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DETECTION OF ALZHEIMER'S DISEASE BASED ON PHASE SYNCHRONIZATION MEASURES IN EEG SIGNALS.

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ABSTRACT: Changes in electroencephalography (EEG) signals of an Alzheimer's disease (AD) patient starts at an early stage but clinically, the most critical task is its early detection. Most notable effect of AD on EEG is the perturbations in the synchronization of these signals between different parts of the brain. This study aims to efficiently detect the amount of perturbation in synchronization AD has on EEG; while using a cost effective data acquisition system, EMOTIV EPOC and implementing low computational algorithms. The acquired signals were filtered via wavelet de- noising; followed by phase synchronization feature extraction through Global Field Synchronization (GFS). GFS seeks to determine a dominant phase and its magnitude of presence across all the electrodes of the data acquisition system in a single run; making this technique global in nature when compared to coherence, being local in nature (two electrodes in an instant). Quadratic Discriminant Analysis (QDA) and Support Vector Machine (SVM) were used for classification resulting in the accuracies of 75.16 ± 1.16% and 87.00 ± 0.95% respectively. EEG signals of AD patients showed a significant decrease (with $p<0.05$) in phase synchronization when compared to those of control subjects especially in the gamma band for all 14 channels.

Keywords: Alzheimer's disease (AD), electroencephalography (EEG) signals and global field synchronization (GFS).

INTRODUCTION

Brain diseases and their spreads are increasing on a worldwide scale with a startling rate. About 60% to 70% of dementia cases are related to AD worldwide. In Pakistan, the situation is no different. As estimated by Gadit et al., about 6% population of Pakistan has depression, 1.5% schizophrenia, 2-3% dementia, 1-2% epilepsy and 1% Alzheimer's disease (AD) (Gadit and Khalid, 2002). This research is on the detection of AD, which is one of the most common form of dementia. It is caused by the degeneration of neurons in the brain (neurodegeneration) which changes the patient's memory, conduct and the ability to think clearly *(*Alzheimer's Association, 2016) Up until the current progress of medical advancements, there does not exist a cure for this disease, however, there are prescriptions, which can defer the symptoms.

There are different causes of AD. The most common of them include genetics *(*Alzheimer's Association, 2013), tau hypothesis *(*Chen *et al*., 2012) and amyloid hypothesis (Hermann *et al.*, 2005, Jeong, 2004). Whatever be the reason, genetic mutation (Gore and Peterson, 2001) tau protein abnormalities (Gomathi *et al.*, 2003) or Aß deposition generally all changes exhibits early symptoms of AD by the age of 40 (Konig *et al.,* 2001). Onset of any dementia starts from a condition known as Mild Cognitive Impairment (MCI). People diagnosed with MCI have an increased risk of developing AD. It is typically classified into three progressive stages – mild (early-stage), moderate (middle-stage) and severe (last-stage) (Dammers *et al*., 2008). In MCI and mild-AD stage, the memory loss does not affect the daily life of the individual. In the later progressive stages, the patient becomes increasingly dependent on the caretaker(s) (Brookmeyer *et al*.,2007; Konig *et al.*, 2005) that is, due to memory loss; the patient would have difficulty in, say, navigating around the house. AD can be diagnosed by different medical trials; but the diagnosis can itself be very cumbersome and the results are usually confused with what normal aging symptoms might be. The physiological tests for diagnosis include Mini Mental State Examination (MMSE) (Hornero *et al*., 2008), neurological examination (Mary *et al*., 2008) and increasingly, EEG recordings, to name a few. There are several reasons as to why AD diagnosis is important. If a diagnosis is positive, it will help the family or caretaker(s) to plan for the financial assistance with respect to the progress of disease and gives them time to become well informed about the disease. If the diagnosis were negative, this would allow having enough time to treat reversible stages of other diseases; such as thyroidal problems (Snowdon *et al*., 1997). In addition, early diagnosis may provide enough time for different research programs to progress, which may allow the disease to be treated at an age where it is just about to display its symptoms (Delorme *et al*., 2007).

In the past vicennium, researches based on electroencephalography signals have become of high

interest for multiple reasons. EEG signals are brain potentials, which can give information regarding brain functioning and recent

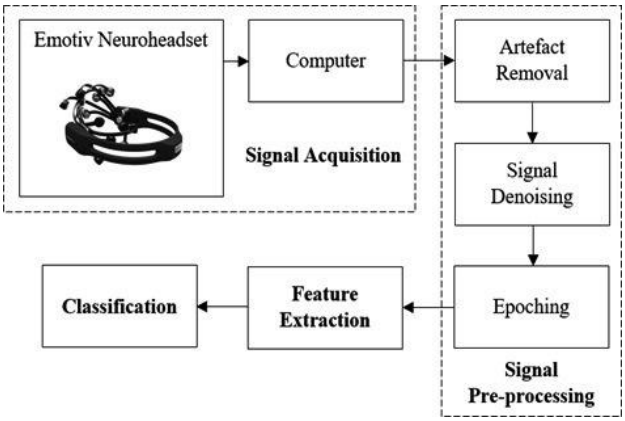

Fig. 1. Workflow starting from the EEG data acquisition using Emotiv, followed by the EEG signal pre-processing to get rid of noise and other potential artefacts. Applying GFS to extract phase synchronization features from the EEG signal of both the patients and control group. Classification algorithms were implemented to classify the extracted EEG features and detect the AD based on phase synchronization.

MATERIALS AND METHODS

This section describes the approach used to efficiently detect the amount of perturbation in synchronization in EEG signals. Fig. 1. shows the block diagram of the workflow starting from EEG signal acquisition, pre-processing to get a noise free signal to extract features and lastly the classification to distinguish between the healthy and diseased EEG signals.

Subjects: A total of 66 subjects were considered for the study, out of which 33 (24 males, 9 females) served as control group (healthy individuals) and the remaining 33 subjects (22 males, 11 females) were patients of Alzheimer's disease. The patients were referred from outpatient memory clinic of Railway Hospital (Islamabad and Rawalpindi, Pakistan). The control group had people ranging from 50 -92 years of age, with an average age of 62.4 ± 8.4 years. The ages of subjects with apparent symptoms of AD spanned from 50 - 94 years of age, with an average age of 65.9 ± 12.6 years. All participants were subjected to multidisciplinary clinical test performed by clinicians and were evaluated on diagnostic staging scales Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Their combined results were then used to categories the subjects as control or patient. All patients were diagnosed with MMSE value of less than 25. MMSE and MoCA are tests, which assess different cognitive domains. These tests evaluate attentiveness of a person along with their concentration. It also estimates conceptual thinking, orientation, language, executive functions and calculations of the subject. The results are recorded in the form of scores, ranging from 0 to 30, in each test. Scores greater than 25 conclude the subject has no significant deficits. Reduced scores are interpreted as significant deficits, which are usually associated with AD. Following these assessments, the subjects were asked to proceed to the recording of EEG signals. They were asked to follow a specified protocol, which is discussed in the next section. Subject statistics are given in the Table 1.

EEG Data Collection: The EEG signals were collected via Emotiv EPOC® Headset with 14 channels and 2 references. Channel names based on the international 10-20 electrode location system are: AF3, F7, F3, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, AF4, with Common Mode Sense/Driven Right Leg (CMS/DRL) references in the P3/P4 locations. This device is capable to sample EEG signals at a rate of 2048Hz with a resolution of 14 bits. Having a bandwidth from 0.2-43 Hz with digital notch filters at 50 Hz and 60 Hz, filtering of the signals is performed digitally with the help of a 5th order Sync filter. This headset connects wirelessly to a computer where the data is sent with a sampling rate of 128Hz.

The signals were obtained from each of the 14 electrodes of the headset for a total of 120 seconds. The protocol followed is described as follows. For the first 30 seconds, the participants were asked to keep their eyes closed. In the next 30 seconds, they were instructed to open their eyes and stare directly ahead, at a stationary object. This procedure was conducted two times, to complete the 120 second data collection, with a total of 60 seconds for eyes closed and equally so for eyes open. This is done to remove any ambiguities which may arise due to the evoked potentials. It has been generally observed that alpha activity is induced due to the closing and opening of eyes; being dominant with eyes closed. The Beta activity increases with eyes open (Czigler *et al*., 2008).

Signal Pre-processing: Once the EEG signals from subjects were acquired, they were imported to MATLAB(r) software for signal de-noising and epoching. Wavelet de-noising was performed on each of the 14 channels that were recorded from a subject. Multilevel decomposition of eight levels was performed which resulted in coefficients for the five bands; namely delta, theta, alpha, beta and gamma. These coefficients were then compiled to form the final de-noised EEG signal. Once de-noising of EEG signals was completed, artefacts from the EEG signals were removed. Epochs were created, each with length of 4 seconds giving a total of

512 samples to work with. Multiple epochs ensure the results obtained have reduced error; a direct benefit of averaging. These epochs were then used for the feature extraction.

TABLE 1: Subject Statistics

Subject no.	Control Group			Patient Group		
	Sex	Age	MMSE	Sex	Age	MMSE
1	M	66	25	M	67	24
2	M	52	26	M	80	24
3	M	72	26	M	65	20
4	M	70	28	M	65	24
5	M	92	28	M	65	20
6	M	64	26	F	70	22
7	M	62	26	F	60	20
8	F	55	29	F	65	24
9	F	53	30	F	60	24
10	M	65	26	F	50	24
11	F	57	26	M	60	23
12	M	60	25	M	76	22
13	M	65	25	F	55	19
14	M	65	29	M	50	24
15	M	57	26	M	56	24
16	M	53	25	M	58	20
17	F	55	29	F	50	16
18	F	65	25	F	56	21
19	M	56	25	M	92	22
20	M	68	27	F	51	24
21	F	65	27	M	52	24
22	M	50	26	F	60	22
23	M	55	29	M	52	22
24	M	55	27	M	94	24
25	M	64	30	M	78	17
26	F	60	28	M	88	14
27	F	71	27	M	65	24
28	M	72	25	M	70	22
29	M	69	25	M	85	24
30	M	58	28	M	75	24
31	M	55	30	M	65	19
32	F	61	29	M	82	24
33	M	73	25	F	60	24

Feature Extraction and Classification: As mentioned in the earlier section, each of the epoch was subjected to global field synchronization (GFS). Since GFS is calculated for a singular frequency, 4 frequencies from each band were selected with equal spacing. Once the GFS values were obtained, average GFS values were calculated for each band. These values were then used to train two different classifiers; Quadratic Discriminant Analysis (QDA) and Support Vector Machine (SVM).

Statistical analysis was performed on the bases of analysis of variance using two-way ANOVA. For this, the independent variable was taken to be the magnitude of impairment that is the mean of GFS for all bands.

RESULTS AND DISCUSSION

De-noising of EEG Signals: The EEG signals acquired from Emotiv headset were pre filtered by the digital filters present in the headset. The raw and filtered signals in Fig. 2 shows data from one of the electrodes (AF4) of the headset when placed on a control subject. Notice how the raw signal is corrupted with higher frequency noise. The filtered signal has a more refined look to which, while retaining the gamma band frequency, has the noise removed.

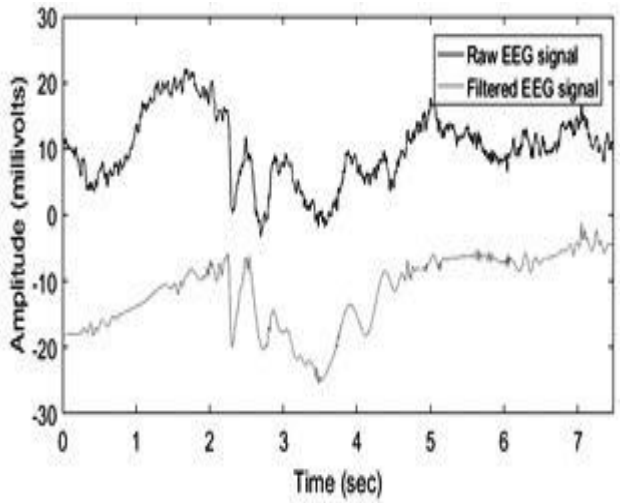

Fig. 2. In the raw EEG signal (above) noise is very apparent in the form of higher frequency. The filtered EEG signal (below) has done away with the noise as can be seen.

GFS: The data recorded gives us the following estimates. In the delta band, it was found the GFS was considerably decreased in the patients (0.597±0.041) when compared to healthy individuals (0.701±0.080). The theta band also showed a similar trend, with lower GFS values for AD patients (0.560±0.037) and higher for the healthy individuals (0.678±0.086). The trend follows in alpha band where the values for healthy individuals and patients were 0.655±0.095 and 0.546±0.035. The more significant drops in GFS values were found in beta and gamma band where, for the AD patients, were 0.508±0.041, and for healthy individuals the values were 0.614±0.091; whereas for gamma band the values for AD were 0.502±0.042 and for healthy individuals, the values were calculated to be 0.632±0.116. These results show that the overall affect the AD has on the synchronization is more dominant in the beta and gamma band. The chart in Fig. 3 shows bar chart of the mean with standard deviations of GFS values obtained for the five bands of EEG signal from controls and patients. It can be seen in the graph that the onset of AD does affect the entire frequency range of EEG.

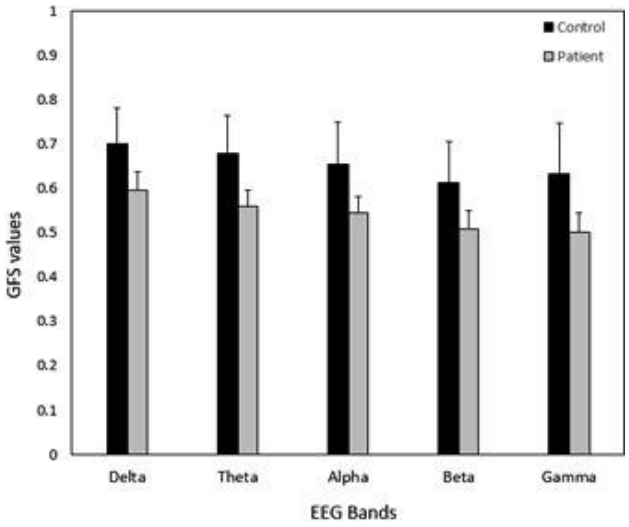

Fig. 3. Mean (±SD) of GFS values obtained for the five bands of EEG signals from control and patients showing decreased GFS values for patient and higher values of GFS for control group.

T-test was performed in order to observe statistical difference in the GFS values between the control group and the patient group. Table 2 contains p values from the test. The ANNOVA tests of the compiled GFS values show significant differences for all bands, F = 303, p<0.000001, SS=10.65, MSe=0.04

TABLE 2:

		Control				
		Delta	Theta	Alpha	Beta	Gamma
Patient	Delta	< 0.05	< 0.05	< 0.05	0.3178	0.1044
	Theta	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
	Alpha	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
	Beta	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
	Gamma	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

Classification: Two classifiers for this research were trained. Each, having a different pattern of recognition, resulted in somewhat dissimilar accuracies, though not majorly significant. The performance of classifiers can be interpreted form the ROC (receiver operating characteristic) curves. ROC curves are defined for binary classifiers and the parameters used to determine the performance include true positive rate and false positive rate (König *et al.*, 2005). True positive rate (TPR) answers the question, in this scenario, how often the classifier classifies the subject as an AD patient when classifying for AD patients. The false positive rate (FPR) displays that for classifying for healthy individuals, how often the classifier incorrectly identifies a subject as an AD patient and not a healthy subject.

Upon training the two classifiers (i.e. QDA and SVM), the following results were obtained. QDA gave an accuracy of 75.16±1.16% whereas SVM produced a more reliable accuracy of 87.00±0.95%. Overall, SVM performed much better than QDA with higher accuracy, lower FPR value and higher TPR value as seen in Table 3.

TABLE 3:

		Accuracy	ROC (FPR)	ROC (TPR)	AUC
Classifier	QDA	75.16±1.16%	0.054±0.012	0.958±0.014	0.996±0.005
	SVM	87.00±0.95%	0.024±0.012	0.964±0.012	0.996±0.005

Conclusion: EEG from both groups were acquired, processed and analyzed. Phase synchronization was chosen as a biomarker and for that GFS was used to obtain phase readings. EEG signals were acquired from exactly those parts of the brain which is hypothesized to have a greater neurodegeneration due to Alzheimer's disease which include parietal and temporal lobes along with regions of frontal cortex. Principle component analysis was done to determine the magnitude of spread of the phases along a particular axis. This technique is still a novel method, which has potential in not only determining phase synchronization in biopotentials but also outside the human anatomy.

In a nutshell, one can use this approach to set phase synchronization as a biomarker for detection of Alzheimer's disease, or can fed an EEG signals to the trained classifier to either classify the signals as healthy or affected EEG. Possible future lines of research include using other non-linear analysis techniques with large patient population from other areas to help physicians to quantize affected EEG for the early diagnosis of the Alzheimer's disease.

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