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Machine learning to detect brain lesions in focal epilepsy

Andrea Perera-Ortega[1], Alireza Sedghi[1], Jonah Isen[1], Sjoerd B. Vos[2,3], Parvin Mousavi[1], and Gavin P. Winston[4,5]

[1]Medical Informatics Laboratory, School of Computing, Queen's University, Kingston, Canada
[2]Centre for Medical Image Computing, University College London, London, United Kingdom
[3]Neuroradiological Academic Unit, Queen Square Institute of Neurology, University College London, London, United Kingdom
[4]Department of Medicine & Centre for Neuroscience Studies, Queen's University, Kingston, Canada
[5]Department of Clinical and Experimental Epilepsy, Queen Square Institute of Neurology, University College London, London, United Kingdom

ABSTRACT

PURPOSE: Identifying areas of abnormality on MRI brain scans in individuals with focal epilepsy is fundamental to the diagnosis and treatment of the condition. However, in about a third of patients with focal epilepsy, brain scans appear to be normal (MRI-negative) as human observers cannot detect any abnormality with current imaging technology. The objective of this paper is to provide a novel approach in presenting localization using machine learning in order to locate areas of abnormality on patients with focal epilepsy on a per-voxel basis by comparing them with healthy controls. As a proof-of-concept, the technique is first applied to patients with visible lesions providing a ground truth (MRI-positive), but future work will extend this to MRI-negative subjects.

METHODS: Our data consists of multi-modal brain MR images from 62 healthy control subjects and 44 MRI-positive patients with focal epilepsy. We utilized a support vector machine (SVM) as our probabilistic classifier and train it with two classes of data. We generate probability maps applying our machine learning classifier on all voxels of a test subjects to visualize the predictions. Overlap scores are used to evaluate the classifier performance in MRI-positive patients.

RESULTS: Our model reached 83% specificity, 91% sensitivity, and an Area Under the Curve (AUC) of 0.896 for the task of voxel-based classification of normal versus abnormal voxels. In addition, Dice scores of up to 0.66 were achieved for the overlap measure of lesion probability map and the ground truth labels annotated by a neurologist.

CONCLUSION: We demonstrated a novel approach in presenting localization using machine learning techniques to localize focal epilepsy lesions from multi-modal MR images.

Keywords: Machine learning, focal epilepsy, support vector machine, magnetic resonance imaging

1. INTRODUCTION

Epilepsy is a common and serious neurological disorder that affects around 1% of the population. Around one third of patients who suffer from focal epilepsy, a type of epilepsy in which seizures originate from one hemisphere of the brain, continue to have seizures despite taking medication. Surgery to remove the abnormality causing the seizures can be an option in refractory focal epilepsy, but it is critical that the abnormal region is accurately identified. The problem arises when MRI scans appear normal for these patients. This does not suggest that the patient is healthy, but rather that the current image scanning technology and human observers cannot clearly identify these areas. These cases account for a third of patients with focal epilepsy. This means that patients who do not improve with medication and also have no identifiable regions of abnormality in the brain must undergo expensive and invasive testing in order to be considered for surgery.[1]

Previous studies have shown that voxel-based imaging techniques in which individual patients are compared to a group of healthy controls on a voxel-wise basis can be helpful in identifying areas of abnormality;[2–4] however, these approaches have low sensitivity and specificity. More recent approaches have used machine learning techniques to detect focal epilepsy. Focke *et al.*[5] trained a support vector machine (SVM) classifier to lateralize (determine if the abnormality originates from the left or right side of the brain) temporal lobe epilepsy (TLE) images in MRI-positive patients and demonstrated changes in distributions of morphological Grey Matter (GM).

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A study by Keihaninejad *et al.*[6] also trained an SVM classifier to lateralize TLE and included MRI-negative patients; however, only regional brain volumes were used in the analysis and other modalities such as T1-weighted images or diffusion tensor images were not considered. In another study, Bennett *et al.*[7] extracted volumes and intensity asymmetries as features from multimodal clinical MRI (T1-weighted, T2-weighted, FLAIR) to train a random forest classifier (RFC) to lateralize TLE into right or left TLE. Although demonstrating promising results, the focus of these studies involved training classifiers to lateralize TLE, but more specific localization of abnormalities was not provided.

This research improves upon the previous studies by combining additional MRI modalities with a machine learning approach in order to provide further localization of abnormalities in patients with focal epilepsy with an aim for improved specificity. This approach involves training an SVM classifier to automate the separation and annotation of individual voxels based on MR images from normal and epileptic subjects as normal or abnormal in order to locate specific areas of importance. Additionally, the areas of importance are visualized to show spatial patterns based on the probabilities of each voxel being normal or abnormal by generating probability maps from test subjects. Overlap metrics for the probability maps are calculated to determine how well the classifier can distinguish between normal and abnormal voxels. By establishing this approach with MRI-positive patients as a proof-of-concept, we hope to later extend this model to detect invisible areas of abnormality in MRI-negative patients by comparing them to patients with visible abnormalities (MRI-positive).

2. MATERIALS AND METHODS

2.1 Data

We use data from 44 patients with medically refractory focal epilepsy undergoing presurgical evaluation at the National Hospital for Neurology and Neurosurgery, London, United Kingdom. The use of this data for research was approved by the National Hospital for Neurology and Neurosurgery and the UCL Queen Square Institute of Neurology Joint Ethics Committee, and written informed consent was obtained from all subjects. We acquired T1-weighted MRI data and diffusion-weighted MRI, which provided fractional anisotropy (FA) and mean diffusivity (MD) from Diffusion Tensor Imaging (DTI), and neurite density index (NDI) and orientation dispersion index (ODI) from Neurite Orientation Dispersion and Density Imaging (NODDI) modelling (processed as in Winston *et al.*[8]). The diagnosis of epilepsy was determined by clinical consensus from their medical records. These individuals have visible and detectable lesions on their MR-images (MRI-positive) and were categorized as the discrete group. Additionally, data from 62 healthy controls without any history of neurological or psychiatric disease was collected using the same neuroimaging protocols.

2.1.1 Data Pre-processing

We performed pre-processing on all images using SPM12[9] in MATLAB 2019b. First, the T1-weighted images were segmented into their Grey Matter (GM) and White Matter (WM) constituents. We use the GM image in our analysis, which was smoothed and normalized to MNI space. We also co-registered the diffusion MRI data for each subject to their T1-weighted image. Here, the non-diffusion weighted scan from the diffusion MRI data (which is T2-weighted) was used to register to the T1-weighted images. We applied the derived transformation to all the diffusion parameter maps (FA, MD, NDI, ODI) as shown in Figure 1 and then smoothed and normalized them similarly to GM images. Finally, the discrete lesion masks (manually drawn by a neurologist) were also normalized to MNI space.

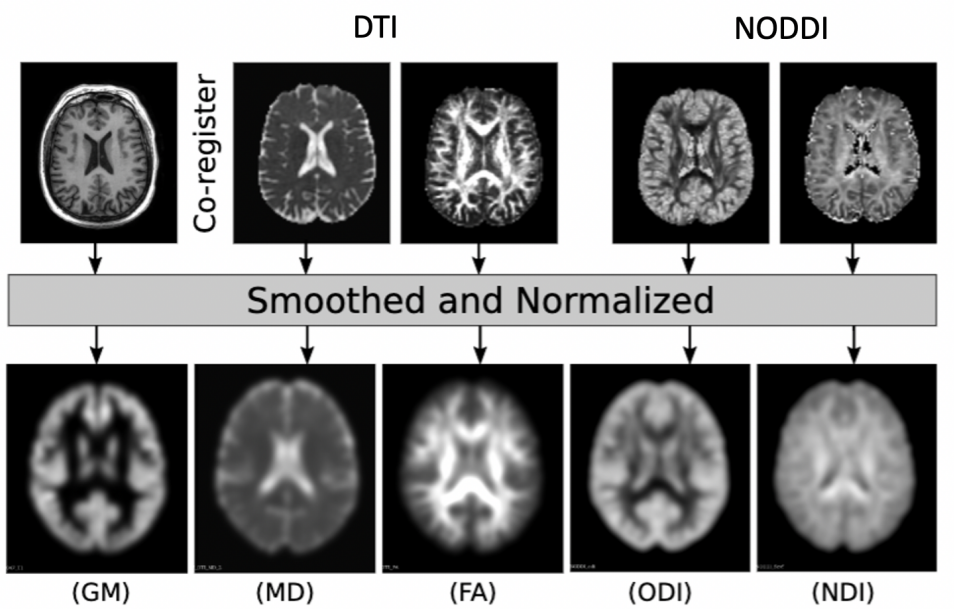

Figure 1. An overview of the preprocessing pipeline of the raw MR images before feature extraction, using a control patient's images. Grey matter (GM) image was segmented from the original T1-weighted scan. In addition, the fractional anisotropy (FA), and mean diffusivity (MD) from Diffusion Tensor Imaging (DTI), along with neurite density index (NDI) and orientation dispersion index (ODI) from Neurite Orientation Dispersion and Density Imaging (NODDI) modalities were all co-registered to the original T1-weighted image.

To extract features for training the SVM, we calculated the Z-score maps for each control and discrete patient images (5 modalities) by standardizing each voxel in each scan. Next, we applied the lesion masks to the Z-score maps to generate training data for SVM. Since the control group subjects do not have any regions of abnormal voxels, lesion masks were selected randomly from the discrete group and applied to the control images to extract areas of healthy voxels for comparison. Six outlier discrete patients were removed due to their significantly larger lesion size. Finally, we generated features from 25 control and 27 discrete patients for training. For testing, we used features of mutually exclusive 18 control and 11 discrete patients.

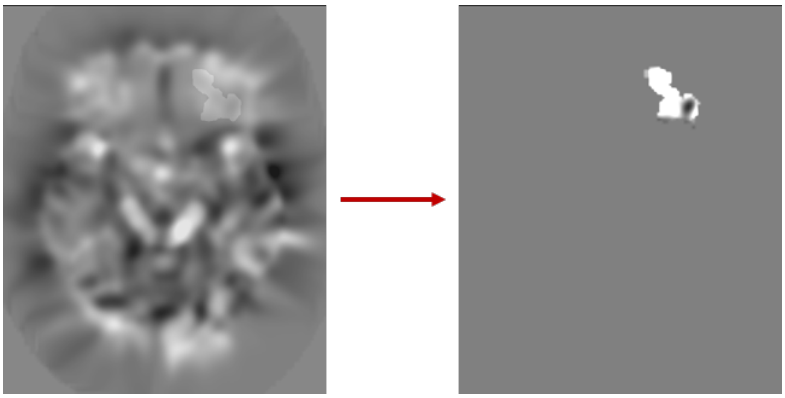

Figure 2. This figure depicts an example of the process of applying the lesion mask onto the Z-map for a discrete patient for the NODDI NDI modality. The result is a lesion image with the corresponding Z-score values from where the lesion was extracted from. This process was repeated for all patients in all modalities. These will be the features used to train the SVM.

2.2 Classification of Focal Epilepsy Lesions

2.2.1 Training

A Support Vector Machine (SVM) was used to efficiently combine features that were derived from the five MRI modalities. We utilized a radial-basis function (RBF) as the kernel function for our SVM. We performed a grid search to find optimal values for SVM parameters gamma and C. These values were found to be 0.1 and 0.0077, respectively. The output of our SVM corresponds to the probability of a voxel belonging to the abnormal class. The SVM was trained using stratified 5-fold cross-validation on 26,838 control voxels and 26,340 discrete voxels in the training set. Probabilistic outputs were generated to assess the accuracy and generate probabilistic color maps.

2.2.2 Evaluation

The model was evaluated during testing using an unseen set of test data, which was untouched during training. To assess the overall accuracy, we calculate the mean and standard deviation of the 5 folds. In addition, the specificity of the models (true negative rate) and sensitivity (true positive rate) were quantified and the corresponding ROC curve was calculated. Finally, we threshold the output probabilities to generate a predicted mask, which we will use for calculating the overlap measures with the ground truth labels.

Probability maps for the individual test patients were generated for visualization purposes. This process was done by using the trained model to predict the class for each voxel. To ensure that only the voxels inside the brain were considered as part of the probability map, a brain mask was created using the segmentation editor inside 3D Slicer[10] to remove the non-brain voxels.

To calculate an overlap metric, the Dice coefficient was used to quantify the similarity between the predicted areas of abnormality and the actual lesion. Since we trained our model on a voxel-based intensities, we limit our Dice calculation to the area of abnormality by considering a spherical object of similar size to the lesion around it. Although this approach disregards false-positives distant from the lesion, it quantifies the level of accuracy around the area of suspicious abnormality. We experiment with 3 threshold values to generate a binary mask of prediction. For instance, for the threshold of 0.5, all probabilities greater than or equal to 0.5 were converted to 1 and all values less than 0.5 were converted to 0. The Dice score is also calculated with thresholds of 0.8 and 0.94. After experimenting with different threshold values, there were no further improvements past the value of 0.94.

3. RESULTS AND DISCUSSION

Performing prediction on the unseen test data, we were able to correctly classify 13,697 out of 16,347 normal voxels from the control group, achieving 83% specificity. For the discrete group, our model was able to reach 91% sensitivity, correctly classifying 7,856 voxels out of 8,612 abnormal voxels.

The resulting Dice scores from assessing the overlaps of the probability maps and real lesions can be separated into two groups. The first group (63% of the test patients) are those whose Dice increased significantly as the threshold value increased. An example (case 1) is shown in Figure 3 on the top with Dice scores of 0.55, 0.60, 0.66 for thresholds of 0.5, 0.8, 0.94, respectively. The Dice score increasing significantly with increase of the threshold values suggests that the model is classifying abnormal voxels with a high degree of confidence.

Although our voxel-based analysis demonstrated good results in the classification of the focal epilepsy lesion, further analysis considering the neighboring voxels needs to be performed. In the future, we will perform post-processing of the predictions as a means to address the correlation in the prediction of the neighboring voxels. Finally, more complex region-based approaches will be investigated, such as Convolutional Neural Networks.

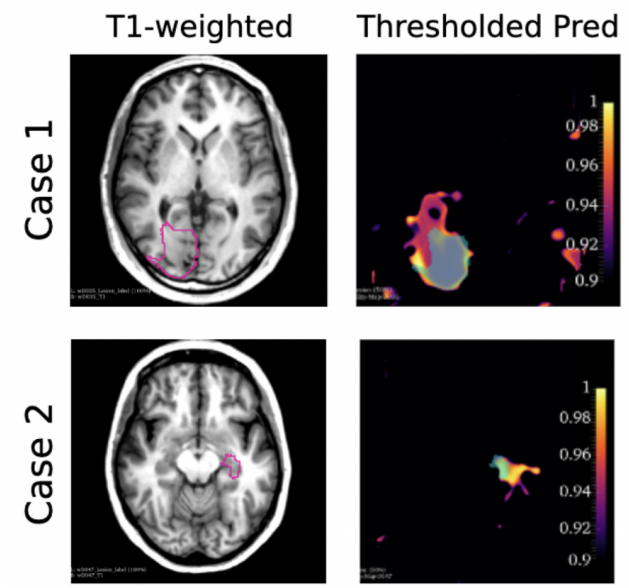

Figure 3. This figure depicts two MRI-positive focal epilepsy patients. These images show the original T1-weighted scans annotated with the ground truth lesion in pink. Additionally, the thresholded SVM predictions are shown to the right with the ground truth mask overlaid.

4. CONCLUSION

We demonstrated a novel approach in presenting localization using a machine learning method based on SVM to classify individual voxels as normal or abnormal in patients with focal epilepsy who have discrete lesions. We trained our classifier on voxel intensities of multiple MRI images of Grey Matter (GM), and modalities computed from Diffusion Tensor Imaging (DTI) and Neurite Orientation Dispersion and Density Imaging (NODDI). Our model was able to achieve 83% specificity and 91% sensitivity in classification of voxel intensities from 18 control and 11 discrete group test patients.

5. NEW OR BREAKTHROUGH WORK TO BE PRESENTED

We demonstrated a novel approach in presenting localization using machine learning to localize the focal epilepsy lesion from MRI images. We train an SVM-based model on fractional anisotropy (FA), and mean diffusivity (MD) from Diffusion Tensor Imaging (DTI), along with neurite density index (NDI) and orientation dispersion index (ODI) from Neurite Orientation Dispersion and Density Imaging (NODDI) modelling.

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