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Functional Localizers as a tool for clinical mapping

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Acknowledgments

Resumo

São conhecidas diferentes regiões corticais que apresentam maior resposta a estímulos de uma determinada categoria em detrimento de outras. Com o presente estudo recorremos à técnica de ressonância magnética funcional para analisar e caracterizar a actividade de cinco destas áreas funcionalmente distintas, a referir, a *Fusiform Face área* (FFA) a *Occipital Face área* (OFA), o *Superior Temporal Sulcus* (STS), o *Lateral Occipital Complex* (LOC) e a *Parahipocampal Place área* (PPA) enquanto os sujeitos visualizavam imagens de quatro tipos diferentes de categorias (faces, objectos, paisagens e versões scrambled de objectos).

Com este paradigma procurámos caracterizar a presença destas áreas em diferentes indivíduos, respectiva variabilidade de localização e ainda a sua resposta às diferentes categorias de estímulos visuais.

Desta forma, verificámos a existência de variabilidade de localização a três níveis: primeiro todas as regiões excepto o STS esquerdo e direito e a OFA esquerda, foram identificadas entre quase, mas não todos, os voluntários da nossa amostra; segundo, encontrámos, alguma variabilidade nas coordenadas de localização não só entre os diferentes voluntários como entre diferentes estudos; terceiro, demonstrámos a existência de dominância hemisférica das áreas selectivas para faces mas não para as restantes.

Finalmente a nossa análise estatística permitiu-nos não só demonstrar a preferência de resposta de cada área relativamente ao estímulo esperado como ainda demonstrar a selectividade alta de LOC mas não de FFA e PPA que, para além de uma resposta ao seu estímulo preferencial, apresentavam também reposta significativa à categoria de objectos.

Abstract

A number of cortical areas are known to show greater response to a particular category of stimulus over others. Here we used functional magnetic resonance to analyze the activity of the functionally distinct areas Fusiform face area (FFA), Occipital Face area (OFA), Superior Temporal Sulcus (STS), Lateral Occipital Cortex (LOC) and parahipocampal place area (PPA) while subjects viewed images of four different categories (faces, objects, places, and scrambled versions of objects).

On doing so we hoped to characterize the presence of these areas across different individuals, its localization variability and their response the different stimuli categories.

We verified the existence of localization variability at three different levels. First, all the regions, except the left and right STS and the left OFA, were present amongst almost but not all the subjects scanned; second we found relative variability of localization coordinates between subjects and studies; and third we showed right hemispheric dominance of face selective areas but not of the PPA or LOC.

We also conducted statistical tests that allowed us to demonstrate the regions' expected category preference but we demonstrated that only the LOC is strongly selective as opposed to the FFA and PPA which, apart from response to their preferred category, also respond significantly to the category of objects.

Index

Abbreviations

FFA – Fusiform Face area

OFA – Occipital Face area

STS – Superior Temporal Sulcus

LOC – Lateral Occipital Cortex

PPA – Parahipocampal Place area

Fmri – Functional Magnetic Resonance

ROI – Region of interest

rFFA – Right Fusiform Face area

lFFA – Left Fusiform Face area

rOFA – Right Occipital Face area

lOFA – Left Occipital Face area

rSTS – Right Superior Temporal Sulcus

lSTS – Left Superior Temporal Sulcus

rLOC – Right Lateral occipital Complex

lLOC – Left Lateral Occipital Complex

rPPA – Right Parahipocampal Place area

lPPA – Left Parahipocampal Place area

List of figures and tables

Introduction

The belief that a link between neural and mental states exists is the basil stone of cognitive neuroscience which pursuits the goal of discovering such links.

One example that has been broadly studied is the case of visual stimuli recognition. Information progresses from the primary visual cortex (V1) in the occipital cortex, in a posterior to anterior direction, to the prefrontal cortex with a corresponding higher degree of complexity and abstractness. The circuits processing this information appear to be organized in two functionally specialized processing pathways, the ventral stream responsible for identification of stimuli – vision for perception (i.e. What?) – and the dorsal stream responsible for appreciating the spatial relationships among stimuli, as well as visual guidance of movements toward objects in space – vision for action (i.e. where?) (Goodale, Meenan et al. 1994; Ungerleider and Haxby 1994).

Regarding the ventral pathway, a question that one may ask is whether stimuli of different categories are analyzed by specialized functionally distinct cortical areas or whether stimuli discrimination is performed by different functionally overlapping cortical areas. Indeed, the use of functional neuroimaging techniques has allowed identification of several cortical regions that show selectively higher response to one stimuli category than to others. Of these the most robust findings involve face perception.

In 1997 Kanwisher et al. (Kanwisher, McDermott et al. 1997) described an area in the fusiform gyrus that responded significantly more to faces than to objects – the Fusiform face area (FFA). Following studies showed that the lateral region of the inferior occipital cortex – Occipital face area (OFA) ((Gauthier, Tarr et al. 2000)) – and the superior temporal sulcus (STS) (Haxby, Hoffman et al. 2000) are also consistently engaged in facial perception. Gobbini and Haxby propose a model of face recognition comprising a core system that encodes the visual appearance of the face which corresponds to the right FFA (rFFA), OFA

and STS; and an extended system that gives additional information who contributes to face perception composed of groups of neurons in the inferior frontal gyrus, amygdale, pre-cuneus, anterior paracingulate gyrus, and a more anterior portion of the STS, among others (Gobbini and Haxby 2007).

Common objects reportedly activate preferentially a region in the Lateral occipital Cortex termed Lateral occipital complex (LOC) ((Malach, Reppas et al. 1995) whereas images of buildings and landscapes preferentially activate a region in the parahippocampal gyrus (parahippocampal place area (PPA)) (Aguirre, Zarahn et al. 1998; Epstein and Kanwisher 1998).

Despite the existence of many functionally distinct areas in the brain being well acknowledged its localization arises fewer consensuses. In the most robust sense a particular individual and distinguishable brain area would present as a unique anatomical, functional and molecular entity. For instance the primary visual cortex (V1) has been identified anatomically using light microscopy in histological preparations of post-mortem material based on a specific pattern of heavy myelination (stria of Gennari, Gennari 1782); and functionally through retinotopy procedures (Sereno, Dale et al. 1995) with further studies showing close agreement between them (Hinds, Polimeni et al. 2009).

However not all functionally distinct areas correspond to an anatomically identifiable region because each brain's shape is unique and we don't yet dispose of clear anatomical or connectivity markers to define most cortical areas. An alternative solution is to use functional localizer protocols. These correspond to experimental tasks designed to identify consistent patterns of functional response in order to localize "same" brain regions. These grossly identified brain regions can thereafter be subjected to further evaluation thus assessing which specific role they play in cognitive functions (Saxe, Brett et al. 2006). Moreover, Once a consistent brain mapping has been created, functional localizers can be of great utility in

clinical setting mainly for preoperative and even intraoperative (using rtfMRI) brain surgery planning (Weiskopf, Sitaram et al. 2007).

Here we focused on the described functionally distinct FFA, OFA, STS, LOC and PPA and used functional magnetic resonance (fMRI), a non invasive technique that has a good spatial resolution (Kwong, Belliveau et al. 1992), to scan 15 volunteers while they viewed images of four different categories: faces, objects (tools, cars and chairs), places (landscapes and skylines) and scrambled versions of objects. On doing so we attempted to: first, verify the presence of these areas across different individuals and its localization variability; and second to corroborate the supramentioned category preference of their response furthermore characterizing their response to non preferred categories, that is if they respond at all and if there is any difference in the processing of non preferred stimuli.

Materials and Methods

Subjects

15 right-handed subjects (8 females, 7 males, ages 21-41, mean age 26,6 years) voluntarily participated in the study after providing informed consent. All had normal or corrected to normal vision and had no health problem of their knowledge.

The study followed the tenets of the Declaration of Helsinki, informed consent being obtained from all subjects for the protocol, which was approved by our local Ethics Committee.

Stimulus

Four different stimulus categories were tested: faces (unfamiliar); Places (landscapes and skylines); objects (tools, cars and chairs) and scrambled versions of objects (figure 1). Images consisted of 300x300 black and white pictures. Face pictures were taken from a freely available face recognition public database, whereas the sets for the other categories were built in-house.

Controlling the images on low level features such as contrast or complexity was not our concern since our goal was solely to map the existence of category specific cortical regions bearing in mind that further characterization of these areas would demand further work.
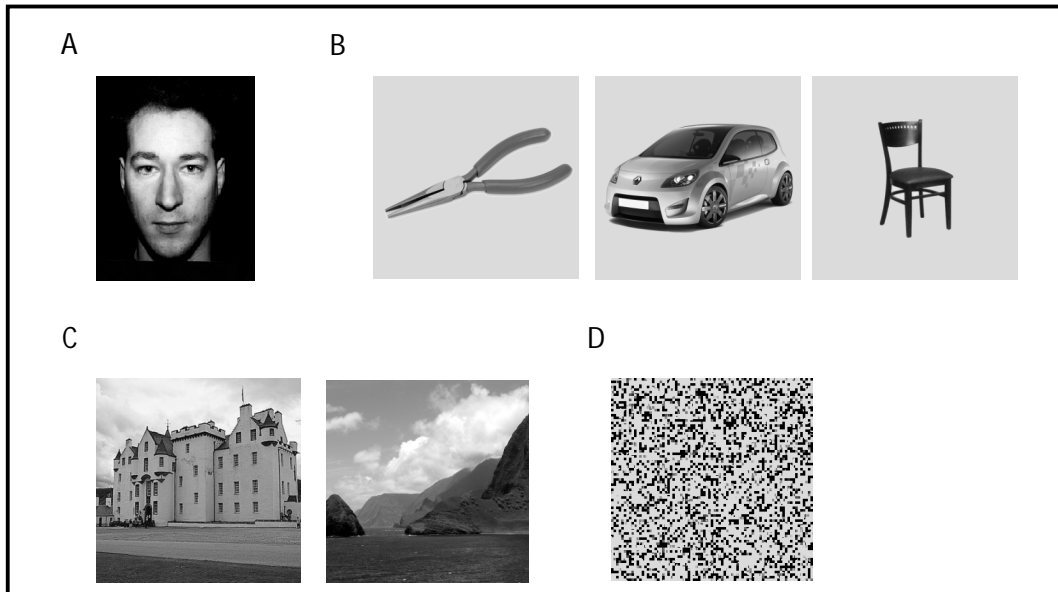
Figure 1 Stimuli examples. A – faces; B – objects; C – places; D – scrambled.

Task design

Stimuli were computer generated and presented on a black background on a screen positioned near the subjects' head and viewed through an angled mirror attached to the head coil subtending approximately 9.48º of the visual field.

Localizer scans consisted of two runs of alternatively viewed blocks of stimuli from a given class (faces, places, objects, scrambled images). Each run had 12 blocks and each block lasted 20s (30 images, 800ms each), separated by 10s fixation baseline intervals. During each block subjects performed a 1-back task to keep stable attention levels. Three repetitions per block were employed.

Data Acquisition parameters

Images were obtained on a Siemens Tim Trio 3T scanner using a 12 channel head coil. Structural images were collected using a T_1 weighted MPRAGE (magnetization-prepared rapid-acquisition gradient echo) (TR = 2300ms , TE = 2.98ms , flip angle = 9º, matrix size = 240x256 , voxel size = 1mm^3). Standard T_2*-weighted gradient-echo echo planar imaging

was used for the functional task runs (TR = 2000ms ; TE = 52ms ; 2x2 in-plane resolution ; 3mm slice thickness with no gap ; flip angle = 90º; matrix size= 114x114; number of slices = 23; 455 measurements for the Color Task and 355 for the simultaneous Response Task). The slices were oriented to obtain a brain coverage spanning from the cerebellum to the inferior frontal and parietal lobes. All runs were acquired in the same session.

Data Preprocessing

Pre-processing steps of motion correction, slice scan-time correction and linear trend removal were performed. Temporal high-pass filtering of 0.00980 Hz (3 cycles in time course) was applied. For all these pre-processing steps BrainVoyager (BV, Brain Innovation, Maastricht, The Netherlands) was used.

Data analysis of the imaging experiments

For each subject, the static localizer time course data from both runs, 1 and 2, was analysed with multi-subject general linear model with faces, objects, places and scrambled as predictors. Setting the significance level at p<0,001 and using a cluster size of approximately 50 mm3 we applied the following contrasts: faces>objects ∩ faces>places ∩ faces >scrambled; Objects>faces ∩ objects >places ∩ objects >scrambled; and places>faces ∩ places>objects ∩ places>scrambled. For this we also used BrainVoyager (BV, Brain Innovation, Maastricht, The Netherlands).

With each contrast we identified, if possible, the regions of our focus in each individual and collectively defined its average coordinates. These results were then compared, at a confidence interval of 95 %, with localizer coordinates of the respective Regions of interest (ROI's) available in literature of reference.

Statistical analysis

Further work consisted in evaluating the response of each ROI to the different stimuli categories (given to us in beta values by running the General linear model). For this we used the statistical analysis software SPSS® (Statistical Package for the Social Sciences), version 20 for Windows®.

We first calculated the average response regarding different stimuli classes for each ROI.

Analysis of normality, due to the size of our sample, was preformed with a Shapiro Wilk-test. Later we compared the activation of the different ROI's to the different stimuli with a Friedman Test. A confidence level of 95 % was used.

Finally we compared the response to the same type of stimulus between the right and corresponding left ROI with a Wilcoxon test and a confidence level of 95 %.

Results

ROI's identification

In Table I we present the left and right coordinates of FFA, OFA, STS, LOC and PPA, of studies of refrence.

Table I right and left coordinates (in talairach space) of FFA, OFA, STS, LOC and PPA of studies of reference. na – not applicable; (a) Anterior part; (b) posterior part.

Study		right			left		
		mean x	mean y	mean z	mean x	mean y	mean z
FFA	(Kanwisher, McDermott et al. 1997)	40	55	10	-35	-63	-10
	(Gauthier, Tarr et al. 2000)	35	-49	-8	-35	-56	-6
	(Fox, Iaria et al. 2009)	35	-48	-19	-37	-43	-20
	(Spiridon, Fischl et al. 2006)	31,3	-55,8	-5,9	-50,1	-69,2	-7,5
	(Ewbank, Schluppeck et al. 2005)	36	-47	-20	-33	-57	-19
	(Scherf, Behrmann et al. 2007)	40	-41	-21	-38	-44	-19
	(Prince, Dennis et al. 2009)	48	-48	-17	-45	-52	-20
OFA	(Gauthier, Tarr et al. 2000)	31	-75	0	-30	-77	0
	(Fox, Iaria et al. 2009)	40	-75	-9	-38	-73	-15
	(Spiridon, Fischl et al. 2006)	17,6	-86,6	-5,2	na	na	na
	(Ewbank, Schluppeck et al. 2005)	25	-66	-10	-18	-64	-6
	(Scherf, Behrmann et al. 2007)	46	-66	-4	-47	-70	6
	(Prince, Dennis et al. 2009)	45	-80	-6	-37	-84	-12
STS	(Fox, Iaria et al. 2009)	53	-44	4	-50	-55	8
	(Scherf, Behrmann et al. 2007)	53	-50	11	-53	-52	14
LOC	(Malach, Reppas et al. 1995)	42,8	-72,7	-18,2	na	na	na
	(Spiridon, Fischl et al. 2006) (a)	28,6	-48,4	-11,5	-45,4	-52,5	-7
	(Spiridon, Fischl et al. 2006) (b)	30,3	-79,6	-3,2	-58,7	-79,7	9,1
	(Duncan, Pattamadilok et al. 2009)	na	na	na	-41	-78	-9
	(Ewbank, Schluppeck et al. 2005)	33	-66	5	-41	-70	-1
	(Scherf, Behrmann et al. 2007)	46	-62	-4	-40	-66	-7
PPA	(Spiridon, Fischl et al. 2006)	16,3	-43,7	1	-38,7	-55,1	4,2
	(Aguirre, Zarahn et al. 1998)	20,6	-53,8	-9,2			
	(Ewbank, Schluppeck et al. 2005)	25	-42	-19	-26	-44	-18
	(Scherf, Behrmann et al. 2007)	26	-43	-13	-23	-43	-11
	(Prince, Dennis et al. 2009)	30	-48	-4	-30	-44	-7
	(Park and Chun 2009)	30	-44	-14	-27	-46	-15

In our study, one subject showed no activation in any of the ROI's predefined, one other showed no activation in the LOC (left or right) and another showed no activation in the PPA (left or right). Apart from these subjects we identified at least one of the face, object and place specific ROI's (figure 2) in every other subject. Table II presents the summary of the regions identified and their peak coordinates.

Table II right and left mean peak coordinates (in talairach space) of FFA, OFA, STS, LOC and PPA and the number of subjects (n) out of 15 in which they were identified.

Region	n/15	Peak X	95 % CI	Peak Y	95 % CI	Peak Z	95 % CI
rFFA	14	36	[33 ; 40]	-47	[-51 ; -43]	-17	[-20 ; -13]
lFFA	11	-41	[-43 ; -40]	-49	[-54 ; -45]	-19	[-22 ; -16]
rOFA	11	35	[29 ; 40]	-69	[-75 ; -63]	-16	[-21 ; -11]
lOFA	7	-41	[-44 ; -38]	-68	[-75 ; -60]	-16	[-20 ; -11]
rSTS	8	41	[37 ; 44]	-55	[-65 ; -45]	15	[10 ; 20]
lSTS	5	-43	[-50 ; -35]	-55	[-76 ; -34]	13	[8 ; 18]
rLOC	11	40	[36 ; 43]	-70	[-75 ; -65]	-10	[-14 ; -4]
lLOC	12	-46	[-49 ; -42]	-66	[-69 ; -61]	-8	[-13 ; -2]
rPPA	12	22	[19 ; 25]	-49	[-56 ; -46]	-6	[-11 ; -1]
lPPA	13	-24	[-27 ; -22]	-43	[-48 ; -38]	-7	[-10 ; -4]

For the stimulus of faces, the number of right regions of interest identified was bigger than the number of left regions of interest. This tendency was inverted for the stimulus of objects and places.

Three subjects (21%) of those in which the FFA was identified presented only activation in the rFFA; as for the OFA four subjects (36%) showed activity only in the rOFA. Regarding the LOC, two subjects (15%) showed activation only in the lLOC and one (8%) only in the rLOC. Finally, in respect with the PPA, one subject (8%) showed left unilateral activation.

Since the lOFA, rSTS and lSTS were identified in only 8 or less than our sample no further analysis was preformed due to insufficient statistical power.

Comparing the confidence interval, at 95 %, of the peak coordinates of our study with the ones pointed in the studies in table 1 we were able to verify that although correspondence occurred with some it wasn't universal, moreover the confidence intervals for the different peak coordinates showed correspondence with a different number of studies with no apparent rule.

ROI's Response to different stimuli

The average pattern of response of the different ROI's to different stimuli classes is computed in figure 3.

The right FFA showed statistically significant higher activity for faces vs objects (p=0,040), places (p=0,000), and scrambled (p=0,000). It also showed statistically significant higher activity for objects vs places (p=0,028) and objects vs scrambled (p=0,000). For places and scrambled it showed no significant difference of response (p=0,079).

The pattern of response of the left FFA was different in that there was no significant difference of response between faces and objects (p=0,069). Similar to the rFFA response to faces was still significantly higher than to places (p=0,000) and scrambled (p=0,000); response to objects was significantly higher than to places (p=0,032) and to scrambled (p=0,001); and it also did not show significant difference of response (p=0,079) between scrambled and places.

The right OFA showed significantly higher activity for faces vs objects (p=0,021), places (p=0,000), and scrambled (p=0,000). It also showed statistically significant higher activity for objects vs scrambled (p=0,008). It showed no significant difference of response between objects and places (p=0,186) or scrambled and places (p=0,186).

The right LOC responded significantly more to objects than to faces (p=0,002), places (p=0,002) or scrambled (p=0,000). It didn't show any other significant difference of response,

either between faces and places (p=1,000), faces and scrambled (p=0,137) or places and scrambled (p=0,137).

The left LOC showed the same pattern of response. It responded significantly more to objects than to faces (p=0,000), places (p=0,002) or scrambled (p=0,000) and didn't show any significant difference of response between faces and places (p=0,343), faces and scrambled (p=1,000) or places and scrambled (p=0,343).

The right PPA showed a significantly higher response to places than faces (p=0,000), objects (p=0,040) or scrambled (p=0,000). It also responded significantly more to objects than faces (p=0,004) and scrambled (p=0,18). For faces and scrambled it showed no significant difference of response (p=0,635).

The left PPA showed the same pattern of response. It responded significantly more to places than faces (p=0,000), objects (p=0,048) or scrambled (p=0,000); it also showed significantly higher response to objects than to faces (p=0,001) or scrambled (p=0,010); and didn't show any significant difference of response between faces and scrambled (p=0,448).

Right/left ROI's response

Response in the right FFA was significantly higher than in the left FFA for all the categories (faces (p=0,16), objects (p=0,21) and places (p=0,21)) except scrambled to which no difference (p=0,182) was found between hemispheres.

Regarding the LOC there was no significant difference of response for faces (p=0,286), objects (p=1,000), places (p=0,477) or scrambled (p=0,722) between hemispheres.

Finally, concerning the PPA there was, also, no significant difference of response for faces (p=0,875), objects (p=0,754), places (p=0,754), or scrambled (p=0,754) between the two hemispheres.
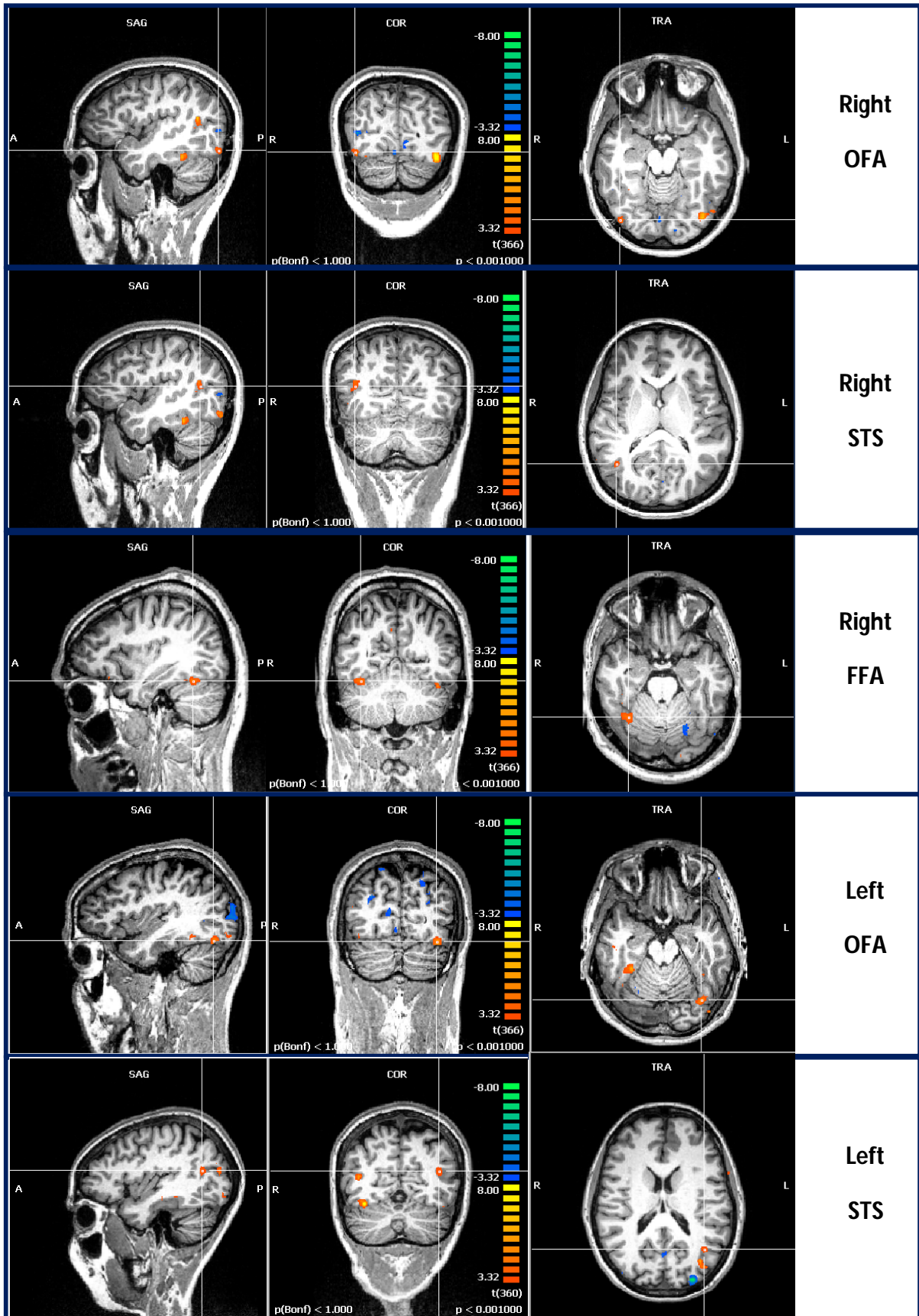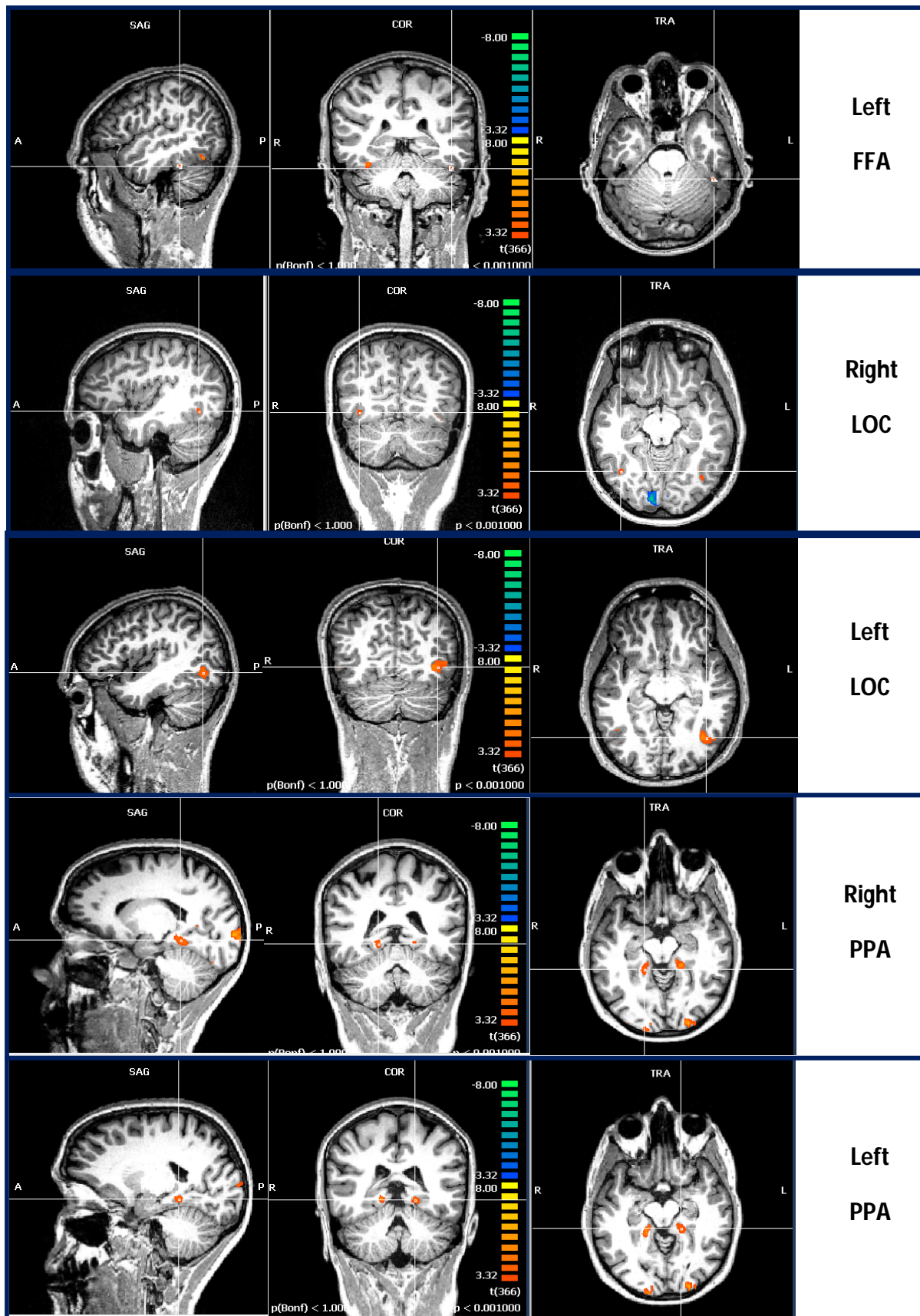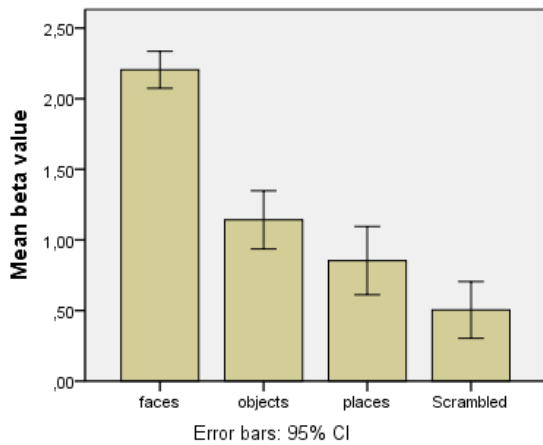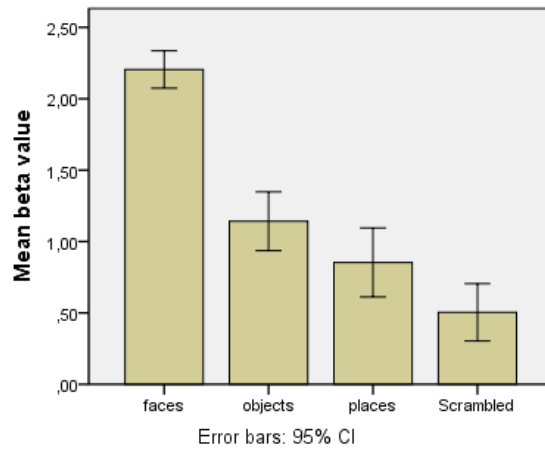
Figure 2 representative fMRI images for the regions of interest mentioned (from left to right: sagital, coronal and transverse planes).
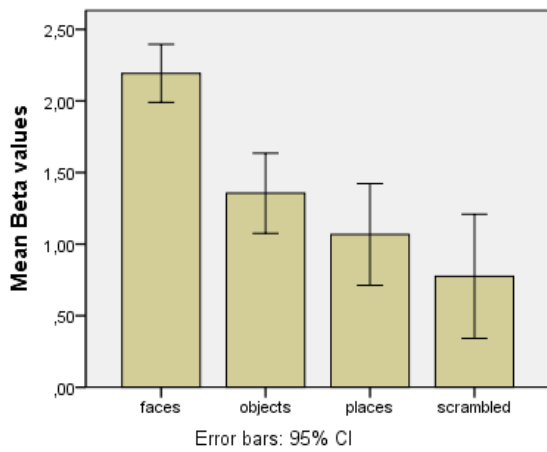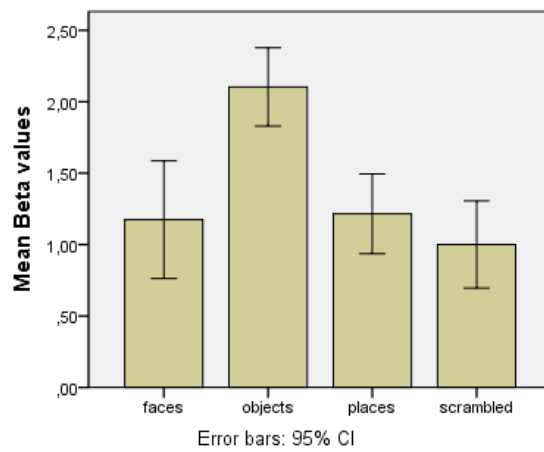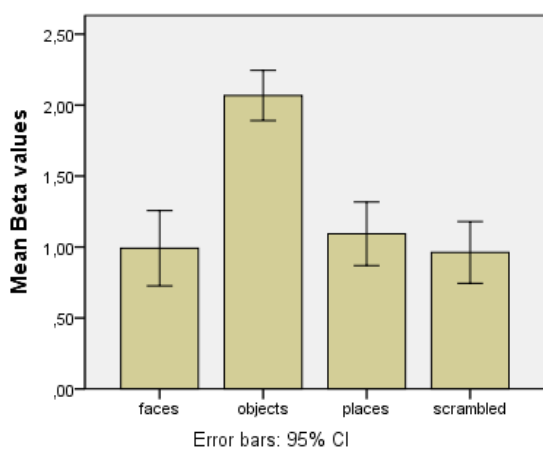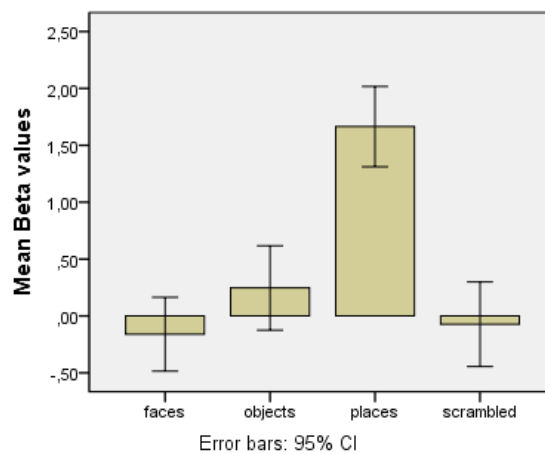
A - rFFA

B - lFFA

C - rOFA

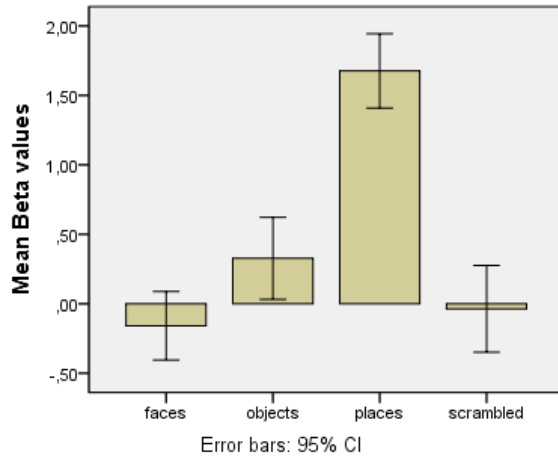D - rLOC

E – lLOC

F - rPPA

E - lPPA

Figure 4 graphical representation of mean parameter estimate of the response to each

category in each ROI.

Discussion

With this study we expected to fulfill three main goals: Verify the presence of the FFA, OFA, STS, LOC and PPA across different individuals and corresponding variability of localization; confirm category-preference of each area; and characterize each area's response to the non preferred categories. On the following sections we discuss these goals while briefly reviewing current knowledge.

1. ROI's Identification and localization variability

1.1 localizer protocol adequacy

Even though functional localizer protocols are a widespread technique in cognitive neuroscience there are some methodological concerns worth mentioning, these refer to: the kind of stimuli used, the task volunteers must perform, the portion of the brain scanned and the statistical criteria employed.

Although the influence of these parameters in localization has not, yet, been extensively studied recent evidence shows that task conditions do not appear to alter the variability of the locations of activations (Berman, Park et al. 2010).

We followed the traditional approach regarding stimuli creation by using inanimate images which although is less effective for identification of face selective ROI's than dynamic stimuli has been proven adequate by a large number of studies (Fox, Iaria et al. 2009; Berman, Park et al. 2010). As a novelty in our study we used simultaneously four categories of stimulus in a total of seven different classes (faces, objects (chais, tools and cars), places (landscapes and skylines) and scrambled versions of objects) instead of the usual just two or three in order to create a more robust localizer, that is one with small differences in the extent, strength and reliability of activation of ROI's and that simultaneously allowed identification of all the ROI's.

The application of a conjunction contrast analysis with *"preferred category > all the other categories of stimulus"* even though may seem too restrictive and does indeed limit the extent of the ROI's identified allowed us to tackle the question of ROI's specificity central to our work. Also it has been suggested by Rossion and colleagues (Rossion, Hanseeuw et al. 2012) that face selective areas other than the FFA are better identified using a more conservative contrast. Last, during data analysis it didn't seem to prevent the localization of the previously defined ROI's across subjects.

In our study we conducted a less than whole brain scan because we were only interested in the previously identified Regions of interest.

The statistical criteria used to define different localizers vary greatly between studies and this does in fact has major influence in the outcome of the localizer. A more lenient threshold allows recognition of a bigger number of clusters responding preferentially to a certain stimulus but may increase the number of voxels comprised by the responsive areas including voxels whose response is weak relative to the center of activation of that area; a stringent statistical threshold, on the other hand, may prevent cluster identification. Indeed the most adequate methodology seems to be using a different statistical threshold for each individual ROI (Rossion, Hanseeuw et al. 2012).

Usual take on this question is reasoning by investigators. We considered previous studies that demonstrated a significant rise of intra-subject variability when using highly selective thresholds ($p < 10^{-4}$ to 10^{-6}) compared to the minimally selective threshold of $p < 0,05$ (Duncan, Pattamadilok et al. 2009) and based on the probability maps obtained during data analysis we decided to use an intermediate threshold of $p < 0,001$, uncorrected.

1.2 FFA, OFA, STS, LOC and PPA identification

Our results showed the presence of the right and left FFA, right OFA, right and left LOC and right and left PPA in the majority of subjects scanned thus supporting the generalized idea that they can be found in the vast majority of normal subjects across the population.

As for the STS (left or right) and the left OFA, they were found in only half or less than our sample. Fox and colleagues (Fox, Iaria et al. 2009) reported a similar result when using static stimuli for localization of the pSTS and showed that this lack of identification was resolved with the utilization of dynamic stumuli, therefore it may happen that this incongruence of localization rests upon inadequacy of stimuli presented. Another explanation may be the contrast analysis or the threshold selected, both of which have already been discussed.

Apart from methodological issues one must consider the possibility that not all subjects present category-selective clusters. Lack of identification of the predefined ROI in at least one of the subjects scanned is the rule rather than the exception in neurophysiologic studies. Surprisingly and perhaps because it usually happens in only a few subjects per study it has never been regarded as relevant.

The presence of face-selective brain networks isn't indeed inate (Scherf, Behrmann et al. 2007; Scherf, Luna et al. 2011). Recalling that all our participants were healthy, it is possible that for a minority of the population a different developmental trajectory happens that explain lack of functional specialization without the usual loss of function, as prosopagnosia, widely reported in literature (Minnebusch, Suchan et al. 2009; Steeves, Dricot et al. 2009); moreover the existence of alternative facial stimuli processing pathways has been reported (Valdes-Sosa, Bobes et al. 2011).

Although it hasn't been studied so far one may hypothesize that this same phenomenon could happen to other types of stimuli, specifically in our case, places and objects. This is a question we believe to be relevant and deserve further study in future especially from larger population studies.

1.3 FFA, OFA, STS, LOC and PPA localization variability

With respect to localization variability three aspects merit consideration: first inter-subject variability in our study, second inter-study variability and third the existence of right/left hemispheric dominance.

The variability of ROI's peak coordinates amongst the subjects scanned in our study was evaluated by analysis of the confidence intervals which showed differences between extremes of between 6 and 15. Over these intervals, the STS presented an abnormally large deviation to mean of peak Y coordinate however the number of subjects in which it was identified doesn't provide enough statistical power to consider these values as a good approximation to the general population. One question thus poses: is this variability significant or not? Answer to this question requires scrutiny of the inter-study variability.

Regarding inter-study variability we were able to verify that it was present, however it is common practice to don't present any dispersion measure for mean peak coordinates and this limited analysis. Our results showed overall correspondence with peak coordinates mentioned in a number of studies but individual differences were found at different levels with no apparent rule.

It is also common practice to refer mean peak coordinates results as "correspondent to others previously referenced in literature" without mentioning how this correspondence analysis was preformed or its strength. Comparing the coordinates of different studies, in spite

of not considering dispersion measures, we reckon that the so mentioned "correspondence" is in fact approximated and arbitrary with, concordant with our results, no apparent rule.

This phenomenon is obviously influenced by the lack of uniformity of localizer protocols, again due to the methodological aspects already mentioned. To what extent is it explained by localizer protocols variance and not by inter-subject variability is another question that needs to be object of further study, especially with larger population samples.

Approach to this dilemma will ultimately provide some enlightening to the actual debate on the accuracy of functional localizer technique (Friston, Rotshtein et al. 2006; Saxe, Brett et al. 2006) to identify specific brain areas. For practical clinical purposes we believe that this variability of peak coordinates is not significant and does not invalidate this technique's value for clinical analysis and preoperative or intraoperative planning (Weiskopf, Sitaram et al. 2007), more important in this case is the identification variability already discussed.

Hemispheric dominance is well supported for face perception related areas not only by study cases of patients with acquired prosopagnosia (De Renzi 1986; Sorger, Goebel et al. 2007) but also neuroimaging studies (Gauthier, Tarr et al. 1999; Rossion, Hanseeuw et al. 2012). As a result it was no surprise to find the right FFA, OFA and STS in more subjects than the corresponding left ROI; and also a significant higher response for every stimuli except scrambled from the rFFA compared to the lFFA.

Hemispheric dominance of object or place perception has however been by far less studied.

With respect to the LOC, our data reinforce neuroimagiological evidence of bilateral activation (Ewbank, Schluppeck et al. 2005; Spiridon, Fischl et al. 2006). With respect to this subject we note that and the sparse study cases in literature refer to patients with bilateral

lesions (Karnath, Ruter et al. 2009) which impair recognition of eventual clues of hemisphere dominance.

Neuroimaging studies usually report bilateral activations of PPA (Epstein and Kanwisher 1998; Spiridon, Fischl et al. 2006; Park and Chun 2009) and although most case studies on pure topographic or landmark agnosia (a condition in which the patient is unable to perceive and identify familiar buildings and landscapes despite maintaining the ability to locate a route) report the necessity of existence of lesion in the right PPA for presentation of the cognitive deficit (Takahashi and Kawamura 2002) Martinaud and colleagues (Martinaud, Pouliquen et al. 2012) recently reported impairment in recognition of houses on two patients out of six who had left PPA lesions. In our study we found no right hemispheric dominance, in fact, one of the subjects scanned showed only activation in the left PPA, but no differences of strength of activation between hemispheres were found. Therefore our data supports the inexistence of hemispheric dominance for the case of the PPA.

2. *ROI's category-preference*

Our approach to ROI's category preference analysis followed two strategies: the first by running a GLM conjunction analysis in which the contrast applied was *"preferred category > all the others"*; and the second by performing a statistical Friedman Test to infer the existence of statistical differences between beta values regarding the different categories in each ROI.

Our results substantiate ROI's category preference in that they all (except the lFFA which is discussed next) showed a significant higher response to the expected preferred category than to all the others.

The left FFA although identified individually with the mentioned contrast in the GLM, on the group analysis with the Friedman test showed no significant difference of response

between faces and objects. We believe that the explanation for this is the fact that the GLM analysis has a higher statistical power than the Friedman test of beta-values. As a consequence the last will not detect the existence of differences when they are small which as discussed in the following section happens in the FFA for these categories of stimuli.

We must admit however that our approach that is using the same dataset for the definition and measurement of magnitude of response of the ROI's may have biased the results. In spite of this we note that our results are coincident with the ones presented by Downing and colleagues (Downing, Chan et al. 2006) on the regions they tested (FFA and PPA).

3. ROI's selectivity

ROI's selectivity analysis was based on their response to the non-prefered categories as measured by the Friedman test.

Regarding the non preferred categories the LOC showed no significant response to any of them. This result supports LOC's selectivity in line with other studies with more limited comparisons (Malach, Reppas et al. 1995).

The FFA and the PPA however showed significant higher response to the category of objects over scrambled and places or faces, respectively.

The FFA's lack of selectivity is not novelty (Downing, Chan et al. 2006; Rossion, Hanseeuw et al. 2012) however it still remains open to debate the reason why this happens. Different hypothesis have been suggested but recent greater amount of evidence, especially by high resolution imaging of the FFA (Grill-Spector, Sayres et al. 2006; Hanson and Schmidt 2011), supports the existence of several subpopulations of voxels selective for different visual stimuli categories.

The right OFA showed a similar response pattern to non preferred categories as the FFA. This doesn't invoke much surprise since they both belong to the core system of face

recognition (Gobbini and Haxby 2007) nonetheless more studies are needed that consider and analyze the other areas of this face recognition system in order to understand fully how it works namely if it is truly a domain specific network or not.

PPA's sensitivity to individual object images is in line with results from previous studies (Downing, Chan et al. 2006; Diana, Yonelinas et al. 2008). The reason for this phenomenon has not been studied with detail so far and it does fall out of the scope of our work. On light of today's knowledge we next purpose two explanations that would need further study.

One possibility for the lack of PPA's selectivity may be, in parallel with the hypothesis discussed for the case of the FFA, the existence of several subpopulations of voxels selective for different visual stimuli categories within the PPA. Indeed Kreiman and colleagues (Kreiman, Koch et al. 2000) by recording the activity of single neurons of the medial temporal lobe while subjects imagined images of different categories of stimuli (including images correspondent with stimuli categories of places and objects) demonstrated that only 17 out of 91 neurons tested in the hippocampus were category selective.

Another hypothesis is that single objects and scenes share similar low-level characteristics to some extent, namely the geometric regularity of lines and the lack of a characteristic pattern as it is recognized for faces (Caldara, Seghier et al. 2006; Schiltz and Rossion 2006). Consequently some of the response may be explained by response to these low-level features. This view is supported by previous work of Andrews and colleagues (Andrews, Clarke et al. 2010) whose results showed that the differences in the amplitude spectrum of places images explained, although in small proportion, the selectivity for places of the PPA.

Conclusion

We tested the response of previously well identified cortical areas, namely the FFA, OFA, STS, LOC and PPA to four different categories of images: faces, objects, places and scrambled versions of objects.

On doing so we were able to verify localization variability on three strands: regarding identification, we verified the presence of these ROI's, except the left and right STS and the left OFA, amongst *almost but not all* the subjects scanned; as for localization coordinates we found relative variability between subjects and studies; finally we confirmed hemispheric dominance of face selective areas but not of the PPA or LOC.

We also demonstrated ROI's expected category preference although our results demonstrate that only the LOC is strongly selective as opposed to the FFA and PPA which, apart from its preferred category, also show significant response to the category of objects.

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