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Machine learning model to characterize seizure development in traumatic brain injury patients. ⋆

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Abstract: Traumatic brain injury (TBI) occurs in 69 million people annually and many patients go on to develop disabling disorders such as post-traumatic epilepsy (PTE). This work focuses on data modeling and analysis for TBI patients who develop seizures. We investigated and analyzed MRI scans using voxel-based morphometry (VBM) to characterize gray level intensity differences between TBI patients who developed seizures and TBI patients who have not developed seizures. We used MRI scans from the Epilepsy Bioinformatics Study for Antiepileptogenic Therapy, which aims to identify epileptogenic biomarkers through an international project involving multiple species, modalities, and research institutions. Using the VBM approach, statistically significant voxel changes were identified between the two clinical groups in different brain regions. Stochastic modeling and statistical analysis of the data in terms of interesting, confounding factors (age and total intracranial volume) and residual variability applied to each voxel independently, are presented. Statistical inference is used to test hypotheses that are expressed as functions of the General Linear Model estimated regression parameters. In addition, we used significant voxels to train a Neural Network (NN) classifier and evaluate the informative power of the proposed approach. The NN was able to distinguish the two clinical groups with an Area Under the receiver operating characteristics Curve of 62%.

Keywords: data analysis, stochastic modeling, neuroscience, post-traumatic epilepsy, magnetic resonance imaging, machine learning, random forest, neural networks, stochastic control.

1. INTRODUCTION

Post-traumatic epilepsy (PTE) is a pathology secondary to traumatic brain injury. PTE is not a homogeneous condition and can appear several years after the TBI with an incidence of up to 50%. PTE is diagnosed when recurrent and unprovoked seizures occur at least one week after TBI. An epileptic seizure is a transient occurrence of signs and symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Seizures may cause sudden and unexplainable emotions, nausea, hallucinations, loss of consciousness, falls and massive muscle spasms which critically compromise the quality of life of the patients and their families Devinsky (2007). However, the mechanism by which trauma to the brain tissue leads to recurrent seizures is unknown and there is currently no treatment that prevents the development of PTE. The Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx) has been devoting extensive efforts to prevent epileptogenesis by identifying validated biomarkers through the study of multimodal and longitudinal data in order to enrich the population eligible for clinical trials Garner et al. (2019b); Dewan et al. (2018). Illness-related brain changes can be detected with structural Magnetic Resonance Imaging (MRI), which has played an increasingly important role for the early diagnosis of neurodegenerative disorders Lebedeva et al. (2017); Amoroso et al. (2018a,c). In this work, we investigated if structural MRI changes at the voxel level can be related to seizure development in TBI patients. Voxel-based morphometry (VBM) is a well-consolidated method for computer-aided, volumetric MRI processing (Ashburner Friston, 2000). Usually applied on T1 MRI images it can successfully detect local gray matter changes related with several neurodegenerative diseases and neurological conditions Kakeda and Korogi (2010). Even though VBM can require a significant computational burden, we decided to use this technique for three main reasons: (i) it allows for the study of the whole brain; (ii) it does not require any Region-Of-Interest (ROI) assumption, thus affording an opportunity for discovery of previously unidentified structural alterations; (iii) it does not depend on ROI segmentation that is particularly challenging for TBI patients who can have large brain lesions Amoroso et al. (2018b). VBM has been used to detect morphological changes related to focal epilepsy, but to the best of our knowledge this is the first VBM study aimed to detect statistical differences in brain anatomy between seizure-free and seizure affected subjects. Specifically, we examined MRI changes due to TBI consequences such as cerebral edemas, hemorrhages, contusions, and

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distortions of brain tissue. Machine learning methods and multivariate data analysis for accurate detection of brain diseases have been receiving an increasing attention Khedher et al. (2015); Abraham et al. (2014). Several validation strategies, classifier models, feature extraction techniques, and selection methods, applied especially to MRI measures, have been explored and have demonstrated their effectiveness in many fields of neuroscience Al Zoubi et al. (2018); Lebedev et al. (2014); Shah et al. (2019). Therefore, to evaluate the discrimination power of VBM, we combined statistical analysis, stochastic modeling, and artificial neural network techniques. Neural network classifiers are adaptive learning algorithms that can handle different types of medical data and integrate into categorized outputs using a nonlinear function of the sum of its inputs. Neural networks have shown promising results in several applications, ranging from image segmentation to pattern recognition, and have been increasingly incorporated in many aided-diagnosis systems within the clinical practice Bron et al. (2015); Amato et al. (2013); Kaymak et al. (2017); Ortiz et al. (2019).

2. MATERIALS AND METHODS

2.1 Materials

In this work, we used 61 T1 magnetization-prepared rapid acquisition gradient echo (MPRAGE) MRI scans of TBI subjects from EpiBioS4Rx. Among these subjects, 22 have had at least one seizure within 6 months of a TBI and 39 have not had any seizures. Additional clinical and demographic information relative to these subjects are summarized in Table 1

Table 1. Sample size, gender, and Glasgow Coma Score (GCS) information are reported for each clinical group. Age and GCS were provided in terms of mean and standard deviation. No statistically significant differences between the two classes were found ($p-values < 0.05$) Jain et al. (2019).

Clinical status	Sample size	Age	Female/Male	GCS
seizure-free	39	37.32 ± 21.33	5/34	10.97 ± 3.98
seizure-affected	22	42.27 ± 18.16	4/18	8.91 ± 4.01

2.2 VBM pipeline

Each MRI scan was first skull-stripped and then oriented and affinely registered to the MNI 152 template using Oxford FMRIB Software Library (FSL) Jenkinson et al. (2012). In this way, we obtained MRI images suitable to run VBM with Statistical Parametric Mapping 12 (SPM12) through MATLAB R2018B Ashburner (2009). The VBM pipeline consists of several steps as shown in Fig. 1. The normalized images were first segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF). Then, we used SPM12 Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) to increase the accuracy of inter-subject matching by estimating the deformations that best align gray matter and white matter images and iteratively registering them with their average gray matter and white matter, respectively Ashburner (2007). Finally, the estimated deformations were used to obtain spatially normalized, modulated and smoothed brain tissue images in the MNI 152 template. Smoothing was carried out with an 8 mm Gaussian kernel Friston et al. (1991).

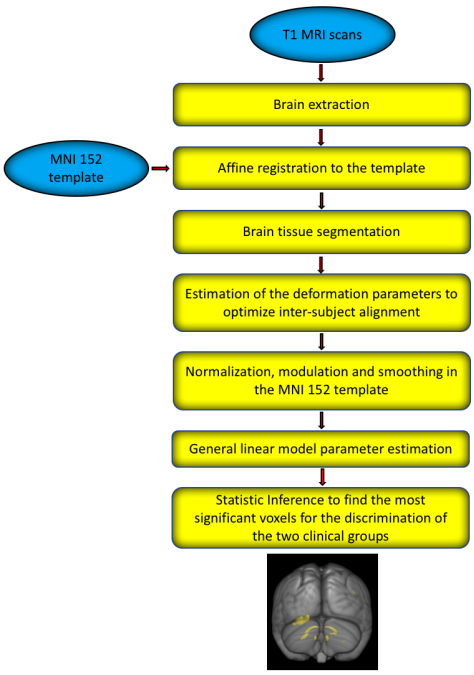

Fig. 1. Flowchart of the VBM pipeline that was used to find the most significant voxels for the discrimination of the two clinical groups: seizure-free and seizure-affected TBI patients.

2.3 Statistical analysis

In the VBM analysis, each voxel v_i (with i voxel position in the brain) was considered as a stochastic variable modeled across the different subjects. Gray matter volume maps, stochastically described as a Gaussian random field, were statistically examined using the General Linear Model (GLM) fitted at each voxel according to random Gaussian field theory Friston et al. (1994). Linear functions or contrasts obtained from the GLM fit were used to test for differences in gray matter volume between seizure-free and seizure-affected patients through a two-sample analysis. Age and total intracranial volume (TIV), obtained from the sum of GM, WM, and CSF, were entered as covariates-of-no-interest. Specifically, F-contrast was used to test the null-hypothesis with a significance probability threshold of $p < 0.05$ family-wise error (FWE) corrected for multiple comparisons at a voxel-level and a spatial extent thresholds of 0 voxels Nichols (2012).

2.4 Anatomical interpretation and informative power

Clusters of significant voxels detected by VBM were used as a mask to identify, on the Talairach atlas Lancaster et al. (1997) (defined on the MNI 152 template), the anatomical regions corresponding to those voxels and thus related to seizure development. We selected the significant voxels from each TBI subject to train a neural network (NN) and evaluate to what extent these voxels can distinguish the two clinical groups. A NN consists of different layers: the input layer that receives the input features, the hidden

layers that learn and model the incoming features and, the output layer that produces the ultimate result. NN classifier was implemented with a 5 unit hidden layer using the latest version of R package nnet. Classification process consisted of 1000 round of stratified cross-validation. Each round included four main steps schematized in Fig. 2: (i) training and validation set were defined by randomly picking 80% and 20% of the stratified dataset, respectively; (ii) important features were selected with a Random Forest classifier in terms of mean accuracy decrease; (iii) training set was used to build classification models with the NN, and (iv) classification models and important features retrieved from the training set were used to classify the validation set with the NN, blind to the diagnosis.

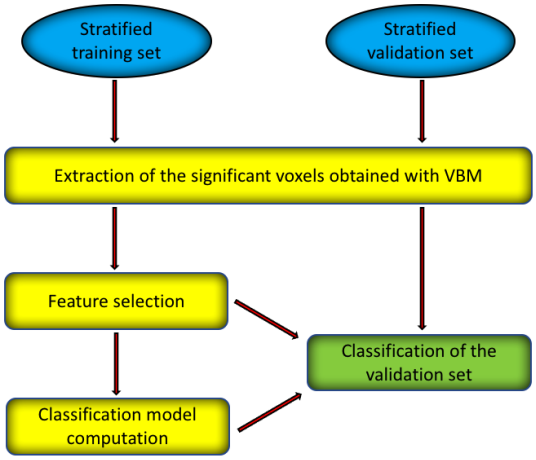

Fig. 2. Flowchart of the steps performed in each cross-validation rounds. Final classification results are computed by averaging the performances of the single rounds over the whole cycle of cross-validations.

3. RESULTS

3.1 Anatomical results

After the FWE correction, we obtained 3645 significant voxels with an F-contrast value greater than 5208.12. Fig. 3 shows axial slice views of some of the voxels that were most significant for the group discrimination, along with the slice position on the sagittal plane. Most of the significant voxels are located in left and right posterior cerebellum (corresponding to semi-lunar lobule, tonsil, uvula and decline gray matter) and in right and left anterior cerebellum (corresponding to dentate nodule, fastigium and culmen gray matter). We found significant voxels also in Brodmann area 8 of the left middle frontal gyrus, right inferior frontal gyrus including orbital part, left and right sub-gyral in the frontal lobe, left temporal lobe, supramarginal gyrus and postcentral gyrus of the right parietal lobe, and right brainstem pons and medulla.

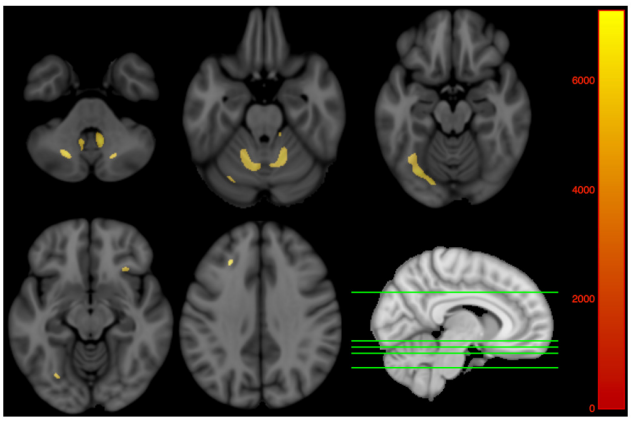

Fig. 3. Axial view of 5 brain slices showing some significant voxels found with the VBM analysis. In the lower right corner, the positions of the axial planes displayed in figure are reported in green along the sagittal plane.

3.2 Classification results

We evaluated the informative power of the significant voxels obtained from VBM in terms of average accuracy, sensitivity, specificity and area under the receiver operating characteristics curve (AUC) computed over all the cross-validation rounds. The NN classifier, trained appropriately on the most significant voxels extracted from each subject of the training set, was able to distinguish seizure-free and seizure-affected TBI subjects of the validation set with a mean accuracy of 0.60 ± 0.02, a mean specificity of 0.54 ± 0.03 and a mean sensitivity of 0.67 ± 0.03. In addition, Fig. 4 shows the mean receiver operating characteristics curve and the mean AUC Hajian-Tilaki (2013).

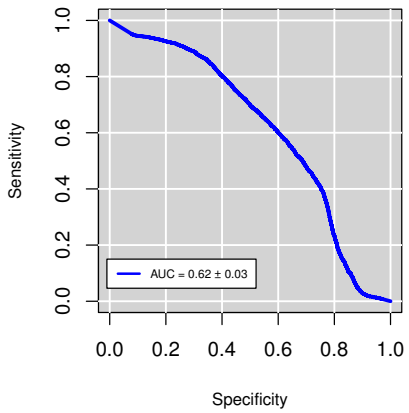

Fig. 4. Neural network classification performance in terms of area under the receiver operating characteristics curve (AUC) obtained using the most significant voxels for discriminating TBI subjects who have developed seizures and TBI patients who have not.

To better investigate the NN functioning and have more insight on the clinical interpretation of the results, we also analyzed the distributions of the classification clinical scores that are shown in Fig. 5.

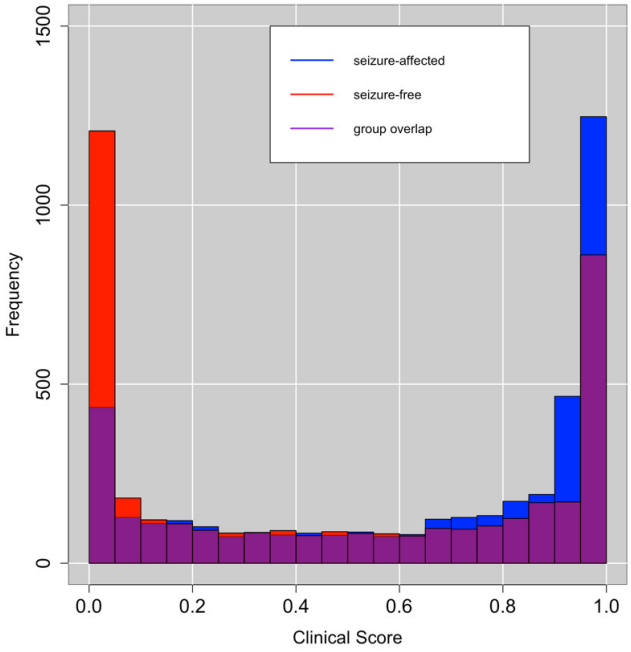

Fig. 5. The classification score distributions using significant voxels obtained with VBM. Each column of the histogram contains the number of seizure-free (red) and seizure affected (blue) TBI patients whose score lies in that bin. Purple bins indicate the overlapping of the two distributions.

From the histograms, we can notice that the NN for the majority of the cases is able to clearly separate subjects belonging to different clinical groups, whereas for some other cases, subjects scores are wrong or close to 0.5. There are incorrect scores especially for the seizure-free class. Specificity, which shows the discriminative power for negative subjects, is lower than sensitivity. This might be due to the fact that many seizure-free subjects are newly recruited and might develop seizure in the next months.

4. DISCUSSION

We used VBM to investigate changes in MRI voxel intensities between two clinical groups: TBI subjects who have developed epilepsy and TBI subjects who have not developed epilepsy. We found statistically significant between-group differences in 3645 voxels. Anatomical regions corresponding to the significant voxels are in accordance with the findings found in literature. Indeed, Irimia et al. (2017) found correlation between post-injury seizure occurrence and tissue loss in middle frontal and postcentral gyri. Riederer et al. (2008) carried out a VBM analysis to study brain changes associated with temporal lobe epilepsy finding reduced gray matter volume in frontal regions, the cerebellum, the left superior temporal gyrus and the postcentral gyrus. In Mueller et al. (2014) and Englot et al. (2018) the role of brainstem structural and functional networks in epilepsy is underlined. Zhang et al. (2012) obtained postcentral gyrus and orbital part of inferior frontal gyrus as significant regions for the classification of normal controls and epileptic patients. Zhou et al. (2019) found disruption of cerebellar-cerebral functional networks in right temporal lobe epilepsy. Salari et al. (2019) studied the brain alterations in epileptic patients compared with normal adults and observed significant changes in right cerbellar volume, left cerebellum cortical thickness and some cerebellar lobules. In addition, we used a NN classifier to assess the effectiveness of these significant voxels in discriminating the two groups. Our machine learning system allowed the distinction of the two groups with an AUC of 0.62 ± 0.03. Classification results seem to reflect GCS overlap of the the two subject populations that share a common area of approximately 80% resulting in a 40% chance of misclassification. Therefore, future studies could aim to examine how GCS correlates with classification scores and how the classification performances change if clinical scores are added to the machine learning model. To the best of our knowledge, this is the first work that uses a VBM approach to distinguish seizure-free and seizure-affected clinical groups. The proposed method underperforms the approaches used in Garner et al. (2019a); La Rocca et al. (2019) where functional and ROI volumes were used to characterize patients who have developed seizures. Nevertheless, our approach can detect subtle changes (i.e. in regions of cerebellum) that were not found with the other two previously cited ROI-based approaches. Thus, even in PTE field as well as in other applications Suk et al. (2014); Amoroso et al. (2018b), VBM has been proved to be very useful to detect MRI alterations that a ROI-based approach is not sensitive to. In upcoming years, EpiBioS4Rx will enroll up to 300 patients, so we expect to improve classification performances as, even though sample size is sufficient to detect some significant differences across the cohort, VBM needs a larger sample of subjects to be less affected by the registration noise. The main purpose of this work is not to give the best performance in the prediction of seizure free and seizure-affected subjects but to investigate the potential of the VBM approach in PTE field with the view to use it in combination with other approaches to improve classification performances. Clinical score distributions show that the NN works properly in most cases but fail for some other cases. Additionally, EpiBioS4Rx will continue following subjects for two years after injury, which may address issues with potential false detections as those shown in Fig. 5. In the future, it would be interesting to investigate if false positives are TBI patients who have developed immediate seizures but will not be diagnosed with PTE, and if false negatives are TBI patients recently enrolled who will develop seizures in the upcoming months.

5. CONCLUSION

Stochastic processes, random field theory, and machine learning techniques were used to investigate the efficacy of VBM to detect subtle structural brain changes between subjects who had at least one seizure after TBI and subjects who had no seizures since the TBI occurred. The VBM approach demonstrated the ability to find statistically significant differences between the two clinical groups in brain regions, which are in accordance with the literature about seizure development. In addition, the significant voxels obtained with VBM allowed the discrimination of the two clinical groups with an accuracy of 60% and an AUC of 62%, proving that VBM in combination with machine learning techniques can be a promising method to predict PTE. In the upcoming months, enrollments of new TBI patients will allow us to make full use of

VBM capabilities and have conclusive results about the predictive power of the proposed approach. The brain is considered to be one of the most complex stochastic systems, and this research provides an opportunity for the control community by bringing together stochastic systems, stochastic control, stochastic modeling, and data science with the goal to characterize seizure development after a TBI.

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