2016-08

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10.1109/embc.2016.7590869
2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)
IEEE

Changes in the EEG Amplitude as a Biomarker for Early Detection of Alzheimer's Disease

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***Abstract*— The rapid increase in the number of older people with Alzheimer's disease (AD) and other forms of dementia represents one of the major challenges to the health and social care systems. Early detection of AD makes it possible for patients to access appropriate services and to benefit from new treatments and therapies, as and when they become available. The onset of AD starts many years before the clinical symptoms become clear. A biomarker that can measure the brain changes in this period would be useful for early diagnosis of AD. Potentially, the electroencephalogram (EEG) can play a valuable role in early detection of AD. Damage in the brain due to AD leads to changes in the information processing activity of the brain and the EEG which can be quantified as a biomarker. The objective of the study reported in this paper is to develop robust EEG-based biomarkers for detecting AD in its early stages. We present a new approach to quantify the slowing of the EEG, one of the most consistent features at different stages of dementia, based on changes in the EEG amplitudes (ΔEEG_A). The new approach has sensitivity and specificity values of 100% and 88.88%, respectively, and outperformed the Lempel-Ziv Complexity (LZC) approach in discriminating between AD and normal subjects.**

Keywords: Alzheimer's disease, dementia, EEG biomarkers, early diagnosis.

I. INTRODUCTION

AD is a progressive, neurodegenerative disorder that affects cognitive brain functions [1]. The rapid increase in the number of people living with AD and other forms of dementia represents a significant challenge to our health and social care systems and to society. Currently, there are over 46.8 million individuals with dementia worldwide at an annual cost of US$818 billion, and this is projected to reach 74.7 million by 2030 with an annual cost of US$ 2 trillion [2].

Early detection of AD is important to enable patients and their families to have proper access to available health and social care [3]. It also makes it possible for patients to gain maximum benefits from new treatments and therapies, as and when they become available, to mitigate against disease progression before irreversible damage is caused to brain cells [4].

Brain changes caused by AD are believed to start 10 to 20 years before the clinical symptoms are observed [4]. There is a need for a reliable, low-cost, easy to use tool for early detection of AD. This requires a biomarker that detects brain changes due to AD in this period. Biomarkers, such as those derived from computerized tomography (CT) and magnetic resonance imaging (MRI) are useful for AD diagnosis, but neuroimaging is expensive, is available only in specialist centres, and it may not be suitable for certain patients (e.g. patients with pacemakers or certain implants [5]).

Potentially, the EEG can play a valuable role in the early detection of AD. Damage to nerve cells/pathways in the brain due to AD causes changes in the information processing activity of the brain and the EEG and this can be quantified as a biomarker [6][7]. Changes in the information processing activity of the brain are thought to be reflected in the information content of the EEG [6][7]. In AD patients, the EEG is characterized by variations in the complexity measures, mean frequency, and in the coherences between cortical regions [8]. EEG has a high temporal resolution and provides valuable information about brain dynamics in AD [9]. Many techniques exist for deriving AD biomarkers from the EEG [10]. However, time domain-based approaches are potentially one of the most reliable ways to derive robust EEG biomarkers for AD [1][6][11].

The slowing of the EEG is one of the most consistent features at different stages of dementia [11][12][13] and the extent of the slowing may be quantified as a biomarker of AD. In this study, we present a new approach to quantify the slowing of the EEG in the time domain by measuring changes in the EEG amplitudes. The changes in the amplitudes over time may be viewed as the mean velocity of the EEG [14]. The approach is easy to implement and is computationally efficient.

We used the new method to discriminate between AD and normal subjects and obtained a sensitivity and specificity values of 100% and 88.88%, respectively. We compared the performance of the new approach to the LZC method. LZC is a nonparametric, non-linear measure of complexity for finite length sequences [15]. The LZC approach produces a good biomarker for AD detection [16] and is used to analyse brain function, brain information transmission, and EEG complexity in patients with AD [17]. The new approach outperformed the LZC approach using the same datasets.

The paper is arranged as follows. In Section II, the methodology used in the study is described. In Section III, the materials (including the datasets and EEG recordings) are described. Section IV presents the results and Section V concludes the paper.

II. METHODOLOGY

In our approach, changes in the amplitudes are used as a measure of the slowing of the EEG. In particular, the sum of the differences between adjacent amplitudes of EEG values per second [14] is determined from:

$$\Delta EEG_A = \frac{\sum \Delta x}{\Delta t} \qquad (1)$$

where Δx represents the difference between adjacent amplitudes of the EEG in one second and Δt denotes the time interval:

$$\Delta x = x_{i+1} - x_i \tag{2}$$

$$\Delta t = t_{i+1} - t_i \tag{3}$$

where x_i and x_{i+1} are the current and next EEG amplitude values, respectively, and t_i and t_{i+1} represent the corresponding times i.

ΔEEG_A is first computed using Equation "(1)" for each EEG channel. The mean ΔEEG_A for the channel is then computed as,

$$M_C = (\sum_{i=1}^{N} \Delta EEG_A) / N \tag{4}$$

where M_C is the mean value of ΔEEG_A, and N is the number of samples for the EEG signal.

The process of deriving the biomarker is divided into two phases – a development phase and a testing phase. In the development phase, two reference feature vectors are created from the mean M_C values for all the EEG channels (one for normal and the other for AD groups). In the testing phase, one feature vector is created for each new subject.

The Euclidean distance measure is then used to discriminate between AD and normal subjects in the classification stage, as,

$$D_i = \sqrt{(V - V_i)^2} \tag{5}$$

where D_i is the distance between the reference feature vector (V) and the feature vector (V_i) for a new or unknown subject i.

The LZC [15][16][17][18][19] biomarker is used to assess the efficiency of the ΔEEG_A biomarker. In the LZC computation, the EEG signal is converted to a binary string as,

$$x(i) = \begin{cases} 0 & if \quad EEG(i) < M \\ 1 & if \quad EEG(i) \geq M \end{cases} \tag{5}$$

where $x(i)$ is the equivalent binary value of EEG(i), i is the index of all values in the EEG signal, and M is the median value of each EEG channel (for each EEG channel there is a median value). The median value is used to manage the outliers.

The binary string is then scanned from left to right till the end to produce new substrings. A complexity counter $c(N)$ is the number of the new substrings. The upper bound of $c(N)$ is used to normalise $c(N)$ to get an independent value from the sequence of length N. The upper bound of $c(N)$ is $N/\log_2(N)$. $c(N)$ is then normalised via $b(N)$ as,

$$C(N) = \frac{c(N)}{b(N)} \tag{6}$$

where $C(N)$ is the normalised value of the LZC, and $b(N)$ is the upper bound of the $c(N)$. The two reference feature vectors of the LZC contain the $C(N)$ for all EEG channels (one for normal, and the other for AD groups). As before, the Euclidean distance measure is used to discriminate between AD and normal subjects during classification.

III. MATERIALS

Two datasets (A and B) were obtained using a strict protocol from Derriford Hospital, Plymouth, U.K. and had been collected using normal hospital practices [11]. Dataset A consists of 3 Alzheimer's patients and 8 age-matched controls (over 65 years old) all of which have normal EEGs as confirmed by a consultant clinical neurophysiologist. Dataset B consists of 24 normal subjects and 17 probable AD, which are not perfectly age matched. In the normal groups, the mean age is 69.4±11.5 (minimum age is 40 and maximum age of 84), and 42% of the subjects are male. In the AD group, the mean age is 77.6±10.0 (minimum is 50 and maximum is 93), and 53% of the subjects are male.

Dataset A was recorded using the traditional 10-20 system in a Common Reference Montage (by using the average of all channels as the reference) and converted to Common Average and Bipolar Montages in software. Dataset B was recorded using the modified Maudsley system that is similar to the traditional 10-20 system.

In both datasets, the EEG recordings include various states such as awake, hyperventilation, drowsy and alert, with periods of eyes closed and open. The sampling rate was reduced from 256Hz to 128Hz by averaging two consecutive samples for storage reasons. Fig. 1 shows the electrode locations in 10–20 system.

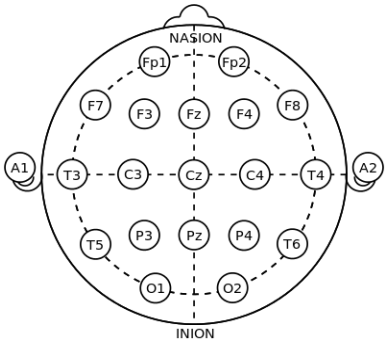

Figure 1. International 10–20 system.

IV. RESULTS AND DISCUSSIONS

Following the approach in [11], complete recordings including artefacts were used without a priori selection of elements 'suitable' for analyses. This was to enable us to have an idea about the robustness and usefulness of the method in practice. Data from a fixed interval (61s to 240s) was used to avoid electrical artefacts, which regularly occur at the beginning of a record, therefore, give a standard three minute data to analyse.

The datasets were divided into AD and normal groups. In the development phase, 39 subjects from dataset B were used (24 normal, and 15 dementia) to create the two reference vectors – one for normal group and one for AD group.

Dataset B was used to create the reference feature vectors because it is larger than dataset A. Consequently, it has more diversity and covered the most problem space.

In the testing phase, 13 subjects were used (2 dementia subjects from dataset A, 3 dementia subjects from dataset B, and 8 normal subjects from dataset B) to create a feature vector for each subject.

The p-values using t-test was computed for mean ΔEEG_A (M_c) between AD and normal groups for each of the 21 electrodes to determine the most significant channels to be used to discriminate between AD and normal groups.

The Euclidean distances between the reference feature vectors and the feature vector of a new or unknown subject is then computed.

We classified a subject as a normal if their vector was closer to the reference vector of normal group than AD. Otherwise, we classified it as AD.

In this study, 6 channels of EEG (PZ, FZ, P4, CZ, F8, and T6) are used to detect AD by calculating the values of mean ΔEEG_A for each channel for each subject. These channels were selected based on an analysis of the mean ΔEEG_A (M_c) values for all channels for AD and normal subjects as shown in Fig. 3, and Table I. The results show that the ΔEEG_A values for ADs are lower than for controls. The reduction in ΔEEG_A values is thought to be due to the slowing in the EEG as a result of AD and this is in keeping with the finding in other studies [7][20].

TABLE I. MEAN ΔEEG_A FOR AD AND NORMAL GROUPS

Seq.	Electrode	Mean ΔEEG_A for AD group	Mean ΔEEG_A for Normal group
1	Fp1	32.423	39.458
2	Fp2	30.717	39.224
3	F7	30.500	35.485
4	F3	27.508	29.255
5	FZ	12.847	27.550
6	F4	25.528	36.906
7	F8	29.014	42.259
8	A1	47.084	38.146
9	T3	41.691	36.914
10	C3	25.190	26.612
11	CZ	12.910	24.082
12	C4	18.822	29.164
13	T4	29.282	40.599
14	A2	35.003	43.115
15	T5	39.464	45.539
16	P3	26.635	34.470
17	PZ	20.170	33.909
18	P4	23.272	34.804
19	T6	34.020	45.597
20	O1	48.508	47.894
21	O2	41.767	43.528

Fig. 3 and Table II show that PZ channel (parietal lobe) has the minimum p-value, followed by FZ (frontal lobe), P4, CZ (central lobe), F8, and T6 (temporal lobe). This illustrates, the gradual slowing of brain wave activity due to AD, starts from the back of the brain (parietal lobe) towards the front (frontal lobe) and from right to the left side and this finding is consistent with the other studies [13][20][21][22][23]. In addition, occipital lobe is the last part of the brain that affected by AD.

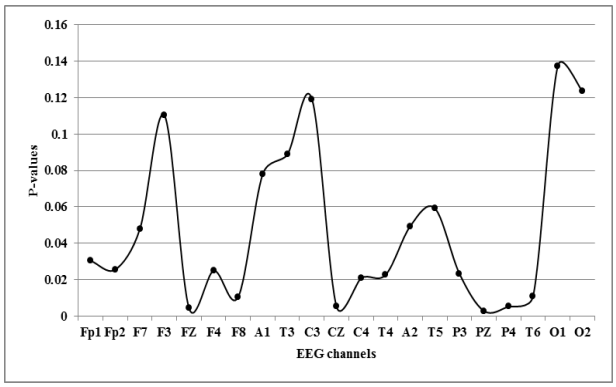

Figure 2. P-values between AD and normal groups.

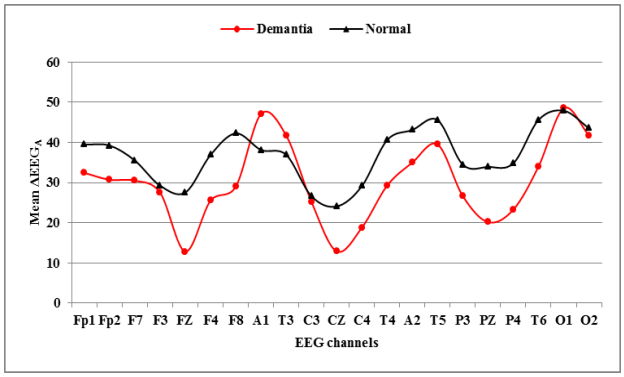

Figure 3. Demonstrates the mean ΔEEG_A for AD and normal groups.

TABLE II. P-VALUES BETWEEN AD AND HEALTHY GROUPS

Seq.	Electrodes	P-values
1	PZ	0.0194
2	FZ	0.0306
3	P4	0.0360
4	CZ	0.0364
5	F8	0.0733
6	T6	0.0764
7	C4	0.1453
8	T4	0.1586
9	P3	0.1633
10	F4	0.1742
11	Fp2	0.1784
12	Fp1	0.2119
13	F7	0.3340
14	A2	0.3454
15	T5	0.4139
16	A1	0.5457
17	T3	0.6204
18	F3	0.7709
19	C3	0.8335
20	O2	0.8649
21	O1	0.9597

The results of our study are consistent with other studies that found out that the slowing of the EEG is a marker for the subsequent rate of cognitive and functional decline in AD patients [12].

The performance of the ΔEEG_A biomarker was assessed by calculating its sensitivity, specificity, accuracy, precision and error rate. We compared the performance of the new approach with that of LZC approach. The results are summarised in Table III. It is seen that the new approach outperforms the LZC approach.

TABLE III. PERFORMANCE RESULTS OF ΔEEG_A, AND LZC APPROACHES

	ΔEEGA	**LZC**
Sensitivity	100.00 %	36.36 %
Specificity	88.8888 %	50.00 %
Accuracy	92.30 %	38.46 %
Precision	80.00 %	80.00 %
Error rate	0.0769	0.615

V. CONCLUSION

Our results suggest that changes in EEG amplitudes, ΔEEG_A is a promising biomarker for AD. As AD subjects have significantly lower ΔEEG_A values., this provides an effective way to discriminate between AD patients and control subjects. Future work will evaluate the new approach using larger EEG datasets.

ACKNOWLEDGMENT

The first author would like to thank The Ministry of Higher Education and Scientific Research (MoHESR) - Iraq for their financial support. Financial support by the EPSRC is also gratefully acknowledged.

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