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Alan Tucholka, Merlin Keller, Jean-Baptiste Poline, Alexis Roche, Bertrand Thirion. Surface-based versus volume-based fMRI group analysis: a case study. MICCAI 2009 Functional NeuroImaging Workshop, Sep 2009, Londres, United Kingdom. 2009. <hal-00776637>

HAL Id: hal-00776637

<https://hal.inria.fr/hal-00776637>

Submitted on 17 Jan 2013

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Surface-based versus volume-based fMRI group analysis: a case study

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Abstract. Being able to detect reliably functional activity in a population of subjects is crucial in human brain mapping, both for the understanding of cognitive functions in normal subjects and for the analysis of patient data. The usual approach proceeds by normalizing brain volumes to a common 3D template. However, a large part of the data acquired in fMRI aims at localizing cortical activity, and methods working on the cortical surface may provide better inter-subject registration than the standard procedures that process the data in 3D. Nevertheless, few assessments of the performance of surface-based (2D) versus volume-based (3D) procedures have been shown so far, mostly because inter-subject cortical surface maps are not easily obtained. In this paper we present a systematic comparison of 2D versus 3D group-level inference procedures, by using cluster-level and voxel-level statistics assessed by permutation, in random effects (RFX) and mixed-effects analyses (MFX). We find that, using a voxel-level thresholding, and to some extent, cluster-level thresholding, the surface-based approach generally detects more, but smaller active regions than the corresponding volume-based approach for both RFX and MFX procedures, and that surface-based supra-threshold regions are more reproducible by bootstrap.

1 Introduction

Studying the localisation and variability of brain activity across subjects is certainly one of the most important aspects of neuroimaging data analysis. The detection and the precise localisation of the BOLD signal are therefore crucial. Clearly, these steps are interacting as the detection of activity across subjects requires first to coregister the subjects brains to a common coordinate system. This step is most commonly performed in 3D space, by applying linear and non-linear warpings such that the anatomical and the functional images are coregistered to a common template, often chosen to be the MNI template. The standard approach to activation detection [1] consists in comparing the images from the different subjects on a voxel-by-voxel basis, computing a statistical map to test the presence of an activation in each voxel of the standard space. The ensuing multiple testing problem can be addressed directly at the voxel-level or

by testing the presence of activity inside clusters defined above a user-chosen threshold [2].

Spatial normalisation is therefore crucial to the whole procedure. Because a very large part of the data originates from the cortex, methods that work on the cortical surface may be more sensitive than those using the 3D data. It is well known that volume-based normalization may introduce inaccuracies in anatomical positioning of functional data, the magnitude of which may be estimated as 1cm in several cortical regions [3]. Several studies have shown that a coregistration based on the cortical surface may better align the functional signal across subjects [4,5,6,7]. For instance, it is difficult to account for the inter-subject variability of gyri size, shape or position in a 3D referential and such differences may displace functional activity to a different gyrus.

In this paper, we investigate whether surface-based approaches, that rely on a cortical surface referential, provide better constraints about the position of functional activity, and more precisely, whether this is reflected in state-of-the-art inter-subject statistical procedures. Following [4], we perform functional analysis on the cortical surface for a group of 25 subjects. The inter subjects analysis relies on matching the subjects cortical surface [4]. Additionally, we systematically compare the 2D and 3D statistical analysis and provide results on the difference in sensitivity of the two approaches for different tests, for a given control of the type I error. More specifically, we use for the comparison mixed- and random-effects inference at the voxel and at the cluster level [8] and assess their bootstrap reproducibility. These statistical analyses provide the cognitive neuroscientist or clinician with solid information on the sensitivity that can be achieved with surface-based methods.

2 Materials and Method

2.1 Data and pre-processing

Data were acquired from 25 subjects who performed a functional localizer protocol as described in [9]. This protocol is intended to activate multiple brain regions in a very short time (128 volumes in 5 minutes) with many experimental conditions to allow the application of many different functional contrasts. Anatomical and functional data was acquired on a 1.5T GE scanner. The functional data was first corrected from the EPI distortions using field maps. Next, a standard pre-processing (correction of differences in slice timing, motion correction and anatomo-functional co-registration) was performed using the SPM5 software on all subjects.

FreeSurfer [4] was used to segment and reconstruct the cortical surface from T1 MRI data of each subject, providing the white matter mesh for both hemispheres (note that the aim of this work is not to evaluate the quality of this segmentation). This provides a common spherical coordinate system for each hemisphere in each subject. Pre-processing of the data includes *i*) segmentation of the white matter on a triangular mesh, *ii*) detection of the deepest sulci,

iii) inflation of the white surface on a sphere (brain-sphere), *iv*) deformation to match the deepest sulci positions on the template model.

All data are then converted to the standard GIFTI format for further processing (to obtain a node-by-node correspondence of the resampled brains): *i*) a regular sphere (icosphere) of diameter equal to the brain-sphere is created, *ii*) this sphere is refolded onto the original cortical surface of each subject while preserving node-to-node correspondence of the icosphere mesh between subjects. The resulting gray/white interface mesh is called resampled mesh.

In Fig. 1, two meshes are presented after affine coregistration to the MNI template of the corresponding T1 images. The cross corresponding to the top of the posterior Sylvian Fissure sulcus on the left subject appears on the right subject in a very different anatomical position. The surface-based correspondence (blue balls) is clearly much more accurate.

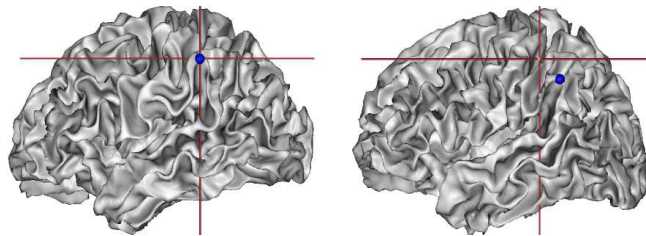


Fig. 1. Definition of the top of the posterior Sylvian Fissure sulcus in two brains in a normalized space (MNI space, affine coregistration). The cross corresponds to the same voxel coordinates. The blue ball correspond to the same node after brain resampling.

An average-brain of the 25 subjects was created for visualisation of the results. Each resampled mesh is coregistered to a normalized space (MNI/Talairach space), then an average brain is obtained by computing the mean 3D position of each node through all subjects in that space.

Functional images were then projected onto the resampled gray/white interface mesh of each subject using the method described in [10]. A General Linear Model (GLM) analysis was applied at each and every node and the activation maps for the *i*) left versus right button presses, *ii*) sentence listening versus sentence reading, *iii*) computation versus reading *iv*) reading versus passive checkerboard viewing contrasts.

2.2 Group data modeling

In this work, $n = 25$ subjects are considered. For each subject i , and at any node of the resampled mesh, let $\hat{\beta}_i$ be the estimation of the BOLD effect related to some some effect of interest (note that this section is easy to generalize to a linear combination, *i.e.* contrast of effects). $\hat{\beta}_i$ is distributed around the true effect β_i : $\hat{\beta}_i = \beta_i + e_i$ with $e_i \sim \mathcal{N}(0, s_i^2)$ where the estimation variance s_i^2 is known from

the first-level General Linear Model (GLM). We assume that $\beta_i = \beta_G + \varepsilon_i$ where $\varepsilon_i \sim \mathcal{N}(0, \sigma^2)$ and β_G is the population-level effect. We thus have :

$$\hat{\beta}_i = \beta_G + \varepsilon'_i, \quad \varepsilon'_i \sim \mathcal{N}(0, \sigma^2 + s_i^2), \quad (1)$$

where σ^2 is the between-subject variance. This is a generalization of the RFX model in [1] which neglects the estimation variance, *i.e.* it assumes $s_i^2 \equiv 0$. Both β_G and σ^2 are then estimated by maximizing the log-likelihood of the model specified in Eq. (1) using the Expectation-Maximization (EM) algorithm in [11]. The following log-likelihood ratios are computed to test the positivity of β_G :

$$\mathcal{L}_{MFX} = \frac{\sup_{\sigma^2, \beta_G > 0} \prod_{i=1}^S \mathcal{N}(\hat{\beta}_i; \beta_G, \sigma^2 + s_i^2)}{\sup_{\sigma^2} \prod_{i=1}^S \mathcal{N}(\hat{\beta}_i; 0, \sigma^2 + s_i^2)}, \quad (2)$$

$$\mathcal{L}_{RFX} = \frac{\sup_{\sigma^2, \beta_G > 0} \prod_{i=1}^S \mathcal{N}(\hat{\beta}_i; \beta_G, \sigma^2)}{\sup_{\sigma^2} \prod_{i=1}^S \mathcal{N}(\hat{\beta}_i; 0, \sigma^2)} \quad (3)$$

Note that computing \mathcal{L}_{RFX} is equivalent to performing a t-test.

2.3 statistical calibration

The distribution of the statistics in Eq. (2-3) under the null hypothesis ($\beta_G = 0$) is unknown, but can be estimated very simply by a randomization procedure, in which the statistics are recomputed after a sign swap of the observed effects $\hat{\beta}_i$. Under the hypothesis that the distribution of the true effects is symmetric about 0 under the null hypothesis, this procedure yields an exact (possibly conservative) specificity for the test. In order to control the family-wise error rate (FWER), *i.e.* the probability of detecting one false positive over the search domain, we consider the distribution of the maximal statistic under the null hypothesis. For a chosen FWER α , this yields a voxel- or vertex- level corrected threshold.

A more sensitive approach to detect extended regions consists in first thresholding the statistics map at a given level (corresponding *e.g.* to $p < 10^{-3}$ uncorrected), and then to estimate the distribution of size (area or volume) of the supra-threshold clusters under the null hypothesis. To solve the multiple comparison issue, the size of the maximal cluster is tabulated under the null hypothesis. Once again, the quantile α of this simulated distribution yields a cluster-level corrected threshold.

In order to enable the comparison of volume-based and surface-based approaches, we systematically project the clusters obtained from the volume-based approaches onto the average surface.

3 Results

To compare the surface-based versus the volume-based group-level analysis, we used four different methods (RFX voxel-level, MFX voxel-level, cluster-level

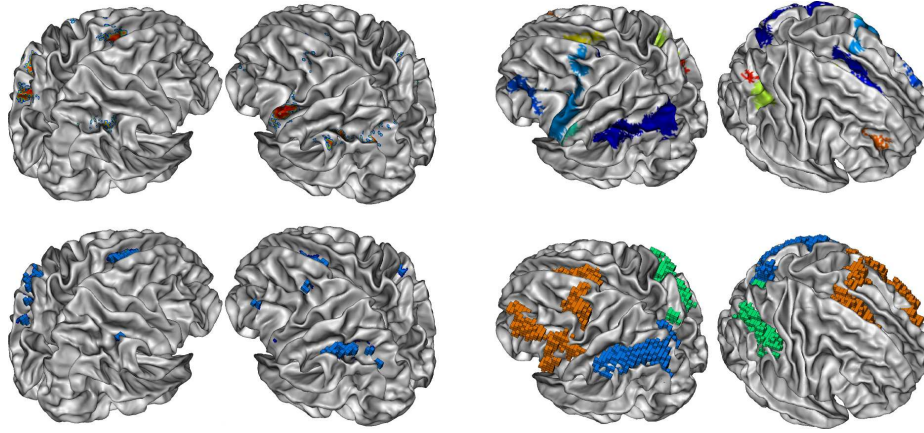


Fig. 2. **Left:** Surface-based (top line) versus volume-based (bottom line) voxel-level RFX group analysis results for the *computation* task. **Right:** Cluster-level RFX group analysis for the *computation* task on the surface (top line) and in the volume (bottom line).

RFX and cluster-level MFX) on four functional contrasts: *computation versus reading*, *reading versus passive checkerboard viewing*, *left versus right button press* and *sentence listening versus sentence reading* that we refer to as *computation*, *reading*, *motor* and *auditory*. The voxel-level analysis finds only a few active voxels with the volume-based method, while the activity map on the surface contains a significant number of active nodes in more brain regions (see e.g. the regions activated for the *computation* task, in the left part of Fig. 2, in particular the bottom part of the pre-central gyrus).

The same tendency can be observed with the cluster-level analysis (see Table 1), although the effect is more subtle (see Fig. 2): The surface-based procedures detected many more functional clusters than the volume-based methods, but these clusters are much smaller. This indicates that:

- Many clusters that are merged in 3D are split into different components on the surface (see Fig. 2); this means that several different functional regions are merged into one cluster in volume-based analyses. While these regions are close in Euclidian distance (in the volume space), there are distant once projected on the surface (e.g. on a different gyrus).
- The size threshold is much *lower* for the surface-based approach than for the volume-based approach, in the sense that the surface-based approach is able to extract finer structures than the volume-based approach.

The MFX statistic never detects any voxels or clusters activated in the volume, while the results on the surface are similar, though weaker than with the RFX statistic. The reduced sensitivity with mixed effects is unexpected and can hint at a first-level model mis-specification, hence a defect of the model design. The results in terms of activated area are given in Table 2; the surface-based

Contrast	Computation		Reading		Left Motor		Auditory	
	RFX	MFX	RFX	MFX	RFX	MFX	RFX	MFX
Surface	14	17	6	7	8	6	4	4
Volume	5	0	4	0	4	0	2	2

Table 1. Comparison of the number of clusters found using RFX and MFX methods on volume-based and surface-based approaches.

Cluster-level								
Contrast	Computation		Reading		Left Motor		Auditory	
	RFX	MFX	RFX	MFX	RFX	MFX	RFX	MFX
Surface	131.6	135.1	26.8	28.9	65.4	63.8	96.6	96.7
Volume	105.1	0	97.6	0	45.3	0	99	109.1

Voxel-level								
Contrast	Computation		Reading		Left Motor		Auditory	
	RFX	MFX	RFX	MFX	RFX	MFX	RFX	MFX
Surface	17.1	15.4	0.5	0.4	23.9	22.7	46.5	46.9
Volume	10.8	0	15	0	15.3	0	46.9	0

Table 2. Comparison of the area of supra-threshold regions in cm^2 of volume-base (after projection) and surface-base approaches, for MFX and RFX statistics, with both cluster-level and voxel-level inference.

approach detects wider regions for the computation task, and less for the reading task when considering RFX. It is generally more sensitive using MFX.

Additionally, we studied the bootstrap reproducibility of the supra-threshold regions in the surface- and volume-based procedures: we created $P = 10^3$ surrogate groups and computed how many time a vertex or a voxel had a p-value below 10^{-3} , uncorrected. We systematically found a higher proportion of consistently supra-threshold regions in the surface-based method as illustrated in Fig. 3. This effect was quantified using the a classification index based on this histogram [12], which was consistently higher for the surface-based approach (data not shown).

4 Discussion

We have shown in this work that surface-base approaches detects activity in more brain regions when voxel-based detection is performed (voxel-level RFX, voxel-level MFX) compared to the volume-based approach. This gain in sensitivity is probably related to two factors:

- The search domain is smaller (*i.e.* it consists in the cortex only), while the volume-based approach tests also white matter and cerebro-spinal fluid regions. This effect is visible in the bootstrap reproducibility histogram shown in Fig. 3. The price to pay is that sub-cortical structures (thalamus, basal ganglia, cerebellum etc.) are not considered in the surface-based representations.

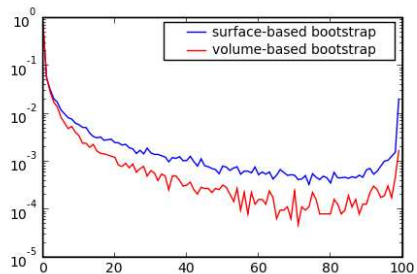


Fig. 3. Bootstrap reproducibility of RFX thresholding procedures for the motor contrast: This is the normalized histogram of the reproducibility map that indicates how frequently a voxel or vertex has a supra-threshold activity, with a threshold corresponding to $p < 10^{-3}$, uncorrected: the surface-based approach has a much higher proportion of consistently supra-threshold regions.

- The coregistration of the data is certainly more accurate, as illustrated in Fig. 1 with an anatomical landmark. Note that this better coregistration could have the effect to reduce the spread of significant regions by removing a spatial uncertainty on their position.

When considering cluster-level statistics, the gain is more subtle, as discussed in the previous section. More precisely, it can be expected that the finer coregistration related to the surface-based approach has a mitigated effect on the detection of large clusters: volume-based approaches tend to join smaller clusters which are close in Euclidean space, but relatively distant on the geodesic (surface-based) representation. It should also be reminded that cluster-level analyses allow only a weak control of false detections: a supra-threshold cluster has the property to contain at least one voxel for which the null hypothesis can be rejected, but does not allow to conclude that all the voxels or nodes in that cluster are indeed active.

Moreover, when considering tasks with asymmetric activity, such as reading, the volume-based approach can miss significant activity in weakly-activated hemisphere, compared to the surface-based approach (data not shown).

However, in surface-based approaches, if the resolution is not fine enough, or if EPI distortions are not perfectly corrected, the functional signal may be diluted to neighbouring gyri, creating false supplementary clusters (as we can see on Fig. 4). An interesting question that can still be addressed is how a surface coregistration procedure based on geometric features such as Freesurfer would compare to representations of the surface that take into account sulcus labelling. Some recent experiments have indeed shown that sulcus-based coordinate systems tend to stabilize the position of some functional landmarks [13].

Conclusion Performing fMRI group analysis on the cortical surface instead of the brain volume may benefit to the detection of some foci of activity, and thus

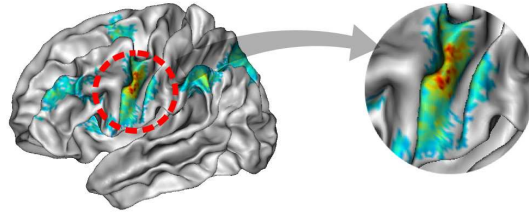


Fig. 4. The activity on the pre-central gyrus has also been projected on the neighbouring gyrus (post-central gyrus).

yield more specific, and possibly more sensitive analysis than standard volume based approaches. It may thus reveal sharper contrasts in the functional data and thus provide more reliable markers of brain functional anatomy. It will also be important to assess whether surface-based analysis better discriminates population of controls and patients than standard volume-based methods.

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