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A Novel Approach to Aid the Diagnosis of Schizophrenia using P300 Component of EEG Signals

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***Abstract*—Schizophrenia is a psychiatric disorder in which the individual's sense of reality is altered. Currently there are no tests that can absolutely diagnose the disorder. Our aim is to develop a computer aided diagnostic(CAD) tool by tapping the EEG signals from the scalp of the head and extracting the P300 event related potentials(ERPs). This CAD tool can be used to objectively aid in the diagnosis and distinguish between Healthy Controls (HC) and subjects of Schizophrenia (Sz).**

The proposed methodology consists of four different stages: EEG preprocessing, feature extraction, feature selection and classification. EEG data of 8 schizophrenic and 8 normal subjects were considered for an auditory odd ball task and visual odd ball task. Features are extracted and are analyzed in both time and frequency domain. These features have been subjected to a feature selection algorithm called principal component analysis and the selected features will be used to train three classifiers. The accuracy of these three classifiers will be compared which include linear discriminant analysis, support vector machines and multi-layer Perceptron and the classifier with the highest accuracy is selected to test the data and perform plotting. The accuracy and efficiency of multi-layer Perceptron classifier was found to be better compared to the other methods discussed.

***Index Terms*—Schizophrenia, electroencephalography, P300, ERPs, auditory oddball task, machine learning, neural networks, receiver operating characteristics, support vector machines, multi-layer perceptron.**

I. INTRODUCTION

Schizophrenia is a serious chronic psychiatric disorder that is characterized by a failure to understand what is real. It is a disorder that affects how an individual think, feels and behaves. The people with this disorder are not in touch with the reality and are very disabling. The symptoms of schizophrenia include positive, negative and cognitive symptoms. Positive symptoms refer to the psychotic disorders like delusions, hallucination, thought and movement disorders. Negative symptoms are those associated with disruptions in the normal emotions and behavior like keeping away from the outside world etc.

Currently, there is no physical or lab test that can absolutely diagnose the disorder. A psychiatrist usually

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arrives at the diagnosis based on the clinical symptoms observed. Hence the subjective component involved in the diagnosis of the disorder is very high. Thus, this paper aims at explaining an objective that can be implemented and used in the objective diagnosis of the corresponding disorder. This paper explains the design of a diagnostic tool using Matlab that may be used to obtain an objective opinion to aid the doctors in the diagnosis of the disorders. The experiment involves tapping into the EEG signals from the scalp of the head. The EEG signals obtained will be processed to extract the P300 component of the EEG waves. P300 is an event related potential (ERP) that appears in an individual 300ms after the onset of a response to a stimulus.

Event related potentials are a time locked event of the activity of electrical signals that occur on the cerebral surface indicating the distinct features of cortical processing [4]. The P300 wave can be divided into two types, the P3a and P3b component. The P3b sub-component has known to be established reliable bio marker for the diagnosis of the fore mentioned disorder [5][6]. The P300 has enough discriminant power to differentiate between the Sz and HC groups [5]. This can be carried out by proper analysis of the EEG signal and proper extraction and analysis of the P300 component extracted using an auditory oddball task [7]. P300 comprises of an early attention [7] process stemming from a frontal working memory representational change to produce the P3a. The attention-driven stimulus signal is then transmitted to temporal and parietal structures related to P3b. These resulting potentials can be dissociated with paradigmatic manipulations and are generated when perceptual stimulus discrimination occurs. The amplitude of P300 indexes [8] the neural power and cognitive processes. The latency of the P300 component indexes neural speed and brain efficiency.

With CAD gaining popularity and9usage9machine learning tools from EEG and fMRI in schizophrenia, mental9disorders and9other9related9illnesses, are gaining importance [9] [10] in9recent years. These, along with physical activity correlation will help in an objective and reliable diagnosis of the disorder and will prove to be a very helpful tool. It will help in the preliminary9analysis and in9gaining an early control over the disorder9and its associated symptoms [11] [12]. Previous works [13] have illustrated using the method of wavelet transforms to perform classification of healthy and schizophrenic controls. They have achieved a sensitivity and specificity of 0.71 and 0.66. Similarly, other works like in [14] have used the property of Fourier transforms to classify the EEG data into respective classes.

The data acquisition from the subjects will be performed by the use of an auditory oddball task and a visual oddball task. Neuromax NMX – 32 instruments will be used to record the data. After the acquisition of the EEG signals, the signals will be preprocessed by applying three different kinds of filters. The filtered data is then epoched to obtain the proper time segments. The epoched data will be further epoched in the time frame of 300 to 800ms to obtain the P300 ERP. An ICA algorithm of the type kurtosis is applied to the extracted components for the purpose of Dimensionality reduction.

The dimensionally reduced data is then used to extract a total of 20 features out of which 17 features correspond to the time domain and 4 features belonging to the frequency domain. The computed values are put in the form of a 20×20 matrix in which each row corresponds to a feature and each column corresponds to a particular channel of EEG.

In order to perform classification, it is necessary to select the appropriate features and this is done using linear discriminant analysis (LDA) and principal component analysis(PCA). The is the classified using Support vector machines and multi-layer perceptron artificial neural networks. The network will be trained to take the data and provided the output as to whether the fed data belongs to a subject of schizophrenia or not. 3D scalp maps are the plotted to visualize the ignited areas of the brain using the EEGLAB toolkit in Matlab.

II. Materials and Equipment needed

EEG of 16 subjects was recorded using the Neuromax NMX-32 EEG machine developed by Medicaid systems. It is a 32 channel EEG machine in which 22 channels are dedicated for making EEG measurements. The tones for the auditory oddball task were generated using the NCH suite software. Three auditory tones that comprise the target tone, distractor and standard tone were generated for test purposes. A sponge ball is will be given to the subject while performing the odd ball task. The subjects will be asked to squeeze the ball at the onset of the target tone. For recording both the P3a and P3b sub components, the EEG signals are recorded with a sampling rate of 256Hz. During this the subjects will be made to hear a series of tones and asked to identify the odd tone of 500Hz. A set of speakers along with a laptop were used to play the tones in a closed environment while the subject lay on bed with the EEG electrodes attached to the scalp.

The data recorded was processed using Matlab [15], The Mathworks Inc., Natick, Mass. USA. The preprocessing is done manually and also using the EEGlab toolbox in Matlab. The neural network will be trained using the Neural Network toolbox and Statistics and Machine learning toolbox, The Mathworks Inc., Natick, Mass. USA. EEG electrodes were placed on the scalp based on the international 10-20 system. The EEG data is passed through the stages shown in figure. 1 to obtain the proper binary classification using pattern recognition.

III. METHODOLOGY

The EEG data is passed through the stages shown in figure.1 to obtain the proper binary classification using pattern recognition. Pattern recognition is used to classify the data as accurately as possible. Each block in the figure 1 explains the different steps involved in the processing of the data in order to build a good enough binary classifier.

IV. SUBJECTS

A total of 16 subjects have been taken for the study. Out of these subjects, 8 were Schizophrenia diagnosed subjects and the rest were healthy controls. Gender, age and family background of the healthy controls was taken in to consideration before proceeding with the data acquisition. Only those healthy controls that did not have a family history of the disorder and satisfied the age criteria were taken into consideration. The Subjects of schizophrenia (Sz) had been diagnosed based on the DSM – V criteria as a standard which stands for the Diagnostic and Statistical Manual of Mental Disorders. [2]

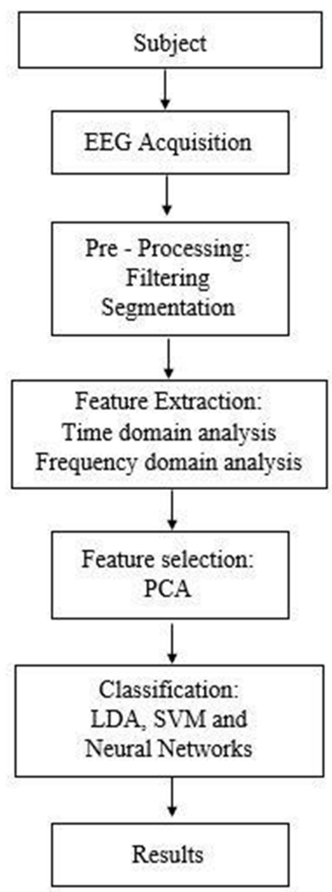

Figure 1. Flowchart of the proposed methodology to be implemented for binary classification of the data.

Since our project involved the inclusion of human trials it was required that our project be reviewed and accepted by the Ethical review committee, BGS GIMS, Kengeri, Bangalore, where we have received the subjects and performed the tests on them. The EEG machines as well as the participants for the test have been provided by BGS GIMS hospital, Bangalore.
Prior written consent has been taken from both the subject and the caretaker before performing the tests. The consent form had details regarding the test to be conducted emphasizing that it will be non-invasive and non – interventional in nature. The operating of the EEG machine was studied by us and we have operated it to take the readings from the subjects for a period of 120 seconds. The subject will be given binaural tone bursts of 2 seconds of the target tone and 2 more seconds of the distractor tone and a standard tone of 4 seconds separating these two tones.

V. Data Acquisition

EEG signals were recorded while subjects performed an auditory odd-ball task (AOD). To give rise to both the P3a and P3b waves, EEGs were recorded at a sampling rate of 256Hz while the subjects had to undergo a 3-stimuli auditory odd-ball task, which comprised a 500Hz target tone, a 1000Hz distractor tone and a frequent 2000Hz standard tone. Participants heard binaural tone bursts (2s duration, 90 dB intensity) presented in a controlled stimuli synchronous onset of 4000ms and 2000 ms. The tones were played for a time frame of 120 seconds for the task. The Participants were instructed to keep their eyes closed to avoid the eye movement and were asked to press a sponge ball or a mouse button using the dominant hand whenever they heard the target tone, discarding all the non-attended target tones.
Participants were told to keep quiet, relax and keep their eyes closed and also relax their jaw. Prior advice was given to the subjects before recording the EEG signals in which most power came from brain signal and not others. This was done to avoid the muscular and the eye artifacts as much as possible. The purpose of closing the eyes was to reduce and minimize eye movement noise due to muscular electrical signals (micro-saccadic eye movements).
The recordings were made using the Neuromax NMX -32 EEG machine (seen in figure. 2), with the electrodes fixed according to the 10 – 20 international system (fig. 3). An EEG electrode gel was used to fix the electrodes to the scalp of the head.

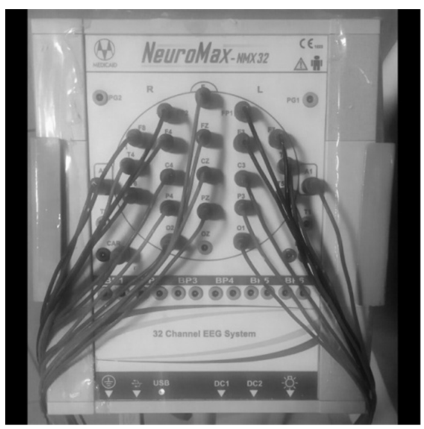

Figure 2. The Neuromax portable 32 channel EEG

The international 10-20 system as seen in fig. 3 is a standard system that shows the approximate position where the electrodes have to be placed on the scalp of the head. The odd numbered electrodes have to be placed on the left hemisphere and the even numbered electrodes have to be placed on the right hemisphere. The electrodes are fitted with the EEG gel that has to be applied to the electrodes before fitting it to the positions on the scalp of the head. Figure 3 shows the international 10-20 system of electrode placement.

VI. Preprocessing

EEG pre-processing stage follows the data acquisition stage and it is a critical one since it allows filtering of the data collected and also the removal of artifacts from the recorded brain signals thus giving us an ‘as clean as possible' cognitive wave. Evoked related potentials (ERPs) are components of the EEG that are believed to be of low frequency content, mainly appearing in the alpha frequency region in EEG [16]. Alpha waves lie in the frequency of 8-13Hz. Ordinary brain EEG activity is averaged out using time epochs to try to extract the non-zero mean average ERP, in particular those in the P3b wave. The first step involves direct filtering of the EEG data.

First, a low pass filter of 15 Hz is applied to filter out the high frequency noise signals and other high frequency bands. This is done so because our prime focus are the alpha waves being generated [17]. The filtered signal is again passed through a high pass filter of 1Hz to remove the DC bias component at low frequencies around 0Hz. The 50 Hz line is removed using a notch filter from frequencies of 49-51Hz.

The second step in preprocessing involves extracting the segments of data where the events have been generated. In particular we focus on extracting only the samples that have been recorded during the target tone. The segments we then joined to get only the extracted P300 component sections. The signal was again segmented and epoched to a time frame of 800ms starting from -200ms from the start of the tone to 600ms.

After this the P300 epoched data was subjected to Independent Component Analysis (ICA). ICA will perform separation of a multivariate signal to numerous additive sub-components. It is mainly applied here for removal of artifacts and Dimensionality reduction. ICA of type kurtosis measures the level of peakedness or the spikiness of a distribution and is 0 for a Gaussian distribution.

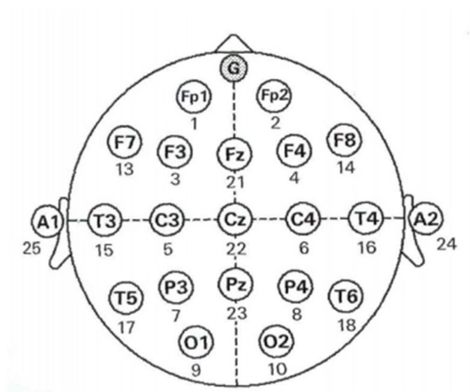

Figure 3. The 10-20 international system for electrode placement

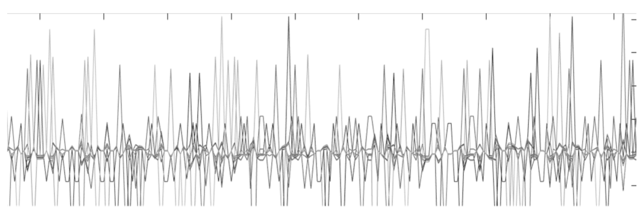

Figure 4. ICA extracted output

VII. FEATURE EXTRACTION

Feature extraction involves computing of several features of the extracted waveforms. Features have been extracted in both time and frequency domain. 16 Time domain features and 4 frequency domain features have been computed. First group of features were computed in the time domain. P300 occurs with a latency between 300 to 600ms after the target tone is presented. So, most of the time domain features are calculated in regard to this time interval.

The second group of features were computed in the frequency domain. The time domain signal is converted to frequency domain using Fast Fourier transforms. To determine the power spectral entropy (PSE), the power spectral density is first calculated and then its entropy is determined [18]. The PSE gives a measure of the disorganized nature of the brain activity.

VIII. Feature Selection

The features computed from EEG signals in previous section are rather numerous when computed for 20 channels. Also, several of these parameters could be irrelevant or redundant in the context of differentiating between both classes of subjects, SZ and HC. For these limitations, machine learning theory states that the important limitations such as over-fitting, generalization and computer load will occur. For these reasons, it is important for us to identify automatically the highly discriminant sub-optimal feature subsets, which is known as Information Theoretic feature selection [19]. Feature selection can be performed by the use of principal component analysis (PCA) and also Linear discriminant analysis. Both these features are available in the statistical and machine learning toolbox in Matlab. This will make sure that only the highly discriminant features are selected for classification. The features will be selected based on the number of components specified for PCA or using max variance computations. These methods will select the most discriminant features from each feature grouping matrix.

IX. Classification

The last stage of the experiment involves the binary classification of the input data between HC and SZ subjects. We have used highly discriminant nonlinear classifiers like support vector machines (SVM) and Multi-layer perceptron. The MLP classifier was implemented using the Neural Network MatLab Toolbox [20]. The neural network has 18 hidden layers. Here 70% of the subjects were used for training purposes, 15% were used for validation and 15% for testing purposes. The supervised machine learning algorithm was used was the well-known Scaled Conjugate Gradient (SCG) algorithm [21] taking the square error as the training performance measure.

The SVM classifier [22] was implemented using the statistics and machine learning toolbox. The test matrix was constructed and every column was assigned a class. All the rows were taken as predictor variables and the last row was taken as response variable that contained the class of that column. Each column represented a sample and the rows represented the features. The kernels that were implemented in the SVM were the linear kernel and quadratic kernel. The ROC [23] plot and the confusion matrix is then constructed and the accuracy of the classifier is determined. The linear discriminant analysis classifier is also implemented the corresponding graphs and values have been computed. The ROC plot and the confusion matrix plot are seen.

X. Results and Discussion

A. Results of Feature Extraction

Out of all the features extracted, no all the features will be of use to us. Many of the features may prove to be redundant for the computation and performing of the classification. But, there are also certain highly discriminant features that help us to perform classification with a strong basis. Some of these features include the absolute value of the P300 wave, thus showing that P300 wave can be used as a reliable potential biomarker. The absolute values of the P300 wave for both the HC and Sz have been listed in table 2 and 3. As it can be seen, the absolute values of the P300 component of a SZ subject are relatively high compared to the readings obtained from normal subjects. Similarly, the PSE value and also the latency values are found to be very distinct when a comparison is made. The median frequency values also show a huge variation between the two groups. The median frequency values are relatively less for a Sz subject compared to a HC subject

B. Classification Results

The classification was successfully performed using three different approaches or algorithms. A comparison was made in relation to the accuracies that were obtained and the best classification algorithm was chosen to pass the test data.

C. Linear Discriminant Analysis

Linear discriminant analysis was performed by vertically concatenating all the 20 columns of the matrix to obtain a single column of data containing 420 rows. Each column represented a subject’s sample data and all the samples were horizontally concatenated. Binary Class numbers are assigned to each row to specify which class it belongs to. The ROC and percentage of accuracy can be seen in fig. 5

D. Support Vector Machine

The implementation of the SVMs was the same as that of LDA. Both were implemented using the classification learner toolbox in Matlab. Upon training the machine, SVM provided an accuracy of 82.4% with an AUC of 0.93. The accuracy of the machine trained with 421 variables and its ROC looks similar to that of LDA.

E. Multi-layer Perceptron Neural Network

The Input data in the form of a matrix is given as an input to the neural network. The target data consisting of just two rows indicates which of the subject belonging to a column belongs to which class. The number of hidden layers have been specified to be 18. 70% of the dataset is used for training, 15% for validation and 15% for testing.

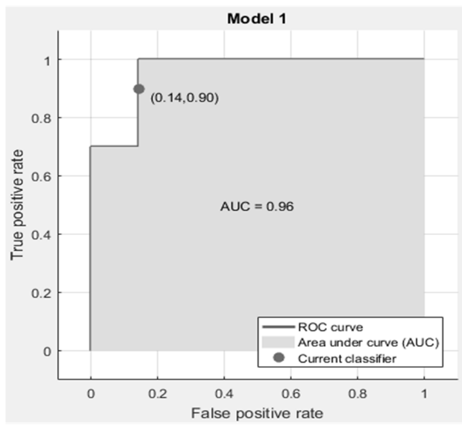

Figure 5. The accuracy and ROC curve for the LDA classifier

This classifier has attained an accuracy of 94.1% and AUC of 0.97. This can be seen in the confusion matrix shown in fig.6.Thus, this is the classifier that is chosen to test the data and finally perform binary classification. The test data is then passed to the neural network as a parameter by converting the neural network into a function. The network will return a value of with 01 or 10 which is the result of the classification. Thus, depending on the output obtained we can determine whether a subject is schizophrenic or not.

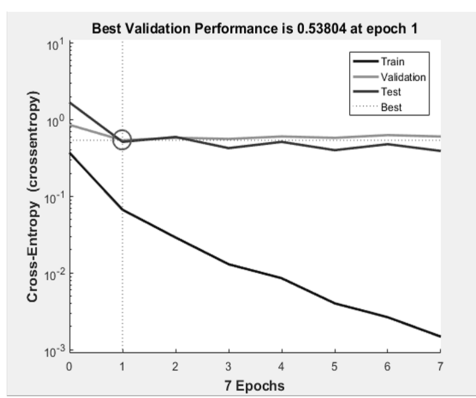

Figure 6. The Performance plot of the MLP classifier.

F. Plotting of Scalp Maps using EEGLAB

EEGLAB, a toolbox in MATLAB, was used for 2D and 3D plots. First the data in EDF format was imported to EEGLAB [15]. Next the sample rate of 256 Hz was set, followed by importing events from data channel. Later this data was filtered, epoched and subjected to Independent Component Analysis. The following plots were performed: 3D plot representing latency, largest ERP component and power spectral density and frequency plot. The following 3D plots in figure 9 and 10 show the variations in the latency in the occurrence of the P300 component.

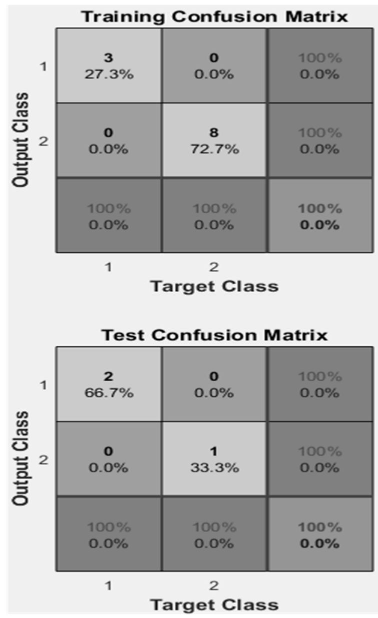

Figure 7. Confusion matrix showing training and testing results

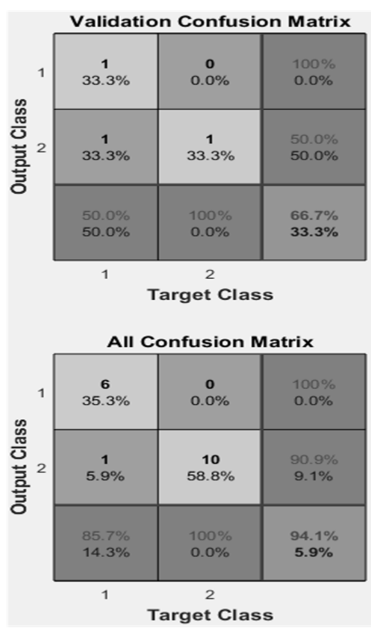

Figure 8. The confusion matrix showing validation and overall accuracy of MLP classifier

This shows that the schizophrenia affected subjects have a delayed latency and amplitude of P300 component when compared to a healthy control. The plots in the figure 11 and 12 show the largest ERP components that have been recorded and plotted from both the schizophrenic and healthy controls. The number of ERPs is found to be more in healthy controls and also the amplitude of the corresponding ERPs is more compared to those of schizophrenic subjects. This supports the literature survey that the P300 components in Schizophrenic subjects are less than those in healthy controls. When the event occurs, the occurrence of the P300 component latency is around 0 to 34 ms but the same when observed in a Schizophrenia affected subjects shows that the latency is around 40- 65 ms late.

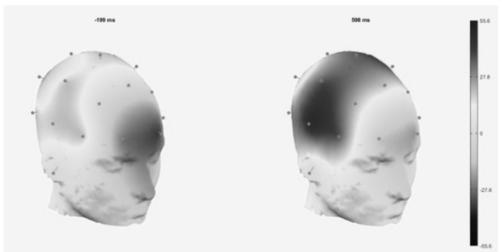

Figure 9. 3D Plot of latency in SZ

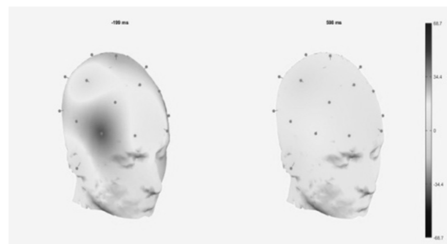

Figure 10. 3D Plot of latency in HC

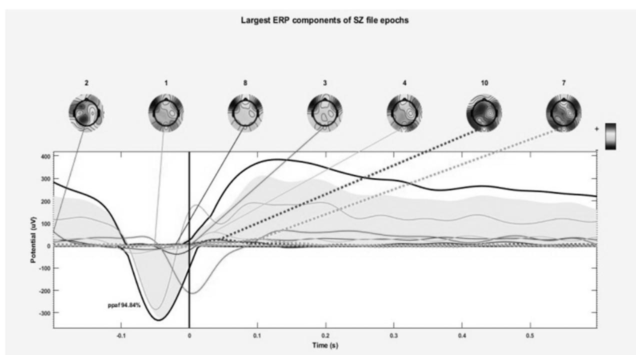

Figure 11. Largest ERP component of SZ

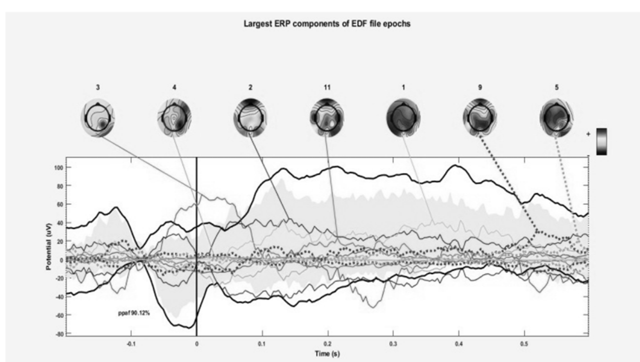

Figure 12. Largest ERP component of HC

XI. Conclusion

We have proposed an end-to-end effective CAD system to help in diagnosing schizophrenia showing promising results from the analysis of the P3b evoked EEG signals during and auditory odd-ball task. The data from the subjects was collected and fed to the Matlab software which processes the data. This in turn was used to extract the features of the P300 wave and feature selection is performed.

Subjects were asked to perform auditory and visual odd-ball task to tap EEG signals. P300 wave, an event related potential was extracted from EEG signal. These signals were preprocessed by filtering and segmentation. Using ICA undesired artifacts were removed and only the required components were retained. Later 21 distinct features in both frequency and time domain were calculated. These features were adopted to 3 machine learning algorithms: LDA, SVM and neural networks and were implemented to test and compare the classification rates. The accuracies of these algorithms were 88%, 82% and 94.2% respectively. Since the accuracy of the MLP classifier was found to be the highest, it was used to test the data. The test data is then fed to the MLP classifier that performs the binary classification of data. The output returned by the classifier is either 10 or 01 which tells us whether the subject under test is affected by schizophrenic

The frequency and component maps were plotted using the EEGlab toolbox available in MATLAB to visualize the probable regions of the brain that are excited when the auditory oddball task was performed and the concerned regions of the brain associated with the disorder are identified.

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