Atlas-based classification algorithms for identification of informative brain regions in fMRI data

Juan E. Arco[1], Paloma Díaz-Gutiérrez[1], Javier Ramírez[2], María Ruz[1*]

[1] Mind, Brain and Behavior Research Centre (CIMCYC),
[2] Department of Signal Theory, Networking and Communications, University of Granada, Granada 18071, Spain,

Abstract

Multi-voxel pattern analysis (MVPA) has been successfully applied to neuroimaging data due to its larger sensitivity compared to univariate traditional techniques. Although a Searchlight strategy that locally sweeps all voxels in the brain is the most extended approach to assign functional value to different regions of the brain, this method does not offer information about the directionality of the results and does not allow studying the combined patterns of more distant voxels.

In the current study, we examined two different alternatives to searchlight. First, an atlas-based local averaging (ABLA, Schrouff et al., 2018) method, which computes the relevance of each region of an atlas from the weights obtained by a whole-brain analysis. Second, a Multiple-Kernel Learning (MKL, Rakotomamonjy et al., 2008) approach, which combines different brain regions from an atlas to build a classification model. We evaluated their performance in two different scenarios where differential neural activity was large vs. small, and employed nine different atlases to assess the influence of diverse brain parcellations.

Results show that all methods are able to localize informative regions where differences were large, demonstrating stability in the identification of regions across atlases. Moreover, the sign of the weights reported by these methods provides the sensitivity of multivariate approaches and the directionality of univariate methods. However, in the second context only ABLA localizes informative regions, which indicates that MKL leads to a lower performance when the atlas does not match the actual brain functional parcellations. These results could improve by employing machine learning algorithms to compute atlases that fit specifically the brain organization of each subject.

Keywords: Multi-voxel pattern analysis, Multiple Kernel Learning, Searchlight, Atlas-based local averaging, fMRI, permutation testing.

1. Introduction

The use of machine learning in neuroscience has considerably increased in the last few years. There are many previous studies that have employed these methods in clinical contexts, providing tools for computer-aided diagnosis of different neurological

* Corresponding author

disorders, such as Alzheimer's (Arco et al., 2015), Parkinson's disease (Choi et al., 2017), epilepsy (Del Gaizo et al., 2017) or brain computer interfaces in quadriplegic patients (Blankertz et al., 2007; Nurse et al., 2015). In this case, obtaining the maximum decoding performance is the main aim, whereas the source of information is not of interest. On the other hand, these methods can also be used for a better cognitive understanding of the human brain, where the main aim is not the prediction itself but the identification of the regions involved in specific cognitive functions. Hebart and Baker (2017) remarked the importance of isolating the use of multivariate decoding for prediction from its use in interpretation, and the need of considering them as two independent frameworks. In the interpretation context, Multi-voxel pattern analysis (MVPA) has replaced the traditional univariate methods due to the larger sensitivity that it provides (Haynes and Rees, 2006; Norman et al., 2006). Moreover, this method localizes where information is contained based on the distribution of spatial patterns instead of evaluating mean differences as univariate approaches do. However, MVPA brings some crucial points to be considered: is it possible to use these techniques in a different context from which they were developed for? If so, would it be necessary to modify the existing algorithms to accomplish the new goals? Finding the most adequate method for each specific context is of vital importance, and in the current investigation we aimed to compare the sensitivity of different approaches and to propose some variations to assess the suitability of these methods in the cognitive neuroscience field.

From the identification perspective, the simplest approach is to use a region of interest (ROI) based on *a priori* knowledge, so that classification is only performed in the voxels contained in the region. The performance of the algorithm highly depends on how well the regional hypothesis fits the observed data. Haxby et al. (2001) demonstrated that the representations of faces and objects were differentially distributed in the ventral temporal cortex, whereas Haynes and Rees (2005) showed that there is an orientation-selective processing in the primary visual cortex (V1). Other studies detected distributed patterns of activity in the visual cortex (Cox and Savoy, 2003; Kamitani and Tong, 2005), whereas Poldrack (2007) highlighted the Type 1 error reduction when a statistical test is applied to each ROI. However, when there is not a straightforward hypothesis regarding the regions involved in specific computations, the whole brain may need to be explored. The main drawback of whole-brain analyses is related to the curse of dimensionality: in fMRI studies, there are usually many more features (e.g. voxels) than samples (e.g. images or volumes), which complicates the definition of a classification model to separate the two classes (Fort and Lambert-Lacroix, 2005). Alternatively, feature-selection methods find a subset of informative features (e.g. voxels in fMRI) that will be the input of the subsequent classification. As an example, *t*-tests can be used to restrict the voxels fed to the classifier to those that differ between the classes. Previous studies have employed this method to localize the regions associated with different pathologies and psychological contexts (Arco et al., 2015; Balci et al., 2008; Haynes and Rees, 2005; De Martino et al., 2008; see Mwangi et al., 2014, for a detailed review).

One of the most appealing approaches for identification of cognitive informative regions is the Searchlight technique (Kriegeskorte et al., 2006), a method that offers results potentially easier to interpret due to its larger spatial precision and no need to define a specific ROI. Searchlight produces maps of accuracies from small spherical regions centered on each voxel of the brain. For each sphere, a classification analysis is performed, and the decoding performance is assigned to the central voxel. There are many studies that have successfully used this technique (e.g. Chen et al., 2017; Cichy et al., 2016; Coutanche et al., 2011; González-García et al., 2017; Loose et al., 2017; Qiao et al., 2017). However, it also has some disadvantages and limitations to consider. Searchlight performance depends on the size of the sphere; the larger the radius of the sphere, the larger the number of significant voxels, even when the size of the informative regions stayed fixed (Etzel et al., 2013; although see Arco et al. 2016). Another drawback is that the accuracy of the classification within a certain sphere is associated with the central voxel, which obviates the possibility that only a few voxels of the total in the sphere truly contain information. As a result, some voxels may be marked as significant only because they are at the center of a sphere that contains informative voxels, leading to somewhat distorted results (see Figure 3 in Etzel et al., 2013 for an extreme example). Another problem is its large computational cost. Each Searchlight analysis entails a massive number of classifications (one for each voxel of the brain), increasing the computational time compared to other simpler approaches. This time cost increases exponentially when different values of the parameters associated with the classifier are evaluated to find the one with the largest performance (grid search) and also when permutation tests are used to evaluate the statistical significance of the results.

There are other alternatives based on atlas that do not suffer from this large computational cost. This is the case of Multiple Kernel Learning (MKL, Lanckriet et al., 2004), a method that uses *a priori* knowledge of brain organization to guide the decision of the classifier. Specifically, this approach extracts information from brain parcellations provided by an atlas to maximize the performance of the classification algorithm, and ranks the regions according to their importance in the decision. A crucial aspect is the two-level hierarchical model that this approach entails. The regions used for classification have an associated weight, which indicates their contribution to the model. Voxels within each region have a similar weight value. Thus, MKL offers information both at the region and at the voxel level. Previous studies have used this method in the context of neuroimaging, e.g. to discriminate between Parkinsonian neurological disorders (Adeli et al., 2017; Filippone et al., 2013), identification of attention deficit hyperactivity disorder (ADHD) patients (Dai et al., 2017; Qureshi et al., 2017) and localization of informative regions (Schrouff et al., 2018). This approach leads to a sparse solution, which means that only a subset of regions is selected to contribute to the decision function (similarly to feature-selection methods). However, this decreases its ability to detect informative regions, which is not recommended when identification of informative areas is the main aim. Schrouff et al. (2013a) proposed another decoding-based method based on local averages of the weights from each region defined in an atlas. This is known as Atlas-based local averaging (ABLA). First, a whole-brain classification is performed, leading

to a weight map summarizing the contribution of each voxel. Then, the weights defined in each region of the atlas are averaged and normalized by the size of the region. This yields a score of the informativeness of each region. This means that this approach builds only one classification model since the summary of the weights is done *a posteriori*. In contrast, MKL combines the different regions of the atlas as part of the learning process, so that using a different atlas will result in a different classification, with the subsequent increase in computational cost compared with ABLA.

Previous research has usually employed atlas-based methods in classification contexts, where the main aim is to obtain the largest accuracy as possible. However, the validity of these approaches in an identification scenario (where the goal is to find the informative brain regions during a certain cognitive function) is yet unknown. Therefore, in this study, we aimed at evaluating the performance of different atlas-based approaches in an fMRI experiment, in two contexts with differential changes in neural activity. To do so, we modified the MKL and ABLA methods to better fit the requirements of an identification context instead of a classification one, and compared the results to those obtained by Searchlight. Specifically, we proposed an L2-version of MKL, which avoids sparsity by allowing all regions of the corresponding atlas to contribute to the model. Moreover, to assess the suitability of these approaches we employed nine different atlases to examine how different brain parcellations influenced the identification of informative regions of MKL and ABLA. We predicted that L2-MKL and ABLA would be more sensitive than L1-MKL, and that they would show a larger overlap with Searchlight results. For a contrast with large differences in the neural activity, we expected overlap between the significant regions obtained by all the approaches. However, this overlap would decrease for the contrast testing more subtle difference in neural activity. In this case, we hypothesized that the specific organization of the brain proposed by each atlas would highly affect the identification of significant regions.

2. Material

2.1 Participants

Twenty-four students from the University of Granada (M = 21.08, SD = 2.92, 12 men) took part in the experiment and received an economic remuneration (20-25 euros, depending on performance). All of them were right-handed with normal to corrected-to-normal vision, no history of neurological disorders, and signed a consent form approved by the local Ethics Committee.

2.2 Image Acquisition

fMRI data were acquired using a 3T Siemens Trio scanner at the Mind, Brain and Behavior Research Centre (CIMCYC) in Granada (Spain). Functional images were obtained with a T2*-weighted echo planar imaging (EPI) sequence, with a TR of 2000

ms. Thirty-two descendent slices with a thickness of 3.5 mm (20% gap) were obtained (TE = 30 ms, flip angle = 80°, voxel size of 3.5 mm^3). The sequence was divided in 8 runs, consisting of 166 volumes each. After the functional sessions, a structural image of each participant with a high-resolution T1-weighted sequence (TR = 1900 ms; TE = 2.52 ms; flip angle = 9°, voxel size of 1 mm^3) was acquired.

We used SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) to preprocess and analyse the neuroimaging data. The first 3 volumes were discarded to allow for saturation of the signal. Images were realigned and unwarped to correct for head motion, followed by slice-timing correction. Afterwards, T1 images were coregistered with the realigned functional images. Then we used slice timing correction to account for differences in slice acquisitions. To better preserve the spatial configuration of activations in individual subjects, images were not smoothed or spatially normalized into a common space.

2.3 Design

The task contained two events in each trial, first a word (positive, negative or neutral in valence) and second two numbers, to which participants had to respond. They performed a total of 192 trials, arranged in 8 runs (24 trials per run), in a counterbalanced order across participants. Each trial started with the word for 1000 ms, followed by a jittered interval lasting 5500 ms on average (4-7 s, +/0.25). Then, the numbers appeared for 500 ms followed by a second jitter interval (5500 ms on average, 4-7 s, +/0.25). The first event (words), was modelled as the duration of the word and the variable jittered interval, yielding a global duration ranging from 5 to 8 seconds. The second event (numbers) was modelled as an impulse function (Dirac delta), i.e. with zero duration, as explained in Henson (2005). The different duration of the events corresponds to the cognitive nature of the underlying processes, extended in the case of the preparation triggered by the words and short in the case of the quick decision linked to the monetary offers.

To test the reliability of the different approaches (sensitivity and overlap of the significant regions with those obtained by Searchlight), we focused on two different classification analyses. First, we aimed at discriminating between the neural activity associated with accepting *vs.* rejecting offers (from now on, *decision* classification). The hand used to respond was counterbalanced across participants, which means that odd subjects used the right/left hand to accept/reject an offer, whereas in even subjects the order was the opposite. Second, we focused on distinguishing the positive *vs.* negative valence of the words (e.g. Lindquist et al., 2015; from now on, *valence* classification) that were equated in number of letters, frequency of use and arousal (Gaertig et al., 2012). We employed a Least-Squares Separate (LSS) model to obtain an accurate estimation of the neural activity (Turner et al., 2012). This method is based on iteratively fitting a new GLM for each trial with two predicted BOLD time courses: one for the target event and a nuisance parameter estimate that represents the activation for the rest of the events. Previous studies have shown that this is the best approach for isolating the activity in contexts like this experiment (Abdulrahman and Henson, 2016; Arco et al., in press),

where overlap and collinearity are large.

2.4 Atlases

In this study, we used 9 atlases to assess the reliability of the informative regions obtained by the three atlas-based classification methods. They differ in three main aspects: the information (anatomical, functional or multimodal) that they use to cluster the brain regions, the number of resulting regions (from 12 to 400) and the algorithms that implement the parcellation (a wide spectrum, from the *k*-means clustering to Bayesian models).

2.4.1. BASC Cambridge

This atlas was computed from group brain parcellations generated by the BASC (Bootstrap Analysis of Stable Clusters) method, an algorithm based on *k*-means clustering to identify brain networks with coherent activity in resting-state fMRI (Bellec et al., 2010). These networks were generated from the Cambridge sample from the 1000 Functional Connectome Project (Liu et al., 2009). Based on this framework, different atlases were built depending on the number of networks defined (Urchs et al., 2015). In this study, we used four versions with 12, 20, 36 and 64 regions.

2.4.2 AICHA

This atlas covers the whole cerebrum and is based on resting-state fMRI data acquired in 281 individuals (Joliot et al., 2015), and also relies on *k*-means clustering. One interesting feature is that it accounts for homotopy, relying on the assumption that a region in one hemisphere has a homologue in the other hemisphere. This leads to 192 homotopic region pairs (122 gyral, 50 surcal and 20 gray nuclei).

2.4.3 Brainnetome

Fan et al (2016) introduced an atlas based on connectivity using in vivo diffusion MRI (dMRI) and fMRI data acquired in 40 subjects. It divides the human brain into 210 cortical and 36 subcortical regions, providing detailed information based on both anatomical and functional connections. The number of regions was computed by using a cross-validation procedure to maximize consistency across subjects (Fan et al., 2014; Liu et al., 2013). All functional data, connections and brain parcellations are freely available at http://atlas.brainnetome.org.

2.4.4 Yeo2011

A clustering algorithm was used to parcellate the cerebral cortex into networks of functionally coupled regions. The method employed assumes that each vertex of the

cortex belongs to a single network (see Yeo et al., 2011). Different brain networks exhibiting brain coactivations were identified from fMRI data of 1000 subjects. There are two versions available depending on the number of networks considered (7 or 17). We employed the latter for the subsequent analysis as it offers a more detailed parcellation of the brain. This atlas is preinstalled in Lead-dbs toolbox (http://www.lead-dbs.org).

2.4.5 Harvard-Oxford

Clustering in this atlas was performed with the automatic algorithm presented in Desikan et al. (2006), which subdivides structural magnetic resonance data of the human cerebral cortex into gyral based regions of interest (ROI). Its validity was evaluated by computing correlation coefficients and mean distances between these results and manually identified cortical ROIs. Forty-eight cortical regions were obtained from data of 37 subjects. The resulting atlas is freely distributed with FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/).

2.4.6 Schaefer

This atlas adds novel parcellations and a larger precision to the brain networks published in Yeo et al., (2011) by using a local gradient approach to detect abrupt transitions in functional connectivity patterns (Schaefer et al., 2017). These transitions are likely to reflect cortical areal boundaries defined by histology or visuotopic fMRI. The resulting parcellations were generated from resting-state fMRI based on 1489 participants (see original paper for further details). There are several versions of this atlas depending on the number of regions the brain is divided into (400, 600, 800 or 1000), but we selected the first one to maintain reasonable speed on computation analyses.

3. Methods

In this study, we considered four different algorithms based on linear classifiers. First, the atlas-based local averaging method (ABLA) presented in Schrouff et al. (2018). Second, an L1-MKL version of the algorithm introduced in (Rakotomamonjy et al., 2008) and implemented in the PRoNTo toolbox (Schrouff et al., 2013a). Third, a modification of the L1-MKL to use an L2-nom instead of an L1 (from now on, L2-MKL) to avoid the sparsity that L1 leads to and the subsequent decrease in detecting informative regions. Finally, we used a Searchlight approach as a reference to contrast the validity of these methods.

3.1 Atlas-based local averaging (ABLA)

This method is used after performing a whole-brain analysis in which all voxels of the brain are used as input to the classification algorithm. A linear classifier leads to a

weight map where each value corresponds to the contribution of each voxel to the decision function. ABLA computes a normalization of the average weight for each region of an atlas that summarizes the importance of this region in a certain classification context. From a mathematical perspective, it is possible to specify a linear SVM (Bennett and Blue, 1998; Burges, 1998) classification rule f by a pair of $(\boldsymbol{w}, \boldsymbol{x})$, from equation:

$$f(x) = \langle \boldsymbol{w}, \boldsymbol{x}_i \rangle + b \qquad (1)$$

where $\boldsymbol{w}$ is the weight vector, $\boldsymbol{x}_i$ is the feature vector and b is the error term. Thus, a point x is classified as positive if $f(x) > 0$ or negative if $f(x) < 0$. The decision function is based on a linear rule that maximizes the geometrical margin between the two classes, and can be obtained by solving the optimisation problem described in Boser et al. (1992):

$$\frac{1}{2}\|\boldsymbol{w}_m\|^2 + C\sum_i \xi_i \quad \text{subject to} \quad y_i(\langle \boldsymbol{w}, \boldsymbol{x}_i \rangle + b) \geq 1 - \xi_i \quad \forall_i \xi_i \geq 0 \quad \forall_i \qquad (2)$$

The solution to the optimization problem can be written as:

$$\boldsymbol{w} = \sum_{\boldsymbol{i=1}}^{\boldsymbol{n}} y_{\boldsymbol{i}} \alpha_{\boldsymbol{i}} \boldsymbol{x}_{\boldsymbol{i}} \qquad (3)$$

after applying the Lagrangian multipliers. Substituting the value of $\boldsymbol{w}$ in Equation 1, it is possible to rewrite the decision function in its dual form as

$$f(\boldsymbol{x}_i) = \sum_{\boldsymbol{i=1}}^{\boldsymbol{n}} y_{\boldsymbol{i}} K(\boldsymbol{x}, \boldsymbol{x}_i) + b \qquad (4)$$

where α_i and b represent the coefficients to be learned from the examples and $K(\boldsymbol{x}, \boldsymbol{x}_i)$ is the kernel function characterizing the similarity between samples $\boldsymbol{x}$ and $\boldsymbol{x}_i$.

Once the significant model was obtained, we extracted the weight maps that guided the decision of the classifier. Then, we computed the normalized weight for each region in the atlas as the average of the absolute value of the weights contained in each region, as explained in Schrouff et al. (2018). Equation 5 summarizes mathematically this computation:

$$NW_{ROI} = \frac{\sum_{v \in ROI} |W_v|}{m_{ROI}} \qquad (5)$$

with v representing the index of a voxel in the weight map, W_v its weight and m_{ROI}, the number of voxels in region ROI.

3.2 Multiple Kernel Learning

This method combines the information from the different brain regions of an atlas to build the classification model, in contrast to the use of the corresponding brain organization *a posteriori* done in ABLA. Specifically, MKL combines different kernels

and optimizes their contribution to the model to obtain the highest performance. As a result, this approach offers information at two levels: regions and each voxel within them. Mathematically, the decision function is computed as a linear combination of all these basis kernels as stated in Lanckriet et al. (2004):

$$K(\boldsymbol{x},\boldsymbol{x}') = \sum_{m=1}^{M} d_m K_m(\boldsymbol{x},\boldsymbol{x}') \quad \text{with} \quad d_m \geq 0, \sum_{m=1}^{M} d_m = 1 \qquad (6)$$

where M is the total number of kernels.

The decision function of the MKL problem is very similar to the SVM one described in Equation 1 but adding the sum of the different kernels from the corresponding atlas:

$$f(\boldsymbol{x}_i) = \langle \boldsymbol{w}_m, \boldsymbol{x}_i \rangle + b$$

The MKL version considered in this study is based on the formulation presented in Rakotomamonjy et al. (2008), where a solution can be obtained by solving the following optimization problem:

$$\text{minimize} \quad \frac{1}{2}\sum_m \frac{1}{d_m} \|\boldsymbol{w}_m\|^2 + C\sum_i \xi_i \quad \text{subject to}$$

$$y_i(\sum_m \boldsymbol{w}_m, \boldsymbol{x}_i + b) \geq 1 - \xi_i \quad \forall i \xi_i \geq 0 \;\; \forall i \sum_m d_m = 1, \; d_m \geq 0 \;\; \forall m \quad (7)$$

where d_m is the contribution to the decision function of each region (see Rakotomamonjy et al., 2008 for a detailed explanation of this method).

This MKL variation optimizes, in a simultaneous manner, the contribution to the decision function of every voxel within a region and the contribution of the region as a whole, in a two-level hierarchical model. On the other hand, the L1-norm (Tibshirani, 1996) constraint on d_m enforces sparsity on some kernels, resulting in a zero-contribution of these regions: information from a region that is present in another is automatically discarded in one of them. Mathematically:

$$S = \sum_{i=1}^{n} |y_i - f(x_i)| \qquad (8)$$

Thus, the L1-norm is based on minimizing the sum of the absolute differences between the target value (y_i) and the estimated values ($f(x_i)$). This hierarchical model leads to two different weight maps: one that summarizes the contribution to the model of each region (region level), and another that provides the contribution of each voxel within its corresponding region (voxel-level). The sparsity that this method entails can be very interesting in classification problems (Arco et al., 2015; Khedher et al., 2017; Plant et al., 2010), but the sparsity that L1-norm leads to can potentiate the instability of the selected regions and decrease the sensitivity in identification contexts (Baldassarre et al., 2017). For this reason, we applied a different version of MKL based on L2-norm instead of L1. In this case all regions defined by the atlas are used to build the model. Mathematically:

$$S = \sum_{i=1}^{n}(y_i - f(x_i))^2 \quad (9)$$

Thus, the L2-norm relies on minimizing the sum of the square of the differences between the target value (y_i) and the estimated values ($f(x_i)$).

In both versions of the MKL, we applied two preprocessing steps before classification: first, we applied a mean-centering to all kernels from each region of the atlas, a very common step in machine learning. This operation relies on subtracting the voxel-wise mean for each voxel across samples, which is computed on the training data to maintain the independence between the training and test subsets. Then, we normalized the kernel dividing each sample by its norm. Regions from which kernels are computed usually have different sizes, and larger regions would have a larger contribution to the model simply because of its larger size. This operation guarantees that all regions have an equal chance regardless of their sizes.

3.3 Searchlight

This method was introduced by Kriegeskorte et al. (2006) to identify the location of the neural activity that contains information about a given classification. It defines a sphere with a certain radius so that only the voxels inside this sphere are used to build the classification model. Performance is associated with the central voxel of the sphere. This procedure is repeated for all voxels in the brain, yielding a map of accuracies. Its main drawback is its local-multivariate nature: it extracts patterns of information from a reduced number of voxels, and this number is much smaller than the one obtained when the brain is evaluated as a whole.

In each sphere, we employed a support vector machine (SVM) classifier with a linear kernel due to its simplicity and the high performance reported by previous studies (Misaki et al., 2010; Pereira et al., 2008). A mathematical description of the SVM algorithm is provided in Section 3.1. We used a 12-mm radius sphere to strike a balance between sensitivity and spatial precision: smaller sizes may not detect some informative voxels whereas larger values can boost false-positives rates (Arco et al., 2016; Chen et al., 2011).

3.4 Performance and statistical significance.

We performed a nested cross-validation to train the model and optimize the hyper-parameters of the classifier (soft-margin parameter, C), both in the ABLA and in the two MKL versions: L1-MKL and L2-MKL. In these situations, the C hyperparameter range was [10^{-5}:10^{5}]. Regarding Searchlight, we used a standard soft-margin parameter of C=1 for each SVM classifier due to the large performance that it provides according to previous studies (Chanel et al., 2016; Dosenbach et al., 2010; Fan et al., 2008). The dataset comprised an fMRI experiment divided into 8 independent runs. To maintain the

independence between training and testing, we used a *leave-one-run-out* cross validation for the external loop (all methods) and the internal loop (MKL and SVM), using the balanced accuracy to evaluate the performance of the model. For a binary classification, the balance accuracy is computed as the average of the accuracy obtained in the images belonging to each experimental condition individually, which increases the robustness of the performance evaluated when there is a different number of images of each class.

Statistical significance was assessed with the method proposed by Stelzer et al. (2013), with a slight difference when the procedure was applied to Searchlight or the atlas-based approaches. In the first one, the significance was computed from accuracy maps, whereas in the other methods weight maps were used instead. First, the labels of the images were randomly shuffled. Then, the corresponding classification method (ABLA, MKL or Searchlight) was applied. This procedure was repeated 100 times in a within-subject classification, resulting in 100 permuted accuracy/weight maps per participant (accuracy for Searchlight and weight for the rest). A map from each individual was randomly picked following a Monte Carlo resampling with replacement (Forman et al., 1995), averaging the permuted maps and obtaining a permuted group map. This procedure was carried out 50000 times to build an empirical chance distribution. A voxel/region was considered significant if no more than 50 samples of the empirical distribution had a larger value than the one obtained without shuffling the labels, which corresponds to a cluster-defining primary-threshold of p=0.001 (50/50000). Once the image was thresholded, an empirical distribution of the cluster sizes of the 50000 permuted maps was built to compute the required family-wise error rate at the cluster level. After associating a p-value to each cluster, an FWE correction was applied (p=0.05) on all-cluster p-values to correct for multiple comparisons at the cluster level.

3.5 Comparison of different atlases

Following the procedure proposed by Schrouff et al. (2018), we computed the Pearson correlation between the weight maps obtained by the different atlases. Since ABLA organizes the weights *a posteriori* in regions from a whole-brain classification, it is only possible to compute this correlation for L1-MKL and L2-MKL. To do so, we calculated the overlap between the significant voxels obtained by each atlas, yielding a value ranging from 0 to 1. We employed permutation tests to assess the significance of the correlation coefficients using a similar framework as described in Section 3.4.

4 Results

In this section, we report the results obtained by the three approaches evaluated in this study: Atlas-based local averaging (ABLA), and the two versions of Multiple Kernel Learning (L1-MKL and L2-MKL). We compared the weight maps of these three methods with the accuracies map obtained by Searchlight by computing the overlap between significant voxels. Moreover, for L1 and L2-MKL we show the stability of the selected

regions across atlases by computing a correlation between their overlapping-significant weight maps, using permutation tests to assess the significance of these correlations. We did not compute this correlation for the ABLA method because weights are exactly the same for all atlases. Additionally, we include the results obtained by these methods in two classification contexts that lead to large or subtle differences (*decision* and *valence*) to test the generalizability of the results of the different approaches.

4.1 Influence of the classification methods

Table 1 summarizes the results for ABLA, L1-MKL and L2-MKL, respectively, in the *decision* classification in terms of accuracy and overlap between the significant regions obtained by each method and those obtained by the Searchlight. The first method yielded a maximum overlap of 70.58% and an accuracy of 81.51%. For L1-MKL, the accuracy increased to 89.37%, reducing the overlap to 21.36%. The accuracy obtained by the L2-MKL method was 74.74%, with the same overlap of 21.36 led to an overlap of 48.39% and an accuracy of 64.73%. The accuracies reported correspond to the values obtained in the maximum overlap scenario, which does not mean that these accuracies were the absolute maximum itself. In fact, we found that the approach that yielded the maximum accuracy was not usually the same that obtained the maximum overlap. We further discuss the implications of this finding in Section 5.1.

In the *valence* classification, the ABLA method obtained a maximum overlap of 41,49% and an accuracy of 51.77 %. This last value is considerably lower than the one obtained in the *decision* classification and it likely reflects the subtle differences in the neural activity associated with the valence of a word. We observed that after applying the L1-MKL method, none of the significant voxels overlapped with the significant results obtained by Searchlight. Similarly, a maximum overlap of 3.81% was obtained when the L2 version of the MKL was employed, with a corresponding accuracy of 49.14%. Table 4 summarizes the results obtained by the three different methods used.

4.2 Influence of the atlases

For the *decision* classification, Table 1 and Figure 1 show the significant results obtained by the ABLA method. Regions marked as informative for different atlases are very similar. The largest overlap score with Searchlight was obtained by the Harv-Oxf atlas (70.58%), whereas the minimum value was derived from the Camb64 division of the brain (21.36%). In L1-MKL, the largest and lowest overlap values were obtained by the same atlases as with ABLA, and results are shown in Figure 2. However, the minimum overlap corresponded to the atlas with the maximum accuracy, Camb64. Results obtained by L2-MKL were quite similar in terms of overlap and accuracy (see Figure 3). Again, the parcellation derived from the Camb64 atlas yielded the largest accuracy and minimum overlap score (74.74% and 21.36%, respectively), whereas Harv-Oxf obtained a good accuracy value and the largest overlap (70.65% and 77.84%, respectively).

Table 4 and Figure 7 include the significant results associated with the nine different atlases and classification methods in the *valence* context. In this case, results were highly affected by the atlas used. Results show a large consistency in the significant regions obtained by ABLA and Searchlight when the Cambridge12 atlas was employed. The brain parcellations provided by AICHA and Harv-Oxf also identified informative regions that were similar to the ones obtained by previous research, (e.g. ventromedial prefrontal cortex, Arco et al, 2018; Lindquist et al., 2015). Nonetheless, results were highly different for L1-MKL. Specifically, the significant voxels obtained were completely different for each atlas (see Figure 8). Regarding L2-MKL, results are very similar. In fact, none of the nine atlases that we employed led to an accuracy that surpassed the chance level, so that the subsequent model did not provide useful information about where the information regions were located. Figure 9 summarizes the results obtained by the L2-MKL method.

4.3 Stability of the weights across atlases

We compared how similar the weight maps were across the different atlases for L1-MKL and L2-MKL, for the two classification analyses. In the *decision* classification, Table 2 summarizes the correlation between the significant weight maps for the L1-MKL. The correlation values obtained by the first 6 atlases (Camb12, Camb20, Camb36, Camb64, AICHA and Yeo2011) range from 0.882 to 0.974. The weight maps derived from the Harvard-Oxford atlas also yielded a large similarity to these 6 atlases This correlation obtained almost a maximum value between the first 6 atlases (Camb12, Camb20, Camb36, Camb64, AICHA and Yeo2011), with values ranging from 0.882 to 0.974. Harvard-Oxford also obtained a large similarity to these 6 atlases, but this correlation decreased when the Brainnetome atlas was employed. By contrast, the Schaeffer atlas led to very different weights compared to any of the other atlases. L2-MKL yielded very similar weight maps regardless of the atlases used. It is worth noting the large correlation between each pair of atlases (see Table 3), even with the Schaefer atlas that yielded very different weights when L1-MKL was applied. We can see how similar the different weights are: only maps provided by Yeo2011 and Brainnetome are slightly less similar to those obtained by the four Cambridge atlases, whereas both show a large correlation with the others. The rest of the atlases present correlation values close to 1. Different atlases lead to very similar results, highlighting the robustness of L2-MKL in the identification of informative regions. Moreover, this finding shows the low influence that the brain parcellation has in the results, which validates the use of these atlas-based methods even when a prior hypothesis about the brain organization in a specific process is missed.

Regarding the *valence* classification, we could compute the correlation between AICHA, Harv-Oxf and BN for L1-MKL because they were the only atlases that shared some informative voxels, yielding a maximum overlap of 0,428. Results obtained by L2-MKL also showed a reduced overlap between the weight maps and we could only correlate the significant results of AICHA, Yeo2011 and Schaefer atlases. In this case, the maximum

correlation was obtained by Yeo2011 and Schaefer, yielding a value of 0.99 (see Table 5). Nevertheless, this value was obtained from an extremely small region since significant results provided by these two atlases were considerably different. We further discuss these results in Section 5.

4.4 Directionality of the weights

In the *decision* classification, it was very useful to evaluate not only the source of information from the weight maps but the sign of these weights. Due to the nature of the contrast, it was expected that weights were organized according to their sign in a specific hemisphere for each group of subjects. Figure 4 shows the distribution of the significant voxels depending on the sign of their weights for the ABLA method. As expected, participants who accepted the offer with the right hand and rejected it with the left hand (odd group) show a cluster of positive weights in the left hemisphere and a cluster of negative weights in the right hemisphere. On the other hand, these results are shifted when results from even participants were evaluated (weights associated with accept an offer are found in the right hemisphere, whereas negative weights are present in the left hemisphere). These results are consistent with those obtained by the univariate results. Specifically, results from the odd group are quite similar from the Acceptance>Reject contrast, and results from the even group have a lot of similarities with the Acceptance<Reject contrast. Figures 5 and 6 exhibit the signs of the significant voxels for the L1-MKL and L2-MKL methods, respectively. It is worth noting that the three atlas-based methods (ABLA, L1-MKL and L2-MKL) take into account the differences at the global activation level as univariate approach does. Regardless of the differences in the spatial location of the information (already commented in a previous section), the weights follow the same distribution than the ABLA approach.

5 Discussion

In this study, we aimed at evaluating methods, alternative to Searchlight, to localize the informative regions involved in cognitive functions. We extracted the weight maps from three atlas-based classification approaches (ABLA, L1-MKL and L2-MKL) and evaluated the statistical significance of each region. We used these methods in two different contexts. In the first one, where the two classes generated large differences in neural activity, L2-regularization resulted the best option for identification purposes. Moreover, atlas-based approaches showed a large stability in the informative regions found regardless of the atlas employed, which highlights the adequacy of these methods. In contrast, when the differences in the activity associated with each class were much subtler, only the ABLA approach showed certain stability in the informative regions across the atlases. However, both L1-MKL and L2-MKL were highly affected by the specific brain organization reflected in the atlases.

5.1 Influence of the classification methods

We have found that maximum accuracy and overlap do not usually concur, especially when detecting subtle differences in neural activity. In the *decision* classification, we found differences across the methods in terms of overlap and accuracy. L1-MKL usually obtained a larger accuracy than ABLA and L2-MKL for the different atlases, but a lower overlap with Searchlight results. According to these results, we can separate the different approaches in two groups: on the one hand, ABLA and L2-MKL; on the other, L1-MKL. The reason for this difference is the regularization used by each method: while ABLA and L2-MKL use an L2-norm regularization, L1-MKL employs an L1. L1-norm provides sparse solutions since it only selects a subset of regions that contain predictive information, while the rest are automatically driven to zero. This can be helpful from the classification standpoint since it leads to larger accuracies: When a lower number of features are considered, the dimensionality of the data is reduced, which facilitates finding the optimal solution to the classification problem. However, our results show that the model with the largest overlap is not usually the most accurate. This is consistent with previous studies, e.g. the extreme case reported by Sona et al. (2007). They proposed a model for decoding subjective perception of participants from their neural data while viewing movie segments. They found a framework that yielded a large performance, but the regions that guided the classifier were partially contained in the ventricles and other regions with large physiological noise. This means that their algorithm performed consistently well in the classification task, but it did not provide any useful information for a better understanding of the human brain. Our results support the need of clearly separating the use of multivariate decoding for prediction and for identification (Hebart and Baker, 2017) in addition to highlight the importance of selecting the methods that best fit the desired aim.

In the *valence* classification, we also found differences across the methods in terms of overlap and accuracy, but in this case these differences were even larger. ABLA was the only method that obtained some overlap with the voxels marked as informative by Searchlight, whereas L1-MKL and L2-MKL hardly detected those significant regions. The key of this finding is the classification problem itself. Evaluating whether a participant responded with the right/left hand to a stimulus generates large differences in neural activity and it is easy for a classifier to find a hyperplane that maximizes the separation of the two classes. This is the reason why the accuracies and the overlap are larger in the *decision* classification. On the other hand, isolating regions with a differential involvement in valence processing is much harder, as shown by recent metanalytic approaches (Lindquist et al., 2015), so the accuracies in this case are much lower.

Our results show that ABLA provides a larger overlap than all the other methods in the two classification problems, especially in the *valence* one. This discrepancy must be due to the different framework that ABLA relies on. Both L1-MKL and L2-MKL consider the regions provided by the atlas to build the model as part of the learning process. Hence,

if the parcellations derived from the atlas do not match the actual organization of the brain in the context under study, the resulting model would be suboptimal since it is based on non-valid assumptions about effective brain parcellations. On the other hand, ABLA builds the classification model from a whole-brain approach, which means that the atlas parcellations do not have any influence in the learning process. Instead, the brain organization is incorporated after building the model to summarize how informative each region is. For this reason, ABLA leads to a better performance when non-accurate atlases are employed, although it is supposed to have a lower ability to detect informative regions compared with methods based on MKL when the atlas leads to a realistic approximation of the brain subdivisions.

5.2 Influence of the atlases

Results show that specific brain parcellations of each atlas impact the spatial accuracy of the different methods only when differences in neural activity are small, but not when these are large. In the *decision* classification, there was a large consistency among the significant regions obtained by all methods across the different atlases. These results carry important implications. Atlas-based approaches are assumed to have a large dependency on the way brain parcellations are computed. In fact, their use is sometimes automatically discarded when there is a clear hypothesis about the brain organization in a specific context. Our results evidence that atlas approaches can identify informative regions even when the concrete one used does not perfectly match the actual configuration of the brain, provided the differences in the neural activity in the context under study are large. However, according to the results obtained in the *valence* classification, there are other contexts where these atlases are not accurate enough to guarantee a good performance in the identification of the sources of information. This is probably related to the size and the specific shape of the region involved in a certain cognitive function, such as the ventromedial prefrontal cortex (vmPFC) associated with the *valence* classification. The only region that ABLA marked as significant in the Camb12 parcellation is the one that contains the vmPFC, so that this method was able to identify where the information was located. Nevertheless, this region has a massive size in this atlas, and these atlas-based methods consider each region as a whole, and thus a large number of voxels are marked as significant only because they are in the same region as the one that is really informative. However, using atlases with more subdivisions implies that these regions are much smaller. This complicates that the organization proposed by the atlas matches the actual shape and location of a small structure as the vmPFC, leading to a reduced sensitivity and spatial accuracy.

The number of subdivisions of an atlas also influenced the performance of the three algorithms evaluated. In the *decision* classification, the optimum value in terms of overlap was obtained by the 36 regions that the Camb36 atlas is divided into. We hypothesize that the number of regions is also important to obtain these results. Using an atlas with few subdivisions means that it is more likely to find an informative region, despite the small ratio between the voxels that are really significant and the total number of voxels that

comprise the region. Instead, a large number of parcellations means that the classifier has to be much subtler in the identification of informative regions. The parcellations derived from Schaeffer add larger precision and subdivisions to the brain networks published by the Yeo2011 atlas. However, results show a better performance in terms of sensitivity when the simplest approach was used. These results strongly indicate that using atlases that do not properly match the actual brain organization is similar to choosing a large Searchlight sphere where only a few voxels within this sphere are informative (Etzel et al., 2013). Using a large radius increases the probability of marking as significant voxels that are not, increasing the false-positives rate. Thus, it is important to use an atlas that properly matches the brain organization when aiming to identify subtle differences in the neural activity.

5.3 Stability of the weights across atlases

We have found a large correlation between the significant weight maps obtained by different atlases in the *decision* classification. The magnitude of the weight of a specific voxel quantifies the contribution of this voxel to the model, and its sign informs us about its relationship to the *Accept* or to the *Reject* class. For the L1-MKL approach, we found large correlation values for all atlases except for the Schaefer one. This means that for most of atlases, the resulting weights associated with each model are very similar, which highlights the stability of the classification methods regardless of the atlas used. Interesting, we found the largest correlations in the weight maps obtained by the four Cambridge atlases, which are all derived from the same clustering algorithm (BASC). This result supports the idea that the mathematical framework employed to delimitate the different brain regions is important, since it can influence the success of the subsequent analyses. On the other hand, the poor performance of L1-MKL when the Schaefer atlas is used can be due to the conjunction of a sparse method and an atlas with a large number of regions, as mentioned in the previous section. It is important to note that our results do not invalidate the use of ambitious atlases aiming at obtaining a detailed parcellation of each cortical region. However, if these parcellations do not accurately match the actual brain organization (e.g. computing an atlas separately for each participant from his/her neural data), sparse solutions are not recommended. Unlike L1-MKL, L2-MKL obtained a large correlation score between each pair of atlases (see Table 2). Thus, L2-MKL adapts to different idiosyncrasies and leads to a common solution for different brain mappings. This means that the weight maps that guide the classification are essentially the same regardless of the atlas used, so that it is possible to successfully employ this approach even without a clear hypothesis about the brain organization in a specific context.

Nevertheless, these results are only valid when there are large differences in the neural activity associated with the two classes to distinguish from. Our findings in the *valence* classification differ substantially from those obtained in the *decision* classification. L1-MKL results (summarized in Table 5) show that we could hardly compute the correlation between two pairs of atlases: the first one, AICHA and Harv-Oxf; the second, AICHA and BN. In addition, none of the significant results provided by these atlases share any

voxel with the Searchlight results, which illustrates that weight maps are similar from a mathematical perspective, but make a null contribution to the neuroscience standpoint. Results obtained by L2-MKL are summarized in Table 6 and conclusions derived from them are essentially the same than L1-MKL. We could only compute the correlation between two pairs of atlases: Schaefer-AICHA and Schaefer-Yeo2011. From these three atlases, Schaefer is the one that leads to a larger overlap with Searchlight: 3.81%. However, none of these significant voxels are shared by AICHA and Yeo2011. This reflects that the two versions of MKL are not able to identify informative regions in contexts where differences in the neural activity between the two conditions are minimum.

5.4 Directionality of the weights

One of the main advantages of using weights instead of accuracy is the directionality that they provide. We have evaluated the sign of each weight within the significant regions for each of the three atlas-based methods for the *decision* classification, where it is easy to evaluate whether the sign of the weight is correct or not from a psychological standpoint. In this experiment, participants used one hand to accept an offer and the other one to reject it. The decoding analysis should mark as informative motor-related areas since the only difference in the classification evaluated is the hand used. However, it is worth remembering that the hand employed was counterbalanced across participants: odd subjects used their right/left hand to accept/reject an offer, whereas for even subjects the order was shifted. We obtained exactly the expected results: the three approaches led to a map in which weights were organized according to their sign. For odd participants, regions associated with the acceptance of an offer (use of the right hand) were localized in the left hemisphere, with a positive sign. On the other hand, regions that contained information when the offer was rejected (left hand) were found in the right hemisphere, with a negative weight. More importantly, the informative regions for even participants shifted: positive weights were found in the right hemisphere, whereas weights with a negative sign were found in the left hemisphere. These results are very similar to those obtained by the univariate approach (see Figure 6): regions with a larger activation when participants accept/reject an offer match the sign of the weights of the different multivariate methods. However, atlas-based approaches use normalized data, which eliminates the differences in the global activation levels associated to each condition. Thus, these methods identify areas that show a different spatial distribution of the information, while the univariate approach purely relies on differences in the activation level.

6 Conclusion

In this study, we compared three different atlas-based approaches to Searchlight to assess their ability to identify informative brain regions for cognitive contrasts that generate

either large or small differences in neural activity. We have shown for the first time that these methods can be used as an alternative to Searchlight since they localize informative regions when there are large differences between the neural activity associated with the two classes to distinguish from. These results are consistent across atlases. Moreover, the use of weight maps provides additional information to accuracies, combining the sensitivity of decoding analyses and the directionality of univariate results. However, results change drastically when the differential neural activity is much lower. Methods based on MKL are highly affected by the discrepancy of actual brain organization and the one proposed by the atlases. On the other hand, ABLA is the only approach that identifies informative regions in accordance with previous research. Our results pave the way for finding a method that leads to a large spatial accuracy in the identification of subtle changes of neural activity. Future studies are needed to widen the findings of this study by evaluating the performance of these methods when the brain parcellations are specifically computed for each participant, which may substantially improve the neuroanatomical functional precision. This combination might boost their sensitivity and widen their adequacy in different contexts, especially when an accurate parcellation is crucial.

Funding

This work was supported by the Spanish Ministry of Science and Innovation through grant PSI2016-78236-P to M.R and the Spanish Ministry of Economy and Competitiveness through grant BES-2014-069609 to J.E.A. This research is part of J.E.A's activities for the PhD Program in Information and Communication Technologies of the University of Granada.

Acknowledgments

We are grateful to Janaina Mourao-Miranda for her kind help during the development of the algorithms employed in the current research.

References:

Abdulrahman, H., Henson, R.N., 2016. Effect of trial-to-trial variability on optimal event-related fMRI design: Implications for Beta-series correlation and multi-voxel pattern analysis. NeuroImage 125, 756-766.

Adeli E., Guorong, W., Saghafi, B., An, L., Shi, F., Shen, D., 2017. Kernel-based joint feature selection and max-margin classification for early diagnosis of Parkison's disease. Sci. Rep. 7, 41069.

Arco, J.E., González-García, C., Díaz-Gutiérrez, P., Ramírez, J., Ruz, M., (in press). Influence of activation pattern estimates and statistical significance tests in fMRI decoding analysis. Journal of Neuroscience Methods.

Arco, J.E., González-García, C., Ramírez, J., Ruz, M., 2016. Comparison of different methods for brain decoding from fMRI beta maps. Poster presented at 22nd Annual Meeting of the Organization for Human Brain Mapping, Geneve, (Switzerland).

Arco, J.E., Ramírez, J., Puntonet, C.G., Górriz, J.M., Ruz, M., 2015. Short-term prediction of MCI to AD conversion based on longitudinal MRI analysis and neuropsychological tests. Innovation in Medicine Healthcare, 385-394.

Baldassarre L., Pontil, M., Mourão-Miranda, J., 2017. Combining Accuracy and stability for model selection in brain decoding. Frontier in Neuroscience 11:62.

Balci, S.K., Sabuncu, M.R., Yoo, J., Ghosh, S.S., Whitfield-Gabrieli, S., Gabrieli, J.D., Golland, P., 2008. Prediction of successful memory encoding from fMRI data. Med Image Comput Comput Assist Inter. 11, 97-104.

Bellec, P., Rosa-Neto, P., Lyttelton, O.C., Benali, H., Evans, A.C., 2010. Multi-level bootstrap analysis of stable clusters in resting-state fMRI. NeuroImage 51, 1126-1139.

Bennet, K.P., Blue, J.A., 1998. A support vector machine approach to decision trees. 1998 IEEE International Joint Conference in Neural Networks Proceedings.

Bode, S., Haynes, J.-D., 2009. Decoding sequential stages of task preparation in the human brain. Neuroimage 45 (2), 606-613.

Boser, B.E., Guyon, I., Vapnik, V., 1992. A training algorithm for optimal margin classifiers. Proceedings of the Fifth Annual Workshop on Computational Learning Theory, 144-152.

Burges, C., 1998. A tutorial on support vector machines for pattern recognition. Data Mining and Knowledge Discovery 2, 121-167.

Chanel, G., Pichon, S., Conty, L., Berthoz, S., Chevallier, C., Grèzes, J., 2016. Classification of autistic individuals and controls using cross-task characterization of fMRI activity. Neuroimage: Clinical 10, 76-88.

Chen, Y., Namburi, P., Elliott, L., Heinzle, J., Soon, C., Chee, M., Haynes, J., 2011. Cortical surface-based searchlight decoding. NeuroImage 56, 582-592.

Chen J., Leong, Y.C., Honey, C.J., Yong, C.H., Norman, K.A., Hasson, U., 2017. Shared memories reveal shared structure in neural activity across individuals. Nature neuroscience 20(1), 115-125.

Choi, H., Ha, S., Im, H. J., Paek, S. H., & Lee, D. S., (2017). Refining diagnosis of Parkinson's disease with deep learning-based interpretation of dopamine transporter imaging. NeuroImage: Clinica 16, 586–594.

Cichy, R.M., Pantazis, D., Oliva, A., 2016. Similarity-based fusion of MEG and fMRI reveals spatio-temporal dynamics in human cortex during visual object recognition. Cerebral Cortex 26(8), 3563–3579.

Coutanche, M.N., Thompson-Schill, S.L., Schultz, R.T., 2011. Multi-voxel pattern analysis of MRI data predicts clinical symptom severity. NeuroImage 57(1), 113-123.

Cox, D.D., Savoy, R.L., 2003. Functional magnetic resonance imaging (fMRI) "brain reading": detecting and classifying distributed patterns of fMRI activity in human visual cortex. NeuroImage 19, 261-270.

Craddock, R.C., James, G.A., Holtzheimer III, P.E., Hu, X.P., Mayberg, H.S., 2012. A whole brain fMRI atlas generated via spatially constrained spectral clustering. Hum Brain Mapp. 33(8), 1914-28.

Dai, D., Wang, J., Hua, J., He, H., 2012. Classification of ADHD children through multimodal magnetic resonance imaging. Front. Syst. Neurosci. 6(63).

De Martino, F., Valente, G., Staeren, N., Ashburner, J., Goebel, R., Formisano, E., 2008. Combining multivariate voxel selection and support vector machines for mapping and classification of fMRI spatial patterns. NeuroImage 43, 44-58.

Del Gaizo, J., Mofrad, N., Jensen, J. H., Clark, D., Glenn, R., Helpern, J., & Bonilha, L. (2017). Using machine learning to classify temporal lobe epilepsy based on diffusion MRI. Brain and Behavior, *7*(10), e00801.

Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 31, 968-980.

Dosenbach, NU., Nardos, B., Cohen, A.L., Fair, D.A., Power, J.D., Church, J.A., et al., 2010. Prediction of individual brain maturity using fMRI. Science 329(5997), 1358-61.

Etzel, J.A., Zacks, J.M., Braver, T.S., 2013. Searchlight analysis: promise, pitfalls, and potential. Neuroimage 78, 261-69.

Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., L, A.R., Fox, P.T., Eickhoff, S.B., Yu, C., Jiang, T., 2016. The Human Brainnetome Atlas: A Ne Brain Atlas Based on Connectional Architecture. Cerebral Cortex 26, 3508-3526.

Fan, L., Wang, J., Zhang, Y., Han, W., Yu, C., Jiang, T., 2014. Connectivity-based parcellation of the human temporal pole using diffusion tensor imaging. Cereb Cortex 24, 3365-3378.

Fan, R.-E., Chang, K.-W., Hsieh, C.-J., Wang, X.-R., Lin, C.-J., 2008. LIBLINEAR: A library for large linear classification. J. March. Learn. Res. 9, 1871-1874.

Filippone, M., Marquand, A.F., Blain, C.R.V., Williams, S.C.R., Mourão-Miranda, J., Girolami, M., 2013. Probabilistic prediction of neurological disorders with a statistical assessment of neuroimaging data modalities. The annals of applied statistics 6(4), 1883-1905.

Forman, S., Cohen, J., Fitzgerald, M., Eddy, W., Mintum, M., Noll, D., 1995. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn. Reson. Med. 33, 636-647.

Fort, G., Lambert-Lacroix, S., 2005. Classification using partial least squares with penalized logistic regression. Bioinformatics 21, 1104-1111.

Gaertig, C., Moser, A., Alguacil, S., Ruz, M., 2012. Social information and economic decisión-making in the ultimatum game. Front Neurosci 6 (103).

González-García, C., Arco, J.E., Palenciano, A.F., Ramírez, J., Ruz, M., 2017. Encoding, preparation and implementation of novel complex verbal instructions. NeuroImage 148, 264-273

González-García, C., Mas-Herrero, E., de Diego-Balaguer, R., Ruz, M., 2016. Task-specific preparatory neural activations in low-inference contexts. Brain Structure & Functions 8, 3997-4006.

Haxby, J.V., Gobbini, M.I., Furey, M.L., Ishai, A., Schouten, J.L., Pietrini, P., 2001. Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science 293(5539), 2425-30.

Haynes, J.-D., Rees, G., 2006. Decoding mental states from brain activity in humans. Nat. Rev. Neurosci. 7, 523–534.

Haynes, J.-D., Rees, G., 2005. Predicting the orientation of invisible stimuli from activity in human primary visual cortex. Nat Neurosci. 8(5), 686-91.

Hebart, M.N., Baker, C.I., 2017. Deconstructing multivariate decoding for the study of brain function. NeuroImage, https://doi.org/10.1016/j.neuroimage.2017.08.005

Henson, R., 2005. Design efficiency in fMRI. URL http://imaging.mrc-cbu.cam.ac.uk/imaging/DesignEfficiency#
VII._Should_I_treat_my_trials_as_events_or_epochs_.3F

Joliot, M., Jobard, G., Naveau, M., Delcroix, N., Petit, L., Zago, L., Crivello, F., Mellet, E., Mazoyer, B., Tzourio-Mazoyer, N., 2015. AICHA: An atlas of intrinsic connectivity of homotopic areas. Journal of Neuroscience Methods 254, 46-59.

Kamitani, Y., Tong, F., 2005. Decoding the visual and subjective contents of the human brain. Nat Neurosci. 8(5), 679-85.

Khedher, L., Illán, I.A., Górriz, J.M., Ramírez, J., Meyer-Baese, A., 2017. Independent component analysis-support vector machine-based computer aided diagnosis system for Alzheimer's disease with visual support. International Journal of Neural Systems 27(3), 8 1650050.

Kriegeskorte, N., Goebel, R., Bandettini, P., 2006. Information-based functional brain mapping. PNAS 103, 3863-3868.

Lanckriet, G.R.G., Cristianini, N., Bartlett, P., El Ghaoui, L., Jordan, M.I., 2004. Learning the Kernel Matrix with Semidefinite Programming. Journal of Machine Learning Research 5, 27-72.

Lindquist, K., Satpute, A., Wager, T., Weber, J., Barrett, L., 2015. The brain basis of positive and negative affect: evidence from a meta-analysis of the human neuroimaging literature. Cereb Cortex 26(5), 1910-1922.

Liu, H., Qin, W., Li, W., Fan, L., Wang, J., Jiang, T., Yu, C., 2013. Connectivity-based parcellation of the human frontal pole with diffusion tensor imaging. J Neurosci. 33, 6782-6790.

Liu, H., Stufflebeam, S.M., Sepulcre, J., Hedden, T., Buckner, R.L., 2009. Evidence from intrinsic activity that asymmetry of the human brain is controlled by multiple factors. Proceedings of the National Academy of Sciences 106 (48).

Loose, L.S., Wisniewski, D., Rusconi, M., Goschke, T., Haynes, J.-D., 2017. Switch-independent task representations in frontal and parietal lobe. Journal of Neuroscience 37(33), 8033-8042.

Misaki, M., Kim, Y., Bandettini, P., Kriegeskorte, N., 2010. Comparison of multivariate classifiers and response normalizations for pattern-information fMRI. NeuroImage 53(1), 103-18.

Moser, A., Gaertig, C., Ruz, M., 2014. Social information and personal interests modulate neural activity during economic decision-making. Frontiers in Human Neuroscience 8, 31.

Mourão-Miranda, J., Bokde, A.L.W., Born, C., Hampel, H., Stetter, M., 2005. Classifying brain states and determining the discriminating activation patterns: Support Vector Machine on functional fMRI data. NeuroImage 25, 980-995.

Mwangi, B., Tian, T.S., Soares, J.C., 2014. A review of feature reduction techniques in neuroimaging. Neuroinformatics 12(2), 229-244.

Norman, K.A., Polyn, S.M., Detre, G.J., Haxby, J.V., 2006. Beyond mind-reading: multi-voxel pattern analysis of fMRI data. Trends Cognit. Sci. 10, 424–430.

Pereira, F., Mitchell, T., Botvinick, M., 2008. Machine learning classifiers and fMRI: A tutorial overvie. NeuroImage 45, S199-209.

Plant, C., Teipel, S.J., Oswald, A., Böhm, C., Meindl, T., Mourão-Miranda, J., Bokde, A.W., Hampel, H., Ewers, M., 2010. Automated detection of brain atrophy patterns based on MRI for the prediction of Alzheimer's disease. NeuroImage 50(1), 162-74.

Poldrack, R.A., 2007. Region of interest analysis for fMRI. Soc Cogn Affect Neurosci. 2(1), 67-70.

Qiao, L., Zhang, L., Chen, A., Egner T, 2017. Dynamic trial-by trial recoding of task-set representations in the frontoparietal cortex mediates behavioral flexibility. Journal of Neuroscience 37(45), 11037-11050.

Qureshi, M.N.I., Oh, J., Min, B., Jo, H.J., Lee, B., 2017. Multi-modal, multi-measure, and multi-class discrimination of ADHD with hierarchical feature extraction and extreme learning machine using structural and functional brain MRI. Front Hum Neurosci. 11(157).

Rakotomamonjy, A., Bach, F., Canu, S., Grandvalet, Y., 2008. SimpleMKL. Journal of Machine Learning 9, 2491-2521.

Rondina, J.M., Hahn, T., de Oliveira, L., Marquand, A.F., Dresler, T., Fallgatter, A.J., Shawe-Taylor, J., Mourão-Miranda, J., 2014. SCoRS—A method based on stability for feature selection and mapping in neuroimaging. IEEE Trans Med Imaging 33(1), 85-98.

Sakai, K., 2008. Task set and prefrontal cortex. Annu. Rev. Neurosci. 31, 219-245.

Schaefer, A., Kong, R., Gordon, E.M., Laumann, T.O., Zuo, X.-N., Holmes, A.J., Eickhoff, S.B., 2017. Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. Cerebral Cortex, 1-20.

Schrouff, J., Monteiro, J.M., Portugal, L., Rosa, M.J., Phillips, C., Mourão-Miranda, J., 2018. Embedding anatomical or functional knowledge in whole-brain multiple kernel learnig models. Neuroinformatics 16, 117-143.

Schrouff, J., Cremers, J., Garraux, G., Baldassarre, L., Mourão-Miranda, J., Phillips, C., 2013a. Localizing and comparing weight maps generated from linear kernel machine

learning models. IEEE Explore, http://ieeexplore.ieee.org/document/6603572/.

Schrouff, J., Rosa, M.J., Rondina, J.M., Marquand, A.F., Chu, C., Ashburner, J., Phillips, C., Richiardi, J., Mourão-Miranda, J., 2013b. PRoNTo: Pattern Recognition for Neuroimaging Toolbox. Neuroinformatics 11(3), 319-337.

Sona, D., Veeramachaneni, S., Olivetti, E., Avesani, P., 2007. Inferring cognition from fMRI brain images. Int. Conf. Artif. Neural Netw. 869-878.

Stelzer, J., Chen, Y., Turner, R., 2013. Statistical inference and multiple testing correction in classification-based multi-voxel pattern analysis (MVPA): Random permutations and cluster size control. NeuroImage 65, 69-82.

Tibshirani, R., 1996. Regression shrinkage and selection via the lasso. Journal of the Royal Statistical Society 58(1), 267-288.

Turner, B., Mumford, J., Poldrack, R., Ashby, F., 2012. Spatiotemporal activity estimation for multivoxel pattern analysis with rapid event-related designs. NeuroImage 62(3), 1429-1438.

Urchs, S., Dansereau, C., Benhajali, Y., Bellec, P. Group multiscale functional template generated with BASC on the Cambridge sample. https://figshare.com/articles/Group_multiscale_functional_template_generated_with_BASC_on_the_Cambridge_sample/1285615

Yeo, B.T.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zöllei, L., Polimeni, J.R., Fischl, B., Liu, H., Buckner, R.L., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 106, 1125-1165.

Table 1: Summary of the results obtained for the different methods and atlases in the *decision* classification.

Method	Atlas	Accuracy (%)	Significant voxels	SL voxels defined in atlas	Overlap with SL (%)	Regions	Significant regions
ABLA	Camb12	81.51	4704	4302	61.69	12	1
L1-MKL	Camb12	86.2	4704	4302	61.69	12	1
L2-MKL	Camb12	72.43	2654	4302	61.69	12	1
ABLA	Camb20	81.51	3692	4302	58	20	1
L1-MKL	Camb20	85.02	3692	4302	58	20	1
L2-MKL	Camb20	65.21	2598	4302	58	20	1
ABLA	Camb36	81.51	982	4302	21.36	36	1
L1-MKL	Camb36	89.37	982	4302	21.36	36	1
L2-MKL	Camb36	74.74	1000	4302	21.36	36	1
ABLA	Camb64	81.51	3740	4302	63.34	64	1
L1-MKL	Camb64	84.62	982	4302	21.36	64	1
L2-MKL	Camb64	70.31	7613	4302	21.36	64	1
ABLA	AICHA	81.51	1802	3291	48	192	5
L1-MKL	AICHA	86.76	636	3291	19.23	192	1
L2-MKL	AICHA	69.53	2867	3291	60.13	192	11
ABLA	Yeo2011	81.51	2731	3137	56.39	17	1
L1-MKL	Yeo2011	87.34	2731	3137	56.07	17	1
L2-MKL	Yeo2011	71.35	2731	3137	56.39	17	1
ABLA	Harv-Oxf	81.51	4609	3389	70.58	48	2
L1-MKL	Harv-Oxf	85.02	4609	3389	70.58	48	2
L2-MKL	Harv-Oxf	70.65	6531	3389	77.93	48	5
ABLA	Brainnetome	81.51	2051	3057	47	246	9
L1-MKL	Brainnetome	78.77	904	3057	21.56	246	4

L2-MKL	Brainnetome	66.53	1129	3057	28.39	246	5
ABLA	Schaefer	81.51	1558	3137	42.9	400	23
L1-MKL	Schaefer	77.84	465	3137	14.5	400	6
L2-MKL	Schaefer	71.61	1926	3137	51.35	400	28

Table 2: Correlation between the significant weight maps across the different atlases after applying the L1-MKL method in the *decision* classification.

L1-Multi Kernel Learning									
Atlas	**Camb 12**	**Camb 20**	**Camb 36**	**Camb 64**	**AICHA**	**Yeo2011**	**Harv-Oxf**	**Brainnetome**	**Schaefer018**
Camb12	1	0.974	0.906	0.936	0.889	0.937	0.539	0.383	0.144
Camb20	0.974	1	0.908	0.951	0.934	0.947	0.564	0.552	0.125
Camb36	0.906	0.908	1	0.975	0.933	0.911	0.497	0.568	0.1
Camb64	0.936	0.951	0.975	1	0.963	0.933	0.542	0.573	0.081
AICHA	0.889	0.934	0.933	0.963	1	0.882	0.61	0.549	0.088
Yeo2011	0.937	0.947	0.911	0.933	0.882	1	0.566	0.528	0.193
Harv-Oxf	0.539	0.564	0.497	0.542	0.61	0.566	1	0.172	0.051
Brainnetome	0.383	0.552	0.568	0.573	0.549	0.528	0.172	1	0.109
Schaefer	0.144	0.125	0.1	0.081	0.088	0.193	0.051	0.109	1

Table 3: Correlation between the different atlases after applying the L2-MKL method in the *decision* classification.

	L2-Multi Kernel Learning								
Atlas	**Camb 12**	**Camb 20**	**Camb 36**	**Camb 64**	**AICHA**	**Yeo2011**	**Harv-Oxf**	**Brainnetome**	**Schaefer018**
Camb12	1	0.927	0.94	0.926	0.845	0.768	0.837	0.72	0.829
Camb20	0.927	1	0.958	0.973	0.776	0.71	0.795	0.64	0.762
Camb36	0.94	0.958	1	0.981	0.795	0.721	0.789	0.663	0.776
Camb64	0.926	0.973	0.981	1	0.805	0.738	0.798	0.67	0.783
AICHA	0.845	0.776	0.795	0.805	1	0.948	0.94	0.904	0.973
Yeo2011	0.768	0.71	0.721	0.738	0.948	1	0.897	0.857	0.945
Harv-Oxf	0.837	0.795	0.789	0.798	0.94	0.897	1	0.849	0.945
Brainnetome	0.72	0.64	0.663	0.67	0.904	0.857	0.849	1	0.889
Schaefer	0.829	0.762	0.776	0.783	0.973	0.945	0.945	0.889	1

Table 4: Summary of the results obtained for the different methods and atlases in the *valence* classification.

Method	Atlas	Accuracy (%)	Significant voxels	SL voxels defined in atlas	Overlap with SL (%)	Regions	Significant regions
ABLA	Camb12	51.77	2095	911	41.49	12	1
L1-MKL	Camb12	48.44	0	911	0	12	0
L2-MKL	Camb12	50.71	0	911	0	12	0
ABLA	Camb20	51.77	0	911	0	20	0
L1-MKL	Camb20	48.18	0	911	0	20	0
L2-MKL	Camb20	50.74	0	911	0	20	0
ABLA	Camb36	51.77	0	911	0	36	0
L1-MKL	Camb36	49.74	0	911	0	36	0
L2-MKL	Camb36	49.22	406	911	0	36	1
ABLA	Camb64	51.77	341	911	7.14	64	1
L1-MKL	Camb64	46.88	549	911	0	64	1
L2-MKL	Camb64	51.75	0	911	0	64	0
ABLA	AICHA	51.77	663	729	20.58	192	5
L1-MKL	AICHA	47.1	780	729	0	192	5
L2-MKL	AICHA	52.83	35	729	0	192	1
ABLA	Yeo2011	51.77	0	709	0	17	0
L1-MKL	Yeo2011	46.15	0	709	0	17	0
L2-MKL	Yeo2011	50.97	1010	709	1.7	17	1
ABLA	Harv-Oxf	51.77	439	715	21.4	48	1
L1-MKL	Harv-Oxf	47.18	145	715	0	48	1
L2-MKL	Harv-Oxf	48.33	0	715	0	48	0
ABLA	Brainnetome	51.77	438	738	7.99	246	3
L1-MKL	Brainnetome	43.34	349	738	0	246	3

L2-MKL	Brainnetome	51.19	137	738	0	246	1
ABLA	Schaefer	51.77	61	708	4.8	400	1
L1-MKL	Schaefer	46.24	123	708	0.14	400	2
L2-MKL	Schaefer	49.14	302	708	3.81	400	6

Table 5: Correlation between the significant weight maps across the different atlases after applying the L1-MKL method in the *valence* classification.

	L1-MKL								
Atlas	**Camb 12**	**Camb 20**	**Camb 36**	**Camb 64**	**AICHA**	**Yeo2011**	**Harv-Oxf**	**Brainnetome**	**Schaefer018**
Camb12	1	-	-	-	-	-	-	-	-
Camb20	-	1	-	-	-	-	-	-	-
Camb36	-	-	1	-	-	-	-	-	-
Camb64	-	-	-	1	-	-	-	-	-
AICHA	-	-	-	-	1	-	0.217	0.428	-
Yeo2011	-	-	-	-	-	1	-	-	-
Harv-Oxf	-	-	-	-	0.217	-	1	-	-
Brainnetome	-	-	-	-	0.428	-	-	1	-
Schaefer	-	-	-	-	-	-	-	-	1

Table 6: Correlation between the significant weight maps across the different atlases after applying the L2-MKL method in the *valence* classification.

	L2-MKL								
Atlas	**Camb 12**	**Camb 20**	**Camb 36**	**Camb 64**	**AICHA**	**Yeo2011**	**Harv-Oxf**	**Brainnetome**	**Schaefer018**
Camb12	1	-	-	-	-	-	-	-	-
Camb20	-	1	-	-	-	-	-	-	-
Camb36	-	-	1	-	-	-	-	-	-
Camb64	-	-	-	1	-	-	-	-	-
AICHA	-	-	-	-	1	-	-	-	0.975
Yeo2011	-	-	-	-	-	1	-	-	0.99
Harv-Oxf	-	-	-	-	-	-	1	-	-
Brainnetome	-	-	-	-	-	-	-	1	-
Schaefer	-	-	-	-	0.975	0.99	-	-	1

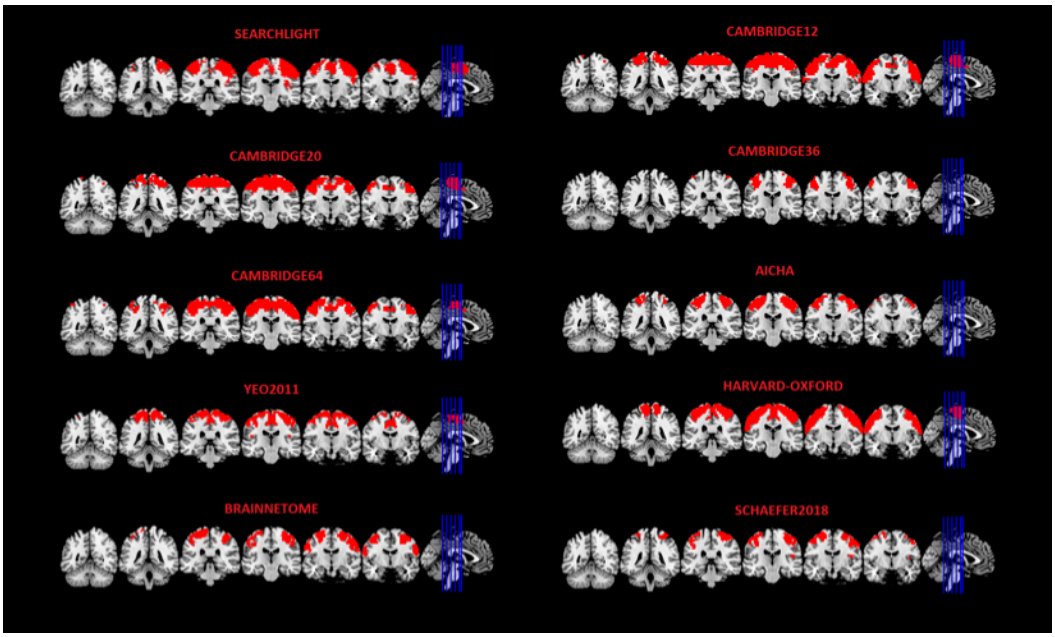

Figure 1: Significant voxels obtained by the Searchlight approach and the ABLA method for all the atlases used in the *decision* classification.

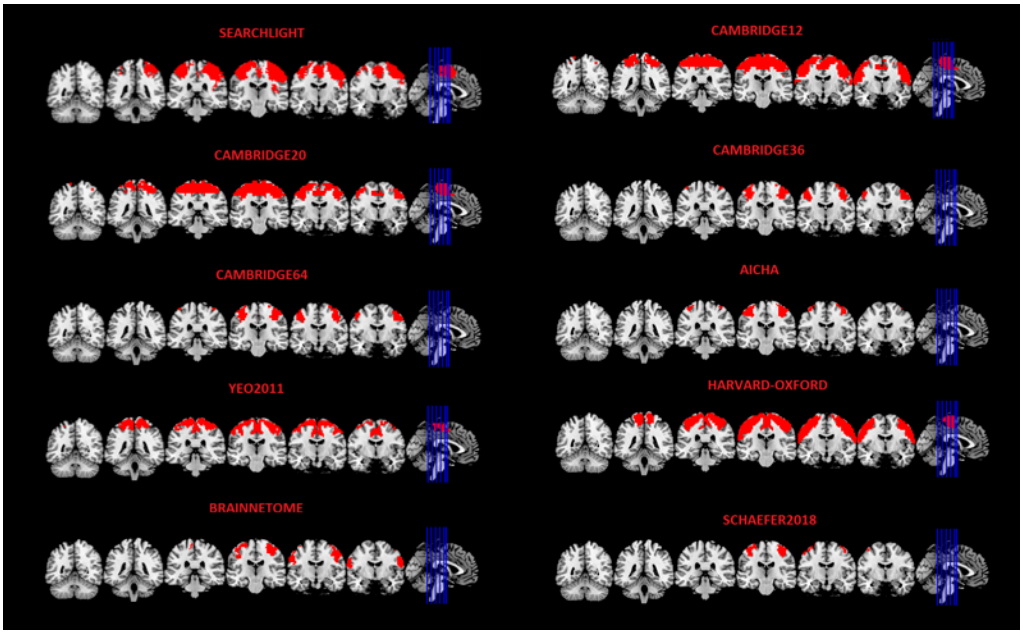

Figure 2: Significant voxels obtained by the Searchlight approach and the L1-MKL method for all the atlases used in the *decision* classification.

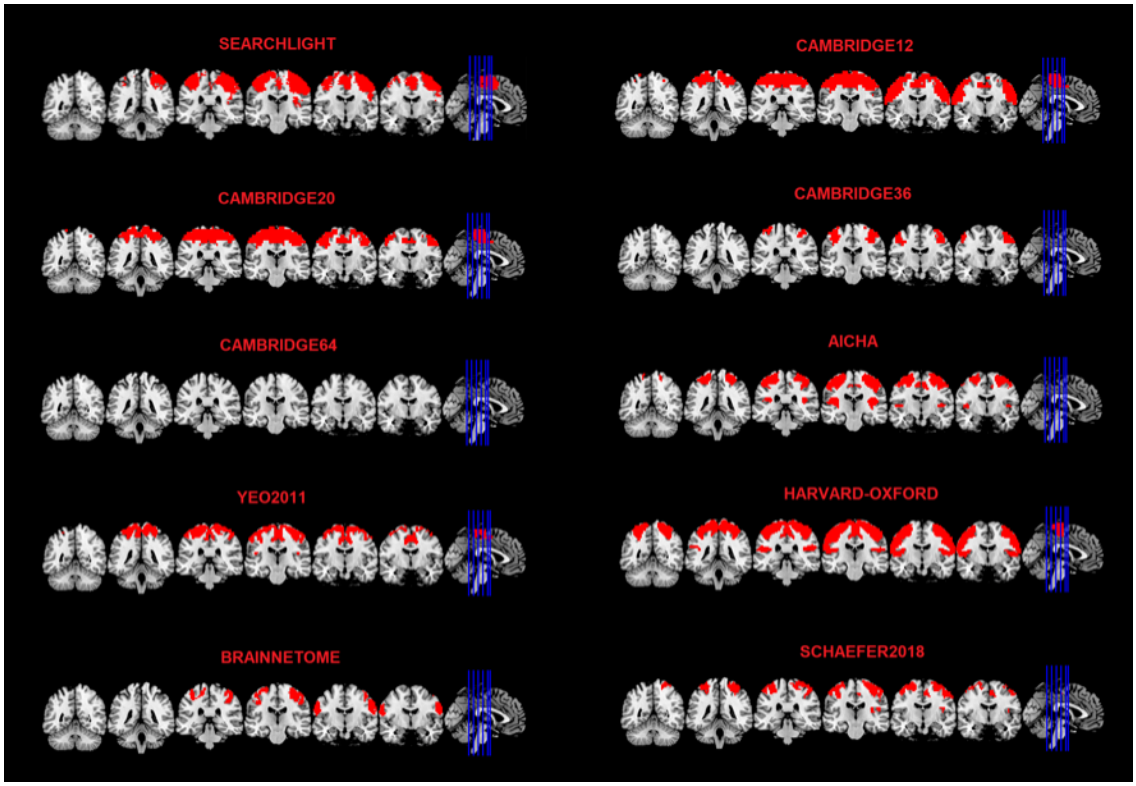

Figure 3: Significant voxels obtained by the Searchlight approach and the L2-MKL method for all the atlases used in the *decision* classification.

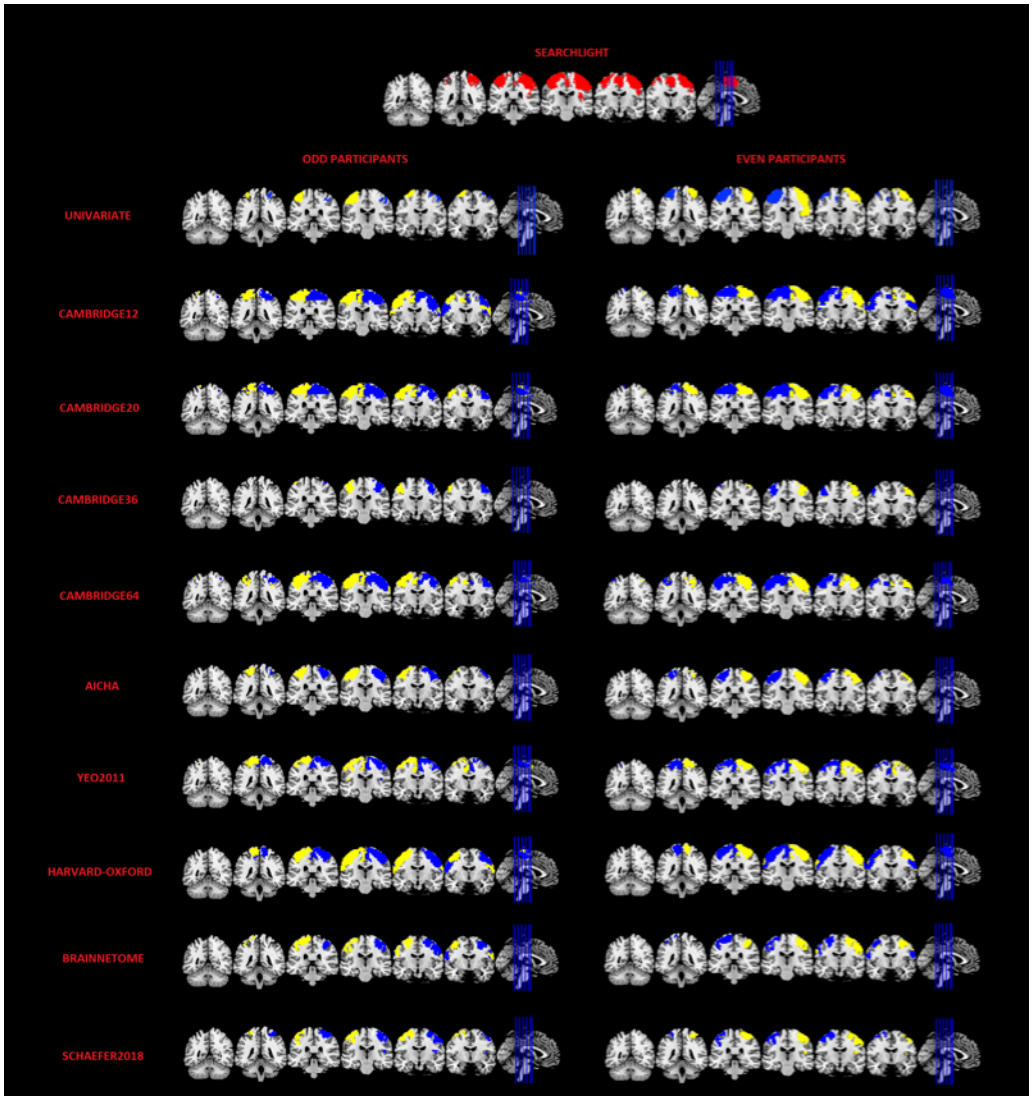

Figure 4: Summary of the results obtained for the *decision* classification by Searchlight, ABLA and univariate approaches. The latter two show large differences between the two groups considered (odd/even participants). Searchlight only provides information about the significance of each voxel itself, so that no separation between groups was considered.

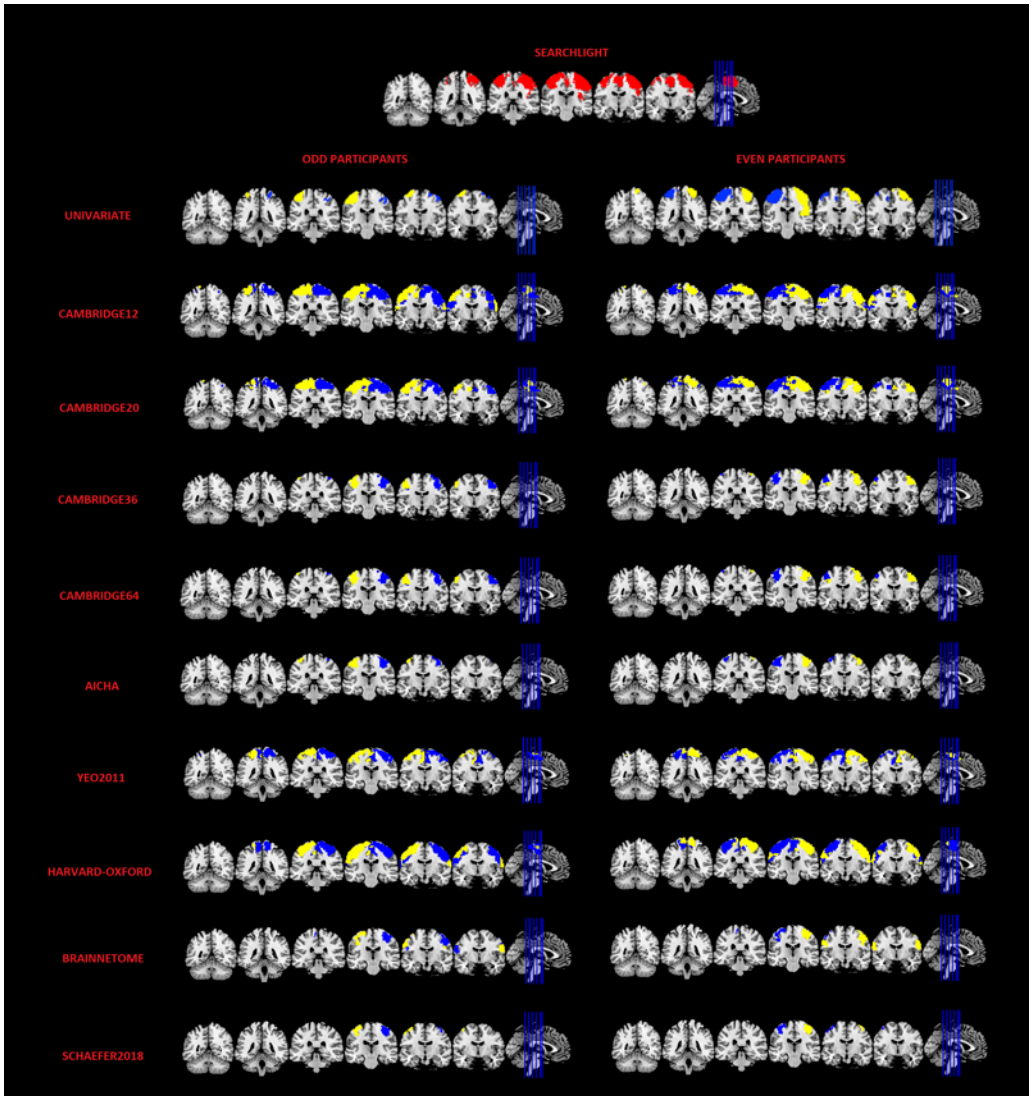

Figure 5: Summary of the results obtained for the *decision* classification by Searchlight, L1-MKL and univariate approaches. The latter two show large differences between the two groups considered (odd/even participants). Searchlight only provides information about the significance of each voxel itself, so that no separation between groups was considered.

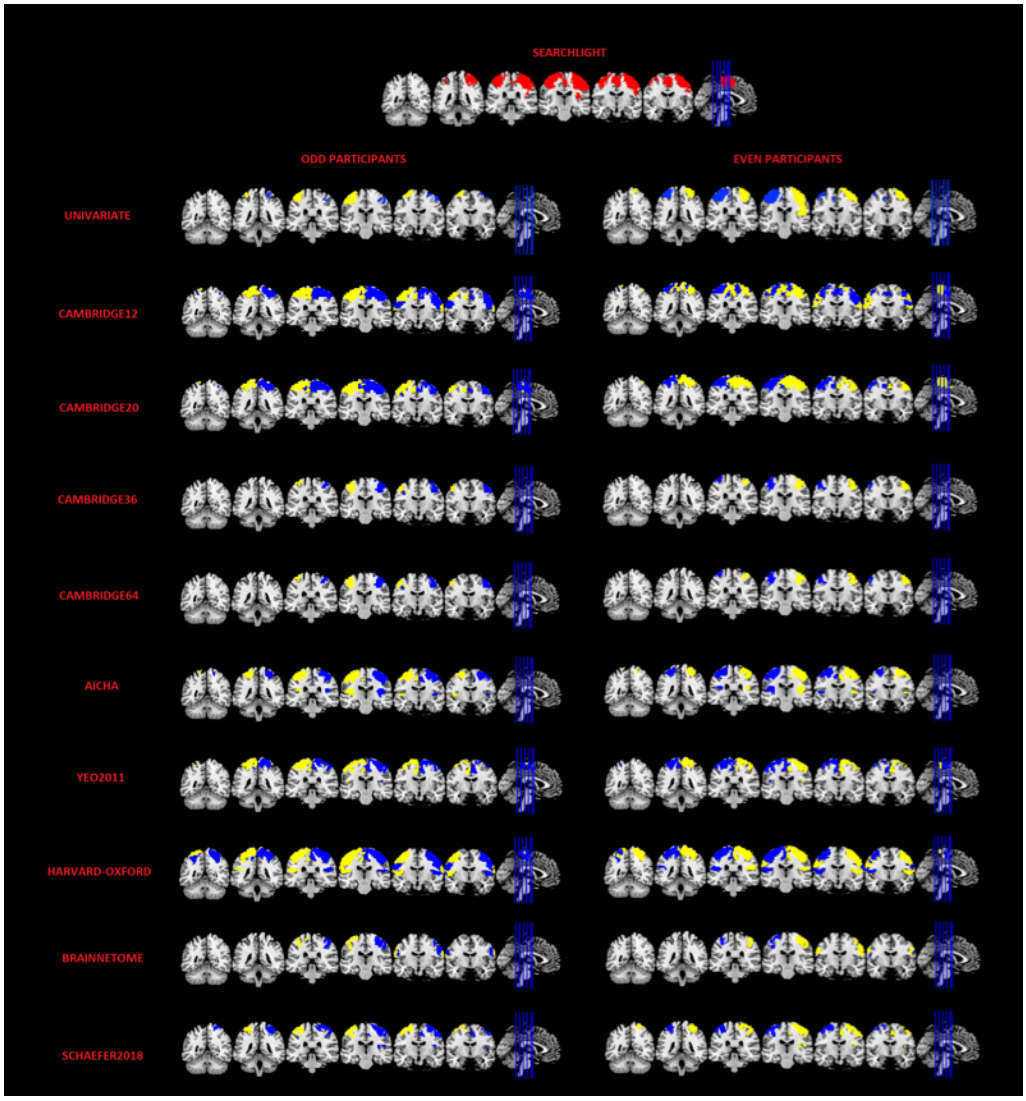

Figure 6: Summary of the results obtained for the *decision* classification by Searchlight, L2-MKL and univariate approaches. The latter two show large differences between the two groups considered (odd/even participants). Searchlight only provides information about the significance of each voxel itself, so that no separation between groups was considered.

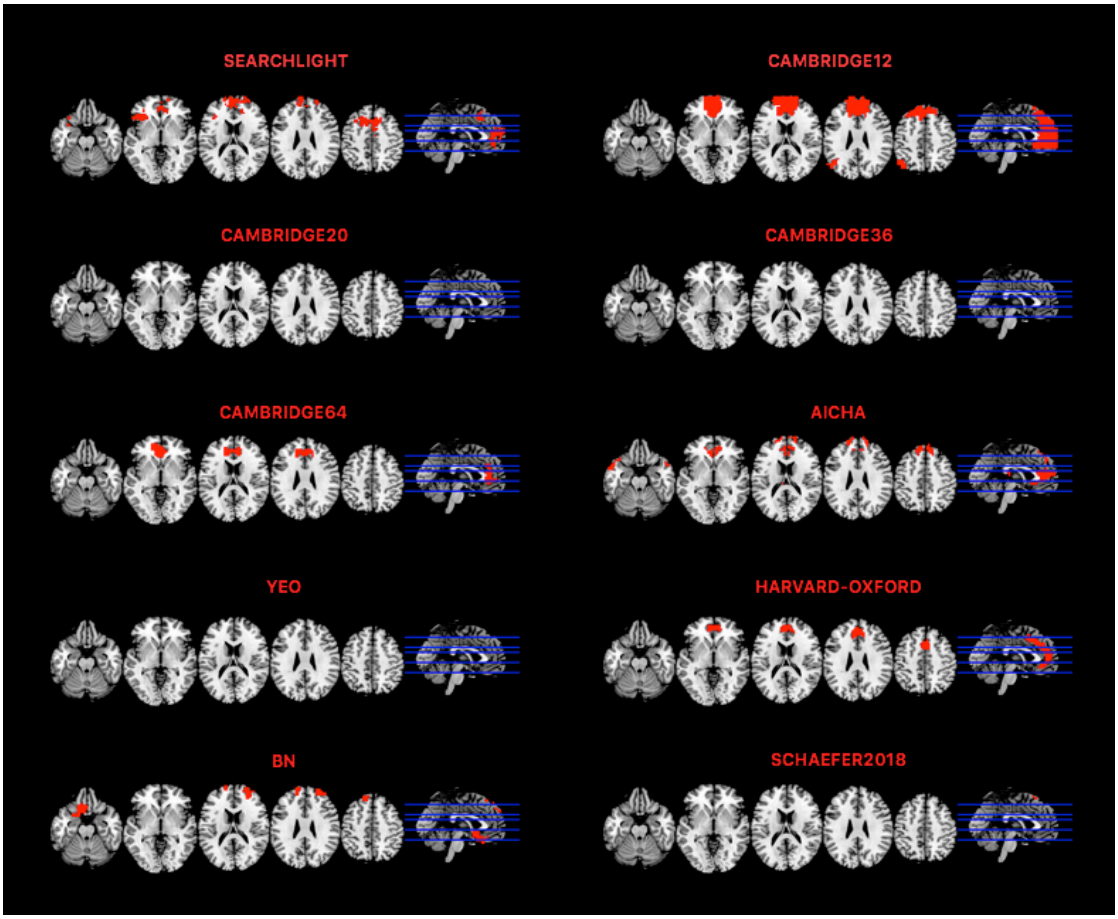

Figure 7: Significant voxels obtained by Searchlight and ABLA method for all the atlases used in the *valence* classification.

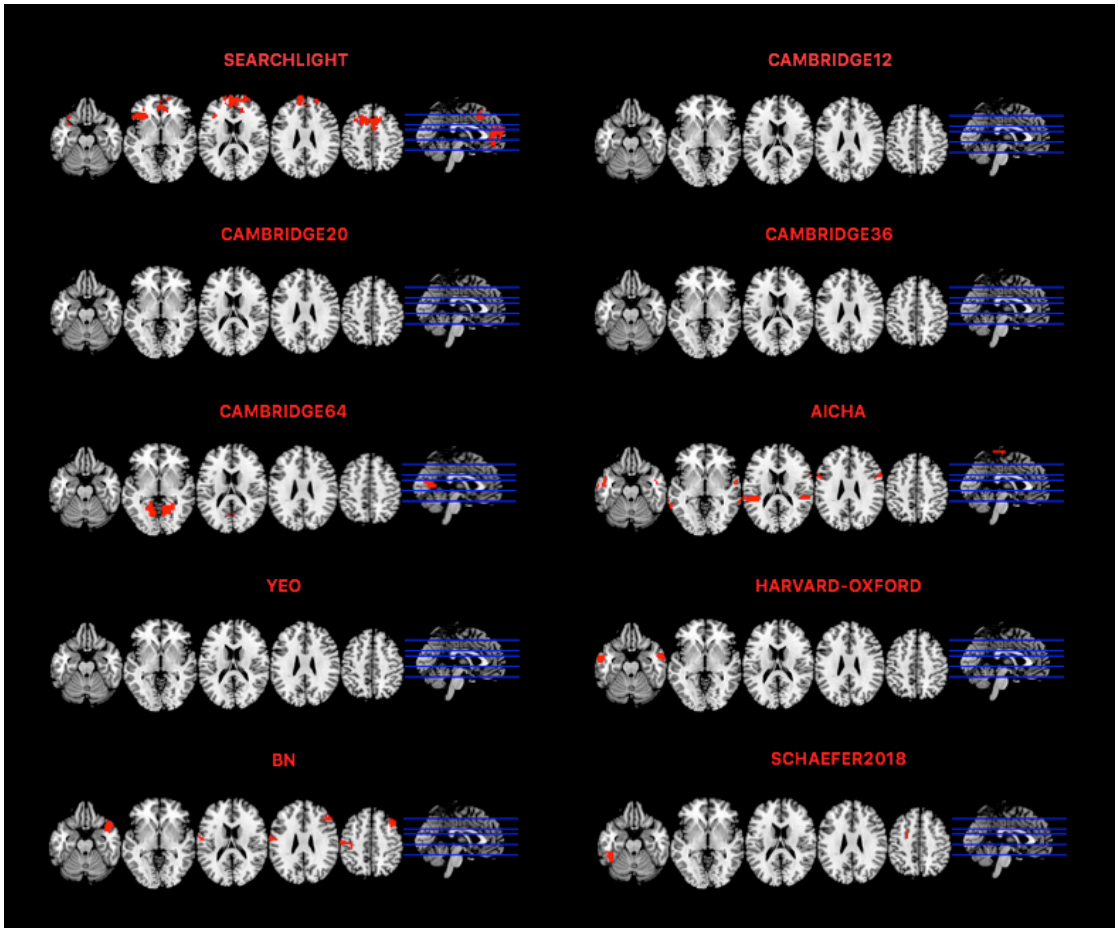

Figure 8: Significant voxels obtained by Searchlight and L1-MKL methods for all the atlases used in the *valence* classification.

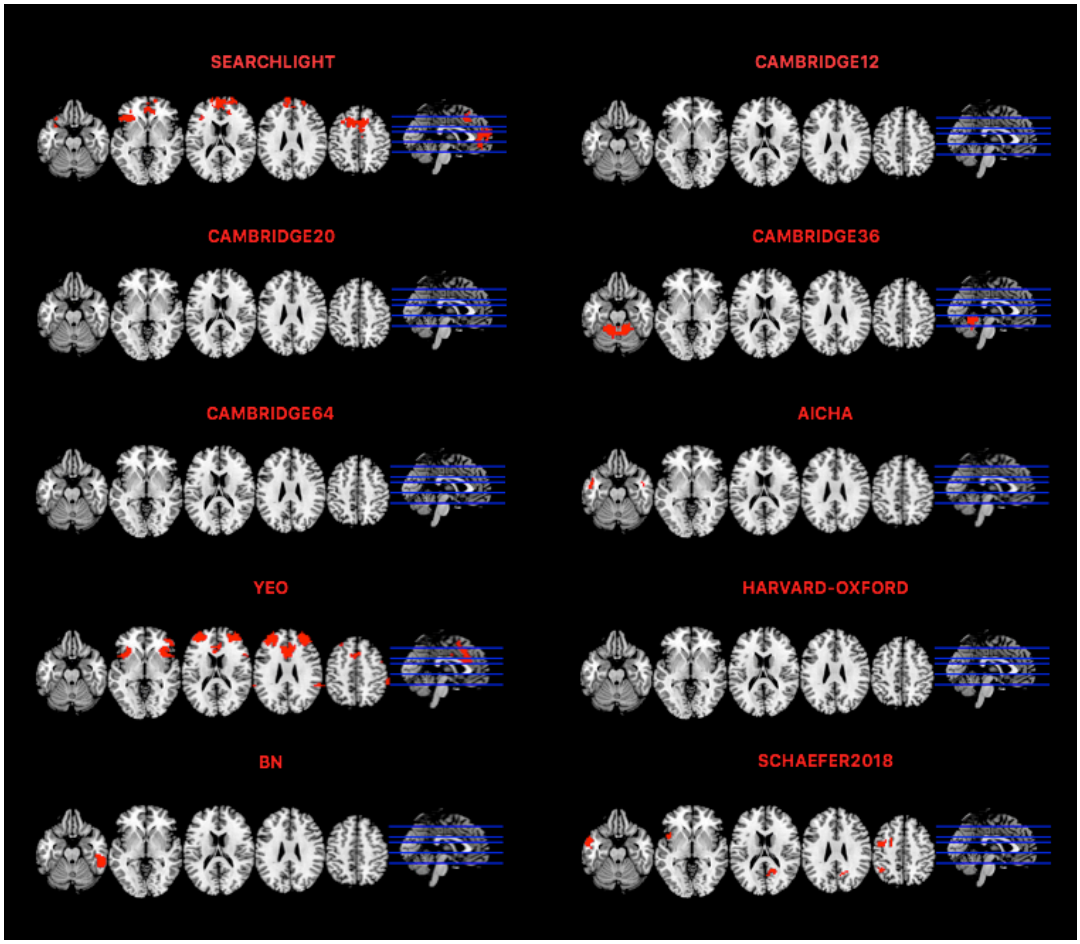

Figure 9: Significant voxels obtained by Searchlight and L2-MKL method for all the atlases used in the *valence* classification.