanner) the optimal order is almost exclusively 1.

In short, in BrainVoyager QX (Version 2.2, Brain Innovation, Maastricht, The Netherlands), Granger Causality Maps (GCMs) are computed with respect to a single selected reference region (here the 'FFA') and maps the sources of influence to that region and targets of influence from that region in every voxels of the brain. Three terms are computed: the influence from the 'FFA' to every voxels (RefVox), the influence from every voxels to the 'FFA' (VoxRef) and the instantaneous correlation between the 'FFA' and every voxels without direction (Inst). In Roebroeck et al., (2005), it is said that the most unbiased view on directed interactions is given by the difference (RefVox-VoxRef) (= the dGCM) which has positive value for voxels where influence from the 'FFA' dominates and a negative value for voxels where influence to the 'FFA' dominates[56]. The great advantage of that method is that temporal information in the data is used to define the existence and the direction of influences WITHOUT a directed graph model of assumed regional connections against other effective connectivity methods requiring preselection of the interactive regions and assumptions about the existence and direction of influences between the regions (as in Fairhall and Ishai, 2007). Also, this method is not ambiguous as other model-free approaches which investigate the correlation between measured time course of different brain area (functional connectivity, see Friston et al., 2003) WITHOUT possible assumptions about the sense of influence.

[56] The value is influenced by the strength and the speed of the relation between each voxels and the 'FFA'.

Granger Causality Maps (GCMs) were computed for the 'FFA' in the following experiment:

Stimuli

Four categories of stimuli were used: photographs of Faces, Cars, and their phase-scrambled versions: Scrambled Faces and Scrambled Cars (Figure 6. 5).

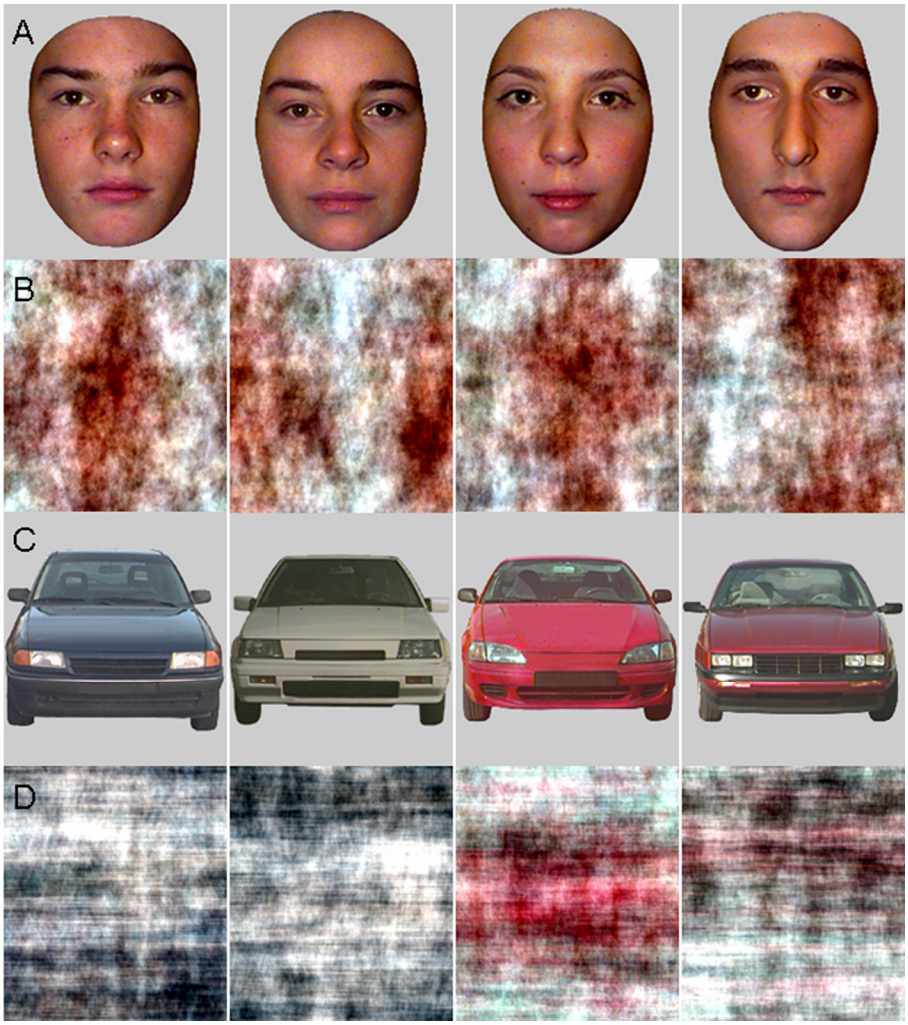


Figure 6. 5. Stimuli: Faces (A), Cars (C), and their phase-scrambled versions: Scrambled Faces (B) and Scrambled Cars (D).

The Face condition consisted of 43 pictures of faces (22 females) cropped so that no external features (hair, etc.) were revealed. All the faces were shown in frontal view. There were inserted in a grey rectangle to form a rectangular image (Figure 6. 5). Similarly, the Car condition consisted of 43 pictures of different cars in a full-front view also embedded in a grey rectangle. Faces and cars

were presented in colour and equalized in luminance. The scrambled stimuli were made using a Fourier phase randomization procedure [FFT with phase replaced by phase of a uniform noise (amplitude conserved in each frequency band (see e.g. Sadr and Sinha 2004)] that yields images preserving the low-level properties of the original image (i.e. luminance, contrast, spectral energy…), while completely degrading any category-related information (Figure 6. 5). Pictures of faces/cars and the phase scrambled face/car pictures subtended equal shape, size and contrast against background.

Paradigm

Participants performed three runs of 11 min 13 sec duration. In each run, there were 6 blocks of 18 sec duration for each of the 4 types of stimuli. Blocks were separated by a baseline condition (cross fixation) of 9600 ms. In each block, 24 stimuli of the same condition were presented (750 ms per stimuli, no ISI) on a black background screen, with 2 or 3 consecutive repetitions of the exact same stimulus in each block (target trials). This gave a total amount of 144 stimuli per category per run. The stimuli and the fixation cross were presented centrally, but stimulus location varied randomly in x (6%) and in y (8%) direction at each presentation (5.5° and 6.2° as visual angle degrees in the x and y direction, average location is centred). Participants performed a one-back identity task (two or 3 targets per block; 30 targets for each condition in total). Patient PS did the experiment two times (10 months between the two sessions).

Imaging acquisition parameters

Functional MR images of brain activity were collected using a 3T head scanner (Siemens Allegra, Siemens AG, Erlangen, Germany), with repeated single-shot echo-planar imaging: echo time (TE) = 50 ms, flip angle (FA) = 90°, matrix size = 64x64, field of view (FOV) = 224x224 mm², slice order descending and interleaved, slice thickness = 3.5 mm. Repetition time (TR) was 1250 ms, 19 slices. A three-dimensional (3D) T1-weighted data set

encompassing the whole brain was acquired to provide detailed anatomy (1 mm^3) thanks to aADNI sequence (TR = 2250 ms, TE = 2.6 ms, FA =9°, matrix size = 256 × 256, FOV = 256 × 256 mm^2, 192 slices, slice thickness = 1 mm, no gap, total scan time = 8 min 5.

Data analysis of the imaging experiments

The fMRI signal was analyzed using BrainVoyager QX (Version 2.2, Brain Innovation, Maastricht, The Netherlands). The same experiment was used as localizer and for GCM analysis. Prior to analysis, the functional data sets were subjected to a series of preprocessing operations. This preprocessing consisted of a linear trend removal for excluding scanner-related signal, a temporal high-pass filtering applied to remove temporal frequencies lower than 3 cycles per run, and a correction for small interscan head movements by a rigid body algorithm rotating and translating each functional volume in 3D space (Friston et al., 1995a,b). In addition to these preprocessing the data were also corrected for the difference between the scan times of the slices. This step is of crucial importance for GCM and should be performed before anything else in particularly before the 3D motion correction. No temporal smoothing was done to not deteriorate the temporal resolution of the data. All anatomical as well as the functional volumes were spatially normalized [Talairach-transformation (Talairach and Tournoux, 1988)] and the statistical maps computed were overlaid to the 3D T1-weighted scans in view to calculate Talairach coordinates for all relevant activation clusters. All coregistrations were done manually and the corrections of the movement were optimized (sinc interpolation) but one of the 8 subjects had to be excluded.

First, the functional data were analyzed using one multiple regression model (General Linear Model; GLM) consisting of predictors, which corresponded to the particular experimental conditions of the experiment. The predictor time courses used were computed on the basis of a linear model of the relation between neural activity and hemodynamic response, assuming a rectangular neural response during phases of visual stimulation (Boynton et al. 1996). In order to localize the 'FFA' (and the other clusters of the core system, Haxby et al., 2000), the conjunction of

the contrasts **[(F-O) and (F-SF)]** between the three runs was computed. This procedure ensured the control for both high-level and low-level differences between faces and objects and that activations identified were consistent across the three runs. The threshold was fixed at q(False Discovery Rate)<0.05.

Second, Granger Causality Maps (GCM) were computed for the 'FFA', more precisely for the 100 most activated voxels of the 'FFA'. As advised in Roebroeck et al., (2005), the size of the 'FFA' was kept small to avoid risk of loss of temporal details and avoid a large cluster of voxels activated in the same contrast but differently effectively connected]. After successful computation of the GCMs, the dGCMs for the face condition were masked with the thresholded (at p<0.02) instantaneous GCM to remove some of the observed vessels effects and thresholds for the dCGMs were computed thanks to a bootstrap method and a false discovery rate (Roebroeck et al., 2005). For the patient PS, the set of dGCMs were computed not only for the face condition but also for the SO condition not used in our contrast of localization. If the influence found in a dCGM for one condition is different from the influence in a dCGM for other condition, thus, that this influence is modulated by experimental conditions, the differences in structural hemodynamics are not the underlying reason for the influence found. The structural hemodynamic variation could not vary with the experimental conditions. Finally, the results of the dGCMs were plotted in the core system (right pSTS, right and left 'OFA' and left 'FFA' if they exist) and in one template of the early visual cortex non specific to faces and centred on V1 available in Brain Voyager QX (4792 voxels of 1*1*1 mm^3 around the calcarine).

3.6.3. Results

3.6.3.1. Patient PS

To isolate face-specific responses and remove any potential low-level visual difference between faces and nonface control stimuli, we contrasted faces *vs.* nonface objects in conjunction with the contrast faces *vs.* phase-scrambled pictures of faces. Consistent with previous observations, there were significant activations at [q(False Discovery Rate) < 0.05] to faces in the 'FFA' (36 -55 -22, 994 voxels and 39 -53 -22, 905 voxels for the 'FFA' in the first and second session) and pSTS (47 -63 6, 1080 voxels and 49 -62 7, 875 voxels for the pSTS in the first and second session) of the right hemisphere for PS. These areas were normal in size and anatomical location as previously reported for normal observers (e.g., Kanwisher et al., 1997; Gauthier et al., 2000a) and for PS (Rossion et al., 2003a; Sorger et al., 2007; Dricot et al., 2008). There was also a smaller significant activation in the left inferior occipital cortex for PS (-40 -74 -19, 256 and -38 -72 -22, 59 voxels for the left 'OFA' in the first and second session), as found in some previous studies of the patient (Sorger et al., 2007). In summary, the missing components of the core network (Haxby et al., 2000) of face preferential activation in PS' brain (left 'FFA' and right 'OFA') were areas located in structurally damaged tissue (Figure 6. 6)[57].

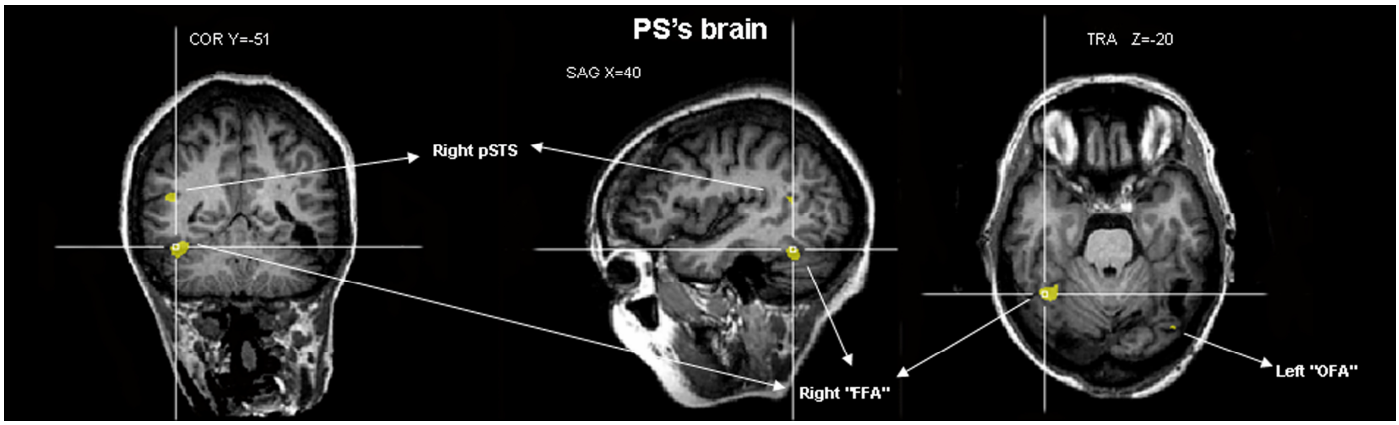


Figure 6. 6. Localisations of the face preferential activations in the patient PS's brain.

[57] There were other areas activated by the conjunction contrast, but unlike the FFA, OFA and pSTS they were not the focus of the present study.

Left 'OFA'

In the two different sessions, the left 'OFA' is influenced by the right 'FFA' during the face condition: 144 voxels on 256 (56.25%) in session 1 (Figure 6. 7) and 23 voxels on 59 (38.92%) in session 2 (Figure 6. 8) exceed the statistical significance [in the scrambled object condition we have only 43 (16.80%) and 7 voxels (11.86%) respectively (Figure 6. 9 and 10) and the direction of influence in the condition face is not due to the differences in structural hemodynamics]. No voxels of the left 'OFA' have influence on the right 'FFA'.

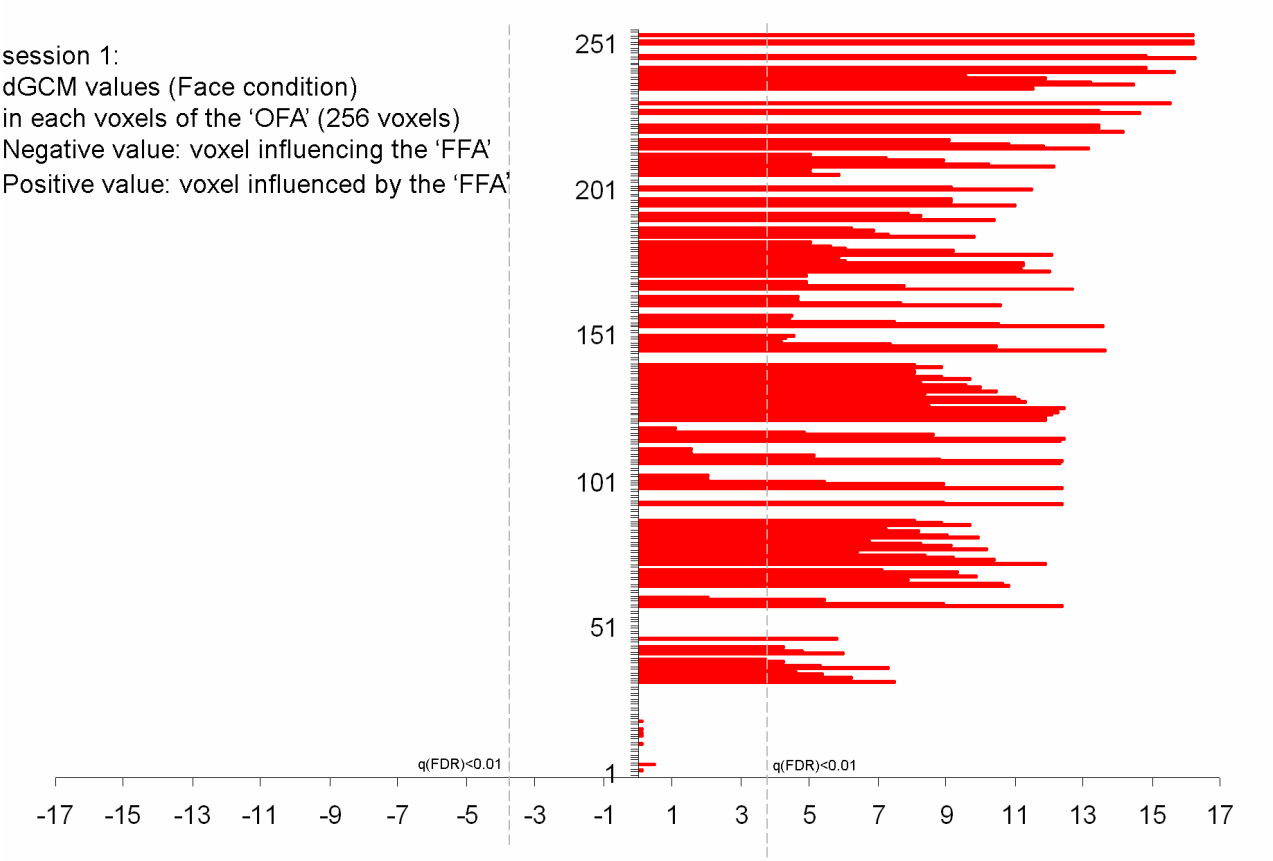


Figure 6. 7. In the functionnaly defined left 'OFA' (session 1), the major influence is from the 'right 'FFA' to the left 'OFA' when the patient PS has to process faces.

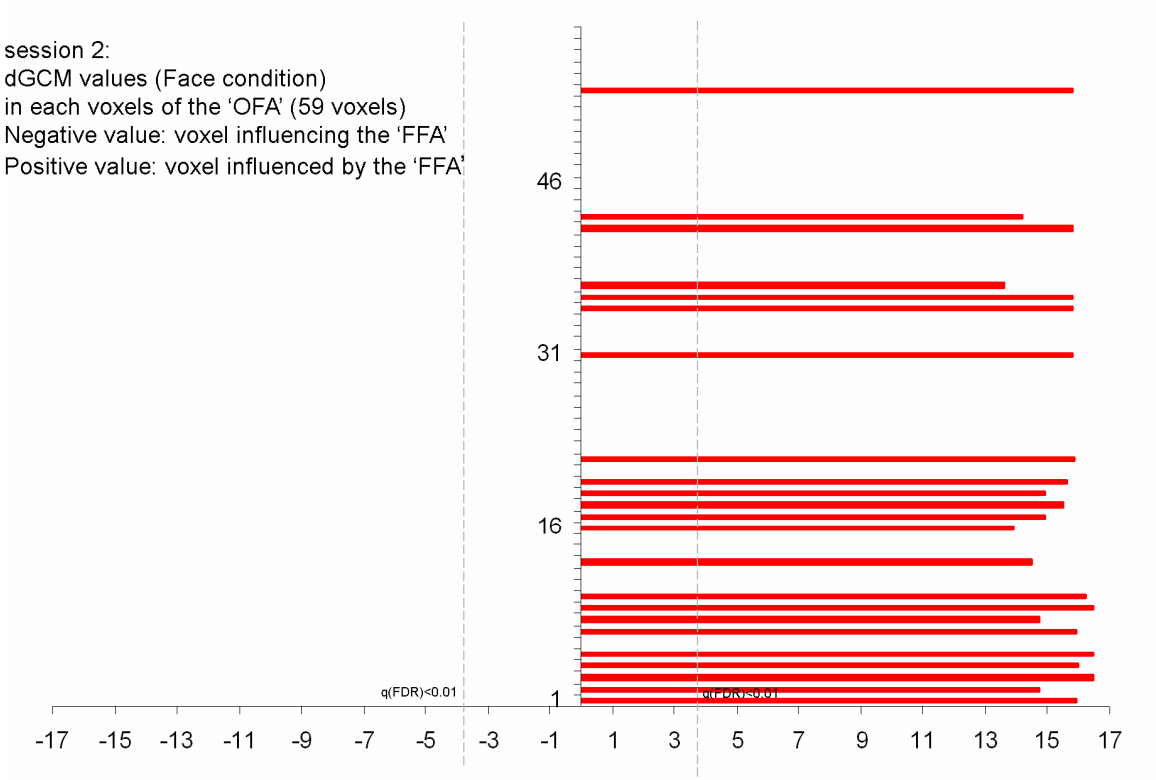


Figure 6. 8. In the functionally defined left 'OFA' (session 2), the major influence is from 'right 'FFA' to left 'OFA' when the patient PS has to process faces.

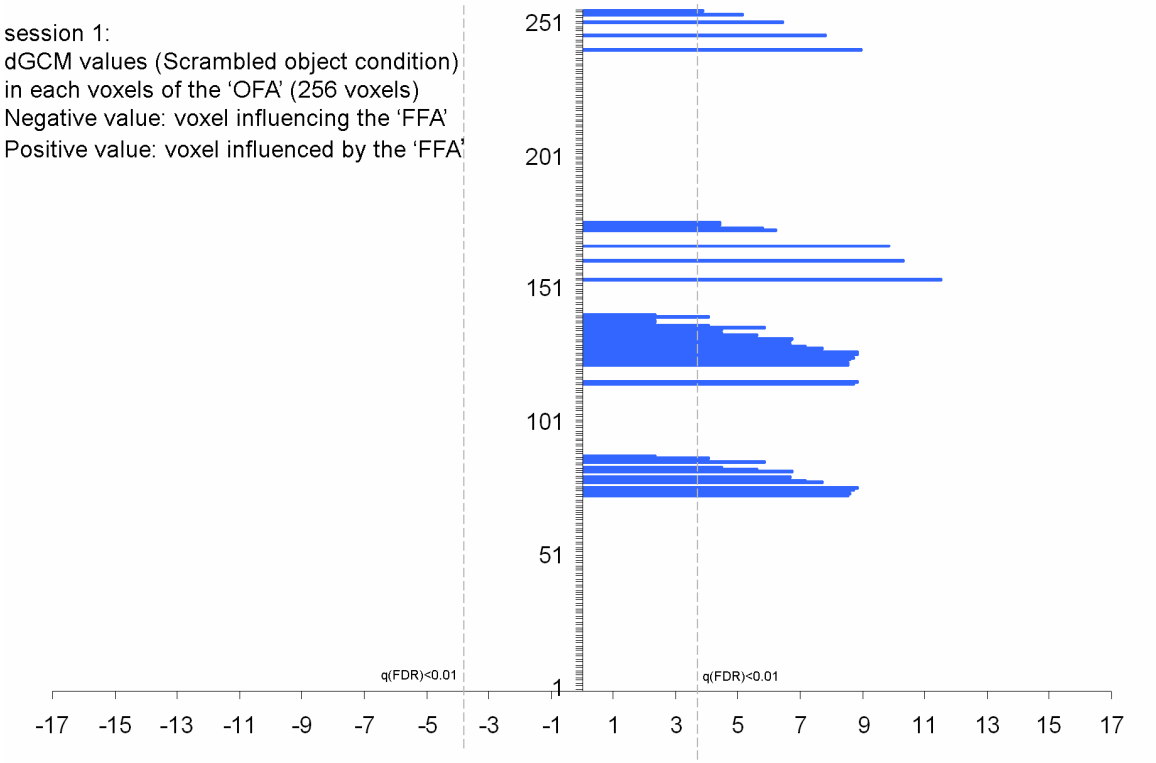


Figure 6. 9. When the patient PS has to process scrambled objects in the session 1 there is almost no exchange between the right 'FFA' and left 'OFA'.

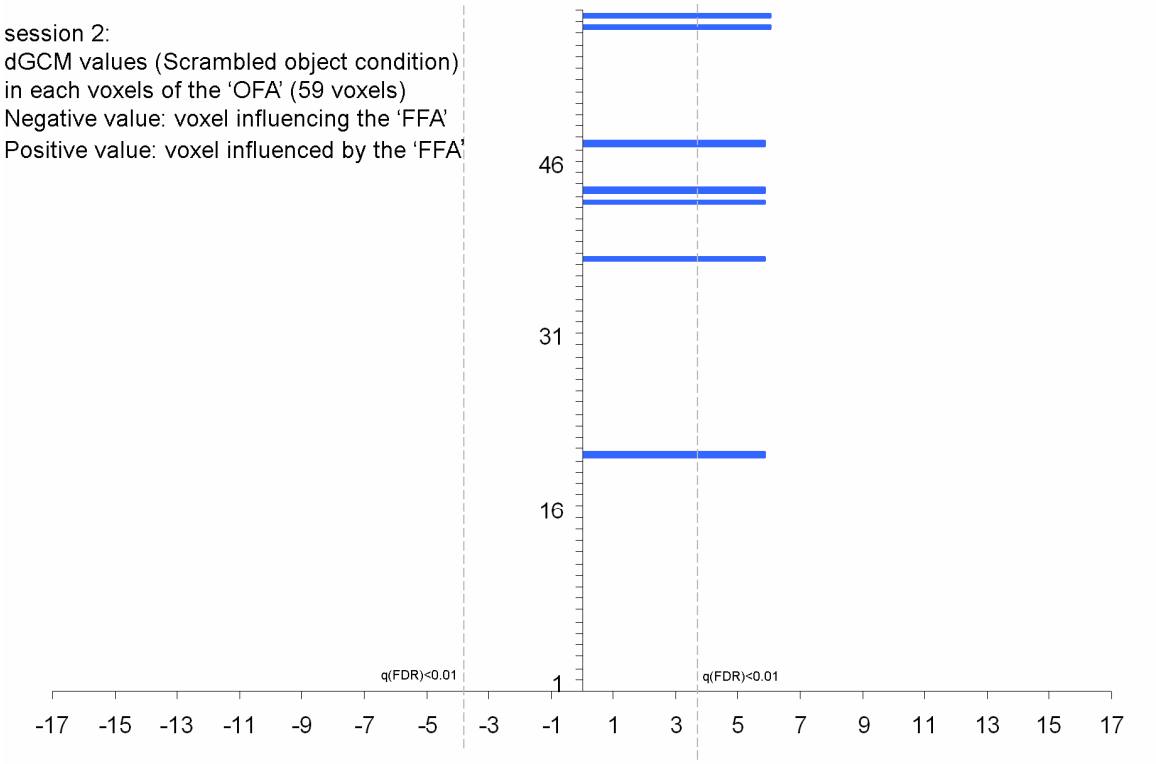


Figure 6. 10. When the patient PS has to process scrambled objects in the session 2 there is almost no exchange between the right 'FFA' and left 'OFA'.

pSTS

In the two different sessions, one part of the right pSTS is influenced by the right 'FFA' and one part is influencing the 'FFA' during the face condition. 49 voxels on 1080 (4.54%) in session 1 (Figure 6. 11) and 49 voxels on 875 (5.6%) in session 2 (Figure 6. 12) exceed the positive statistical significance (they are influenced by the 'FFA') and 44 and 118 respectively (4.10% and 13.49%) exceed the negative statistical significance (they influence the 'FFA'). In the scrambled object condition, we have no voxels reaching the significance.

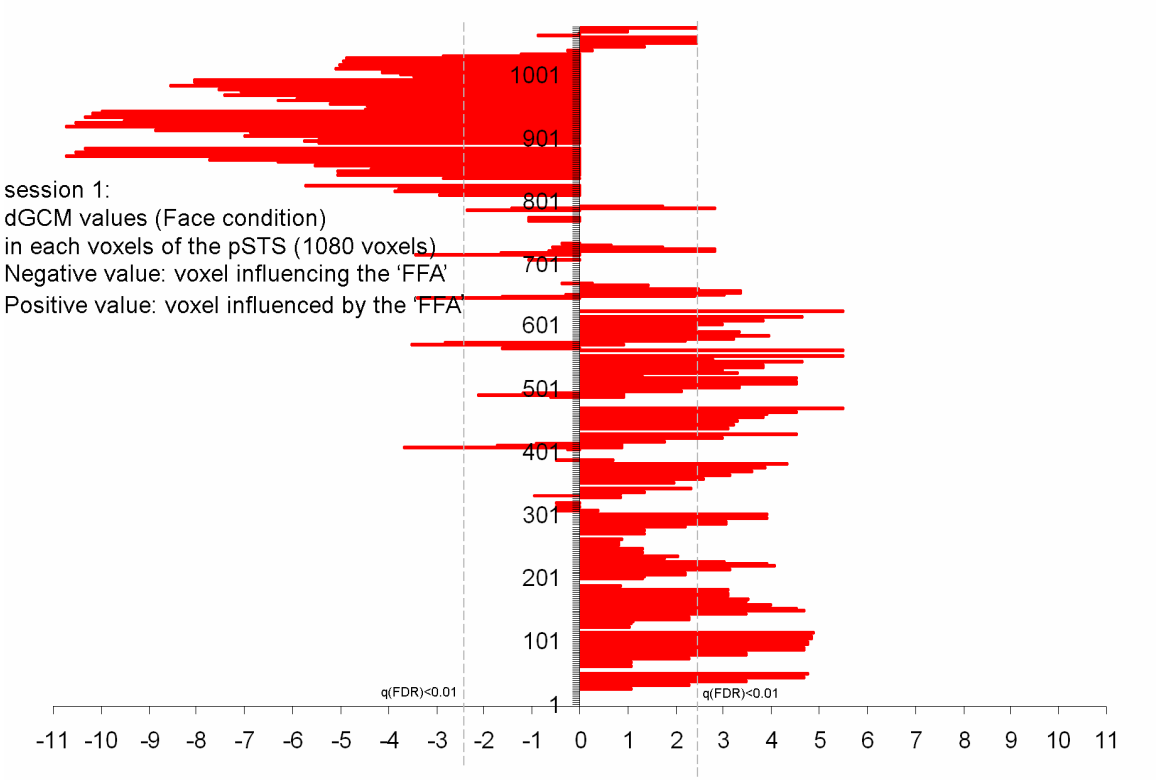


Figure 6. 11. In the functionally defined pSTS (session 1), there is a mutual influence between pSTS and 'FFA' when the patient PS has to process faces.

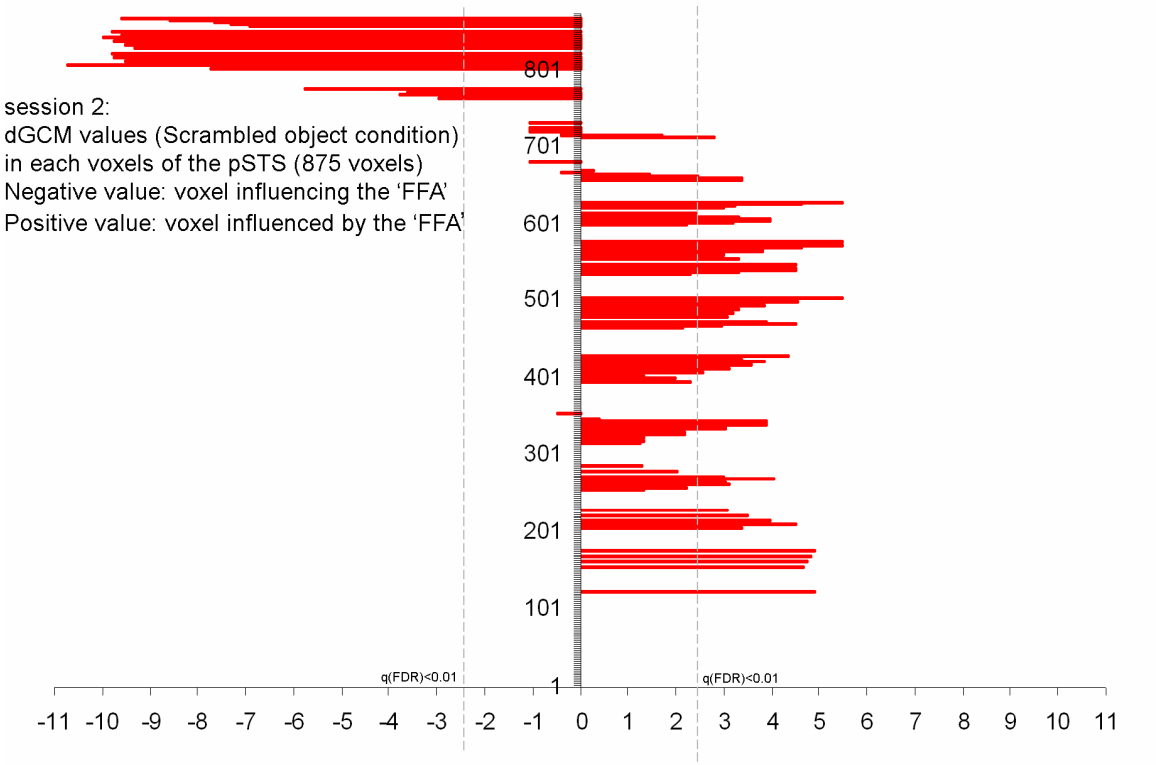


Figure 6. 12. In the functionally defined pSTS (session 2), there is a mutual influence between pSTS and 'FFA' when the patient PS has to process faces.

Early visual cortex around V1

The region (4792 voxels anatomically defined on one Brain Vogager brain template) is not a face region: the contrast F-O is not significant (0.7 and 0.06 in the session 1 and 2 respectively). However, the contrast SF-F is significant (0.0001 and 0.00001 in the session 1 and 2 respectively) maybe due to top-down selection or inhibition of non pertinent information or restriction to one part of the visual field. In the two different sessions, we can find some sub-clusters influencing the 'FFA' during the face condition. 59 voxels in session 1 (1.23%, Figure 6. 13) and 157 voxels in session 2 (3.27%, Figure 6. 14) exceed the negative statistical significance (they influence the 'FFA'). In the scrambled object condition, we have only 12 (0.003%) and 0 voxels respectively (Figure 6. 15 and Figure 6. 16) reaching the significance. We find also voxels influenced by the 'FFA' but the numbers of voxels is similar between the two conditions: 404 (8.43%, Face condition) and 424 (8.85%, Scrambled object condition) for the session 1 (Figure 6. 13 and Figure 6. 15) and 94 (1.96%, Face condition) and 89 (1.86%, Scrambled object condition) for the session 2 (Figure 6. 14 and Figure 6. 16).

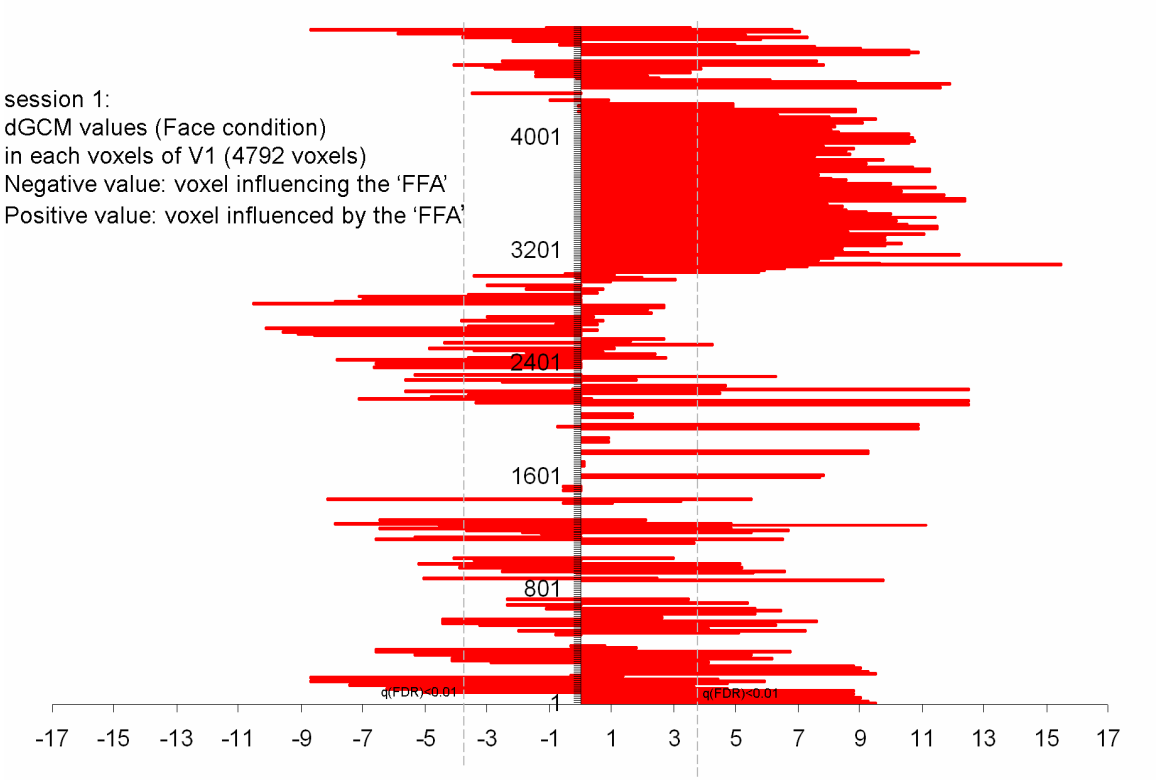


Figure 6. 13. In the anatomically defined V1 (session 1), we can find influence from that region on the right 'FFA' when the patient PS has to process faces.

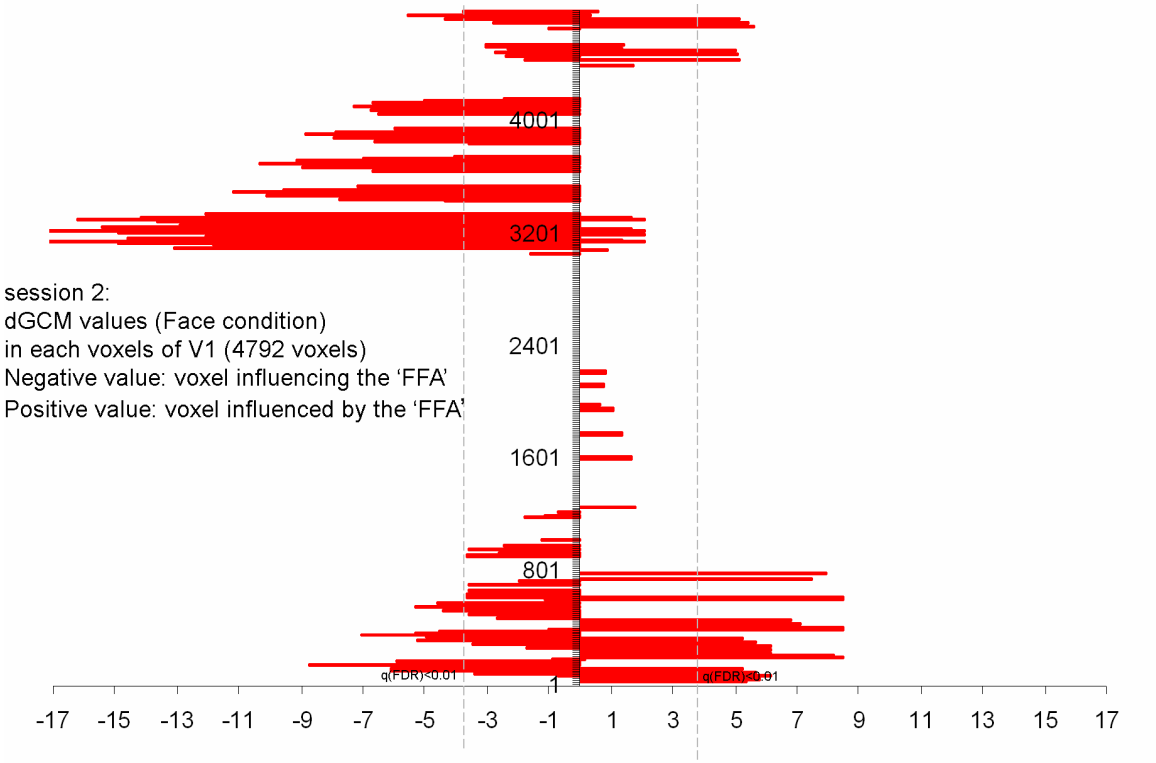


Figure 6. 14. In the anatomically defined V1 (session 2), we can find influence from that region on the right 'FFA' when the patient PS has to process faces.

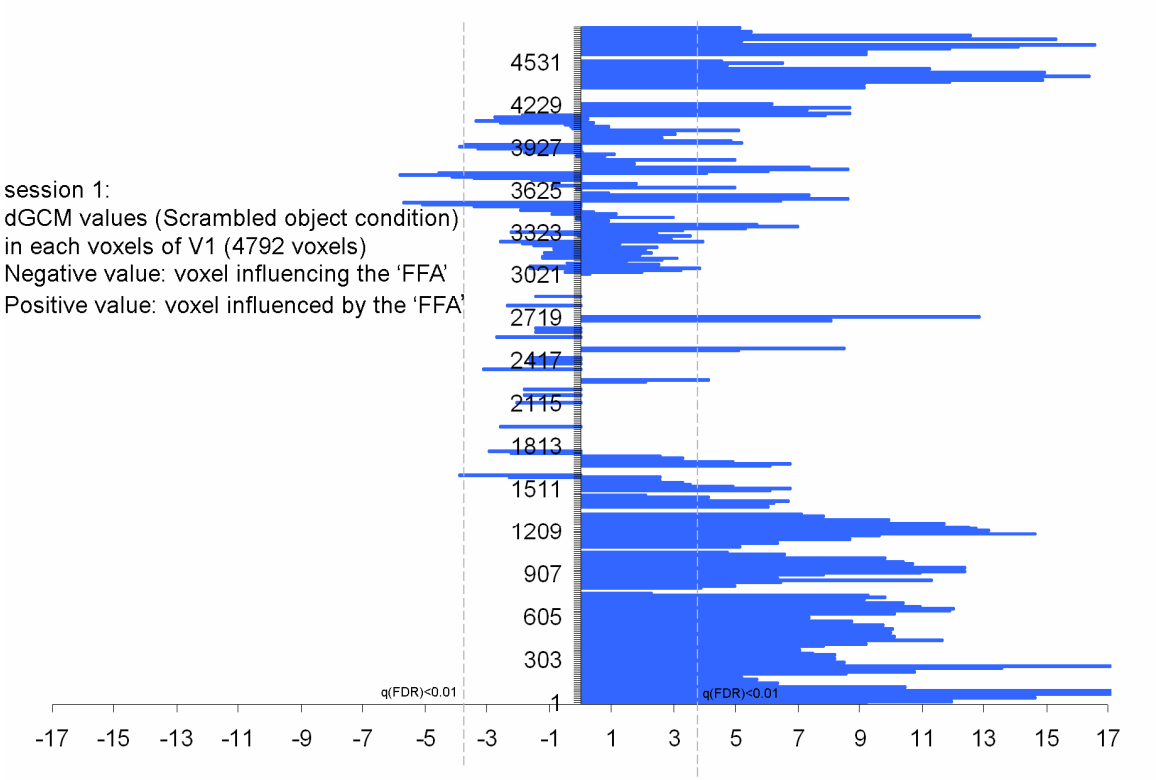


Figure 6. 15. In the anatomically defined V1 (session 1), we find lesser influence from that region on the right 'FFA' when the patient PS has to process scrambled objects in place of faces (Figure 6. 13).

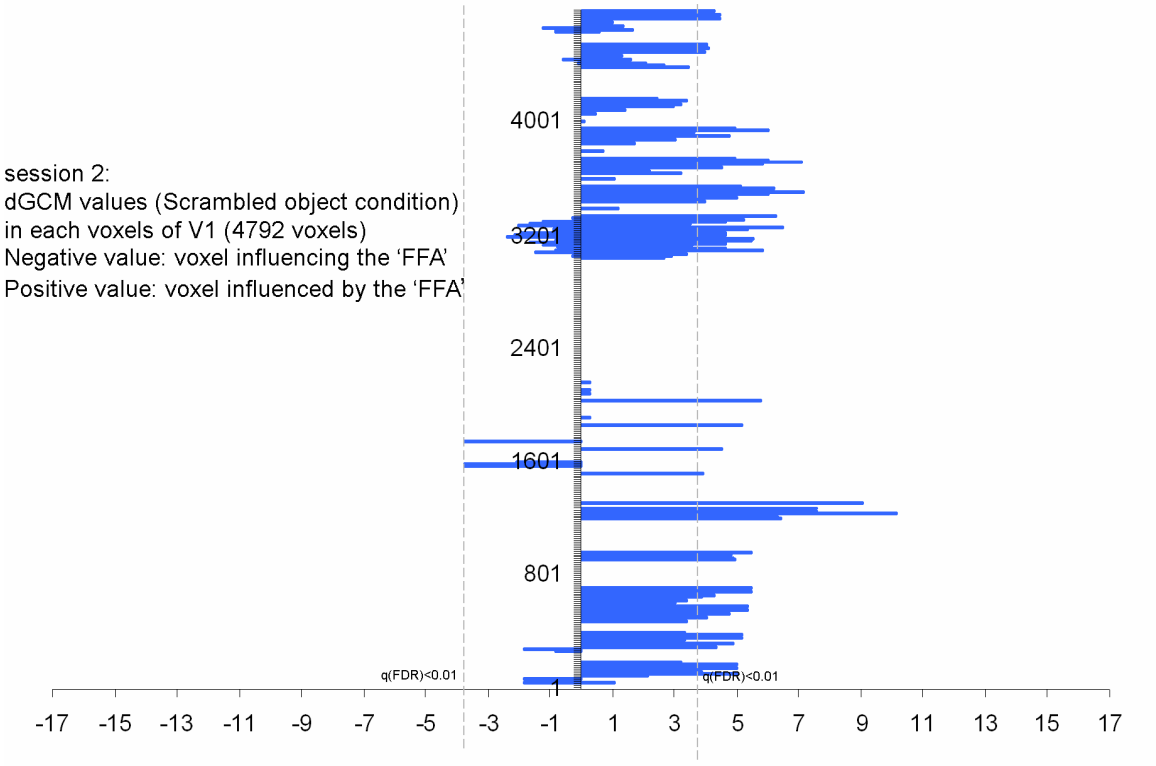


Figure 6. 16. In the anatomically defined V1 (session 2), we find lesser influence from that region on the right 'FFA' when the patient PS has to process scrambled objects in place of faces (Figure 6. 13).

The way to the 'FFA'

Even if the influence of early visual cortex to the right 'FFA' is maybe not direct, the way 'early visual cortex' to left 'OFA' to right 'FFA' is not compatible with our results. Indeed, our GCMs can be interpreted with respect to the 'FFA': we can at least say that all the regions with negative dCGM values influence all regions with positive dCGM values via the 'FFA'. Although simulations have suggested (Roebroeck et al., 2005) that interactions with a smaller temporal delay than the TR can still be detected, they also showed that the detection capacity decreases as the TR gets further away from the influence delay. This means that the way from early visual cortex to 'FFA' must be quite fast (about 20 ms following our TR). Finally, we can notify that the pSTS and the 'FFA' have a slightly mutual influence.

3.6.3.2. Control subjects

Normal participants showed activation at q(FDR)<0.05 (see Supplementary Table 6. S1 for details) in the right and left FFA (mean Talairach coordinates: 37.9+/-5, -45.5+/-5, -20.0+/-4 for the right FFA and -40.5+/-, -50.6+/-6, -17.1+/-4 for the left FFA), in the right and left 'OFA' (34.4+/-8, -77.4+/-6, -12.3+/-4 for the right 'OFA' and -35.0+/-3, -81.9+/-6, -10.0+/-6, for the left 'OFA'[58]) and in the right pSTS (45.7+/-5, -43.0+/-8, 7.4+/-5). The region around V1 (4792 voxels anatomically defined on one Brain Vogager brain template) is not a face region in our 7 subjects: the contrast F-O is not significant for 5 of our 7 subjects (p=0.16, p<0.01 (S2), p<0.01(S3), p=0.71, p=0.20, p=0.64, p=0.11) and the contrast SF-F is very significant for all of them (ps<0.0001 at least).

Left 'OFA' (Table 6. 1)

The left 'OFA' is influenced by the right 'FFA' during the face condition: 52.71% of the size of the region exceeds the positive statistical significance (average % of the subjects). On the other hand,

[58] We don't find the left 'OFA' in subject S3.

only 0.93% of the voxels of this region have influence on the right 'FFA' and the difference in the two possible directions of influence is highly significant: pair-t_7=4.26, p<0.005. There is no difference with the patient PS[59]: t(Crawford and Garthwaite, 2002) = -0.15; p= 0.89 and t(Crawford and Garthwaite, 2002)=-0.44, p=0.67 respectively for each of the influence.

Table 6. 1. Percent of the voxels of the left 'OFA' exceeding the positive (being influenced by the right 'FFA') and negative statistical significance (having influence on the right 'FFA').

	Percent of the left 'OFA' influenced by the 'FFA'	**Percent of the left 'OFA' influencing the 'FFA'**
S1	65.00	0.00
S2	70.29	0.00
S3	0.00	0.00
S4	73.56	5.17
S5	73.95	0.00
S6	75.85	1.33
S7	10.34	0.00

pSTS (Table 6. 2)

The pSTS is quasi not influenced by the right 'FFA' during the face condition: 0.64% of the size of the region only exceeds the positive statistical significance. The influence from de pSTS on the 'FFA' is slightly higher (10.94%) but the difference is not significant pair-t_7=-1.18, p=0.28. There is no difference with the patient PS[60]: t(Crawford and Garthwaite, 2002) = -0.09; p= 0.93 for the -pSTS to right 'FFA'- direction but the way –right 'FFA' to pSTS- is slightly more important for PS (but also little: 0.05%...): t(Crawford and Garthwaite, 2002)=2.40, p=0.053.

[59] Mean of the two PS's sessions.

[60] Mean of the two PS's sessions.

Table 6. 2. Percent of the voxels of the pSTS exceeding the positive (being influenced by the right 'FFA') and negative statistical significance (having influence on the right 'FFA').

	Percent of the pSTS influenced by the 'FFA'	Percent of the pSTS influencing the 'FFA'
S1	4.51	0.00
S2	0.00	0.00
S3	0.00	14.95
S4	0.00	0.74
S5	0.00	60.87
S6	0.00	0.00
S7	0.00	0.00
PS	5.07	8.78

Early visual cortex around V1 (Table 6. 3)

In the early visual cortex around V1, 12.22% of this region is influenced by the right 'FFA' during the face condition and 9.65% of the region influence 'FFA' directly. The difference between the two directions is not significant pair-t_7=0.73, p=0.49 and there is no difference with the patient PS[61]: t(Crawford and Garthwaite, 2002) = -1.02; p= 0.35 and t(Crawford and Garthwaite, 2002)=-1.00, p=0.36 respectively for each of the influences. Notice that in each of our subjects we can always find some early visual regions non specific to faces having influence on the right 'FFA' without going by the 'OFA's.

Table 6. 3. Percent of the voxels of V1 exceeding the positive (being influenced by the right 'FFA') and negative statistical significance (having influence on the right 'FFA').

	Percent of the V1 influenced by the 'FFA'	Percent of the V1 influencing the 'FFA'
S1	14.29	9.89
S2	17.45	9.49
S3	8.99	14.96
S4	12.40	22.06
S5	9.87	3.92
S6	21.18	3.61
S7	1.36	3.61
PS	5.20	2.25

[61] Mean of the two PS's sessions.

Right 'OFA' (Table 6. 4)

As for the left 'OFA', the right 'OFA' is influenced by the right 'FFA' during the face condition: 68.28% of the size of the region exceeds the positive statistical significance and only 0.21% has influence on the right 'FFA'. The difference in the two possible directions of influence is highly significant: pair-t_7=6.86, p<0.0005.

Table 6. 4. Percent of the voxels of the right 'OFA' exceeding the positive (being influenced by the right 'FFA') and negative statistical significance (having influence on the right 'FFA').

	Percent of the right 'OFA' influenced by the 'FFA'	Percent of the right 'OFA' influencing the 'FFA'
S1	52.63	0.00
S2	92.31	0.00
S3	20.62	0.00
S4	84.27	0.00
S5	85.89	0.00
S6	56.51	1.47
S7	85.71	0.00

Left 'FFA' (Table 6. 5)

45.62% of the voxels belonging to the left 'FFA' is influenced by the right 'FFA' and 10.15% influences this last region. The difference is almost significant: pair-t_7=2.28, p=0.06. We can notice that this difference become significant if we only take in consideration the most right lateralized subjects: pair-t_3=5.19, p<0.0139 (S1, S2, S3, S6).

Table 6. 5. Percent of the voxels of the left 'FFA' exceeding the positive (being influenced by the right 'FFA') and negative statistical significance (having influence on the right 'FFA').

	Percent of the left 'FFA' influenced by the 'FFA'	**Percent of the left 'FFA' influencing the 'FFA'**
S1	42.39	3.72
S2	93.81	0.00
S3	74.76	0.00
S4	24.79	46.72
S5	21.94	16.79
S6	50.84	0.79
S7	10.78	2.99

The way to the 'FFA'

As we said for the patient PS, even if the influence of early visual cortex to the right 'FFA' is not direct, the way 'early visual cortex' to right (or left) 'OFA' to right 'FFA' is not compatible with our results.

3.6.4. Conclusion

Here we have shown that the face-related activation found in the right hemisphere of our brain damaged patient PS may not originate from posterior areas of the other hemisphere, such as the left 'OFA', through callosal connections. We found indeed a right 'FFA' activation for faces influencing the controlateral activation of the left 'OFA' and influenced by early visual areas. Moreover, the patient PS has exactly the same organisation than the control subjects: a direct way from early visual cortex to the right 'FFA'.

Acknowledgements

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de Recherche Concertées). BR is supported by the Belgian National Foundation for Scientific Research (FNRS).

Supplementary materials:

Supplementary methods

DTI images were acquired using a 3T head scanner (Siemens Allegra, Siemens AG, Erlangen, Germany) with a sequence developed by Allard Roebroeck: echo time (TE) = 83 ms, repetition time (TR) = 9400 ms, Bandwidth = 2790 hz/pixel, matrix size = 128x128, field of view (FOV) = 256x256 mm^2, 75 slices, 80 directions, bo=1000 s/mm^2 (resolution $2mm^3$, total scan time = 12 min 41 par run). Eight runs were acquired in two different sessions (6 months between sessions). The tracking in PS's brain has been based on the face regions found thanks to the localizer described in our first experimental chapter (see chapiter 3.1.3.2.).

The data were analyzed with BrainVoyager QX (Version 1.9.10, Brain Innovation, Maastricht, The Netherlands) and Matlab version 2007b. The recorded volumes presenting artefacts were carefully eliminated and the different runs were averaged with Matlab to increase the signal-to-noise ratio. To create the Mean Diffusivity (MD) and the Fractional Anisotropy (FA) maps, the DTI data were coregistred with the 3D anatomy of the patient without Talairachization (the distorsions imposed by the Talairachization are indeed incompatible with the DTI). The determinist tracking was made from the regions of interest that were slightly widened by one or two voxels beyond the border white- grey matter. Only the fibers with FA > 0.2 were considered and a deviation angular of less than 50 ° was required.

3.6. Granger causality mapping in a brain-damaged prosopagnosic patient incompatible with a feedforward hierarchical model of the face recognition

Supplementary Table 6. S1. Talairach Coordinates and size of the regions at q(FDR)<0.05 for the 7 control subjects.

	Talairach Coordinates				
	x	y	z	size (mm^3)	
Right 'FFA'	37.38	-45.62	-18.06	613	S1
Left 'FFA'	-42.83	-49.55	-18.98	618	
Right 'OFA'	22.42	-80.21	-14.37	19	
Left 'OFA'	-34.35	-79.9	-16.8	20	
Psts	40.92	-28.59	0.24	599	
Right 'FFA'	38.17	-43.88	-17.29	1032	S2
Left 'FFA'	-39.42	-58.54	-15.93	921	
Right 'OFA'	33.64	-84.77	-9.2	1249	
Left 'OFA'	-35.35	-80.49	-6.25	138	
pSTS	44.49	-49.8	15.11	91	
Right 'FFA'	40.99	-44.56	-22.25	1103	S3
Left 'FFA'	-42.05	-37.1	-21.64	614	
Right 'OFA'	47.94	-67.62	-12.46	97	
Left 'OFA'	-	-	-	-	
pSTS	45.59	-36.97	9.41	194	
Right 'FFA'	44.21	-51.26	-18.23	331	S4
Left 'FFA'	-45.54	-48.74	-11.95	351	
Right 'OFA'	30.8	-81.25	-18.29	89	
Left 'OFA'	-32.27	-87.87	-12.68	348	
pSTS	45.14	-54.84	3.54	135	
Right 'FFA'	31.97	-39.4	-17.41	100	S5
Left 'FFA'	-34.7	-56.73	-11.92	679	
Right 'OFA'	39.67	-71.1	-8.06	326	
Left 'OFA'	-30.4	-90.04	0.43	430	
pSTS	39.47	-43.26	7.36	276	
Right 'FFA'	34.49	-51	-16.56	1399	S6
Left 'FFA'	-45.01	-46.89	-18.33	1133	
Right 'OFA'	31.83	-76.19	-6.95	814	
Left 'OFA'	-39.95	-78.97	-11.46	675	
pSTS	45.98	-39.16	5.43	51	
Right 'FFA'	43.89	-50.16	-26.24	45	S7
Left 'FFA'	-42.57	-43.21	-19.71	334	
Right 'OFA'	41	-77	-18	7	
Left 'OFA'	-37.78	-73.94	-12.82	174	
pSTS	47.75	-50.25	6	4	

4. DISCUSSION GÉNÉRALE ET CONCLUSIONS

Au cours de notre thèse, nous avons tenté de clarifier la neuro-anatomie fonctionnelle de la reconnaissance des visages et en particulier de préciser le réseau neuronal sous-tendant leur perception.

En résumé, plutôt que d'adhérer aux modèles hiérarchiques classiquement représentés dans la littérature visage (Haxby et al., 2000 ; Gobbini & Haxby, 2007 ; Fairhall & Ishaï, 2007), nous avons étayé un modèle inversé (Rossion, 2008 ; Figure 9 du chapitre 2.5.) qui propose que l'activation première de la ''FFA'' soit indépendante de l'activation de l' ''OFA'' située pourtant postérieurement.

Inspiré des premières recherches et de l'intuition remarquable de Justine Sergent (Sergent, 1986) et en accord avec les développements actuels dans la compréhension de la reconnaissance des objets (Hochstein et al., 2002, entre autres) ainsi qu'avec les récentes études chez le singe (Freiwald et al., 2009), ce modèle postule également qu'une représentation globale et grossière du visage dans la ''FFA'' (composée de neurones au champ récepteur large) soit ensuite raffinée par des interactions avec les neurones de l' ''OFA'' (composée de neurones au champ récepteur de plus petite taille) lors de l'individualisation des visages.

Les visages, quelle que soit leur représentation -photos réalistes, visages de type Mooney ou faits de fruits et légumes comme ceux peints par Arcimboldo, caricatures, visages composés de basse fréquence spatiale, etc.- sont d'abord détectés et catégorisés comme « un visage » de façon holistique par la ''FFA'' qui perçoit automatiquement de manière simultanée les composants ET les relations basiques entre ces composants que doit comporter un visage (deux yeux au-dessus du nez, lui-même au-dessus de la bouche). Cette détection holistique dont sont capables les deux patientes prosopagnosiques décrites dans nos études (et le patient GG testé récemment dans notre laboratoire, Busigny et al., in press) activerait la ''FFA'' de manière rapide mais relativement grossière

(Goffaux et al., 2010; voir aussi Sugase et al., 1999, Sripati & Olson, 2009 pour des études chez le singe) depuis les aires visuelles précoces sans doute par le faisceau longitudinal inférieur. Cette représentation grossière servirait de « template » ou de guide à une individualisation holistique nécessitant l'intégration précise de multiples traits et de relations spatiales pour gérer les différences même très subtiles entre des visages et cela, grâce à l'aide de régions plus postérieures aux champs visuels plus étroits.

Cette individualisation holistique basée sur une seconde vague d'activations au moins partiellement en provenance de l' ''OFA'' par une boucle réentrante dans la 'FFA' ferait défaut à nos deux patientes dont les ''OFA''s n'existent plus. Les faibles capacités résiduelles de reconnaissance des visages de la patiente PS ne reposent d'ailleurs que sur un traitement focalisé sur la bouche (Caldara et al., 2005 Orban de Xivry et al., 2008; Van Belle et al., 2010) car elle est incapable de traiter la région des yeux étant donné les multiples traits et relations spatiales qui doivent y être intégrés finement avec l'aide de l' ''OFA'' (pupille, iris, paupières, cils, sourcils, distance interoculaire, distance par rapport au nez, distance par rapport au front,…). Ce traitement analytique sur la bouche se ferait dans des régions non spécifiques aux visages comme la partie ventrale droite du LOC (Grill-Spector et al., 2001; Malach et al., 1995) qui est la seule région où la patiente présente de l'adaptation aux visages quand elle réussit à en discriminer.

La détection faciale et l'individualisation spatiale seraient ainsi sous-tendues par des circuits neuronaux se chevauchant dans la ''FFA'' droite qui jouerait le rôle clé à la fois dans le codage holistique grossier et dans le codage holistique individualisant mais qui aurait besoin, pour ce dernier traitement, de l'aide du reste du réseau visage. La ''FFA'' droite est en effet non seulement la région activée le plus fortement lors de la détection holistique, en particulier d'un stimulus comme un Mooney, mais aussi celle où la perception individuelle holistique fine se marque le plus fort (Schiltz & Rossion, 2006; Schiltz et al., 2010, Andrews et al., 2010). De plus, si la ''FFA'' est, paradoxalement, la région visage la moins spécifique (de haut niveau) de part sa sensibilité aux

propriétés de bas niveau des visages[62] (couleurs et fréquences spatiales, voir notre chapitre 3.1), elle ne présente cependant pas plus d'activité pour une série de visages brouillés différents que semblables (absence d'adaptation aux visages brouillés ; Andrews et al., 2010). La ''FFA'' est sans doute aidée dans sa détection des visages par leurs fréquences spatiales voire leurs couleurs mais elle n'est pas destinée à discriminer des objets de bas niveaux. Quant à l' ''OFA'', en tout cas celle que nous avons trouvée en utilisant un paradigme expérimental permettant un contrôle et une vérification des propriétés de haut et bas niveaux, elle est de haut niveau et ne présente pas de sensibilité aux propriétés de bas niveau des visages. En effet, activée « en second » par la détection d'un « template » visage par la ''FFA'', il n'est pas crucial qu'elle puisse agir comme simple détecteur de visage. Nous pensons par ailleurs que même si certaines études ont montré au moyen de classificateur que la catégorisation d'un visage est possible sans la ''FFA''(Haxby et al., 2001; O'Toole et al., 2005) ou avec des patients prosopagnosiques présentant une ''FFA'' droite lésée anatomiquement (Barton et al., 2002) soutenant donc une approche distribuée, cela n'est vrai que pour les stimuli non ambigus qu'ils ont testés et différents de ceux utilisés par exemple dans notre étude 3.3. (visages Mooneys) qui nécessitent une perception holistique et pour lesquels la ''FFA'' est indispensable (encore qu'on ne peut pas exclure un rôle suffisant du pSTS).

Remarquons aussi que si nous nous sommes attaché principalement aux régions visages communément reconnues pour leurs rôles dans la perception des visages afin de critiquer le modèle hiérarchisé du « core system » (Haxby et al., 2000 ; soit la ''FFA'', l' ''OFA'' et le pSTS que nous avons cherché par ailleurs à définir le plus correctement possible), nous voudrions souligner une dernière fois la complexité du réseau visage et le côté « plus étendu » de la critique des modèles purement hiérarchiques. Haxby et al., (2000) puis Gobbini & Haxby (2007) dans leur description

[62] La 'FFA' droite est aussi plus activée par les objets que par les objets brouillés. Haxby Haxby et al. (2000) et plus tard Weiner et al. (2010) penchent d'ailleurs vers un réseau de reconnaissance d'objets et de visages distribué et commun en partie soit un codage distribué des catégories d'objets visuels. Selon eux, des régions qui ne répondraient pas préférentiellement à une catégorie d'objets pourraient cependant jouer un rôle dans l'identification d'un stimulus de cette catégorie (pour les objets dans la ''FFA'' et pour les visages dans les régions objets). Il est vrai qu'à l'échelle spatiale de la fMRI, il y a sans doute un entrelacement de sous-populations neuronales dominantes et nombreuses pour une catégorie avec des sous-populations moins nombreuses pour une autre.

d'un réseau sous-tendant la reconnaissance des visages, proposaient, en plus du « core system », l'existence d'un « extended system » (cortex paracingulaire antérieur, jonction temporopariétale, cortex temporal antérieur, précuneus, amygdale, insula et le striatum ; voire aussi le gyrus frontal inférieur, l'hippocampe et le cortex orbitofrontal rajoutés par Ishaï et al., 2005) plus multimodal incluant des tâches de stockage et de récupération d'informations biographiques, sémantiques et/ou émotionnelles (voir aussi Fox et al., 2009 ; Ishai, 2008 ; Tovée, 1998; Tsao et al., 2006 ; Tsao et al., 2008 ; Pinsk et al., 2009 et Tsao et al., 2006; 2008 chez le singe). Les mécanismes neuronaux de reconnaissance des visages largement distribués dans un réseau de nœuds interconnectés peuvent donc laisser penser que mémoire et perception[63] ou émotion et perception sont plus intimement liées que prévu dans les modèles et que ces liens demandent à être caractérisés plus profondément comme le soulignent d'ailleurs Gobbini & Haxby (2007). De plus, lors de notre première analyse (chapitre 3.1.) et alors que la tâche est un simple one-back sur des visages inconnus, nous activons déjà la plupart de ces régions. Il apparaît également à travers d'autres études que des activations parallèles et synchronisées, top-down et bottom-up, entre toutes ces régions seraient responsables de notre capacité à reconnaître des visages sans effort : Bar soulignait en 2003 le rôle de guide du cortex préfrontal pour la reconnaissance d'objets dans la voie occipito-temporale ; Barbeau et al. (2007), grâce à des électrodes intracérébrales chez des patients épileptiques, montraient, cette fois pour les visages, des activités aussi précoces dans le gyrus frontal inférieur que dans la ''FFA''. Remarquons aussi qu'au niveau anatomique, le faisceau occipito-frontal inférieur et le faisceau longitudinal inférieur, voies rapides et myélénisées, respectivement vers le gyrus frontal inférieur et la ''FFA'' semblent deux bons candidats pour permettre des activations rapides de ces deux régions. Reddy et al. rapportaient, également en 2007, l'influence de l'attention « top-down » liée à la tâche dans une étude où le gyrus fusiforme s'activait en condition de tâche double pour des visages pertinents malgré que les ressources attentionnelles soient focalisées sur un autre stimulus,

[63] Les étapes perceptives et mnésiques seraient plus imbriquées que ne le laissait supposer le modèle de Bruce & Young (1986) qui séparait ces deux étapes. L'impossibilité pour la mémoire à récupérer ou former une information pourrait à ce titre entraîner des difficultés de perception.

activité beaucoup plus importante que lorsque le visage pouvait être entièrement ignoré car sans intérêt pour la tâche. Selon eux, réduire l'attention focale « bottom-up » ne suffisait pas à réduire les réponses neuronales, tant que l'on ne retirait pas en même temps l'attention « top-down » liée à la tâche. A l'image, du modèle de Rossion (2008) pour le cœur du système des visages, on est là assez loin de mécanismes hiérarchisés et séquentiels.

Pour appuyer ce modèle, il serait, par ailleurs, intéressant de se demander plus en détail si les activations top-down et bottom-up, entre les régions visages diffèrent entre une simple tâche de détection de visage (sans identification demandée ou même possible) et une tâche d'identification. Réutiliser la technique des Grangers Causality comme on l'a fait au chapitre 6 de notre partie expérimentale avec notamment les stimuli de notre chapitre 3 (Mooneys faces)[64] nous semblerait donc la prochaine expérience à faire[65]. Elle permettrait de prouver que l'influence de la ''FFA'' sur l' ''OFA'' augmente lorsque la tâche nécessite une identification. Il serait d'ailleurs intéressant de rajouter, dans les limites possibles de temps d'enregistrement d'un volume cérébral pour qu'il reste compatible avec le timing de la technique des Granger Causality, le gyrus frontal inférieur.

Reste que dans la voie ventrale (notre propre étude, chapitre 1, Pinsk et al., 2009 et Tsao et al., 2006), l'existence de plusieurs clusters visages au niveau individuel pose question. Les questions de savoir d'une part pourquoi tant d'aires visages sont distribuées spatialement le long de la voie ventrale et d'autre part quels sont leurs rôles respectifs restent ouvertes. Nous pensons que la neuro-imagerie couplée à l'enregistrement cellulaire chez le singe est actuellement l'outil le plus adéquat pour répondre, d'autant que cette technique aidera aussi à comprendre plus précisément le couplage neurovasculaire (Sirotin & Das, 2009) et les phénomènes d'adaptation.

En guise de conclusion finale, nous espérons que cette thèse aura contribué à resouligner l'importance d'une synergie étroite entre des disciplines telles que la neuropsychologie cognitive,

[64] Les stimuli utilisés par Goffaux et al. (2010) seraient aussi très appropriés.
[65] Plutôt qu'un « block design », un « event-related design » nous semble plus adéquat pour aléatoirement mêler les stimuli où l'identification est ou non possible.

en particulier des patients cérébro-lésés, et l'ingénierie pour aider à la compréhension de la structure et du fonctionnement du système nerveux.

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Experimental Psychology Society: Cambridge Meeting April 2-4, 2008.
Abstract: Behavioral and neural evidence for preserved holistic face detection in acquired prosopagnosia.
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Vision Sciences Society: 7th Annual Meeting May 11-16, 2007. Sarasota, Florida.
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