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Classification of chronic pain using fMRI data: Unveiling brain activity patterns for diagnosis

Rejula VIJEYKUMAR[1], **Anitha JEEVANAYAGAM**[1], **Belfin ROBINSON**[1,2,*]
[1]Department of Computer Science and Engineering, Karunya Institute of Technology and Sciences, Coimbatore, India.
[2]Department of Neurology, School of Medicine, University of North Carolina at Chapel Hill, North Carolina, USA

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Abstract: Millions of people throughout the world suffer from the complicated and crippling condition of chronic pain. It can be brought on by several underlying disorders or injuries and is defined by chronic pain that lasts for a period exceeding three months. To better understand the brain processes behind pain and create prediction models for pain-related outcomes, machine learning is a potent technology that may be applied in Functional magnetic resonance imaging (fMRI) chronic pain research. Data (fMRI and T1-weighted images) from 76 participants has been included (30 chronic pain and 46 healthy controls). The raw data were preprocessed using fMRIprep and then parcellated using five various atlases such as MSDL, Yeo'17, Harvard, Schaefer, and Pauli. Then the functional connectivity between the parcellated Region of Interests (ROIs) has been taken as features for the machine learning classifier models using the Blood Oxygenation Level Dependent (BOLD) signals. To distinguish between those with chronic pain and healthy controls, this study used Support Vector Machines (SVM), Boosting, Bagging, convolutional neural network (CNN), XGboost, and Stochastic Gradient Descent (SDG) classifiers. The classification models use stratified shuffle split sampling to fragment the training and testing dataset during various iterations. Hyperparameter tuning was used to get the best classifier model across several combinations of parameters. The best parameters for the classifier were measured by the accuracy, sensitivity, and specificity of the model. Finally, to identify the top ROIs involved in chronic pain was unveiled by the probability-based feature importance method. The result shows that Pauli (subcortical atlas) and MSDL (cortical atlas) worked well for this chronic pain fMRI data. Boosting algorithm classified chronic pain and healthy controls with 94.35% accuracy on the data parcellated with the Pauli atlas. The top four regions contributing to this classifier model were the extended Amygdala, the Subthalamic nucleus, the Hypothalamus, and the Caudate Nucleus. Also, the fMRI data parcellated using a cortical MSDL atlas was classified using the XGboost model with an accuracy of 87.5%. Left Frontal Pole, Medial Default mode Network, right pars opercularis, dorsal anterior cingulate cortex (dACC), and Front Default mode network are the top five regions that contributed to classify the participants. These findings demonstrate that patterns of brain activity in areas associated with pain processing can be used to categorize individuals as chronic pain patients or healthy controls reliably. These discoveries may help with the identification and management of chronic pain and may pave the way for the creation of more potent tailored medicines for those who suffer from it.

Key words: Biomarkers, chronic pain, machine learning, fMRI, neuroimaging, classification

*Correspondence: researchbelfin@gmail.com

1. Introduction

Chronic pain is a continuous or recurrent pain that lasts for several months or longer, usually longer than customary for ordinary recovery[1]. It differs from acute pain [2, 3], which is a short-term pain usually caused by injury or tissue damage and tends to go away as the injury heals. Many conditions, including arthritis [4], fibromyalgia [5], nerve damage, cancer [6], and back problems [7], can cause chronic pain. It can also result from an injury or infection that has not fully healed. Chronic pain can be debilitating and significantly affect a person's quality of life [8], leading to depression [9], anxiety[10], and social isolation [11]. It often requires a multidisciplinary approach to treatment, including medication, physical therapy, cognitive-behavioral therapy, and other interventions [12].

Several noninvasive imaging modalities have been used to understand chronic pain, including magnetic resonance imaging (MRI) [13], functional MRI (fMRI) [14, 15], positron emission tomography (PET) [16], and computed tomography (CT) [17]. Researchers can discover structural and functional changes related to chronic pain using MRI and functional magnetic resonance imaging (fMRI), which can offer precise brain and spinal cord pictures [20]. Insights into the underlying neurological processes of chronic pain may be gained by using PET to evaluate changes in brain metabolism and blood flow [15]. CT can also be used to identify structural changes in the spine and joints that may be associated with chronic pain [17].

The noninvasive neuroimaging method known as functional magnetic resonance imaging (fMRI) enables researchers to track blood flow changes in the brain related to neuronal activity. fMRI can offer insights into the brain processes underlying the perception of pain since chronic pain is a complex and varied disorder that is frequently challenging to identify and treat [19]. More information of fMRI analysis has been found in the literature [69, 70]. The use of machine learning algorithms to analyze fMRI data and create classification models that can precisely predict if a person is suffering chronic pain based on their brain activity has gained increasing attention in the past few years. One common machine learning technique used in fMRI chronic pain research is pattern classification, where algorithms are trained to differentiate between brain activity patterns associated with pain and those associated with nonpainful stimuli [20, 21]. Regression analysis is another method that may be used to pinpoint the parts of the brain that are most closely linked to outcomes related to pain [22].

Chronic pain manifests in a myriad of ways, with diverse reporting methods available. The treatment course is influenced by a multitude of factors, including hospital resources and patient financial situations. Within the realm of machine learning and deep learning research, a wide array of data sources have been employed, encompassing self-reported data [58–60], Kinematics gait data [61], fMRI [21, 24, 25], Electromyographic (EMG) readings [62], Inertial Measurement Unit (IMU) sensor data [63], Neurosensory analyzer outputs [64], Electroencephalography (EEG) recordings [65], skin conductance level (SCL) measurements [66], and Electronic Health Records (EHRs) [67, 68]. This study deliberately focused solely on fMRI data, as it provides a more pertinent basis for meaningful comparisons between different subjects.

Here is an overview of several recent studies on categorizing chronic pain using fMRI. Based on fMRI brain activity, a support vector machine (SVM) classifier has been used to determine if people suffer from persistent back pain [23]. The study showed that by analyzing brain activity patterns in regions such as the insula, thalamus, and other areas responsible for processing pain, the SVM classifier successfully distinguished between individuals with chronic pain and healthy individuals with an accuracy rate of 92.45%. It is important to note that the study included multimodel data such as brain imaging (resting-state blood-oxygenation-level-dependent and arterial spin labeling functional imaging) and autonomic activity (heart rate variability). Using

the fMRI data, Convolutional Neural Networks (CNN) accurately distinguished between chronic pain and healthy controls in 86.8% of the samples [21]. Another important research used CNN to classify chronic pain patients from healthy controls show an accuracy of 85% to make the classification[71]. The use of machine learning on chronic pain data on various neuroimaging modalities was discussed and summarized previously [25]. This study aims to classify the fMRI healthy controls and the chronic pain patient's data using various machine learning classifiers. The study also aimed to understand the best parcellation scheme for this data. A detailed explanation of materials and methods, results, and discussions were given in the forthcoming sections.

2. Materials and methods

The study aims to distinguish chronic pain sufferers from healthy controls. The study used machine learning algorithms to analyze brain biomarkers for persistent pain. The workflow of the study has been designed to test the Chronic pain fMRI resting state data with various parcellation schemes and various machine learning algorithms to understand the best possible algorithm and parcellation schemes. The design of the study also focused on using hyperparameter tuning to tune the best suitable parameters for each machine learning algorithm. Figure 1 shows the working model's organizational structure.

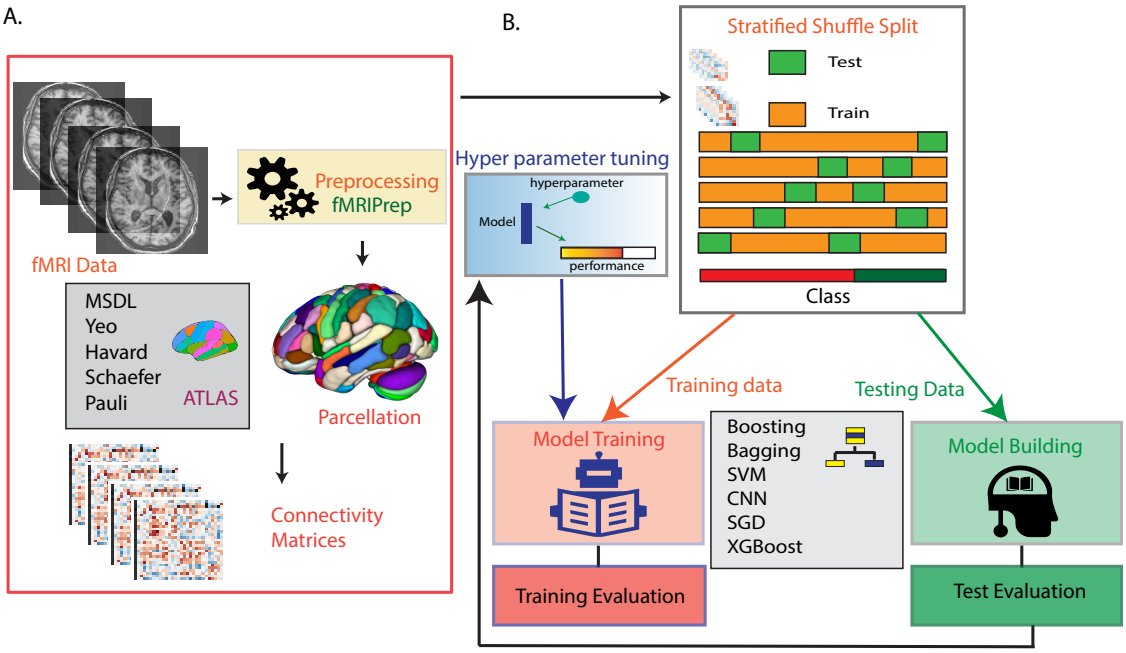

Figure 1. Schematic diagram of the Research flow A. fMRI data input preparation for Machine Learning; B. Machine Learning general flow with hyperparameter tuning and the list of Machine learning classifiers used in the study.

2.1. Dataset

For the investigation, we utilized a dataset sourced from openneuro.org (https://openneuro.org/datasets/ds000208/versions/1.0.1). This dataset is composed of both functional MRI (fMRI) and T1-weighted scans, encompassing data from seventy-six individuals, including both healthy controls and patients with osteoarthritis. Notably, a single resting-state fMRI session was conducted for each of these participants. This data collection was conducted across two consecutive studies, aiming to discern the differential impacts of placebo versus duloxetine

treatments on individuals suffering from chronic pain [19]. The demographic details of the original study have been given as Table 1.

Table 1. Details of the study design in Tetreault et al.'s experiment.

Participant type	Count	Age (Mean±SD)
Healthy control	20	57.9 ± 6.66
2W-Placebo patient	17	56.88 ± 5.68
3M-Placebo patients	20	57.6 ± 9.51
3M-Duloxetine patients	19	59.16 ± 4.61

Within this context, our study was devised as a cross-sectional analysis, with the objective of discerning distinct brain biomarkers that differentiate between states of pain and absence of pain. These brain biomarkers were identified based on the classification of patterns present in the collected data.

2.2. Participants

In this cross-sectional study, the patients and controls who reported experiencing no pain during the scan were grouped as "No pain" patients. In contrast, those who reported feeling pain were grouped as "Pain" patients (refer response column from the metadata file of dataset). The descriptive statistics on the study participant group are given as Table 2. Age variable shows that there is a statistical difference between the Pain and No pain groups (Welch two sample t-test; p = 0.0258; 95% CI [-6.7917, -0.4516977]). At the same time, the gender variable does not show any statistical difference between the two groups (Pearson's Chi-squared test; p = 0.4003). The descriptive statistics were carried out using R Software (version R-4.2.2), Package: dgof (https://cran.r-project.org/web/packages/dgof) library.

Table 2. Participant's descriptive statistics.

	Pain	no pain	ALL
Subjects	30	46	76
Gender	Male: 14 Female: 16	Male = 20 Female = 26	Male: 34 Female: 42
Age	56.5 ± 6.4	60.1 ± 6.9	57.9 ± 6.8

Where, Mean ± Standard Deviation.

2.3. fMRI preprocessing

The data set contains both T1-weighted images (structural) and resting-state blood-oxygen-level-dependent (BOLD) measurement images (functional). This study has used fMRIPrep (https://fmriprep.org/en/stable/), a fMRI data preprocessing pipeline to prepare both structural and functional data for analysis. The fMRIPrep uses standard software packages like FSL, ANTs, FreeSurfer, and AFNI to process the data. Initially, the T1 weighted image followed a workflow to intensity normalization, image alignment, skull stripping, spatial normalization, brain tissue segmentation, and surface reconstruction [57]. Similarly, the BOLD images were preprocessed with processes like time-slice correction, head motion estimation, and distortion reconstruction. Once the T1 weighted image and fMRI images are preprocessed, they will be aligned with each other to collect

the signals on various brain regions [21, 23]. The fMRIPrep belongs to the Neuroimaging PreProcessing tools (NiPreps) ecosystem (https://www.nipreps.org/).

2.4. Brain functional parcellation

The brain is complex because of its spatial heterogeneity and the diverse functions of each region. Brain parcellation is a way to partition the brain into various partitions to understand its entire organization and role. There are various parcellation schemes available to partition the brain into different regions for analysis. This study utilizes five various atlases to analyze the chronic pain data. The atlases used in this study have been tabulated below (Table 3). The region parcellation of atlases used in this study has been presented in the supplementary Figure 1.

Table 3. Atlases and regions

Atlas	Regions of Interest (ROIs)	Region Class
MSDL [29]	39	Cortical
Yeo-17 [30]	17	Cortical
Schaefer [31]	400	Cortical
Harvard [32]	49	Cortical
Pauli [33]	16	Subcortical

2.5. Feature extraction (ROI correlation matrix)

The brain functional connectivity of all the participants used in the study was extracted using the Python Anaconda (Version 22.9.0), Nilearn (0.10.0) library [34]. For this study, the function connectivity (i.e. the correlation between the regions) between the region of interests (ROIs) acts as the feature for the machine learning classifiers used. The feature extraction process takes three different steps. The first step was to remove the initial few slices from the functional image because it might consist of noise and artifacts. From the remaining time series images, the movement confounds were removed using the orthogonal projection method [35]. The second step was to extract the brain activities evident in the various ROIs defined by the parcellation scheme. The third step was to create a correlation matrix marking the activities observed between regions. The correlation matrix was calculated using the dynamic time warping distance (DTW) and correlation between the ROIs. In this study, for each subject five different pair-wise connectivity matrices were created with various parcellation schemes. For example, Subject 1 with MSDL parcellation scheme will have a 39X39 connectivity matrix denoting the pair-wise connectivity measure between the 39 ROIs.

2.6. Machine learning classification models

This study has used six machine learning classification models to identify the best suitable algorithm suited for this chronic pain fMRI dataset parcellated with various parcellation schemes (MSDL, Yeo-17, Harvard, Schaefer, Pauli, See Table 3). The problem proposed here is a binary classification problem to classify controls from chronic pain patients. The classification models used for this study are Support Vector Machines (SVM) [36], Stochastic Gradient Descent (SDG) [37], convolution neural network (CNN) [38], Bagging [39], Boosting [40], and XGboost [41]. The SVM classifier uses a hyperplane to differentiate the groups on a n-dimensional plane. SDG is an approximate and iterative optimization technique which can be used to classify data points. CNN (Convolutional

Neural Network) works by using convolutional layers to automatically learn hierarchical features from image data, enabling effective pattern recognition and object detection. The tree-based classification models like Bagging, Boosting, and XGboost were also used in this study for analysis. The machine learning classification models were utilized from Python Anaconda (Version 22.9.0), sklearn (1.2) library. The deep learning models were implemented using Python with the Keras (2.10.0) and TensorFlow (2.13.0) libraries.

The evaluation of classification algorithms was conducted by comparing their performance metrics, including accuracy, sensitivity, and specificity, which were quantified using the following equations:

Accuracy measures the proportion of correctly classified instances over the total number of instances:

$$\text{Accuracy} = \frac{\text{Number of Correct Predictions}}{\text{Total Number of Instances}} \times 100\%$$

Sensitivity (also known as True Positive Rate or Recall) assesses the algorithms' ability to accurately identify positive instances:

$$\text{Sensitivity} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Negatives}} \times 100\%$$

Specificity calculates the algorithms' proficiency in correctly identifying negative instances:

$$\text{Specificity} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Positives}} \times 100\%$$

These metrics collectively provided a comprehensive appraisal of the classification algorithms' performance, enabling a robust assessment of their discriminatory capabilities in our study.

2.7. Hyper parameter tuning

Almost all the machine learning classifiers are statistical models that expect various parameters to be learned from the data. Once the classification model gets trained by the existing data, the model will be able to fit the model parameters. However, the best parameter fit for the model cannot be learned from the normal learning process. Construction of the best machine learning model for a problem becomes tedious because the algorithm needs the best available parameter for that problem. For Example, for the K- nearest neighbour (KNN) algorithm, the algorithm needs an optimal number of neighbors to fit the model. Hyperparameter tuning is a method where the models can have multiple hyperparameters from which the parameter tuning algorithm chooses the best parameter for the given problem [42]. Grid search cross-validation is a search parameter search approach that searches the best set of parameters from the grid of hyper parameters. For this study, the hyperparameter tuning was done using the GridSearchCV approach utilizing Python Anaconda (Version 22.9.0), sklearn (1.2) library. The tuned parameter for various machine learning classifiers is available in the supplementary information (Supplementary Table 3).

2.8. Training and evaluation

Training the model is a crucial step in the machine-learning process, during which the algorithm learns from the provided training data. Machine learning models excel at processing data swiftly, recognizing patterns, and detecting anomalies more efficiently than humans. In this study, supervised learning algorithms were employed to establish a mathematical relationship between the data features and the corresponding data labels. In our

research, the data feature consisted of connectivity matrices of both pain and control subjects, while the target labels were used to categorize the subjects as either pain or control. After the machine learning algorithm learns from the data features and labels, the resulting models can be evaluated and tested for their performance.

Training a machine learning algorithm means being a systematic, iterative scheme that uses the available dataset to its maximum potential. Before the training, the data need to be preprocessed and formatted concerning the machine learning algorithm's input requirements. Also, the input parameters required for the algorithms need to be determined before the start of the training. As mentioned in the previous section, this study utilizes hyperparameter tuning methods to tune the parameters.

For some studies, the training data is very limited because the size of the population is less. In case of limited data, the resource needs to be allocated carefully for training and testing. Using the same data for testing and training might give overfitting results. To avoid overfitting problems and to use the limited data well, cross-validation is a common way to split the data. A stratified shuffle split is a cross-validator that provides stratified random folds at the same time preserves the ration of samples for each label. This study utilizes stratified shuffle split from Python Anaconda (Version 22.9.0), sklearn (1.2) library. The parameters, number of splitting (n_splits = 5) and random state instance (random_state = 0) were used for this study. We executed 5 distinctive rounds of data division, each encompassing train-test splits. In each iteration, 1/5 (or 20%) of your data is reserved for testing, and the remaining 4/5 (or 80%) are used for training. This process is repeated five times, and the results (e.g., classification accuracy) from each iteration are typically averaged to provide an overall assessment of the model's performance. By design, this approach ensured the retention of the dataset's original class distribution, thereby averting any bias stemming from class imbalance. Moreover, the employed 'random_state' value of 0 guaranteed the replicability of our split configuration for future investigations. This meticulous randomization strategy provided a consistent basis for model training and evaluation across these meticulously predefined partitions, fostering both rigor and reproducibility in our experimentation. The performance evaluation of the classification model can be calculated using various matrices like classification accuracy, confusion matrix, Log Loss, area under the curve, and F-Measure. This study utilizes the classification accuracy and specificity and sensitivity to evaluate the chronic pain classification model (sklearn.metrics (1.2)).

3. Result

The primary objective of this study is to differentiate between individuals suffering from chronic pain and healthy controls through the analysis of the most optimal classification algorithm. Also, this study aimed to understand the regions that are significantly contributing to classify the subjects as chronic pain patients from the healthy controls. The experiment was designed to understand the best parcellation atlas and the best algorithm suitable for the chronic pain fMRI data available. In this study, the methodology employed quantified the outcomes by measuring the accuracy, sensitivity, and specificity of the classifier models utilized. These metrics were used to evaluate and assess the performance of the classification models. A high accuracy indicates that the model can effectively distinguish between different classes or conditions in the dataset. Along with accuracy, sensitivity and specificity are three important metrics that are used to evaluate the performance of a classifier. Sensitivity measures the proportion of true positives (i.e. the number of correctly identified positive cases) among all the actual positive cases in the dataset. Specificity, on the other hand, measures the proportion of true negatives (i.e., the number of correctly identified negative cases) among all the actual negative cases in the dataset. A good classifier should have high sensitivity and specificity values, indicating that it can accurately identify both

positive and negative cases in the dataset. The results clearly show the atlases and algorithms that are perfectly suitable for identifying the biomarkers of chronic pain from the dataset used.

3.1. Analysis on accuracy, sensitivity, and specificity

The study involved parceling the fMRI data of chronic pain subjects into five different parcellation schemes (refer to Table 3 and Supplementary Figure 1). The results displaying the accuracy of various algorithms are presented in Figure 2. Sensitivity and specificity scores from various classifier models, along with different parameter iterations, are visualized in Figure 3 and Figure 4, respectively.

When searching for the best atlas that performed well with the data, both Pauli (region labels in Supplementary Table 1) and MSDL (region labels in Supplementary Table 2) showed superior results with various classification models. For bagging classifiers, MSDL exhibited accuracy ranging from 62% to 78%, while Pauli ranged from 62% to 76%. In both atlases (MSDL and Pauli), most hyperparameters achieved approximately 70% accuracy. Similarly, for boosting classifiers, MSDL showed accuracy ranging from 75% to 89%, whereas Pauli exhibited a range between 70% and 94%. Notably, for CNN, when using the MSDL atlas, the accuracy varied from 40% to 85%, and when using the Pauli atlas, the range of accuracy for various hyperparameters was 30% to 80%. MSDL and Pauli atlases also performed well in other algorithms, showing variation in accuracy from 20% to 80%. However, other atlases such as Harvard, Schaefer, and Yeo did not perform well with the data and the algorithms used. Even with sensitivity and specificity, the MSDL atlas and Pauli atlas parcellations outperformed other parcellation schemes (refer to Figure 3 and Figure 4).

Six various binary classifier models were deployed on the chronic pain data parcellated with five different atlases. The atlas that performed well in terms of accuracy metric with various algorithms is presented in Figure 5. The best classification accuracy classifying chronic pain patients from healthy controls was by the boosting algorithm giving 94.35% accuracy with best parameters {'criterion': 'friedman_mse', 'learning_rate': 0.075, 'loss': 'deviance', 'max_depth': 3, 'max_features': 'log2', 'min_samples_leaf': 0.20, 'min_samples_split': 0.28, 'n_estimators': 10, 'subsample': 0.95}, sensitivity noted 93.5% and specificity recorded as 82%. The chronic pain data parcellated with Pauli atlas rendered the top accuracy in this experiment setup. The XGboost classifier was also performed well with the data parcellated with MSDL atlas rendering 87.5% of Accuracy with hyperparameter {'learning_rate': 0.1, 'max_depth': 3, 'n_estimators': 100}, sensitivity noted 85% and specificity recorded as 80.2%. The CNN classifier resulted in higher accuracy, specificity, and sensitivity noted as 87.80%, 84.0%, and 86.7% respectively. The best accuracy for each algorithm and related parameters, sensitivity, and specificity are tabulated in Table 4. It is important to note that, the Pauli and MSDL atlases give better accuracy with all the algorithms. The top accuracy metric on each classifier model parcellated with Pauli and MSDL atlases shows both parcellation schemes worked invariably well (Figure 2). When boosting classifier is concerned, MSDL also gives 89.76% of accuracy while Pauli gives 94.35% of accuracy. Data parcellated with MSDL atlas gave better accuracy than the data parcellated with Pauli atlas with SDG, CNN, and XGboost Classifiers (refer Figure 5, Table 4).

3.2. Region of interests that contributes to classify chronic pain

The machine learning classification models are used to classify chronic pain patients and healthy controls. Classifying and identifying the chronic pain patients may be the first step in diagnosing the problem but the informatics behind the chronic pain is a matter of importance to treat the problem. Feature importance is a

Table 4. Highest accuracy scores and corresponding parameters for each algorithm.

Algorithm	Atlas	Accuracy	Best Parameter (Parameter Tuning)	Sensitivity	Specificity
Bagging	Pauli	76.4%	{'base_estimator___max_depth': 6, 'max_samples': 0.7}	90.1%	70.1%
Boosting	Pauli	94.3%	{'criterion': 'friedman_mse', 'learning_rate': 0.075, 'loss': 'deviance', 'max_depth': 3, 'max_features': 'log2', 'min_samples_leaf': 0.20, 'min_samples_split': 0.28, 'n_estimators': 10, 'subsample': 0.95}	93.5%	82.1%
CNN	MSDL	87.80%	{'optimizer':'adam', 'learn_rate':0.01, 'momentum':0.04, 'init_mode':normal, 'activation':softmax, 'weight_constraint':3.0, 'dropout_rate':0.5, 'neurons':15}	84.0%	86.7%
SGD	MSDL	85.2%	{'alpha': 0.1, 'loss': 'hinge', 'penalty': 'l2'}	82.2%	43.3%
SVM	Pauli	71.6%	{'C': 10, 'gamma': 1, 'kernel': 'linear'}	62.05%	62.2%
XGBoost	MSDL	87.5%	{'learning_rate': 0.1, 'max_depth': 3, 'n_estimators': 100}	85.03%	80.27%

method in machine learning that assigns scores to the various features used as input based on the way that feature is important in diagnosing the problem. There are various methods one can identify the feature importance score such as decision tree models, statistical correlations, and permutation-based scores. Permutation importance, a method used in this study, provides insights into the features that a model relies on the most. It involves estimating the predictive performance of a pre-trained model on an independent dataset, typically a validation dataset, and recording it as a baseline performance. While permutation importance is not a strict feature selection technique, it helps identify the features that contribute significantly to the model's overall predictive capability.

Table 5. Comparative Analysis of Accuracy (% Acc), Sensitivity (%Sen), and Specificity (%Spec).

Study	Population	Modality	Atlas	Methods	% Acc	% Sen	% Spec
Santana, 2019 [21]	150	fMRI	MSDL	CNN	86.8%	NA	NA
Lee, 2019 [23]	53	fMRI, rCBF, s1CONN	NA	SVM	92.45%	92.45%	92.45%
Chatterjee, 2023 [71]	76	fMRI	NA	CNN	85.20%	NA	NA
Proposed Study	76	fMRI	Pauli	Boosting	94.35%	93.50%	82%
Proposed Study	76	fMRI	MSDL	XGBoost	87.50%	85.00%	80%
Proposed Study	76	fMRI	MSDL	CNN	87.80%	92.30%	86.50%

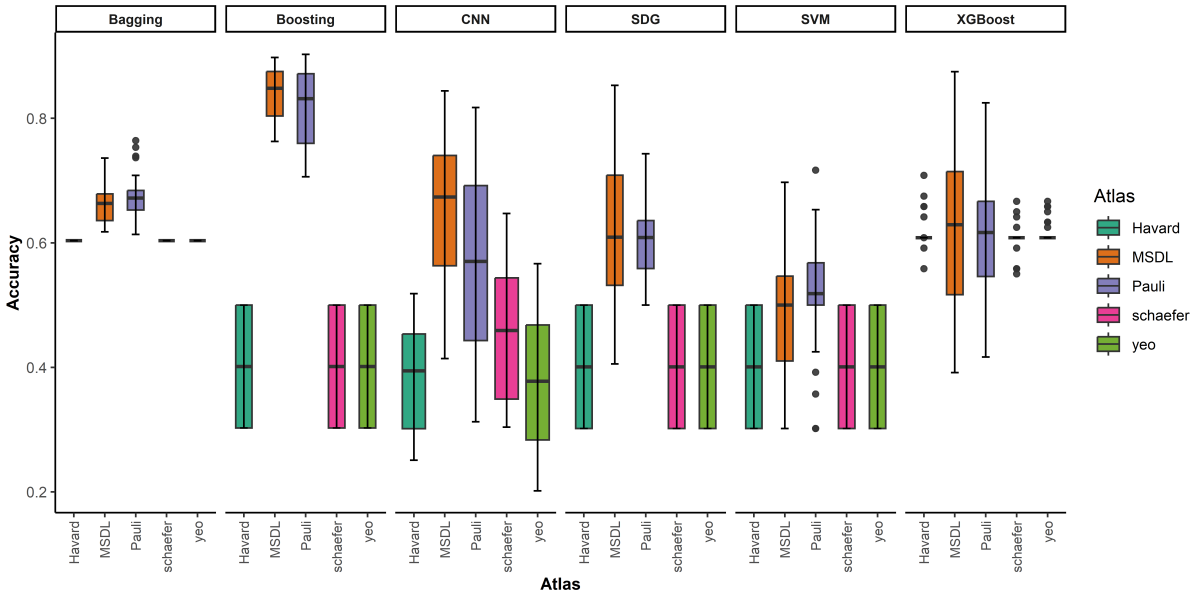

Figure 2. Classifier accuracy to predict chronic pain patients and healthy controls. Atlases (MSDL, Pauli) show relatively variable accuracy across various algorithms. Bagging and Boosting algorithms give better accuracy above 60% when parceled using MSDL and Pauli atlases run across various hyper parameters. Boosting and XGboost algorithms show accuracy above 80% in a few cases.

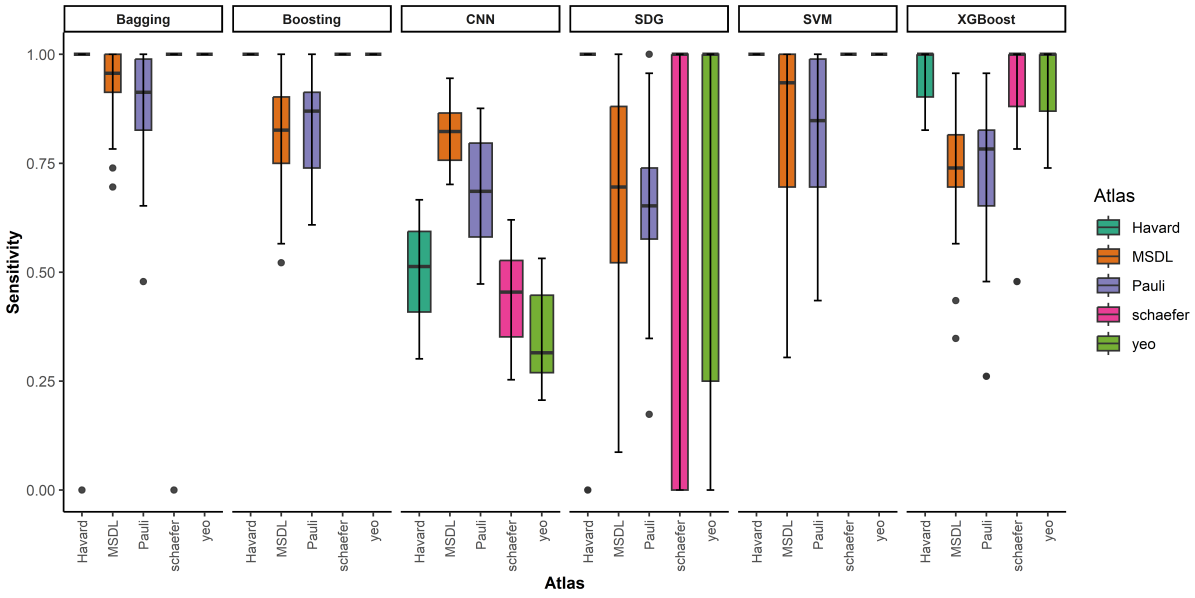

Figure 3. Sensitivity of classification models. The mean Sensitivity of the boosting algorithm looks the best of all algorithms compared to the data parcellated with MSDL and Pauli.

Feature importance analysis was conducted on Regions of Interest (ROIs) derived from both the MSDL and Pauli atlases. The Boosting classifier demonstrated strong performance in both atlases, achieving an accuracy of 89.76% for MSDL and an impressive 94.35% for Pauli.

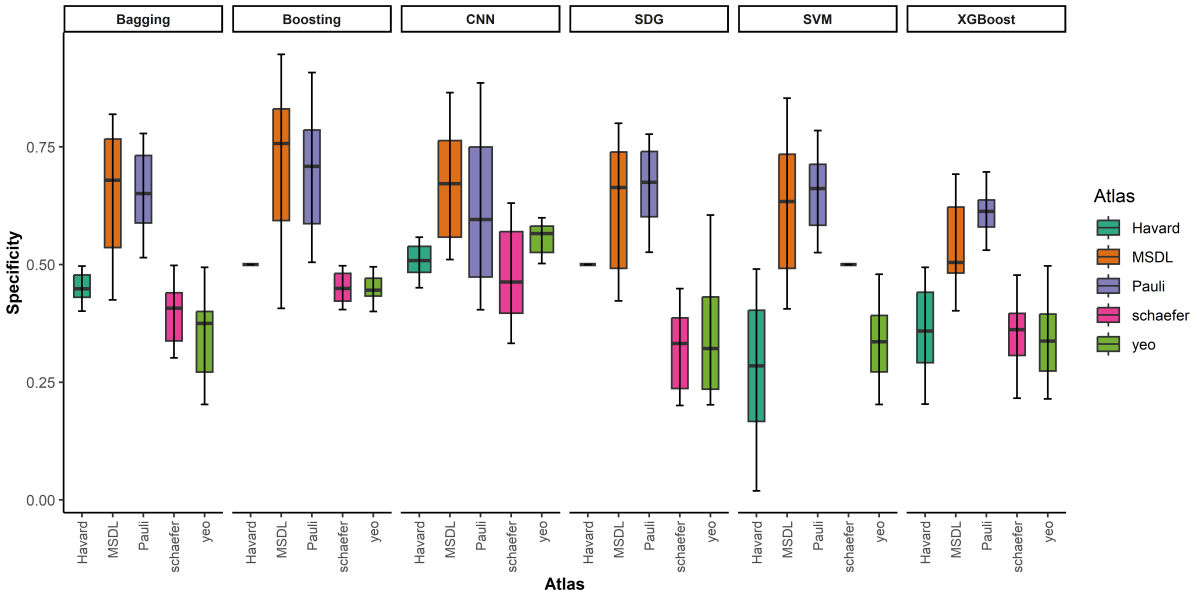

Figure 4. Specificity of classification models. The mean Specificity of the boosting algorithm looks the best of all algorithms compared to the data parcellated with MSDL and Pauli.

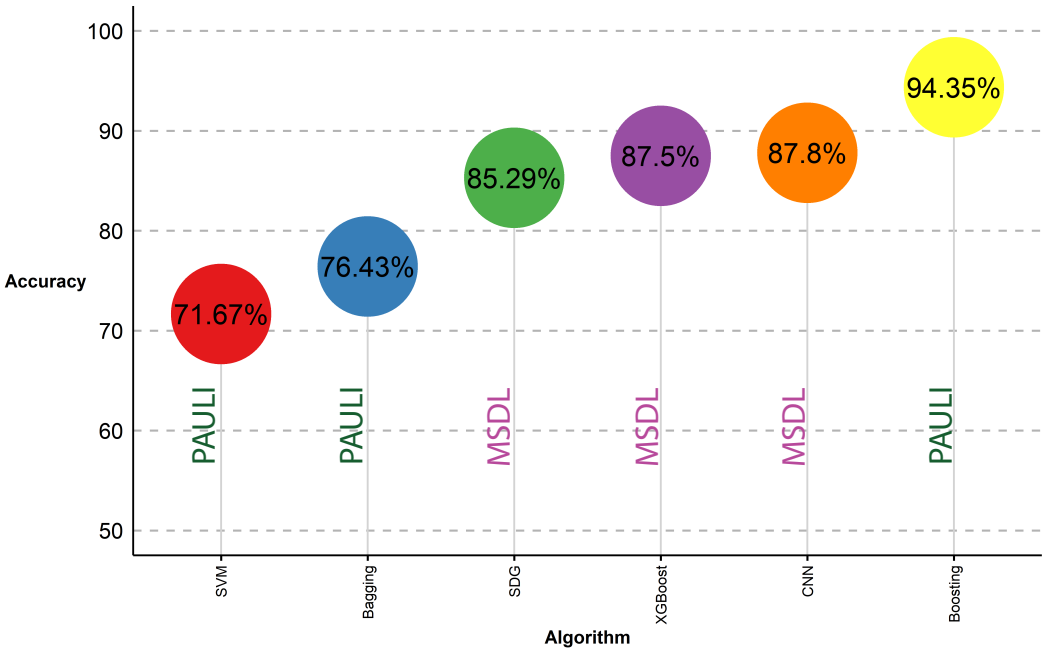

Figure 5. Classification Accuracy metric for various classifiers utilized with the employed parcellation schemes.

To assess the significance of our findings, we compared the results of our fMRI-based chronic pain study with those of previous studies and compiled the comparisons in Table 5, which evaluates accuracy, sensitivity, and specificity. The 'Population' field in Table 5 indicates the number of included fMRI scans in each study, while 'Modality' denotes the type of scan data used. Remarkably, our study showcased superior performance,

achieving the highest accuracy among previously conducted studies. Notably, our SVM algorithm achieved a maximum accuracy of 71.6%, although it falls short of the 92.54% reported in a comparative experiment by [23]. It is essential to highlight that the study by Lee et al. [23] utilized both rCBF (Regional Cerebral Blood Flow) and s1CONN (S1 connectivity) data in addition to fMRI data, which may account for their higher accuracy, sensitivity and specificity compared to our study. A notable point of comparison is a recent study by Chatterjee et al. [71] that employed CNN on the same dataset, albeit with a different experimental design and method. Their study achieved an 85.20% accuracy, whereas our proposed work outperforms it. In our sample setup and method setup, we attained a maximum accuracy of 87.80%, accompanied by sensitivity of 92.30% and specificity of 86.50%. These findings underscore the significant advancements and improvements introduced by our study in accurately distinguishing between pain and nonpain conditions, thereby enhancing the diagnostic capabilities of fMRI-based pain assessments.

Top five regions in cortical and four subcortical regions that contribute to chronic pain were selected as important regions. The subcortical top five ROIs responsible for chronic pain are visualized in Figure 6A. Similarly, the top five cortical regions that are responsible for Chronic pain are visualized in Figure 6B. The top subcortical regions active during chronic pain are amygdala, subthalamic nucleus, hypothalamus, mammillary nucleus, and parabrachial pigmented nucleus. Whereas ROIs like dorsal anterior cingulate cortex, Front Default mode network, Right Temporoparietal Junction, Right Anterior Intraparietal Sulcus, and anterior insular cortex are the important regions that are active in cortical regions in chronic pain patients.

3.3. Discussion

This study aimed to classify fMRI chronic pain data by employing a comprehensive approach. The process began with meticulous data preprocessing, followed by partitioning the fMRI data into distinct regions using five different atlases. Subsequently, we subjected the parcellated data to a range of machine learning classification models to identify the most effective algorithm-parcellation scheme combination for our dataset. To evaluate the classifiers' performance, we utilized a range of metrics, including accuracy, specificity, and sensitivity. Moreover, we employed a probability-based feature importance measure to pinpoint the key features driving the classification.

Our results are highly promising. Using the Pauli atlas in conjunction with the boosting algorithm, we achieved remarkable accuracy (94.35%), impressive specificity (93.5%), and substantial sensitivity (82%). Similarly, the MSDL atlas paired with the XGBoost algorithm yielded strong results with an accuracy of 87.5%, sensitivity at 85%, and specificity of 80.2%. Furthermore, we explored the use of the CNN classifier on data parcellated with the MSDL scheme, achieving an accuracy of 87.80%, sensitivity of 92.30%, and specificity of 86.50%. These outcomes are especially encouraging when juxtaposed with the findings of previous fMRI classification studies related to chronic pain data [21, 23, 71].

The comparative analysis of previously available related studies has been tabulated (Table 5), comparing their findings with the results of the proposed study. Specifically, the analysis focuses on the evaluation of accuracy, sensitivity, and specificity in both the related studies and the proposed study. This comparison allows for a comprehensive assessment of the performance and effectiveness of the proposed study in relation to existing research in the field. The tabulated results provide valuable insights into the advancements and contributions made by the proposed study in improving the classification accuracy and diagnostic capabilities for the given target variables.

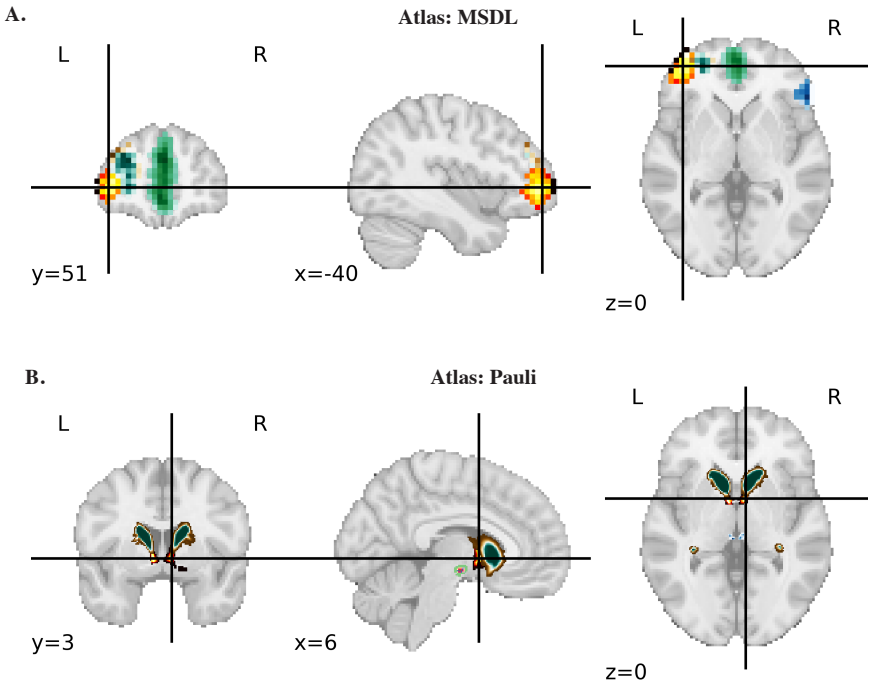

Figure 6. Top ROIs in cortical and subcortical regions responsible for chronic pain.

The machine learning classifier results showed MSDL and Pauli atlas to be better for parcellating this chronic pain fMRI data. The probability-based feature importance measure was implemented to get the top regions that contribute to classifying these patients. The regions identified as top regions in this study are the regions that are involved in chronic pain processing as identified in various previous studies. The top five regions of the MSDL cortical atlas that contributed to classify the chronic pain subjects from the healthy controls are the left frontal pole [43], the medial default mode network [44], the right pars opercularis [45], the dorsal anterior cingulate cortex (dACC) [46] and front default mode network [47]. The data parcellated with Pauli subcortical atlas classified with Boosting algorithm showed the extended amygdala [48–50], subthalamic nucleus [51], hypothalamus [52, 53] and caudate nucleus [54–56] are the top four regions that contributed most for classification.

It is very important to note that chronic pain is a complex condition that can be challenging to classify due to its heterogeneity and comorbidities. Pain can vary greatly in terms of its location, duration, severity, and underlying cause, making it difficult to group into distinct categories. Additionally, comorbidities of chronic pain can further complicate classification. For example, a person with chronic pain caused by arthritis may also have depression, making it difficult to determine whether the pain is primarily due to the arthritis or the depression. Similarly, a person with chronic pain caused by fibromyalgia may also have sleep disturbances, which can exacerbate their pain symptoms. The heterogeneity of chronic pain also makes it challenging to develop effective treatment strategies. What works for one person may not work for another due to differences in the underlying cause and comorbidities of their pain. This highlights the need for a personalized approach to chronic pain management that considers each person's unique circumstances.

4. Conclusion

The study proposed a model that preprocessed fMRI chronic pain data and parcellated it into distinct regions using different atlases. Various machine learning classification models were used to identify the best algorithm and parcellation scheme. The performance of classifiers was evaluated using accuracy, specificity, and sensitivity metrics, and important contributing features were identified. The results showed promising accuracy, sensitivity, and specificity when parcellating data using Pauli and classifying with a boosting algorithm. Similarly, the MSDL atlas showed promising results when classified with XGboost and CNN algorithms. The study's findings are encouraging compared to previous fMRI classification studies on various chronic pain data.

The study's innovation is rooted in its novel methodology for decoding chronic pain dynamics from fMRI data. However, it is essential to acknowledge the inherent limitations of such studies. The intricate nature of chronic pain, coupled with its diverse comorbidities, presents challenges for accurate classification and effective treatment. Additionally, while fMRI offers valuable insights, it may not comprehensively consider psychological and emotional factors that intricately shape pain perception. Despite these limitations, the pursuit of ongoing research and personalized management holds promise for improving outcomes in chronic pain management. Further investigations are necessary to uncover precise underlying mechanisms, thereby identifying potential targets for innovative treatments in the realm of chronic pain.

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