Processing Magnetic Resonance Image Features with One-class Support Vector Machines

Investigation of the Autism Spectrum Disorder Heterogeneity

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Abstract: Support Vector Machine (SVM) classifiers are widely used to analyse features extracted from brain MRI data to identify useful biomarkers of pathology in several disease conditions. They are trained to distinguish patients from healthy control subjects by making a binary classification of image features extracted by image processing algorithms. This task is particularly challenging when dealing with psychiatric disorders, as the reported neuroanatomical alterations are often very small and quite un-replicated within different studies. Subtle signs of pathology are difficult to catch especially in extremely heterogeneous conditions such as Autism Spectrum Disorders (ASD). We propose the use of the One-Class Classification (OCC) or Data Description method that, in contrast with two-class classification, is based on a description of one class of objects only. Then, new examples are tested for their similarity to the examples of this target class, end eventually considered as outliers. The application of the OCC to features extracted from brain MRI of children affected by ASD and control subjects demonstrated that a common pattern of features characterize the ASD population.

1 INTRODUCTION

Several post-processing methods to analyse brain Magnetic Resonance Imaging (MRI) data have been developed and implemented so far to obtain diagnostic models of pathology and useful disease biomarkers. Machine-learning techniques, e.g. those based on support vector machines (SVMs) (Vapnik, 1995), have been shown to be valuable tools to make predictive diagnoses in single subjects in a large variety of diseases. They can be implemented for diagnosis prediction, to assess the disease progression and to evaluate the treatment effectiveness (Orrù et al., 2012). Conventional binary (also called two-class) classification algorithms are applied in most cases. They aim to classify an unknown object into one of two pre-defined categories. In the present study we propose the use of the One-Class Classification (OCC) or Data Description method (Moya et al., 1993), which, in contrast to two-class classification, makes a description of one training class of objects (referred to as the positive class or target class) and detects which (new) objects resemble this target class, thus distinguishing them from examples considered outliers. Using OCC in standard binary classification problems, where objects from both the two classes are at disposal, could result in worse recognition accuracy, as the complete knowledge encoded in the available training set is not fully exploited. However, OCC could provide more robustness in case of difficulties embedded in the nature of data, since they seek to describe properties of the target class instead of minimizing the classification error.

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Table 1: Dataset composition and sample characteristics. *Abbreviations*: ASD, autism spectrum disorders; NVIQ, non-verbal intelligence quotient; std, standard deviation.

Variable	Subject group, mean ± std [range]			
Age (months)	ASD (n=41)		Controls (n=40)	
	49 ± 12 [28-70]		49 ± 14 [24-72]	
NVIQ	73 ± 22 [34-113]		73 ± 22 [31-113]	
	Males (n=21)	Females (n=20)	Males (n=20)	Females (n=20)
Age (months)	50 ± 10 [34-70]	48 ± 13 [28-69]	48 ± 13 [24-70]	50 ± 16 [22-72]
NVIQ	75 ± 22 [40-113]	70 ± 23 [34-113]	73 ± 23 [32-123]	71 ± 24 [31-106]

As a case study, we focused on the analysis of brain features extracted from MRI data of children affected by Autism Spectrum Disorders (ASD), which are complex developmental neuropsychiatric conditions affecting 1 in 68 children in USA (CDCP, 2014), and characterized by impairment in socio-communicative abilities, as well as restricted and stereotyped behaviours. Different approaches have been proposed to date to explore the genetic, clinical and neurobiological heterogeneity of ASD. Several studies aimed to explore the predictive power of MRI data, to find reliable ASD markers (Ecker et al., 2010; Jiao et al., 2010; Ingalhalikar et al., 2011; Calderoni et al., 2012; Zhou et al., 2014; Gori et al., 2015; Retico et al., 2015).

We propose the implementation of OCC to region-based characteristics extracted from structural MRI brain data, in order to measure their performance in the discrimination of patients with ASD with respect to controls in the preschool age. Moreover, we investigate the distribution of "normal" patterns of brain structure to test its homogeneity and its potential to enable the definition of a robust boundary in relation to which the patients with ASD are classified as outliers. Should it not be the case, a consistent neuroanatomical pattern among the ASD patients would be investigated. Finally, the relative contribution of the considered brain features to the decision function is studied to identify the neuroanatomical regions more involved in the OCC boundary definition.

2 MATERIALS AND METHODS

2.1 Samples of Subjects and MRI Data Acquisition

A group of 21 male and 20 female pre-schoolers with ASD [mean age ± standard deviation = 49 ± 12 months; age range = 28 – 70 months] and a group of 40 control subjects matched by gender, age, non-verbal IQ (NVIQ), and socioeconomic status were selected for this case-control study (see Table 1). Participants in the ASD group were recruited in the ASD Unit of IRCCS Stella Maris Foundation (Pisa), a tertiary hospital and research university in Italy. The control group was composed of 20 pre-schoolers with idiopathic intellectual disability (ID), and 20 pre-schoolers without intellectual disability (noID). Subjects with ID were included within the control group in order to obtain a match for NVIQ between patients and controls. T1-weighted MRI data with voxel size of 1.1x1.1x1.1 mm^3 were acquired using a GE 1.5 T Signa Neuro-optimized System (General Electric Medical Systems).

2.2 Data Preprocessing and Feature Extraction

The preprocessing of the entire data set included the volumetric segmentation and cortical reconstruction by the Freesurfer image analysis suite version 5.1.0, (http://freesurfer.net/; Fischl et al., 2004). In the cortical parcellation step, neuroanatomical labels were assigned to each location on the cortical surface according to the Desikan–Killiany–Tourville (DKT) cortical atlas, which divides the cerebral cortex into 62 structures (31 structures per hemisphere) (Klein and Tourville, 2012). The following 5 surface-based features for each structure are computed: *Area* (white surface area in mm^2); *Volume* (gray matter volume in mm^3); *Thickness* (average cortical thickness in mm); *ThicknessStd* (standard deviation of cortical thickness in mm); *Mean-Curv* (integrated rectified mean curvature in mm^{-1}). We remark that the *Volume* is computed according to a surface-based method, as the average of the white and pial surface areas, multiplied by the cortical thickness. In addition we considered the *White Surface Total Area* (in mm^2) and the *Mean Thickness* (in mm) of the cortex in the two hemispheres, thus obtaining a vector of 314 characteristics for each subject.

2.3 One-class Feature Classification

Among conventional binary classification algorithms, Support Vector Machines (SVM) are quite extensively applied tools (Vapnik, 1995). They are a supervised binary classification method that requires a training set of labeled input examples to learn the differences between the two sample classes, and a labeled test set to quantify the classification performance.

In the context of classification of brain images, each input example is a vector $\mathbf{x}$ of features extracted by each input image. The label $\mathbf{y}$ associated to each input example indicates its membership, e.g. “1” for vectors belonging to the patients class, “-1” for controls. Basically, during the training phase an optimization problem is solved to identify the largest-margin hyperplane allowing for an optimal separation of the two classes. The input vectors contributing to the definition of the separating hyperplane are called *support vectors.* Since data are generally not linearly separable a *regularization parameter* C is introduced to control the trade-off between the number of training errors and the generalization ability of the classifier. It is usually set using heuristics or tuned using cross-validation procedures.

The SVM can then predict the classification of an unlabeled input vector by checking on which side of the separating hyperplane the example lies. The SVM belong to the class of kernel methods, which depend on data only through dot products. To achieve good separation results even in case of non-linearly separable classes, the dot product can be replaced by a kernel function, which computes a dot product in some (possibly) higher dimensional feature space. This allows carrying out a linear classification in this feature space, without explicitly mapping in such a feature space the original observations. The separating hyperplane found in the feature space corresponds to a non-linear boundary in the input space. In this case, the prediction of the class membership of an unlabeled input vector is performed by mapping it into the feature space, and checking on which side of the separating hyperplane the example lies. Among the non-linear kernel functions the Radial Basis Function (RBF) Kernel is the most popular. It depends on the Euclidean distance between the examples and is defined as $k(\boldsymbol{x}, \boldsymbol{x}') = \exp(-\gamma\, ||\boldsymbol{x} - \boldsymbol{x}'||^2)$. The parameter γ determines the smoothness of the boundary (in the input space). Like the regularization parameter C, also this parameter γ is usually set using heuristics or tuned using cross-validation procedures.

Schölkopf et al., (2000) presented a new formulation of two-class SVM, where the C parameter was removed and replaced with a new parameter $\boldsymbol{\nu}$ with a more natural interpretation: it is an upper bound to the fraction of misclassification and margin errors and a lower bound on the fraction of support vectors. For certain parameter settings, the results of this new algorithm coincide with the conventional one. Moreover, desirable properties of previous SVM algorithms are retained. Schölkopf et al., (2001) modified the previous approach to address the OCC problem and called the new algorithm *single-class SVM*. During the training phase of a single-class SVM, a hyperplane is placed such that it separates the target set from the origin with maximal margin. Similarly to the standard two-class SVM, when a more flexible data description is required, an implicit mapping of the data into another (possibly high dimensional) feature space is defined, such that the dot product in this feature space can be computed by evaluating a simple kernel function. An ideal kernel function would map the target examples onto a bounded, spherically shaped area in the feature space and outlier objects outside this area. The single-class SVM attributes a new point $\mathbf{x}$ to the target or the outlier class by evaluating which side of the hyperplane it falls on in feature space. As in two-class algorithm, the regularization parameter $\nu \in (0, 1]$ has to be set. It can be interpreted as an upper bound on the fraction of training points outside the estimated region, and a lower bound on the fraction of support vectors.

In this work, we applied single-class SVM with RBF kernel to the vector of 314 characteristics extracted for each subject of our datasets. We performed the single-class classification separately on the male subset, on the female subset and on the entire dataset (see Figure 1).

In the linear-kernel classifiers, the entries of the vector $\mathbf{w}$ can be directly considered as the relative weights of each characteristic for the decision function (Gori et al., 2015). Conversely, in the non-linear case (e.g. with the RBF kernel), the interpretation of the vector $\mathbf{w}$ is non-intuitive, since the separating hyperplane is obtained in the feature space. We used the approach proposed by Schölkopf et al., (1999) to approximate the *preimages* for the single-class SVM with RBF kernel.

Additionally, to understand which features and which neuroanatomical regions drive the SVM boundary definition, we tailored the permutation testing method (Gori et al., 2015; Gaonkar and Davatzikos, 2013; Wanh et al., 2007; Mourão-Miranda et al., 2005) to the case of OCC.

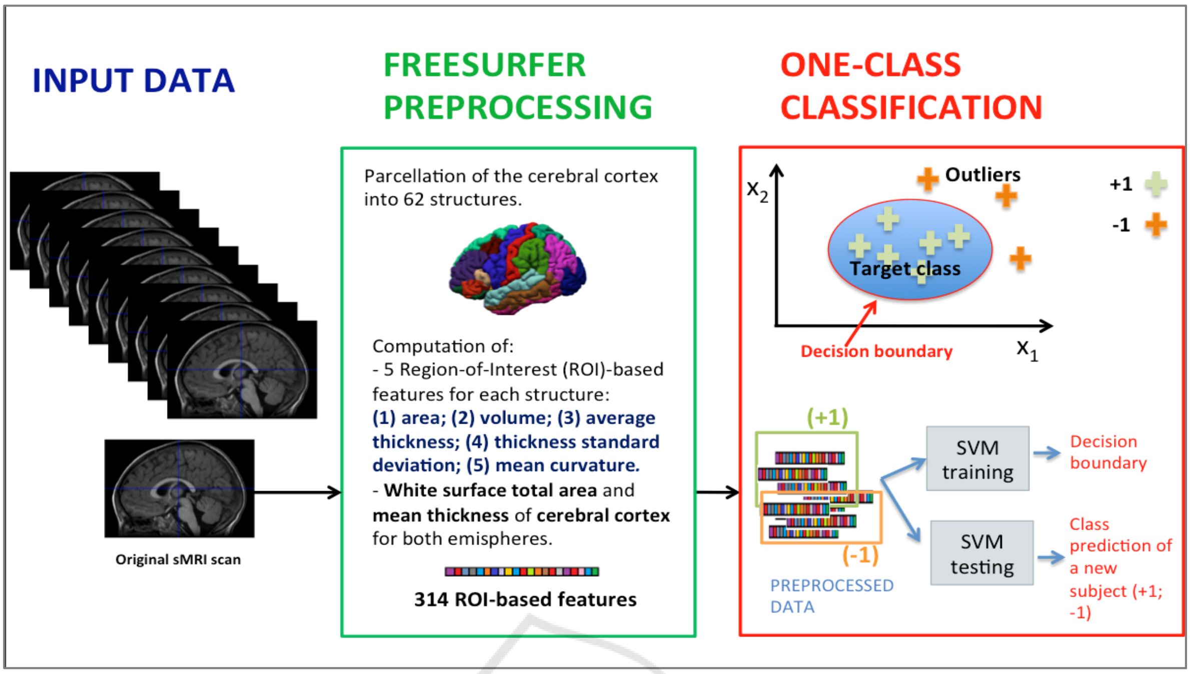

Figure 1: Schematic representation of analysis method. The regional features are extracted from brain sMRI scan of each subject using Freesurfer software. Then, the collected sets of features are classified with one-class SVM applying the LPO-CV procedure. Abbreviations: sMRI, structural Magnetic Resonance; ROI, Region Of Interest.

The performance of the SVM classifiers is evaluated in terms of the sensitivity and the specificity, computed by varying the classifier decisional threshold. These values can be represented in a curve known as Receiver Operating Characteristic (ROC) curve (Metz, 2006). The area under the ROC curve (AUC) is a global index to compare the performance of different classifiers. To ensure an unbiased estimate of the OCC SVM performance we implemented a cross-validation (CV) procedure, leaving one pair of subjects out at each iteration (LPO-CV). The difference with respect to a CV procedure to evaluate binary classification performance lies only in the training step: we simply trained the OCC on only one class (target class) inside the CV, and tested it on the subset of both classes left out for testing.

3 RESULTS

The Freesurfer pipeline was applied to preprocess the MRI of each subject. Patients with ASD and controls were matched on age and NVIQ. To train and test OCC we used RapidMiner (http://rapidminer.com/) advanced analytics platform version 5.3, which includes the single-class SVM as a part of the LibSVM operator.

We first performed single-class classification by setting ν=0.1 and γ using heuristics (i.e. as the inverse of the number of features). Then, we carried out the optimization of the parameters ν and γ, within nested LPO-CV loops.

The intuitive approach for transforming a binary discrimination problem into a single-class task in the context of highly heterogeneous conditions like ASD is to use the control class as target class, figuring that it could enable the definition of a robust boundary, in relation to which the ASD patients would be classified as outliers. Consequently, we first trained a single-class SVM by considering only control examples to form the decision boundary, thus discarding information about the ASD class during the training phase. This would be the optimal approach if the control class had characteristics of homogeneity, since the single-class SVM could capture the control class structure, by adjusting itself to its properties. This would allow recognizing ASD examples as outliers, even in case the available ASD sample is not representative of the real ASD population, due to the extreme ASD heterogeneity. However, the results obtained in this case in terms of AUC were not above the chance level.

Therefore, we repeated the same procedure using the ASD patient group as the target class to investigate whether there was a consistent neuroanatomical pattern among the ASD patients in relation to which the controls would be classified as outliers. The performance achieved by optimizing the parameters ν and γ was: AUC=0.74 for the male subset, AUC= 0.68 for the female subset and AUC=0.64 for the entire dataset.

These results show that the control class does not have characteristics of homogeneity allowing recognizing ASD examples as outliers.

Conversely, there is a common structure among the ASD patients that the single-class SVM could capture.

We also found a slight performance decrease when estimating the OCC performance on the entire dataset, which is not surprising and we ascribed it to the introduction of the gender as an additional heterogeneity factor.

In order to evaluate the potential of single-class SVM with respect to the primary aim of this work, that is the discrimination of ASD versus controls, we carried out also the two-class SVM classification with linear and RBF kernels. The results we achieved were: AUC of 0.74 for males and 0.58 for females by using the linear kernel classification, and 0.68 for male subset and 0.65 for females adopting the RBF kernel.

To understand which of the 314 characteristics (i.e. which brain regions and which of the 5 computed features) are the most relevant to the single-class SVM boundary definition, we trained a OCC SVM with RBF kernel using all the ASD patient group as the target class (with ν=0.1 and heuristic γ) and we applied the algorithm proposed in Schölkopf et al., (1999) to generate the preimage vector **z**. Then, we carried out a permutation testing procedure in the training phase originally tailored to the OCC with 10000 iterations and with ν=0.1 and heuristic γ, separately for the male subset, the female subset and the entire dataset.

We used the Matlab (The MathWorks, Inc.) interface to the LIBSVM package (http://www.csie.ntu.edu.tw/~cjlin/libsvm/) to train the OCC in the permutation testing procedure and the Statistical Pattern Recognition Toolbox (http://cmp.felk.cvut.cz/cmp/software/stprtool/index.html) for Matlab (STPRTool) to generate the preimage.

We show in Figure 2 the brain regions most contributing to the definition of the OCC boundary, as resulting from the permutation test, for male and female subsets, respectively. For the male population the regions visible in Figure 2(a,c) are: left (L) and right (R) medial orbito frontal cortices, L pars triangularis, R pars opercularis, middle temporal cortex and R insula. For the female population the regions visible in Figure 2(b,d) are: L and R caudate anterior cingulate, pars opercularis, posterior cingulated, cuneus; R pars triangularis postcentral gyrus, superior temporal cortex and superior parietal cortex. They are mostly among the network of structural brain alterations widely reported in the population with ASD, including frontal and temporal areas.

Thus, despite the phenotypical heterogeneity in ASD a common neuroanatomical profile that underlies the core features could be detected with the OCC SVM approach.

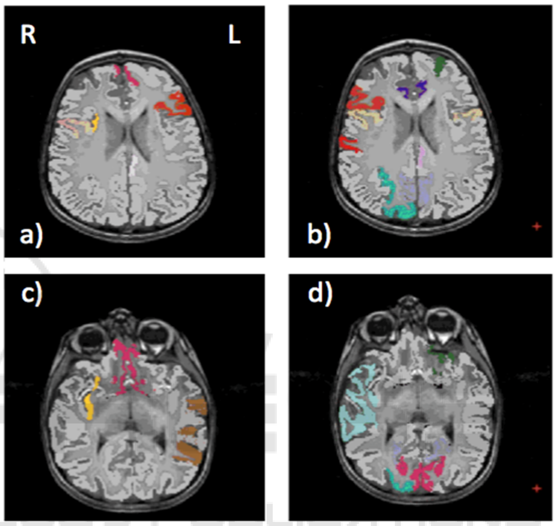

Figure 2. Brain region most contributing to the definition of the OCC boundary. For the male population the regions visible in a) and c) are: left (L) and right (R) medial orbito frontal cortices (pink), L pars triangularis (red), R pars opercularis (mustard), middle temporal cortex (brown) and R insula (yellow). For the female population the regions visible in b) and d) are: L and R caudate anterior cingulate (violet), pars opercularis (mustard), posterior cingulate (light violet), cuneus (magenta); R pars triangularis and postcentral gyrus (red), superior temporal cortex (light blue), superior parietal cortex (cyan).

4 CONCLUSIONS

The usefulness of OCC in the biomedical domain was already proved in a number of applications, including in the domain of psychiatric disorders (Mourão-Miranda et al., 2011). However, to the best of our knowledge, we propose the first application of OCC to the analysis of MRI data of patients with ASD.

The aim of this work was to apply OCC not only to measure its performance in the discrimination of ASD versus controls, but also to investigate whether the distribution of "normal" patterns of brain structure is enough homogeneous to enable the definition of a robust boundary, in relation to which the patients with ASD can be classified as outliers. As an alternative, a consistent pattern among the patients with ASD will provide a boundary in relation to which the controls are classified as outliers. The latter hypothesis was confirmed by our results. We found out evidence that the control group is more heterogeneous and therefore the hypersphere or decision boundary enclosing most of the controls contains data in the ASD range. Vice versa, the ASD group shows a common structure that the SVM OCC could capture.

The present work is a proof of concept that the OCC framework can be applied to neuroimaging data to investigate if consistent patterns of alterations do exist even in heterogeneous populations. Despite the results we found need to be confirmed against a larger population, the approach we present here is a preliminary step aiming to set up a strategy to identify common altered features in specific disorders.

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