UNIVERSIDAD NACIONAL DE COLOMBIA

Morfología funcional de Trastornos del Espectro Autista (TEA)

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A mi hija Salomé Almeida; a mi familia: Elizabeth, Janith, Rosa Mery, María, Rafael y Paula por su apoyo, sus consejos y sus confianza en mí, por creer en mis sueños y por ayudarme a alcanzar mis metas.

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Abstract

We present a morphometry method using models of brains taken from magnetic resonance images (MRI) in T1 sequence using the probability distribution function (PDF), obtained by the histogram of voxel intensity. A measure have been used to calculate the differences between regions of interest taken from brain models. The weights found with these similarity metric are characteristics to train a support vector machine (SVM).

This work shows the utility of this approach in medical imaging applications to make a classification between two classes. The methodology of this work is applied in an experimental group extracted from a public set of brain sMRI data: *Autism Brain Imaging Data Exchange* (ABIDE), classification between patients control and patients diagnosed with Autism Spectrum Disorder (ASD) shows a sensitivity and specificity of 70 %, which is comparable with other studies performed with this neuropathology.
Keywords: Autism Spectrum Disorders, ABIDE, sMRI, Morphometry, Probability Desnsity Function.

Resumen

Presentamos un método de morfometría que usa modelos de cerebros tomados de resonancia magnética nuclear en secuencia T1 usando la función de distribución de probabilidad (PDF por su nombre en inglés), obtenido mediante el histograma de intensidad de voxel. Una medida ha sido utilizada para calcular las diferencias entre regiones de interés tomadas de los modelos del cerebro. Los pesos hallados con esa métrica de similitud son características para entrenar una máquina de soporte vectorial.

Este trabajo muestra la utilidad de este enfoque en aplicaciones de imágenes médicas para hacer una clasificación entre dos clases. La metodología de éste trabajo se aplicó en un grupo experimental extraídos de un conjunto público de datos de sMRI de cerebro: *Autism Brain Imaging Data Exchange* (ABIDE), la clasificación entre sujetos control y pacientes diagnosticados con Trastorno del Espectro Autista (TEA) muestra una sensibilidad y una especificidad del 70 %, la cual es comparable con otros estudios realizados previamente con esta neuropatología.
Palabras Clave: : ABIDE, Clasificación, Función de densidad de probabilidad, Morfometría, Resonancia magnética estructural, Trastornos del espectro Autista.

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1 Introduction

1.1. Autism Spectrum Disorders

Autism Spectrum disorders (ASD) [1] constitute a group of neuroevolutive alterations that represent in a wide variety of clinical expressions, all of multifactorial disorders resulting in the development of central nervous system.

It is estimated that in recent reviews, the median of the global prevalence of the problem is 62/10 000, which means that one child in 160 has an ASD and subsequent disability. This estimate represents average cipher, because the observed prevalence varies considerably across studies.

It only has regional prevalence estimates for the European Region and the Region of the Americas, but not statistically different: in Europe the median rate is 61,9/10000 (range: 30,0 to 116,1 / 10 000), and the Americas 65,5/10 000(range 34-90/10 000). On the contrary, in many areas of the world, particularly in Africa, the prevalence estimates are absent or only provisional. Except China, countries with relatively ample evidence base are high-income countries. They have carried out some studies in middle-income countries, but no data on the prevalence in any of the low-income countries.[17].

It is estimated that about 16 % of the population under 15 years in Colombia has some kind of development disorder, include ASD; according to the Sistema Integral de Información de la Protección Social(SISPRO), in Colombia the following frequencies of diagnosis were recorded in 2013 in the Pervasive Developmental Disorders group (CIE-10: D840-D848):[21]

[1] Use this nomenclature in all document

Table 1-1: Diagnosed Population in Colombia

Diagnosis	**No.People**
D840 – Child Autism	64530
D841 – Atypical Autism	2642
D842 – Rett Syndrome	12
D843 – Pervasive Developmental Disorder-Not Otherwise Specified	13
D844 – ADHD Mental Retardation	19
D845 – Asperger Syndrome	45
D848 – other developmental disorders	109

Autism affects more men than women in a ratio of 3-4: 1, although this ratio is lower in patients with mild mental retardation; by contrast, it is higher in those with a high IQ[12]. In the international classification systems, the ASD are grouped under the epigraph of Pervasive Developmental Disorders (PDD). In all disorders of this group are observed qualitative changes in social interaction, communication deficits and repetitive patterns, restricted and stereotyped behaviour. The prototypical disorder of this group is autism, characterized by the aforementioned triad of signs, but is much more common pervasive developmental disorder not otherwise specified (PDD-NOS), it does not have all the symptoms of autism and usually less severe.[4].

Currently, scientific research has raised a multifactorial interaction in the etiology of autism, including genetic and environmental factors, however, there is no evidence on which and how these environmental factors on genetic susceptibility and development of the central nervous system influence[22]. Some theories suggest that between environmental factors, found viral infections such as rubella, herpes, cytomegalovirus, among others; obstetric complications at childbirth, administering vaccines during the first months of life, intolerance to certain foods and nutrients, consumption of unsuitable products during pregnancy, among others[21]. Is disown in 90 % the causal factor because the scientific community has not succeeded in proving that environmental factors are the cause of the disorder, the other 10 % of cases have been identified in chromosomal and not chromosomal factors.[3].

1.1.1. Signs and symptoms

The triad of signs that are associated with ASD are: a) The abnormal or impaired development in social interaction; b) The existence of problems in communication, which affects the understanding and spoken language, and c) restricted repertoire of activities and interests

of patients[20].

Social Interaction

Patients may have an inability to develop relationships with children of their age. You may lack the spontaneous tendency of normal children to share enjoyment, interests or objectives, such as showing, bringing, or pointing to objects of common developmental age. The lack of social or emotional reciprocity is evident when the child does not actively participate in social games, and prefers to have only activities and uses inappropriate tools for the game.

Communication

Alterations in communication affects verbal and nonverbal skills. Children with ASD may have a significant delay in language acquisition or total absence. Speaking patients do not have the faculty to initiate or sustain a conversation with others, or have a stereotyped language (echolalia), use repetitive words or speak idiosyncratically.

Restricted interests

Children with ASD often have patterns of behaviour, activities and restricted, stereotyped, repetitive interests. The interest is very limited, and patients worry stubbornly however restricted activities can be aligned over and over toys in the same way, or repeatedly imitate a behaviour. A little old autistic child may have a tantrum, caused by slight changes in the environment, such as the order of his toys or placing new curtains in his room. They can show inflexible activities in the form of non-functional routines and rituals, as always follow the same route at home or to go to school.

1.2. Diagnosis of AD

Since there is a large number of syndromes related to autism, it is strictly clinical diagnosis. Most of these early disorders of brain function are not selective, causing the appearance of autistic signs, combined with evidence of neurologic dysfunction[20].

The diagnostic category “autism” was described and implemented in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association “APA”, 1980) within the deep problems that are evident in infancy, childhood, or adolescence, bearing in mind that in the previous two versions symptoms associated with autistic disorder were incorporated into childhood schizophrenia.

The six criteria set out in this manual diagnosis were:

1. Starts before 30 months of age.
2. General absence of responsiveness capacity to other peoples.
3. Serious in the development of language deficit.
4. When speaks, peculiar speech patterns are presented (immediate echolalia, delayed, metaphorical language or pronoun reversal).
5. Bizarre to various aspects of the environment such as resistance to change, peculiar interest or attachments to animate or inanimate objects replies.
6. It is different from schizophrenia because there is absence of delusions, hallucinations, loss of associations and incoherence.

After the third edition, the APA published the revision of DSM-III, adding autistic disorder diagnosis criteria that was grouped into four broad criteria identified by the letters A, B, C and D, consisting of 17 items or items (five in criterion A, six in B, five in C and one in D)[26].

The DSM-IV differences were the five conditions included in the diagnosis of autism and correspond to the following categories[18]:

1. Autistic Disorder (AD)
2. Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS).
3. Asperger syndrome.
4. Rett syndrome.
5. Childhood disintegrative disorder.

Within the group of ASD, AD cases are more frequent and better defined, the rest of ASD are confused with other disorders such as mental retardation, speech disorder, obsessive compulsive disorder and schizophrenia among others. Clinical diagnostic tools developed on the basis of DSM-IV, tried to separate the TA of the other categories, appealing to more objective observations (ADOS - *Autism Diagnostic Observation* and ADI-R - *Autism Diagnostic Interview-Revised*, and others).
The current version of the DSM, the DSM-V, conceptually consolidated the autism, replacing the current name of pervasive developmental disorders by Autism Spectrum Disorder (ASD). This change has a scope that goes beyond a simple semantic adequacy of DSM-IV, as a sustenance for the reformulation of the classification in the logic of the dimensional approach.

The diagnosis of ASD process has as main purpose to characterize, with the highest reliability possible, the behaviour of the individual as belonging to a specific diagnostic category, by identifying comorbid conditions and differentiation of other developmental or mental disorders.
Firstly, relevant information should be collected through a detailed history of the individual. Then it must implement a series of neuropsychological tests to understand better the symptoms and complete the psychological profile of the person.
The most commonly used tests to diagnose or assess the severity of ASD are[2]:

1. **ADI-R (Autism Diagnostic Interview-Revised) Lord et.al (1994)**:

   It is a semi-structured interview designed to diagnose and assess key aspects of ASD as: socialization, communication and restricted interests and stereotyped behaviors. It consists of 93 items and it is applied to parents or people close to the patient by a specialized clinician..

   It is designed for individuals older than 18 months, that has psychometric measures of specificity and sensivity of 75 % - 96 % and 86 % - 100 % respectively.

2. **ADOS-G (Autism Diagnostic Observation Schedule-Generic) Lord et.al (2000)**:

   The ADOS scale is a standardized assessment tool used to diagnose ASD. It evaluates aspects of reciprocal social interaction and communication, play and use of imagination.

   It consists of four modules, which are applied according to the patient's verbal skills. Each item receives a weighted value of 0 (zero, normal) to 3 (three severe symptoms). It must be applied by a specially trained clinician.

   It has a sensivity higher than 90 % and specificity from 80 % to 90 %

3. **CARS (Childhood Autism Rating Scale) DiLalla y Rogers (1994)**:

   It is an observational instrument developed to identify children with autism compared with children with another deficit in the development and determine the severity of symptoms. It is applied in children over two years.

   It consists of 15 scales where the child's behaviours are scored according to chronological age. The sum of the item, placed the child in a continuum from "without autism"to "mild autism"to "severe autism". No training needed for your application.

   It has a sensivity of 100 % and inter-rater reliability is 71 %

4. **M-CHAT (Modified Checklist for Autism in Toddlers)**:

   It is an instrument that aims to properly discriminated children with normal neurodevelopment and girls with autism spectrum disorders before two years of age. In the new version of CHAT number of questions going from nine to 23 was modified.

   It has a sensivity of 95 % and specificity of 99 %

5. **GARS (Gilliam Autism Rating Scale) Gilliam (1995)**:

   It is an instrument used to estimate the severity of symptoms, applies from three to 22 years. It is based on the DSM-IV and the items are grouped into four categories: stereotypes, communication, social interaction and evolutionary changes. It contains 56 items divided into 4 subscales of 14 items. The items in the first three sub-scales are valued using a Likert's scale of 4 points ranging from never seen (0) to frequently observed (3). The items of the sub-scale developmental disorders are evaluated using a dichotomous scale and observed behaviors in the first 36 months of life[5].

1.2.1. Early Diagnosis

ASD do not have a cure and their diagnosis requires a wide deployment of professionals who are properly trained in the assessment of the signs presented in these disorders. After characterizing the disorder, and once the differential diagnosis has been made, it should be ensured that it is as accurate as possible in order to avoid unnecessary waste of time and money (efficient diagnosis); In turn should be concise so as not to cause discomfort to patients and their families. Difficulties in the diagnosis of ASD are reflected in the attribution of imprecise or erroneous descriptive labels that prevent early attention to cases [19].
Even though neuropsychological tests are a valid tool for diagnosing autism at an early age, there is no evidence for the use of medical imaging studies to support such a diagnosis [25]. Neuroimaging represents an opportunity to evaluate the relationships between the functioning of the different areas or regions of the brain and the various cognitive alterations related to this psychopathology, ie the analysis of the structure offers new possibilities to correlate functional brain changes with the present signs in the ASD and, in turn, provide an early intervention to improve the quality of life of both the patient and the people who surround him.

1.3. Medical Imaging in ASD

1.4. State-of-the-Art

Different researches have been done for the purpose of co-relate the functional alterations presented in ASD and the anatomical structures that control these functions.

The first approaches to this theory dating from 1991, where Kemper and Bauman analyzed the brains of six autistic patients, finding the main alterations at the level of the limbic system, cerebellum and inferior olive. These brains showed no major morphological changes; however, there was a decrease in the size of neuronal cells and increasing in neuronal density level of the amygdala and other limbic structures in the brain compared to controls[9].

With the development of new techniques of image processing it has managed to establish more accurately the brain changes in patients diagnosed with ASD.

Webb, Et.Al(2009) Used structural magnetic resonance images (MRI) applied to 85 children between three and four years old, divided into three groups: 45 diagnosed with ASD, 14 children with developmental delay and 26 children with typical development.
In their research they used volumetric measurements of the brain, the cerebellum and vermianos lobes IV, VI-VII and VIII-X using software developed by the Johns Hopkins University that allows simultaneous data visualization and interaction within multiple planes (coronal, axial and sagittal).
The main finding of this study was a significant reduction in the sagittal-media vermian area vermian vermianos lobe lobes IV and VI-VII when children with ASD is adjusted for increases in brain volume or the total cerebellum compared to children typically developing[27].

Schumann, Et.Al(2010) They conducted a study based on MRI scans of 118 children (87 males, 31 females) aged between 12 and 48 months (medium, 30 $\pm$ 10 month). The images were processed using a combination semi anatomy manual guided using software FreeSurfer. When performing a statistical analysis provided by the software, they found that the covariance for all separated by age and gender, subjects showed a significant increase in total brain volume in the ASD group compared to the controls on a 7 % [23].

Jockschat Et.Al(2011) They conducted a meta-analysis of fair changes in brain structure reported in the literature. They used a revised approach to activation likelihood estimation (ALE) for meta coordinates based on the results of neuroimaging. To mitigate small samples used in previous studies, meta-analysis compiles information from 277 patients diagnosed with ASD and 303 healthy controls. They found six sets of convergence indicating changes in brain structure in patients with ASD including the occipital lobe, the paricentral region,

the medial temporal lobe, basal ganglia and the right parietal lobe. The researchers found evidence of structural abnormalities despite the variability of diagnostic criteria and heterogeneity of the method of voxel-based morphology (VBM) and in turn, a dependency between the changes and the age of patients[16].

Jiao Et.Al(2011) In this study, they tested the hypothesis that diagnostic models can distinguish children with ASD from controls based on regional cortical thickness, and that these models have greater accuracies than diagnostic models based on regional volumes. To test this hypothesis, they computed average cortical thicknesses and volumes of 66 structures defined on a brain atlas, for each subject. They then applied four data-mining approaches to generate four diagnostic models based on either regional cortical thicknesses or regional volumes. To avoid a model generation bias, they applied four machine learning methods to generate the diagnostic model; the best classification performance throws an accuracy = 87 %, area under the receiver operating characteristic (ROC) curve (AUC) = 0.93, sensitivity = 95 %, and specificity = 75 %. [8].
The use of support vector machines and machine learning techniques and statistical interpretation of data is common for the analysis of neuroimaging because of its high dimensionality and complexity. These approaches use features derived from volumes as inputs from a supervised classification algorithm that are learned from previously assigned tags. As more features are added to the classification algorithm, its discriminatory power increases; Reducing the dimensionality of a neurological image is a basis for making a comparison between two more classes. The patterns found in each characteristic of the image allow to differentiate the disorders associated with the morphology of the brain.
Yaw Wee Et.Al (2014), they presented a novel approach to identify (ASD) using regional and interregional morphological regions taken of sMRI. [28]

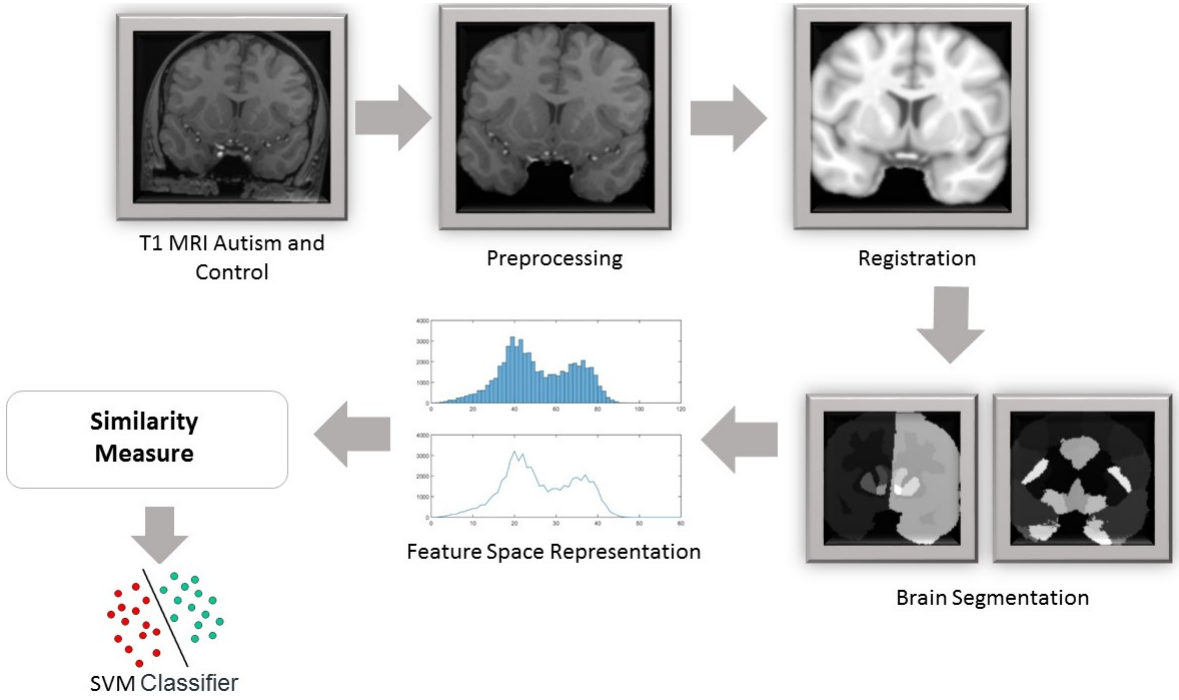
1.5. Proposed Approach

In the present work we propose a methodology that extracts morphological features information of groups of Magnetic Resonance Images (MRI) taken the intensities in order to condense this information into characteristic brain models.

2 Automatic Classification of Autism Spectrum Disorders using low level features

The method comprises as basic steps, pre-processing, elastic registration to represent the brains in the MNI normalized space and characterization of each region by its normalized histogram of intensities. Each of the segmented regions can then be compared with the others by computing the distance between Probability Distribution Functions (Normalized intensity histograms) with the Kullback-Leibler divergence. Finally, a conventional Support Vector Machine (SVM) classifier, using the KL distance as input and a linear kernel, separates the two studied classes. Figure **2-1** outlines the steps of the proposed methodology, next sections describe further detail.

Figure 2-1: Pipeline to proposed methodology



2.1. Pre-Processing

First, the field bias was corrected and the intensity is normalized using the FSLMATH tool provided by the Oxford University[15], since images were not captured with the same resonator. The skull was removed using (Brain Extraction Tool) BET tool [24].

2.2. Registration

The MNI152 space (Stereotaxic Registration Model) [14] was used as template to register the T1 images of both patient groups. The process starts by an affine rigid registration with respect to the MNI152 template, under 12 degrees of freedom. Spatial errors are corrected using FLIRT (FMRIB 's Linear Image Registration Tool)[11]. A more accurate registration is achieved by an elastic registration using the FNIRT[15] tool with a quadratic spline which optimizes the processing time and ensures that the register is as accurate as possible.
Once the template MNI152 has been registered towards the brains, the transformation matrix resulting is used in order to segment all brains in regions of interest using an atlas.

2.3. Feature representation

A drastic dimensionality reduction is achieved by mapping the anatomical structures to a space in which these complex objects can be compared. The different low level characteristics associated to a region should describe either geometrical or structural properties representing the region. Orientation is a very global feature that depends on the particular brain size and shape. Edges in this case are very variable. Intensities in contrast represent the local resonance properties of particular tissue locations and should be in consequence proportional to the amount of tissue[19]. Since the ASD is considered as a complex disorder with variable patterns, this work uses an intensity based descriptor as the distribution of gray values within a particular region using the histogram in order to evaluate the probability distribution function per each region.

2.4. Similarity Measure

2.4.1. Kullback-Leibler Divergence

The Kullback-Leibler (KL) divergence, also known as the relative entropy, is a widely used measure of the difference between probability density functions. Given two discrete probability distributions P and Q, the KL divergence between P and Q is a measure of the information lost when q is used to approximate p and is defined by:

$$D_{KL}(P \parallel Q) = \sum_{i=1}^{N} P(i) ln \left(\frac{P(i)}{Q(i)} \right) \tag{2-1}$$

Provided that $D_{KL}(P\|Q) \neq D_{KL}(Q\|P)$, this measure is not symmetric and cannot be a true metric. The version used in the present investigation corresponds to the blended version as the DKL taken as the mean of the two possible measurements

$$D_{KL} = (\frac{1}{2})\{D_{KL}(P \parallel Q) + D_{KL}(Q \parallel P)\}$$

2.4.2. Gaussian Mixture Models

A Gaussian Mixture Model (GMM) is a parametric probability density function represented as a weighted sum of Gaussian component densities. GMMs are commonly used as a parametric model of the probability distribution of continuous measurements or features in a biometric system, such as vocal-tract related spectral features in a speaker recognition system. GMM parameters are estimated from training data using the iterative Expectation-Maximization (EM) algorithm or Maximum A Posteriori (MAP) estimation from a well-trained prior model.
A Gaussian mixture model is a weighted sum of M component Gaussian densities as given by the equation 2-2,

$$p(x|\lambda) = \sum_{i=1}^{M} w_i g(x|\mu_i, \Sigma_i) \tag{2-2}$$

where x is a D-dimensional continuous-valued data vector (i.e. measurement or features), w_i, i=1, . . . , M, are the mixture weights and $g(x|\mu_i, \Sigma_i)$, i = 1, . . . , M, are the component Gaussian densities.

2.5. Classifier

SVM (Cristianini and Shawe-Taylor, 2000) is a type of machine learning algorithm, originally introduced by Vapnik and co-workers (Boser et al., 1992;

Vapnik, 1998) and successively extended by a number of other researchers. Their remarkably performance with respect to sparse and noisy data is making them the system of choice in a number of applications including the protein function prediction, patters in histopathological images, and others. Those are used for classification, they separate a given set of binary labeled training data with a hyper-plane that is maximally distant from them (known as "the maximal margin hyper-plane").

2.6. Experimental Setup

2.6.1. MRI Data

The data used for the current study is part of the *Autism Brain Imaging Data Exchange* ABIDE. Data were fully anonymized as required by HIPAA regulations [6]. The ABIDE database contains aggregated MRI T1 scans of 539 ASD individuals and 573 typical controls aged 6–65 years which were scanned as part of 20 international studies. Analyses were performed on 2 samples from the database, including only male cases with MRI resolutions of $1 \times 1 \times 1$ and ages between 18 and 35 years, aiming to test on an homogeneous population. The analysis was then carried out with 104 subjects (52 subjects diagnosed with ASD and 52 controls) as shown in Table **2-1**.

Table 2-1: Strict sample phenotypic information.

Group	Age	Total	Mean	Standard Desviation	Variance Coefficient
Autism	18 - 35 years	52	24,3	5,21	21,36 %
Control	18 - 35 years	52	24,6	4,75	19,3 %

2.6.2. Registration

The Harvard - Oxford atlas [13] was used as the reference to segment each brain of the experimental group into 96 cortical (48 per hemisphere) and 21 sub-cortical regions. The lateralized template was elastically registed to each

of the brains. The final labeling was adjusted by a simple Nearest neighbour interpolation.
Overlapping after registration was estimated by a *Dice Score* coefficient, computed as

$$QS = \frac{2|X \cap Y|}{|X| + |Y|} \tag{2-3}$$

Where: X is the MNI152 template and Y the evaluated brain.
Once the elastic registration is performed, each brain is compared with the deformed template to verify that there is a high correspondence. Results are shown in Table **2-2**.

Table 2-2: Overlap Analysis

Group	**Analyzed Cases**	**Register**	**Total Overlap ± SD in %**
Control	52	Affine	95.31 ± 0.78
		Elastic	97.36 ± 0.65
Autism	52	Affine	95.08 ± 0.99
		Elastic	97.27 ± 0.79

3 Results

For each iteration of the validation procedure, the SVM classier returns a value that is often interpreted as the probability of the test subject belonging to the positive class. With the values collected from the whole experimental group, a receiver operating characteristic (ROC) curve was constructed since this is the metrics more used in case of binary classiffication problems. The area under the curve (AUC), a global measure of the classication performance, and the equal error rate (EER), the rate for which both false positive rate (type I error) and false rejection rate (type II error) are equal, were calculated. The EER value means that there is a decision threshold in which it is possible to achieve simultaneously sensibility and specicity rates of 1 EER.

3.1. Using Kullback-Leibler Divergence

Once the cortical and sub-cortical brain regions are segmented, each region defines a set of individual constituted by the 104 cases. Afterward, the histogram of intensities per region is computed and normalized to have the probability distribution function. The number of bins was set to 128, aiming to obtain the best homogeneous intensity representation.
The experimental group is described in Table **2-1**
The Kullback-Leibler divergence to calculate the centroid in the control group is used in order to find, for each ROI,a case that had the minimum distance between them and then take that case as a reference to assess the autism cases and determine whether there are regions where differences are presented.Those distances were compared with the centroid and finally stored in a vector. raphics for each analyzed region; Figure **3-4** and Figure **3-2**, for instance, show the distances obtained between the centroid of Control cases

regarding to Autistic cases evaluated in the cortical region *Right Frontal Pole* and sub-cortical region *Left pallidum*.

Figure 3-1: Graph of all cases the centroid in the cortical region *Right Frontal Pole*

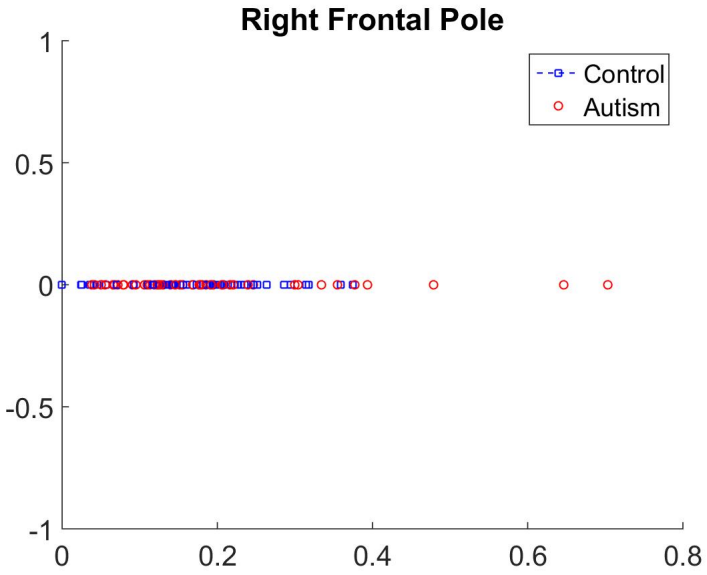
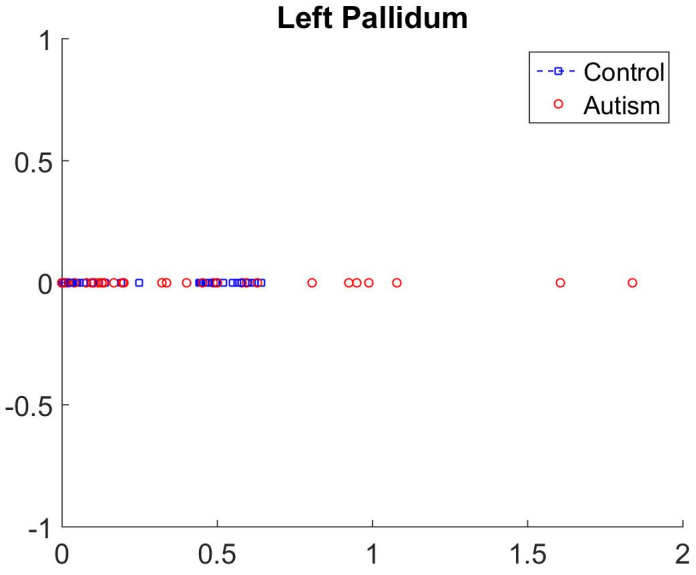


Figure 3-2: Graph of all cases the centroid in the subcortical region *Left pallidum*



Using a Gaussian kernel, the probabilistic model is obtained to adjust the parameters of support vector classification, to achieve this, the method of

cross validation is used taken 75 % of cases (78 in total), the remaining 25 % was used to test the sensitivity and specificity of the method. This process was performed three times in order to obtain the best fit parameters in the SVM.

Once set the classification algorithm was calculated for each region analyzed the area under the curve (AUC) and confirmed using the equal error rate. It is noteworthy that the regions that showed greater accuracy were subcortical regions, especially in the basal ganglia and the amygdala which play an important role in brain morphological changes such autistic patients and as reported in previous researchs.[10]. In Table **3-2** we present some results for classification using the Kullback-Leibler Divergence for cortical and subcortical regions.

The curve in Figure **3-3** has an AUC of 0.67, the good performance of the classier even when our experimental group is relatively small and has an important imbalance of classes, likewise the aging distribution is quite heterogeneous in the two classes.

Figure 3-3: Performance of classification with Area Under Curve (AUC)

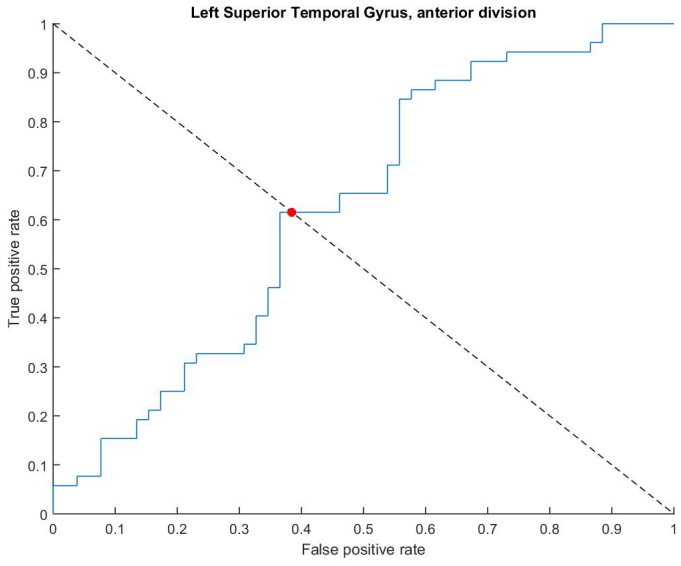


Table 3-1: Area Under Curve and Equal Error Rate for cortical and sub-cortical regions classification were found with Kullback-Leibler Divergence

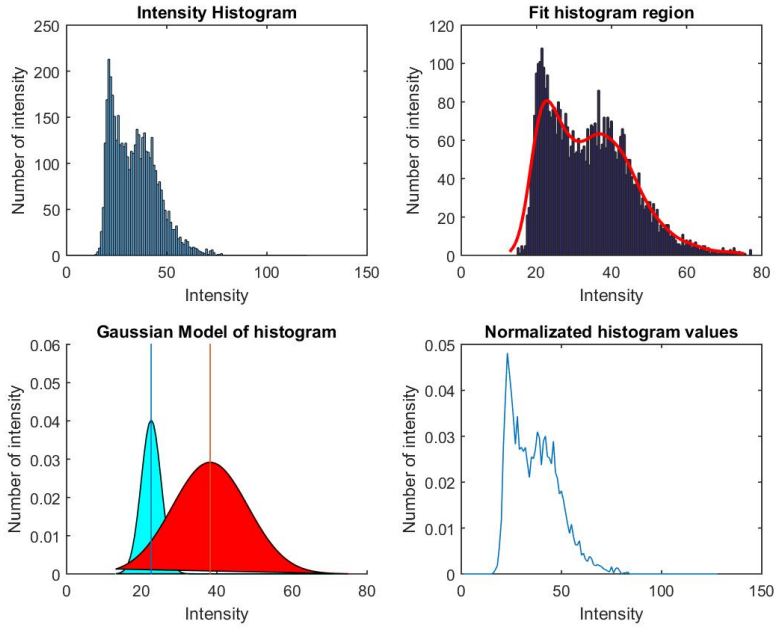
	Region	AUC	EER
Cortical Regions	Right Superior Temporal Gyrus, anterior division	0,670	0,615
	Right Central Opercular Cortex	0,643	0,634
	Left Superior Temporal Gyrus, anterior division	0,635	0,596
	Left Middle Temporal Gyrus, anterior division	0,630	0,596
Sub-Cortical Regions	Right Thalamus	0,609	0,615
	Left Cerebral White Matter	0,601	0,557
	Left Lateral Ventrical	0,595	0,557
	Left Thalamus	0,588	0,557

3.2. Using Gaussian Mixture Model

In this step, the Gaussian Mixture Model(GMM) in order to represent the gray and white matter for each region is used, and the parameters for both probability function are concatenated on a matrix. Graphics for each analyzed region; Figure **3-4**, for instance, show the two Gaussian Distributions (Gray Matter and White Matter).

The algorithm returns the mean and the Standard Deviation for each distribution model; this features are used as weights for the classification step.

Figure 3-4: Graph of two Gaussian distribution obtained for the intensity histogram. The cyan distribution represent the white matter, the red distribution represent the gray mater



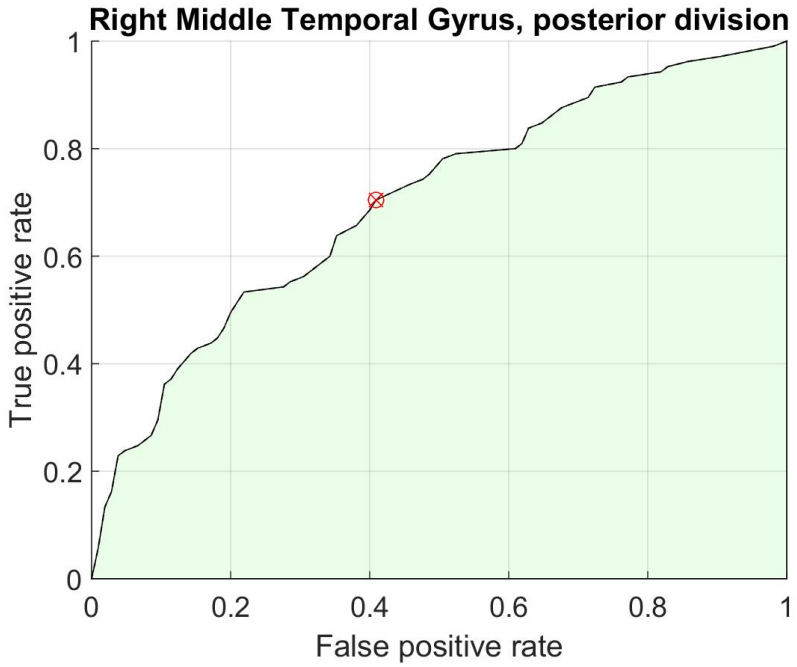
In Table **3-2** we present some results for classification using the Gaussian Mixture Models for cortical and sub-cortical regions.

Table 3-2: Performance of classification for cortical and sub-cortical regions classification were found with Gaussian Mixture Models

	Region	AUC	Sensitivity	Specificity	F Score
Cortical Regions	Right Middle Temporal Gyrus posterior division	0,719	0,704	0,590	0,666
	Left Lateral Occipital Cortex inferior division	0,701	0,647	0,647	0,647
	Left Inferior Temporal Gyrus anterior division	0,686	0,6	0,666	0,620
	Left Cingulate,Gyrus, anterior division	0,676	0,676	0,590	0,648
Sub-Cortical Regions	Left Pallidum	0,653	0,580	0,647	0,600
	Left Amydgala	0,644	0,6	0,628	0,608
	Right Accumbens	0,634	0,561	0,647	0,587
	Right Amydgala	0,602	0,638	0,561	0,614

Figure **3-5** show the most discriminant region found using Gaussian Mixture Model.

Figure 3-5: Area Under Curve (AUC) for the most discriminant region found using GMM



4 Discussion

In this work we presented an useful method to classify patients who have been diagnosed with ASD and they differ from control patients. The variability of the disorder and methods used by clinicians to diagnose could not be entirely reliable. The method used in this research works with low-level features on MRI in order to represent the latent information in it and using a measure of probability distributions functions. We reduced the dimensionality of the presented information in the brain stem which is related to higher order functions structure.
The results obtained correspond to regions reported in the state of the art studied with other methods of image analysis based on high-level features. Cortical regions are still relevant in the study of autism due to the anatomical variability of the brain; the methodology used in this study showed good results, it could be determined differences in cortical regions of autistic patients compared to controls specially in the Right and Left Temporal Gyrus, present on the Broka's and Wernnike's areas, both related with the normal language function, which represents a direct relationship with the signs present in the disorder[7].

4.1. Products

While developing this thesis, two works were presented in international conferences:

- 'A multidimensional feature space for automatic classification of autism spectrum disorders (ASD)' in XII International Symposium on Medical Information Processing and Analysis - SIPAIM (2016)[1].

- 'Gaussian Mixture Models for detection of Autism Spectrum Disorders (ASD) using magnetic resonance imaging.' in XIII International Symposium on Medical Information Processing and Analysis - SIPAIM (2017).

4.2. Future Work

As future work we want to do an inter-class classification to determine automatically the existing classes in Autism spectrum disorder described by the DSM-V, using other descriptor features such as edges, shape and volume of the ROI.

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