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Performance assessment of machine learning techniques for early multiple sclerosis prediction using resting-state FMRI connectivity data

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Abstract

The scientific community is becoming increasingly interested in the use of machine learning to clinical data in order to help diagnosis and prognostic assessment. Nonetheless, selecting the appropriate method was essential for achieving robust and dependable categorization. Our research sought to determine which machine learning techniques performed best in differentiating Multiple Sclerosis patients from control participants, as well as if these techniques may be useful in supporting the early diagnosis of Multiple Sclerosis. The Random Forest, Support Vector Machine, Naïve-Bayes, K-nearest-neighbor, and Artificial Neural Network algorithms are the ones we chose. In order to discover brain networks, we used the Independent Component Analysis on functional MRI resting-state sequences[1]. After identifying 15 networks, we were able to extract the mean signals needed for categorization. To identify the most crucial variables in each algorithm, we carried out feature selection tasks. Based on the early presentation of motor/sensorial abnormalities in Multiple Sclerosis, we demonstrated that the sensory-motor I was the best discriminate network between controls and early Multiple Sclerosis. Furthermore, utilizing simply this network, Random Forest and Support Vector Machine demonstrated identical 5-fold cross-validation accuracies (85.7%) in classification

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performance, making them the top methods. We think that these results may indicate a positive step in the direction of a clinical diagnosis and prognosis.

Keywords: Multiple Sclerosis, MRI resting-state sequences, Support Vector Machine, Artificial neural network.

1. Introduction

Among the several MRI acquisition types, functional magnetic resonance imaging (fMRI) is capable of measuring brain activity by identifying variations in blood flow. There is a connection between cerebral blood flow and neuronal activity; blood flow to a part of the brain that is being used rises. Finding the active areas helped researchers understand how the healthy brain functions, and in an increasing number of studies, this knowledge was used to identify the specific brain regions affected by a certain illness [2]. The resting state fMRI (rs-fMRI) and task-based fMRI were the two types of fMRI studies that might be conducted. The activation of particular brain networks during rest and their interplay were the main subjects of the rs-fMRI investigation. Task-based functional magnetic resonance imaging (fMRI) facilitates the monitoring of blood flow variations throughout distinct networks during certain movements or training regimens. By finding novel biomarkers, these methods helped to enable early detection of neurodegenerative illnesses by comprehending their evolution [3]. The scientific community has been particularly interested in rs-fMRI in order to investigate spontaneous neuronal activity in the human brain at rest. Numerous resting-state fMRI investigations have reliably documented the establishment of functionally connected resting-state networks when the subject is at rest[4]. The robustness of these functionally linked networks within the brain has been demonstrated by these studies, which have consistently identified the same resting-state networks (i.e., default mode network, visual network) despite using different subject groups, methods, and MRI acquisition protocols.

Multiple Sclerosis (MS) is a demyelinating illness that alters the brain's information flow and affects the central nervous system. It can cause a variety of indications and symptoms, such as cognitive, motor, and occasionally mental issues[3]. There are many types of multiple sclerosis (MS), wherein new symptoms develop gradually (progressive forms) or in isolated bouts, with full symptom elimination in between attacks (relapsing-remitting forms, or R-R). Although the exact aetiology of MS was still unclear, it was thought that those who were genetically predisposed to respond to an unknown environmental element may be exposed to it. Since the course of MS was so unexpected and variable, it is now impossible to anticipate how the disease would proceed over time or how severe it will be in any given individual. In this pathology, prompt diagnosis was essential. Several classification techniques have been used in recent years to use histology and RNA data to separate MS from healthy controls.

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2. Pre-processing for MRIs

The automated white matter (WM) lesion segmentation and filling on the corrected T1 and FLAIR, non-linearly co-registered, was performed using LST-toolbox v.2.0.15, with the belief map set to GM and an initial threshold of kappa = 0.15. The number of lesions and the estimated total lesion burden (ml) were computed.

The following tools from the FMRIB's Software Library v.5.0 were used to pre-process all rs-FMRIs: (1) removing T1 equilibrium effects by deleting the first five volumes; (2) stripping the skull from pictures; (3) correcting motion and slice time; (4) denoising using a high-pass temporal filter (128 s); and (5) smoothing the image spatially using a Gaussian kernel of FWHM 8 mm. No subject's greatest translation or maximum rotation in any axis was more than 1 mm. There were no significant statistical differences (t-test, $p < 0.05$) seen in the mean Euclidian distance or the mean Euler angle between the two groups.

T1 segmentation was used to produce the WM and CSF masks, which were then applied to each rs-FMRI to extract the signals. Six motion parameters and the WM and CSF signals were regressed out of the time series. The residual time series for each scan were demeaned and co-registered to the T1 normalized on the MNI 152 standard space after these nuisance factors were eliminated[5].

Using the Infomax technique, we performed an independent component analysis (ICA) on this pre-processed rs-FMRI using the GIFT toolkit v.3.0b. Prior research has shown that the ICA analysis is a reliable method for investigating minute changes in MS. It has been extensively shown that there is a correlation between changes in ICA networks and clinical MS characteristics. ICA is a whole-brain, data-driven method that is strong because of its inherent ability to show dynamics for which there is no temporal model. Additionally, ICA was created to disentangle a multivariate signal into its constituent parts, making the study of a complex of signals easier. Since ICA is used without any previous hypothesis, it overcomes the relative arbitrariness of the ROI selection when compared to the region-of-interest (ROI) technique.

To strike a compromise between the number of components retrieved and the robustness of component spatial maps, an intermediate model order (number of components = 21) was used. After several iterations of independent component decomposition, each of these components remained stable. Specifically, the GIFT toolbox's ICASSO1 plug-in was utilized to determine which components were the most dependable and stable throughout the course of 20 iterations using various beginning circumstances and bootstrapped data sets. With an ICASSO quality rating of 0.97, a dependable solution was found.

	MS (*N* = 18)	CTRL (*N* = 19)	*P-Value*
Gender (M/F)	9/9	9/10	1[a]
Mean Age (Years)	34.17 (22–49)	37.42 (21–64)	0.43[b]
Mean Age At Onset (Years)	32.5 (20–45)		

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Disease Duration (Months)	17.83 (3–36)
Mean EDSS	2.13 (1–4.5)
Mean Lesion Load MRI (Ml)	6.37(28.35–0.141)

Table:1 Clinical and demographic characteristics of the CTRL and MS groups

Two experts visually recognized fifteen mean components. Using voxelwise one-sample t-test, we first examined all 15 mean components, encompassing all subjects—RR-MS as well as healthy controls. GIFT automatically threshold the t-maps from the on-sample t-test, with a default value of 1.5. After that, they were binarized, producing masks for extracting the mean signal of the 15 networks for each participant. We utilized the MarsBaR toolkit for Matlab 2013a to automatically extract this data.

3. Analysis of machine learning

To forecast a category or label in a machine learning classification problem, the data were utilized. Supervised learning is the term for this method, which involves an algorithm using input data to build a model that can correctly categories each observation. A classifier is an algorithm that applies classification. Using a classifier, data may be grouped into groups and distinctions between them can be found. A model may be created to categories data samples into classes by resisting class labels.

The quantity, quality, and type of the features all influence which machine learning method is best to utilize. Various categorization methods are developed by diverse methodologies based on their respective natures. In the current study, Matlab 2013a and the R language (3.3.2) were used to perform machine learning analysis on a dataset consisting of 37 rows (subjects) and 15 features (mean signal in the network). Five distinct classifiers were constructed: Artificial Neural Network (ANN), k-Nearest Neighbour (kNN), Random Forest (RF), Support Vector Machine (SVM), and Naïve Bayes (NB) [6].

To examine the tree decision category, we first constructed an RF method. Then, to evaluate a non-linear category, we used an SVM technique with a Radial Kernel. We then used a kNN classifier, which is a non-linear method based on the Euclidean distance between points, and a linear classifier, NB, as it is one of the more widely used statistical techniques. Ultimately, we constructed an Artificial Neural Network, which serves as a modeling tool capable of simulating complicated input-output relationships that previous analytic functions were unable to describe. It depicts a non-linear structure of statistical data.

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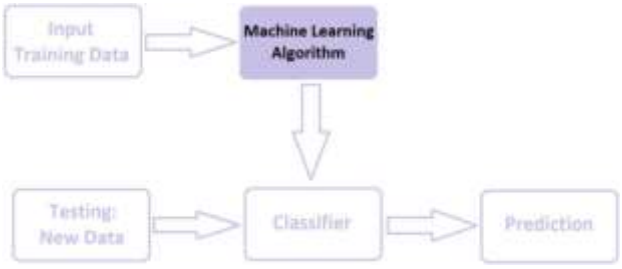

Fig: 1 An illustration of a machine learning classifier

3.1 Support vector machine

Encouragement A machine learning tool called a vector machine is used in a variety of domains, including speech disorders, face recognition, bioinformatics, cancer diagnosis, seizure prediction, and EEG signal categorization. With SVM, it is possible to create the best hyperplane with the biggest margin for dividing data between two groups (see Fig. 2b). A solitary hyperplane suffices to divide two-dimensional data into groups, such +1 or – 1 [7]. This strategy could not be sufficient when the data are nonlinear and exhibit greater complexity, like in the case of biological data, as the data distribution may be informal and a line may not effectively distinguish between classes. Furthermore, when dealing with complicated data, a linear method might result in several mistakes during the classification stage.

When data could not be separated linearly, they were transformed into Feature Mapping, a higher dimensional mapping for classification, which has a specific function Φ(xi) as in equation (1). One can use a Kernel function to determine the value of Φ.

$xiT\ xj = K(xi, xj) = \Phi(xi)T\ \Phi(xj)$ ----------1

The kernel function, denoted as K(xi,xj), is derived from the inner product of two variations, xi and xj. In the first xi space dot product. The computation uses xj, which is transformed into higher space so that it may take the place of dot products as the kernel function.

The radial kernel function (RBF) is among the most often used function kernels. A RBF kernel is defined as follows: given two data samples, denoted by x and λ, which are represented as feature vectors in some input space:

$K(xi, xj) = e^{-1/2} (\frac{x-\mu}{\sigma})^2$ ----------2

where the squared Euclidean distance between the two feature vectors is represented by $(x-\mu)^2$.

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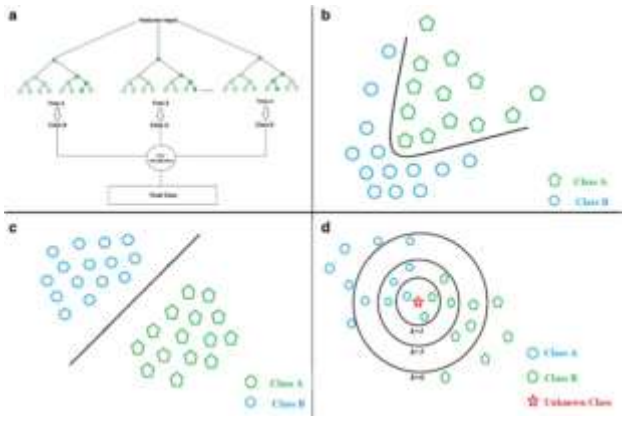

Fig: 2 (a) a decision tree example made using an RF technique; (b) an illustration of a kernel radial in an SVM classification; (c) an example of NB when the data are separable linearly; (d) a KNN example displaying various classifications according to k value

3.2 K-nearest neighbors

One of the most basic categorization techniques is K-nearest-neighbor. When little to no prior knowledge about the distribution of the data is available, it needs to be among the first options considered for a classification research [8]. When determining trustworthy parametric estimates of probability densities proved to be challenging, discriminate analysis became necessary, leading to the development of K-nearest-neighbor classification.

KNN techniques compare each unseen point x to every point xi in the training set by means of a distance function dist (x, xi). After completing the k minimum distances, the label for x is determined by taking the majority over the associated labels, yi. The quantity and distance of the data points are the main problems with the kNN approach. Actually, provided a suitable distance—usually the Euclidean one—is available and the training set's data point count is manageable, a kNN approach performs admirably.

The kNN algorithm's efficiency is mostly determined on the value of k, or the number of nearest neighbours. Cross-validation is one method for determining the ideal value for k, but data inspection is also a necessary step in the process. Larger k values often result in greater precision since they lower total noise. A poor signal-to-noise ratio actually necessitates higher values of k [9]. For most datasets, the k values have typically been in the range of 3 to 10.

The value with the greater classification accuracy in this instance was represented by the k value of 7, which was used while developing the kNN algorithm.

3.3 Naïve Bayes

The simplest classifier is the Naïve Bayes one, which just involves drawing a line to distinguish between the classes that are being investigated [10]. Furthermore, it is a statistical method that is

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increasingly frequently used for classification in data mining problems. It is predicated on the independence assumption between the characteristics in the Bayes theorem.

$$P(A|B) = P(B|A)P(A) \Big/ P(B) \text{----------3}$$

The Bayes theorem makes it possible to determine the likelihood that a random event A will occur given that event B has already occurred. It is necessary to know the a priori likelihood of A, B, and B impacted by A. The number of parameters needed for NB classifiers was linear in the number of variables in a learning issue, making them extremely scalable. Based on the so-called Bayesian theorem, the NB Classifier approach works best when the input dimensionality is large. Even though NB is straightforward, it frequently performs better than more complex categorization techniques. NB has demonstrated its usefulness in text categorization, medical diagnosis, and systems performance management. It is frequently described as "surprisingly" accurate in these domains. Since the classes were not linearly separable, an NB classifier is often not appropriate for non-linear problems.

4. Feature selection

A potent technique for enhancing prediction accuracy and better locating knowledge hidden in high-dimensional datasets is variable and feature selection. Reducing the so-called "curse of dimensionality," which raises the possibility of over fitting and incorrect record categorization, is, in fact, a recognized challenge in classification tasks. When the feature space exceeds the number of records, this issue deteriorates [11]. Finding the optimal subset of features for a given classification model based on variable ranking is highly helpful in enhancing prediction performance.

Because of these factors, we used several feature selection techniques, based on the classifier, to get a ranking of the best predictive networks. We employed the recursive feature elimination (rfe) for the SVM and kNN, the intrinsic feature selection of RF based on the Gini index, and the other algorithm's features weight calculation using the function "varImp" found in the caret package.

Recursive feature elimination involves using an external estimator to apply weights to features (such a linear model's coefficients). Iterative feature selection involves repeatedly taking into account progressively smaller subsets of characteristics. First, all of the characteristics are used to train the estimator, and weights are assigned to each one. Before modeling, the predictors were sorted and the less significant ones were gradually removed. Finding a subset of predictors that can be utilized to create an accurate model is the aim.

While the ANN employs combinations of the absolute values of the weights, the linear classifier (NB) technique delivers the absolute value of the t-statistic for each model [12]. In the end, we rebuilt each of the five classifiers using just the most crucial characteristics.

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5. Discussions

In order to assess how well five distinct machine learning algorithms performed in differentiating between healthy controls and MS patients in order to support the early diagnosis of MS from rs-fMRI data, we trained the algorithms on functional connectivity data extracted from ICA networks. Specifically, we used the RF, SVM, NB, kNN, and ANN techniques on the same dataset of values from ICA networks [15]. After that, each classifier's features were chosen, and the outcomes were compared

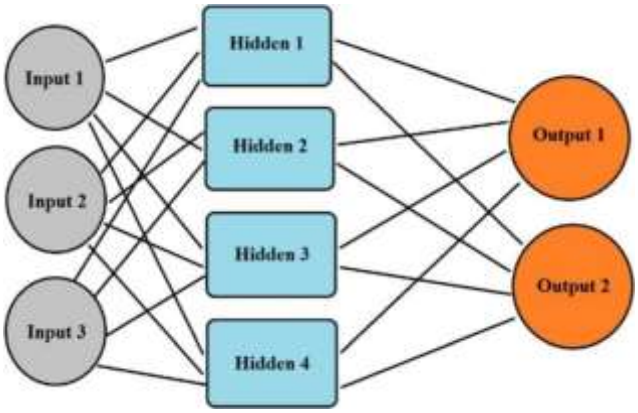

Fig 3: An ANN's internal design with its hidden layers

After being trained on all the characteristics, the five classifiers' 5-fold cross-validation accuracies were incredibly low. Given that the classifiers were developed using various algorithmic techniques, their performance values varied greatly from one another. Accuracy between RF and SVM was comparable. Given that these were the most widely used machine learning algorithms in real-world applications, it was rather fascinating. SVM was often employed when there was a limited quantity of relatively clean, outlier-free data, and when the features were associated.

In contrast, RF performs better when there are more instances of well-randomization, which helps to minimize the occurrence of outliers. In our instance, the pre-processing procedures in which the signals were subjected to several denoising stages in order to eliminate different artifacts, such as WM and CSF masks and head motion, were responsible for the 5-fold cross-validation accuracies of SVM and RF being comparable [11]. Additionally, there weren't many features, and RF was presumably at a considerable disadvantage. In contrast, NB performed poorly (46.6%), which is likely related to its linear character; in contrast, kNN (63.2%) and ANN (69.9%) showed performance that was equivalent to that of SVM and RF.

Classification performance using all networks

Algorithm	Accuracies	Sensibility	Specificity	PPV-NPV
RF	56.5%	53.3%	60%	3–3

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SVM	63.3%	60%	80%	4–2
NB	46.6%	46.6%	46.6%	3–3
kNN	63.2%	66.6%	60%	4–2
ANN	69.9%	53.3%	53.3%	3–3

Table: 2 Calculated for each classifier employing all networks, the Five-Fold Cross Validation Accuracies, Sensibilities, Specificities, Positive Predictive Value (PPV), and Negative Predictive Value (NPV)

Classification performance using only sensori motor I network

Algorithm	Accuracies	Sensibility	Specificity	PPV-NPV
RF	85.7%	100%	66.7%	6–1
SVM	85.7%	100%	66.7%	6–1
NB	71.42%	50%	100%	5–2
kNN	71.42%	50%	100%	5–2
ANN	71.42%	50%	100%	2–3

Table 3: Every classifier's accuracy, sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were determined using just the Sensori Motor I network.

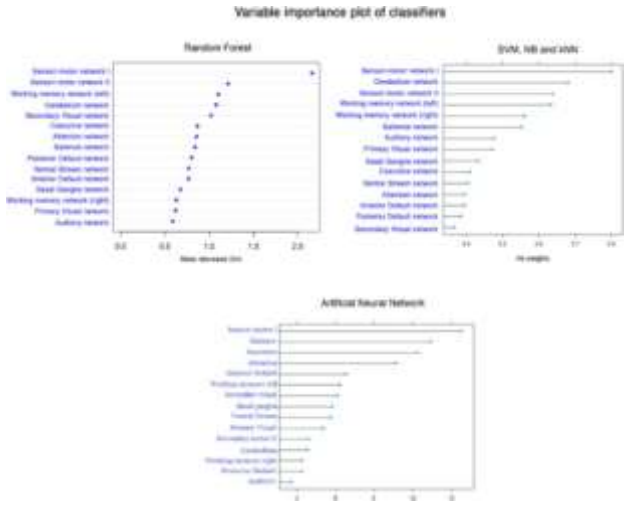

Fig: 4 apply feature selection to the five algorithms. The sensori-motor I network is the most crucial network in any scenario.

6. Conclusions

The use of machine learning to data in the resting state has grown significantly in popularity and attention over the past several years.

Nonetheless, a deeper understanding of these methods was required to apply the appropriate strategy for the problem under consideration in light of the data distribution and feature count. Thus, a separate methodology should be used depending on the ailment under consideration. The goal of the current study was to determine if different types of machine learning approaches could aid in the early detection of multiple sclerosis (MS) based on connectivity data from rs-fMRI. We

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used the following techniques to create five distinct classifiers in order to achieve this goal: SVM, RF, NB, kNN, and ANN. The characteristics taken into consideration came from the examination of 15 well-known networks using resting-state fMRI using GIFT and the MELODIC programme. We demonstrated that the sensori-motor I was the best discriminate network between controls and early MS when comparing all other classification methods with feature selection. Specifically, RF and SVM appeared to be the superior methods in this instance since they demonstrated the preprocessing methodology's resilience by presenting the same accuracies utilizing just this variable. Observation revealed that the cerebellum, working memory networks, and sensori-motor II all had similar significance ratings. These results were consistent with the early signs of motor and sensory impairments in multiple sclerosis.

To sum up, we think that our thorough methodology may highlight minute variations in functional connectivity, which may eventually be used to the clinical setting for prognosis and diagnosis.

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