Quantifying inter-hemispheric differences in Parkinson's Disease using siamese networks

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Abstract. Classification of medical imaging is one of the most popular application of intelligent systems. A crucial step is to find the features that are relevant for the subsequent classification. One possibility is to compute features derived from the morphology of the target region in order to check its role in the pathology under study. It is also possible to extract relevant features to evaluate the similarity between different regions, in addition to compute morphology-related measures. However, it can be much more useful to model the differences between regions. In this paper, we propose a method based on the principles of siamese neural networks to extract informative features from differences between two brain regions. The output of this network generates a latent space that characterizes differences between the two hemispheres. This output vector is then fed into a linear SVM classifier. The usefulness of this method has been assessed with images from the Parkinson's Progression Markers Initiative, demonstrating that differences between the dopaminergic regions of both hemispheres lead to a high performance when classifying controls *vs* Parkinson's disease patients.

Keywords: Deep learning, siamese network, Parkinson's disease, SPECT images.

1 Introduction

Current medical images provide an extremely useful information for the diagnosis of a wide range of diseases. Despite these images have a high quality, their correct interpretation and the subsequent diagnosis is not a straightforward task. The emergence of artificial intelligence has revolutionized the study of different pathologies, given the ability of this kind of techniques for being used within a computer aided diagnosis (CAD) system [12]. When applying to neuroimaging, this tool usually finds relevant patterns that are extremely useful for the identification of neurological disorders. In fact, a high number of studies have developed intelligent systems for this purpose. For instance, these methods have demonstrated a good performance when diagnosing Alzheimer's disease [2, 16, 1, 9]. These works use information contained in magnetic resonance or positron emission tomograpy (PET) images to classify controls *vs* AD patients, in addition to detect the progression from mild cognitive impairment to a severe dementia. In a

similar way, changes associated with Parkinson's disease have also been automatically detected by these alternatives [6, 17, 21]. They usually employ DaTSCAN neuroimages given their suitability for visualizing the dopamine deficiency.

Moreover, classification models focus their analysis on a specific brain region that characterizes the pathology. Besides, the definition of this region of interest considerably reduces the dimensionality of the data, addressing the curse of dimensionality problem associated with statistical classification. After that, the simplest alternative is to evaluate the intensity of the voxels contained in this region. However, it is unlikely that differences in intensity allow to interpret the cognitive state of the patient. Another option is to compute features based on the morphology of the region [11, 26]. Thus, the region is characterized by a series of measurements such as size, position of the centroid, roundness, etc. Despite this alternative has been successfully employed in previous studies, it seems suboptimal for one crucial reason: the relevance of features varies for each individual classification context. This means that some features can be extremely informative in one scenario, but completely irrelevant in a different one. An interesting alternative is to directly model the differences between regions, instead of extracting features associated with each one of them. In this case, a siamese neural network is an excellent choice [14, 8]. According to its name, this architecture consists of two identical neural networks sharing the same structure that compare their individual outputs at the end by using a distance metric. A global output is then generated from this resulting measure.

In this work, we propose an alternative for automatically computing differences between two regions that can be subsequently used for classification. Specifically, our proposal relies on the use of a siamese neural network with two inputs that extracts informative features from both regions. Once the model is trained, the latent space of the dense layer leads to a feature vector that is entered as input of a linear classifier. The proposed methodology has been evaluated using PET images from the Parkinson's Progression Markers Initiative [18]. Specifically, we aim at demonstrating that differences between the dopaminergic regions of both hemispheres can be used as discriminative features to distinguish between controls and patients suffering from Parkinson's disease.

The rest of the paper is organized as follows. Section 2.1 contains a description of the dataset used for the evaluation of the performance of the system. Section 2.2 details the preprocessing applied to this database before entering into the siamese neural network, which is explained in Section 2.3. Results are summarized in Section 3, whereas conclusions and future work are available in Section 4.

2   Material and methods

2.1   Dataset

The method proposed in this work aims at measuring the asymmetry between different brain regions that can be relevant for classification purposes. The database employed in this work contains DaTSCAN SPECT images from 1413 subjects, 1218 from patients suffering Parkinson's disease (PD) and 195 controls (CN) from the PPMI dataset [19]. This repository contains data from an observational clinical study to verify the progression markers in Parkinson's disease. Raw projection data are acquired into a 128 x 128

matrix stepping each 3 degrees for a total of 120 projection into two 20% symmetric photopeak windows centered on 159 KeV and 122 KeV with a total scan duration of approximately 30–45 min. Table 1 summarizes the demographics of the patients in the database. Thus, the goal in this specific context is to evaluate if differences in the shape of the dopaminergic regions can be used to distinguish between PD patients and CN.
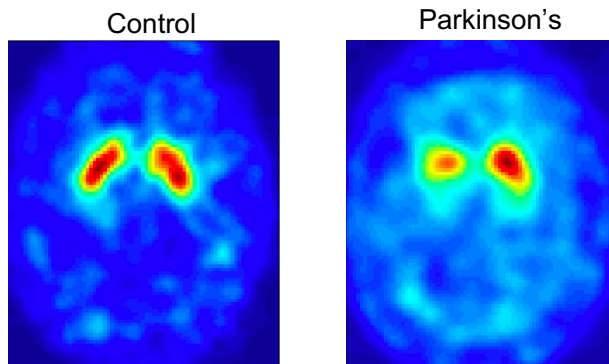

Fig. 1: Slice of the 3D images corresponding to a control (left) and a PD patient (right).

Table 1: Patient Demographics

Evaluation	Sex (M/F)	Mean Age $\pm$ Std
NC	130/65	61.02 ± 11.25
PD	798/420	62.93 ± 9.92

2.2 Preprocessing

DaTSCAN images from the PPMI database were spatially normalized according to the MNI152 template, which is based on the average of 152 scans from normal subjects. We further used SPM12 [27] to preprocess the images, applying affine and local deformations to achieve the best warping between the images with the DaTSCAN template defined in [22]. After that, the regions of interest were selected, which refers to those that reveal dopaminergic activity. As a result, this process led to a reduction in the size of the images, from the original (95, 69, 79) to the final (29,25,41). This final step allows a reduction in the computational cost of the classification system while preserving the information contained in the target regions.

Another crucial aspect is related to the intensity levels of the images. The idea behind these functional images is that the intensity in each pixel provides an indirect

measure of the neurophysiological activity. This means that the same value in two different pixels should correspond to the same drug uptake, whereas abnormal differences in these values can reveal a wide range of pathologies [25, 24, 7]. This paper employs Integral Normalization [13], in order to ensure that there is a clear relationship between intensity levels and drup uptakes, as follows:

$$\hat{\mathbf{I}}_i = \frac{\mathbf{I}_i}{I_{n,i}} \tag{1}$$

where $\mathbf{I}_i$ refers fo the image of the *ith* subject in the database, $\hat{\mathbf{I}}_i$ is the resulting normalized image, and $I_{n,i}$ is the intensity normalization value. This is computed as the mean of the image for each independent subject. Then, the resulting values were standardized in the range [0,1]. Finally, each resulting image is then partitioned into two subimages. The first one contains the dopaminergic region of the left hemisphere, whereas the second includes the dopaminergic region of the right one. These two images for each individual subject are entered into the classification system proposed in this work, which is fully described in next sections.

2.3   Siamese neural network

The siamese architecture was introduced in the 1990s within a signature verification system [5]. A siamese neural network consists of the union of two identical neural networks with exactly the same configuration. This means that they have the same parameters and even share common weights. During the training, each network processes the inputs as an individual feedforward network, processing information in only one direction. Briefly, each neuron of a specific layer processes the input, and sends the output to all the neurons of the following layer. Since both networks share the same weights, they are updated at the same moment through the error back-propagation process. Given that the siamese architecture is based on two individual networks, each one of them receives an input and produces an output in its final layer. The main aspect of this framework is that the outputs of both subnetworks are compared according to a distance measure. Based on this value, the final output of the siamese network is then used to assign a label to the data inputs. The output can be seen as the semantic difference between the projected representation of the inputs [8].

Despite this network has been widely used with the aim of evaluating the similarity between two inputs (e.g. fingerprints [3] or signatures [5]), it can be used as an intermediate stage within a different classification context. Figure 2 depicts a representation of the siamese neural network employed in this work. In our case, we trained the siamese network with the SPECT images of the database described in Section 2.1. The aim in this application context was to test that asymmetry between the dopaminergic regions of each hemisphere differs from PD patients and controls. In other words, our hypothesis is that differences between left and right striatum are relevant to distinguish people who suffer from Parkinson's disease and those that do not. This way, the left and right dopaminergic regions are entered into the two inputs of the siamese network. The model is then trained in order to learn the differences between the two inputs. To do so, the Hinge function [10] is used to compute the loss associated with the distance between the outputs of the two subnetworks, as follows:
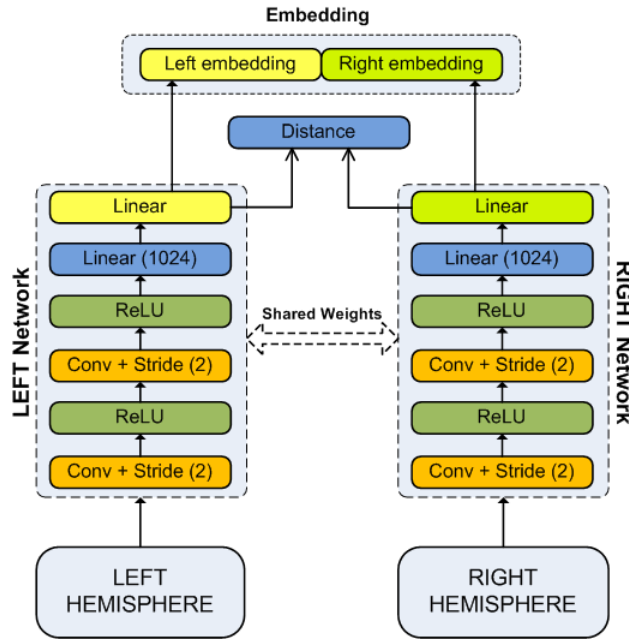
Fig. 2: Architecture of the siamese network used to compute the embeddings.

$$l(y) = \begin{cases} 0 & t \cdot y \geq 1 \\ 1 - t \cdot y & \text{otherwise} \end{cases} \tag{2}$$

where $t = \{-1, 1\}$ corresponds to the actual label and y is the output of the linear layers.

Once the training process is finished, the information contained in the final layer is retrieved. This is obtained as the combination of the output of the lineal layer of each individual branch. This embedding is then used as the feature vector within a classification framework. Specifically, the vectors associated with each individual sample are used to train a linear Support Vector Machine (SVM) classifier. Different metrics from the confusion matrix are employed to evaluate the performance of this scheme. Besides, a 5-fold cross-validation scheme was used to preserve the independence between training and test sets.

3 Results

In this section, we present the results obtained by the proposed method. First of all, we used the T-distributed Stochastic Neighbor Embedding (TSNE) for reducing the dimensionality of the embeddings to two dimensions in order to improve the visualization of data associated with the two classes: PD patients and controls. As Figure 3 shows, the

samples are grouped into two different clusters. It is worth highlighting that there is a clear separation between both classes since most of samples are correctly located. This demonstrates that the information contained in the embedding allows the distinction between the two classes.
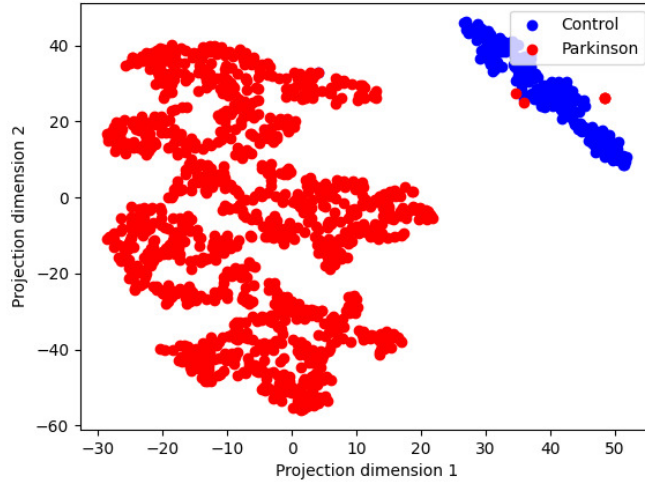

Fig. 3: Projection over the first two dimensions of the embeddings associated with controls (blue) and PD (red).

Table 2 summarizes the performance in terms of different metrics. With reference to balanced accuracy, a 96.78% was obtained, whereas our proposal led to an AUC of 99.16%. This demonstrates the suitability of the proposed method for this classification context. Figure 4 depicts the ROC curve obtained by our method. This graphic provides a visual evidence of the large performance obtained by our proposal. In fact, the large AUC obtained manifests that most of samples are properly assigned to their corresponding class.

Figure 5 provides a crucial information that certifies the separability between the two classes. Figure 5a contains two different clusters, similar to the ones obtained in Figure 3. However, in this case it is represented the pairwise distance between the vectors contained in the dense layers of both branches in the siamese network. It is important to note that this distance is much lower for controls than for PD patients, evidencing that the asymmetry between the dopaminergic regions of both hemispheres is higher in PD patients. Therefore, as Figure 5 states, there is a much higher variability regarding the differences between both hemispheres in PD patients compared with controls. This means that PD patients are extremely different than controls, but they also vary one from each other, as the large variance in the sample shows.

Table 2: Classification results obtained by the proposed method and by other previous works.

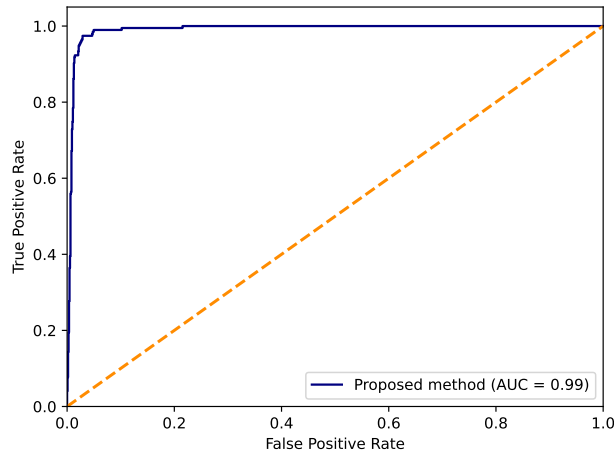| Method	Accuracy	Sensitivity	Specificity	AUC
Ours	**96.78 $\pm$1.99**	**97.66 $\pm$1.65**	**95.90 $\pm$3.84**	**99.16**
[25]	95.00 $\pm$3.00	95.00 $\pm$5.00	95.00 $\pm$4.00	97.00
[20]	94.10 $\pm$4.50	93.30 $\pm$5.80	95.80 $\pm$7.90	94.60
[4]	92.00	94.00	91.00	-
[23]	84.60	71.60	97.50	85.90
[15]	95.20	97.50	90.90	-

Fig. 4: ROC curves obtained for classification using PET, MRI and mixed mode images

4   Conclusions and future work

In this work, we propose a method based on siamese neural networks to assess anatomical differences in medical imaging. These differences are then evaluated in a classification context in order to quantify their relevance as a feature extractor. Once the network is optimized to compute similarities between two different inputs, vectors from the final dense layer are extracted. These features are then entered into a linear SVM classifier, leading to an accuracy of 96.78%

The excellent results manifest the usefulness of the method, paving the way to future research not only in brain imaging but also in other biomedical signals. Additionally, the inclusion of the cosine similarity in the loss function could help in a better computation of the similarities between the two inputs of the neural network. Finally, our findings reveal that differences between two structures can be even more informative
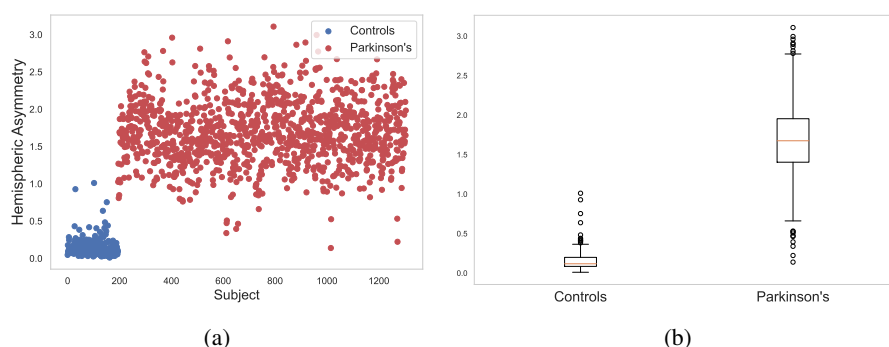
(a)   (b)

Fig. 5: (a) Distribution of the inter-hemispheric distances computed by the proposed model for Parkinson's patients and controls. (b) Boxplots of the distributions of distances in both classes.

that the nature of the regions itself, even when these differences had been considered as irrelevant in the context under study.

Acknowledments

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