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Higuchi Fractal Dimension of the Electroencephalogram as a Biomarker for Early Detection of Alzheimer's Disease

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Abstract— **It is widely accepted that early diagnosis of Alzheimer's disease (AD) makes it possible for patients to gain access to appropriate health care services and would facilitate the development of new therapies. AD starts many years before its clinical manifestations and a biomarker that provides a measure of changes in the brain in this period would be useful for early diagnosis of AD. Given the rapid increase in the number of older people suffering from AD, there is a need for an accurate, low-cost and easy to use biomarkers that could be used to detect AD in its early stages. Potentially, the electroencephalogram (EEG) can play a vital role in this but at present, no reliable EEG biomarker exists for early diagnosis of AD. The gradual slowing of brain activity caused by AD starts from the back of the brain and spreads out towards other parts. Consequently, determining the brain regions that are first affected by AD may be useful in its early diagnosis. Higuchi fractal dimension (HFD) has characteristics which make it suited to capturing region-specific neural changes due to AD. The aim of this study is to investigate the potential of HFD of the EEG as a biomarker which is associated with the brain region first affected by AD. Mean HFD value was calculated for all channels of EEG signals recorded from 52 subjects (20-AD and 32-normal). Then, p-values were calculated between the two groups (AD and normal) to detect EEG channels that have a significant association with AD. k-nearest neighbor (KNN) algorithm was used to compute the distance between AD patients and normal subjects in the classification. Our results show that AD patients have significantly lower HFD values in the parietal areas. HFD values for channels in these areas were used to discriminate between AD and normal subjects with a sensitivity and specificity values of 100% and 80%, respectively.**

Keywords: Alzheimer's disease, EEG biomarkers, Higuchi fractal dimension, early diagnosis.

I. INTRODUCTION

AD is an age-related 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 due to the aging population represents a significant challenge to health and social care systems and to society. Currently, there are over 46.8 million individuals with dementia worldwide with an annual cost of care estimated at US$818 billion. This is projected to reach 74.7 million by 2030 with an annual cost of US$ 2 trillion [2]. However, many dementia sufferers do not receive an early diagnosis. It is estimated that more than 50% of people living with dementia may not have received timely diagnosis [3]. In 2011, only 28 million people out of 36 million received a diagnosis worldwide [4].

An early detection of AD will provide an opportunity for patients to access appropriate health care services [5,6], facilitate the development of effective treatments [7], could be useful for identifying people at risk for progression to AD [8], and may slow cognitive decline [9].

AD starts many years before its clinical manifestations [10]. Reliable, accurate, low-cost, and easy to implement AD biomarkers that can be used to diagnose AD at preclinical stages could be very useful in the care for AD and may assist in the development of new treatments.

Potentially, EEG can play a vital role in the early detection of AD [5,6,7,11,12]. Damage to nerve cells/pathways in the brain due to AD causes changes in the information-processing activity of the brain. These changes are thought to be reflected in the information content of the EEG [5]. The changes can be quantified and used as a biomarker to detect the evolution of AD [13]. The utility of EEG to detect brain signal changes even in the presymptomatic stage of the disease has been demonstrated [13]. EEG is non-invasive, low-cost, has a high temporal resolution and provides valuable information about brain dynamics in AD [5,6,11]. Moreover, EEG biomarkers can be used as the first line of diagnosis to complement other more expensive approaches such as neuroimaging (e.g. MRI) [7].

The gradual slowing of brain wave activity caused by AD starts from the back of the brain and spreads out towards other parts during the preclinical stages [6,8,14,15]. Detecting the brain region that is affected first by AD may be useful in its early diagnosis. HFD is a fast computational method that can track the changes in a biosignal from a measure of its complexity [16,17] and is suited for capturing region-specific neural changes due to AD [18]. In addition, it has been shown to be an efficient method for discriminating between AD patients and normal subjects [13, 18]. Thus, HFD of the EEG is potentially a good biomarker for determining the regions of the brain that are thought to be firstly affected by AD. Smits et al [18] have used HFD for AD detection, but not to track changes in the brain due to AD or to identify those at high risk of AD.

In this study, we have used HFD to derive an EEG-based biomarker of AD which is then used to determine the region of the brain affected first by AD, and to discriminate between AD patients and normal subjects. Determining the brain regions thought to be affected first by AD based on EEG analysis may be useful in early diagnosis of AD. It may also be helpful in the development of a tool that could be used to identify people at high risk of AD. Our results show that AD patients have significantly lower mean HFD values in the parietal area. In addition, the HFD biomarker has sensitivity and specificity values of 100% and 80%, respectively, in distinguishing between AD patients and healthy subjects.

The paper is arranged as follows. In Section II, the materials (including the datasets and EEG recordings) are

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described. In Section III, the methodology used in the study is described. Section IV presents the results and Section V concludes the paper.

II. MATERIALS

This study was based on EEG data that was recorded from 52 volunteers. All the volunteers underwent a strict protocol based on normal hospital practices at Derriford Hospital, Plymouth, UK [11]. The EEG recordings include several states such as hyperventilation, awake, drowsy and alert, with periods of eyes closed and open. For storage reasons, the sampling rate was reduced from 256Hz to 128Hz by averaging two adjacent samples. The duration of each EEG signal is 4 minutes. Fig. 1 shows the channel locations using a 10–20 system.

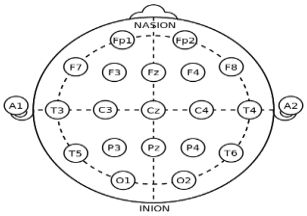

Figure 1. International 10–20 system.

The EEG dataset was divided into two sub-datasets (A and B). The sub-dataset A includes 11 age-matched subjects over 65 years old (3 AD, and 8 normal) and has normal EEGs as confirmed by a consultant clinical neurophysiologist. The sub-dataset A was recorded using the traditional 10-20 system in a Common Reference Montage by using the average of all channels as a reference and the EEG signals were converted to Common Average and Bipolar Montages using software. The sub-dataset B includes 41 subjects who were not perfectly age-matched, 24 subjects were normal (10 males and 14 females) have mean age 69.4±11.5 years (from 40 to 84 years), and 17 were probable AD patients (9 male and 8 female) have mean age 77.6±10.0 years (from 50 to 93 years). All patients were referred to the EEG department of Derriford hospital from a specialist memory clinic. A battery of psychometric tests (including the MMSE [19], Rey Auditory Verbal Learning Test [20], Benton Visual Retention Test [21], and memory recall tests [22]) was performed on all patients at the memory clinic. The classification of subjects with dementia was based on the working diagnosis provided by the specialist memory clinic. All healthy volunteers and AD patients had their EEG confirmed by a consultant clinical neurophysiologist at the hospital as normal and probable mild AD respectively [11].

III. METHODOLOGY

Fractal dimension provides a measure of the complexity of time series such as the EEG. HFD is a fast nonlinear computational method for obtaining the fractal dimension of time series signals [16,17,23] even when very few data points are available [16]. HFD provides a more accurate measure of the complexity of signals compared to other methods (e.g. Maragos and Sun, Katz and Petrosian) [16,24,25].

To compute the HFD [16,17,18] of an N-sample data sequence x(1), x(2), ..., x(N), the data set is divided into a k-length sub-data set as,

$$x_k^m : x(m), x(m+k), x(m+2k), \ldots, x\left(m+\left[\frac{N-m}{k}\right]\cdot k\right) \quad (1)$$

Where [] is Gauss' notation, k is constant, and m=1, 2, …, k.

The length $L_m(k)$ for each sub-data set is then computed as,

$$L_m(k) = \left\{ \left[\sum_{i=1}^{\left[\frac{N-m}{k}\right]} \left| x(m+ik) - x(m+(i-1)\cdot k) \right| \right] \frac{N-1}{\left[\frac{N-m}{k}\right]\cdot k} \right\} / k \quad (2)$$

The mean of $L_m(k)$ is computed to find the HFD as,

$$HFD = \frac{1}{K}\sum_{M=1}^{K} L_m(k) \quad (3)$$

The value of HFD of the EEG begins to decrease around the age of 60 years [18]. However, the reduction is more pronounced in AD patients compared to normal elderly people. HFD has been shown to be sensitive to neuronal dysfunction [26] and so may be used to identify areas of the brain that is affected first by AD. This makes it possible to use it to capture region-specific neural changes due to AD.

In our approach, the process of deriving the HFD EEG biomarker was divided into training and testing phases. In the training phase, 39 subjects were selected randomly from dataset B (15 AD, and 24 normal). Only subjects from dataset B were used in the training phase because of its larger size which meant that it has more diversity and covered most of the problem space. In the testing phase, 13 subjects were selected randomly (2 AD from dataset B, 3 AD and 8 normal from dataset A).

HFD was computed for each EEG channel. As shown in Fig. 2, the feature set of each subject was created by combining their HFD values ($HFD_{n.1}$, $HFD_{n.2}$, …, $HFD_{n.21}$) based on the channel number, where *n* is the subject's number. To construct the reference feature vector for each group (AD or normal), we computed the mean HFD values for each EEG channel as shown in Fig. 2,

$$Mean_{ch} = \frac{1}{s}\sum_{1}^{s} HFD_A \quad (4)$$

where *ch* is the channel number, and *S* is the number of subjects in each group (AD or normal).

Two feature vectors were created, one for AD, and the other for normal. Fig. 2 shows the procedure for creating the feature set for each subject, and the feature vector for each group (AD and normal).

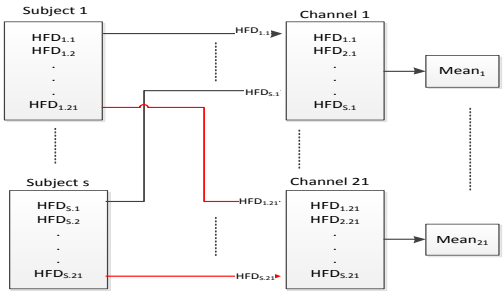

Figure 2. Creating the feature set for each subject, and the reference features vector for each group (AD and normal).

The HFD values for all 21 channels were computed in the training phase and used to construct the two feature vectors for AD and normal groups. Each feature vector includes the averaged HFD values for the all 21 EEG channels.

Fig. 3 shows a plot of HFD values for all 21 channels for all the subjects in the training dataset. These were used to create two feature vectors for AD and normal groups and to determine threshold values that separate the two groups. It can be seen from the figure that there is little or no difference in average HFD values for all 21 channels. This is because the changes in the EEG in AD are qualitatively similar to those of normal subjects [27]. It may therefore be difficult to develop a diagnosis model based on the features of all 21 channels.

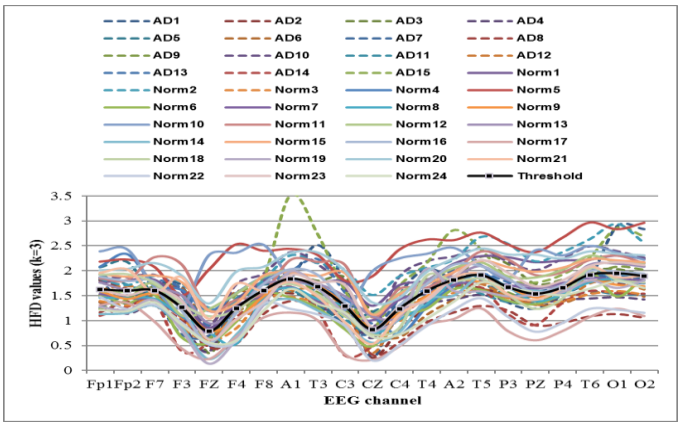

Figure 3. HFD values of the AD and normal and the threshold between them.

Fig. 4 shows the mean HFD values and the threshold values for both AD and normal groups. It can be seen that although there is significant overlap in the HFD values for some EEG channels, but not for other channels. Channels with a high separation of HFD values could be used to discriminate between AD patients and normal subjects. For example, the average HFD values for channels F3, F4 A1, C4 T4 and A2 show no discernible difference, but channels Fp1, Fp2, Fz, Cz, T5, P3, Pz, P4, T6, O1 and O2 show differences between the two groups. It may therefore be possible to discriminate between AD and normal based on the average HFD values in these channels.

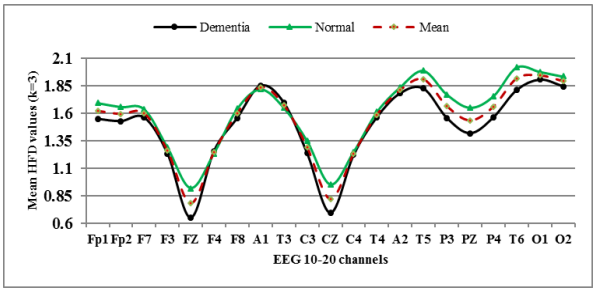

Figure 4. Mean HFD values for AD and normal groups, and the threshold between them.

Fig. 4 shows the mean HFD values of AD patients are lower than in normal subjects.

To determine the region of the brain that is affected first by AD and the most significant EEG channels that may be used to discriminate between AD patients and normal subjects, the p-values of the mean HFD values of AD patients and normal subjects for the all 21 EEG channels were analysed using t-tests. The p-value was used as a criterion to determine the best EEG channels that can be used in the classification. Table I shows the p-values between the two groups (AD and normal).

TABLE I. P-VALUES BETWEEN AD AND NORMAL GROUPS

Channel	P-values
Fz	0.028111522
Cz	0.039124719
Pz	0.059441060
P3	0.072958495
T6	0.096962212
P4	0.104595362
T5	0.163009137
Fp1	0.164677171
Fp2	0.216162653
F7	0.328010598
F8	0.351212252
C3	0.428339823
O2	0.548701678
O1	0.644081467
A2	0.666513881
F3	0.687416694
T4	0.717922825
T3	0.747577598
A1	0.828733195
C4	0.844921141
F4	0.872691805

As shown in Fig 5, the mean p-value for each lobe of the brain was computed to detect which lobe was mostly affected by AD based on HFD analysis. The results show that the parietal lobe has the minimum mean p-value compared to the other lobes of the brain as shown in Fig. 5. This is consistent with the idea that the gradual slowing of the brain wave activity caused by AD starts from the back of the brain and then spreads out to the other parts over the time [6,8,14,15]. Thus, the gradual reduction in the HFD values could be used to determine the brain regions that are thought to be affected first by AD and hence subjects at high risk of dementia.

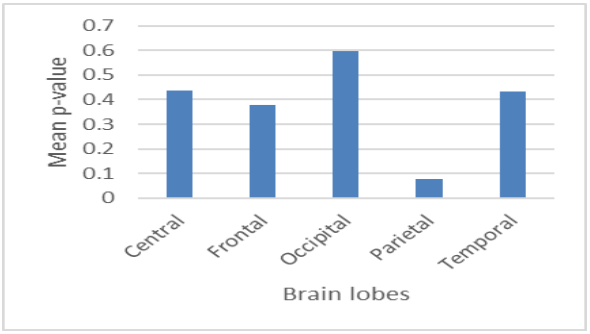

Figure 5. Mean P-values for each lobe of the brain.

Table I shows that some EEG channels have small p-values. HFD of such channels may be used to discriminate between AD patients and normal subjects. From the analysis

of HFD values channels with p-values of less than 0.1 were selected as having high discriminating power in distinguishing between AD patients and normal subjects. We were also interested in determining the minimum number of EEG channels that may be used to discriminate between AD patients and normal subject. We selected five EEG channels (Fz, Cz, P3, Pz, and T6) that satisfied the threshold for p-value as features with the potential to discriminate between the two groups. The average HFD values from the selected channels were used to design a model for AD diagnosis. The channel selection was based on the analysis of the average HFD values for all the channels for the training EEG dataset. Two reference feature vectors were created, one for AD patients and the other for normal subjects. Each reference feature vector includes the average HFD values for the selected channels.

In the testing phase, HFD values from the selected channels (Fz, Cz, P3, Pz, and T6) were computed for each unknown subject whose AD status we want to predict. The HFD values were computed in the same manner used for computing the reference vectors for the two groups of the training dataset. The k-nearest neighbor (KNN) algorithm [28,29] was used to compute the distances between the unknown feature vector extracted from an unseen EEG signal and the two reference feature vectors of AD and normal as,

$$D(w_i, w_j) = Min_{x \in w_i, x \in w_j} \|x - y\| \quad (5)$$

where D is the KNN value representing the distance between the two classes (*x* and *y)*, *i* is the indicator for a known subject (class *x*), and *j* refers to the unseen subject (class *y*). The norm ||x-y|| was calculated using the Euclidean distance measure [29,30]. The Euclidean distance was computed as,

$$E_j = \sum_{l}^{n} \sqrt{((HFD_l)_m - (HFD_l)_j)^2} \quad (6)$$

where E_j is the Euclidean distance between the extracted features for the unseen subject *j* and the reference feature vector, n is the number of channels (n=5), *m* represents the group code (AD or normal), *l* is the channel number, $(HFD_l)_m$ is the mean HFD value of the reference feature vector, and $(HFD_l)_j$ is the mean HFD value for the unseen subject *j*.

The unseen subject is classified as AD if its distance is closer to the AD reference feature vector, else it is classified as normal. The ability to discriminate between AD patients and normal subjects will depend on the proportional distance between the two reference feature vectors of AD patients and normal subjects. The minimum distance will provide the high discrimination rate.

IV. RESULTS AND DISCUSSIONS

In this study, we investigated whether HFD biomarker could be used to determine the region of the brain that is affected first by AD and to discriminate between AD patients and normal subjects. We analysed the HFD values for all EEG channels. The KNN classifier was used to discriminate between the AD patients and normal subjects.

To detect the most part of the brain that is affected due to AD, the p-values between the two groups (AD and normal) were computed. The results show the parietal lobe has the minimum mean p-value compared with the other brain's lobe. This demonstrates the gradual slowing of the brain wave activity caused by AD starts from the back of the brain and then spreads out to the other parts over the time. We can conclude the gradual reduction in the HFD values that could be used to determine the brain regions that are thought to be firstly affected by AD and then may be used to detect the subjects at high risk of dementia.

We selected 5 EEG channels (Fz, Cz, P3, Pz, and T6) to discriminate between AD patients and normal subjects by analysing the mean HFD values for all EEG channels. As shown in Table I, these 5 channels have the minimum p-values (between 0.09 and 0.02).

AD patients can be characterised by the slowing of the brain activity [6]. This slowing is reflected in the EEG signal. The results show that the mean HFD values of AD patients are lower than in normal subjects as shown in Fig 3. The reduction in HFD 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 [5,18,31]. The results of our study are consistent with other studies that found that the slowing of the EEG is a marker for the subsequent rate of cognitive and functional decline in AD patients [5,6,32].

The performance of the HFD biomarker was assessed by calculating its sensitivity, specificity, accuracy, precision, error rate as shown in Table II.

TABLE II. PERFORMANCE RESULTS OF HFD BIOMARKER

Sensitivity	100.00 %
Specificity	80.00 %
Accuracy	84.615 %
F-measure	75.00 %
Error rate	0.1538

Matthew's correlation coefficient (MCC) was computed to measure the quality of the binary classification (AD and normal) in machine learning between the actual and predicted results [33,34]. The MCC of the HFD was 0.6928.

The main advantage of a diagnostic test is to utilise it in the diagnosis. Sensitivity and specificity did not provide clinicians with the probability of the disease in a patient. While the probability of the test provides that and this may help to diagnose successfully. Therefore, there is a need to direct the diagnostic test towards the predictive values. The predictive values of the test rely on the prevalence of the abnormality in the patients being tested (the prevalence can be defined as the probability before the test is performed that a subject has the diseases). The ratio of these probabilities represents the likelihood ratio (LR). LR can be used to estimate the probability of diagnosis by combining the sensitivity and specificity in one measurement to produce that probability [35,36]. The LR provides the advantage of the applied model that was used in the testing [37], the decision can be used to compute the probability of abnormality from other different probabilities [38], and LR points the usefulness of the test for raising certainty about the success of the diagnosis [35]. The LR+ and LR- for HFD were 3.6670 and 0, respectively. A high FPR and FNR will minimize the diagnostic performance of the system [39]. FPR and FNR are 0.272, and 0 for HFD. The positive and negative predictive

values (PPV, NPV) are the purified estimates of the same probability of subjects to give the correct diagnosis [35,36]. The PPV, and NPV for HFD were 0.6000, and 1.0, respectively.

V. Conclusion

Our results suggest that HFD biomarker is a promising biomarker that captures the regions of the brain thought to be affected first by AD in its early stages and could be used to detect subjects at high risk of dementia. As AD subjects have significantly lower HFD values, this provides an effective way to discriminate between AD patients and normal subjects. Potentially, the slowing of the EEG is a marker for the subsequent rate of cognitive and functional decline in AD patients. Future work will evaluate the HFD biomarker using larger EEG datasets.

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References

[1] E. C. Ifeachor *et al.*, "Biopattern analysis and subject-specific diagnosis and care of dementia," in Engineering in Medicine and Biology Society, 2005. IEEE-EMBS 2005. 27th Annual Int. Conf. of the, 2006, pp. 2490–2493.

[2] M. Prince *et al.*, "World Alzheimer Report," 2015.

[3] E. Jammeh et al., "Using NHS primary care data to identify undiagnosed dementia," J. Neurol. Neurosurg. Psychiatry, vol. 86, no. 11, pp. e4–e4, 2015.

[4] M. Prince *et al*., World Alzheimer Report 2011: The benefits of early diagnosis and intervention. Alzheimer's Disease International, 2011.

[5] A. H. Al-nuaimi *et al.*, "Tsallis entropy as a biomarker for detection of Alzheimer's disease," in Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual Int. Conf. of the IEEE, 2015, pp. 4166–4169.

[6] A. H. Al-nuaimi *et al.*, "Changes in the EEG amplitude as a biomarker for early detection of Alzheimer's disease," in Engineering in Medicine and Biology Society (EMBC), 2016 IEEE 38th Annual Int. Conf. of the, 2016, pp. 993–996.

[7] D. Ferreira *et al.*, "Electroencephalography is a good complement to currently established dementia biomarkers," Dement. Geriatr. Cogn. Disord., vol. 42, no. 1–2, pp. 80–92, 2016.

[8] D. V Moretti, "Theta and alpha EEG frequency interplay in subjects with mild cognitive impairment: evidence from EEG, MRI, and SPECT brain modifications," Front. Aging Neuro., vol.7, p.31, 2015.

[9] R. A. Sperling *et al.*, "Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Inst. on Aging-Alzheimer's Asso. workgroups on diagnostic guidelines for AD," Alzheimer's Dement., vol.7, no.3, pp.280–292, 2011.

[10] A. L. Sutton., Ed., Alzheimer Disease Sourcebook, Fifth edit. Detroit: Omnigraphics: Peter E. Ruffner, 2011.

[11] G. Henderson *et al.*, "Development and assessment of methods for detecting dementia using the human electroencephalogram," IEEE Trans. Biomed. Eng., vol. 53, no. 8, pp. 1557–1568, 2006.

[12] D. V. Moretti, "electroencephalography-driven approach to prodromal Alzheimer's disease diagnosis: from biomarker integration to network-level comprehension," Clin. Interv. Aging, vol. 11, p. 897, 2016.

[13] B. Dubois *et al.*, "Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria," Alzheimer's Dement., vol. 12, no. 3, pp. 292–323, 2016.

[14] C. Babiloni *et al.*, "Directionality of EEG synchronization in Alzheimer's disease subjects," Neurobiol. Aging, vol. 30, no. 1, pp. 93–102, 2009.

[15] U. A. Khan *et al.*, "Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer's disease," Nat. Neurosci., vol. 17, no. 2, pp. 304–311, 2014.

[16] A. Accardo *et al.*, "Use of the fractal dimension for the analysis of electroencephalographic time series," Biol. Cybern., vol. 77, no. 5, pp. 339–350, 1997.

[17] H. Preißl *et al.*,"Fractal dimensions of short EEG time series in humans," Neurosci. Lett., vol. 225, no. 2, pp. 77–80, 1997.

[18] F. M. Smits *et al.*, "Electroencephalographic fractal dimension in healthy ageing and Alzheimer's disease," PLoS One, vol. 11, no. 2, p. e0149587, 2016.

[19] M. F. Folstein *et al.*, "'Mini-mental state': a practical method for grading the cognitive state of patients for the clinician," J. Psychiatr. Res., vol. 12, no. 3, pp. 189–198, 1975.

[20] E. S. O. Spreen, A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary, 2nd ed. Oxford University Press, Inc, February 1998, ISBN 0-19-510019-0.

[21] A. L. Benton, "Revised Visual Retention Test: Clinical and Experimental Applications Psychological Corporation," New York, 1974.

[22] G. A. Talland and M. Ekdahl, "Psychological studies of Korsakoff's psychosis: IV. The rate and mode of forgetting narrative material.," J. Nerv. Ment. Dis., vol. 129, no. 4, pp. 391–404, 1959.

[23] T. Higuchi, "Approach to an irregular time series on the basis of the fractal theory," Phys. D Nonlinear Phenom., vol. 31, no. 2, pp. 277–283, 1988.

[24] R. Esteller *et al.*, "A comparison of fractal dimension algorithms using synthetic and experimental data," in Circuits and Systems, 1999. ISCAS'99. Proc. 1999 IEEE Int. Symp. on, 1999, vol. 3, pp. 199–202.

[25] C. Gómez *et al.*, "Use of the Higuchi's fractal dimension for the analysis of MEG recordings from Alzheimer's disease patients," Med. Eng. Phys., vol. 31, no. 3, pp. 306–313, 2009.

[26] F. Zappasodi *et al.*, "Fractal dimension of EEG activity senses neuronal impairment in acute stroke," PLoS One, v.9, no.6, p. e100199, 2014.

[27] G. W. Fenton, "Electrophysiology of Alzheimer's disease," Br. Med. Bull., vol. 42, no. 1, pp. 29–33, 1986.

[28] J. P. M. De Sa, Pattern recognition: concepts, methods and applications. Springer Science & Business Media, 2012.

[29] A. N. Papadopoulos, Nearest Neighbor Search:: A Database Perspective. Springer Science & Business Media, 2006.

[30] D. Michie, D. J. Spiegelhalter, and C. C. Taylor, "Machine learning, neural and statistical classification," 1994.

[31] D. Abásolo *et al.*, "Analysis of regularity in the EEG background activity of Alzheimer's disease patients with Approximate Entropy," Clin. Neurophysiol., vol. 116, no. 8, pp. 1826–1834, 2005.

[32] J. Jeong, "EEG dynamics in patients with Alzheimer's disease," Clin. Neurophysiol., vol. 115, no. 7, pp. 1490–1505, 2004.

[33] S. Raschka, "An Overview of General Performance Metrics of Binary Classifier Systems," arXiv Prepr. arXiv1410.5330, 2014.

[34] DM Powers, "Evaluation: from precision, recall and F-factor to ROC, informedness. markedness correlation". Technical report, School of Informatics and Engineering, Flinders University, Australia; 2007

[35] D. G. Altman and J. M. Bland, "Statistics Notes: Diagnostic tests 2: predictive values," Bmj, vol. 309, no. 6947, p. 102, 1994.

[36] A. K. Akobeng, "Understanding diagnostic tests 1: sensitivity, specificity and predictive values," Acta Paediatr., vol. 96, no. 3, pp. 338–341, 2007.

[37] A. G. Lalkhen and A. McCluskey, "Clinical tests: sensitivity and specificity," Contin. Educ. anaesthesia, Crit. care pain, vol. 8, no. 6, pp. 221–223, 2008.

[38] J. J. Deeks and D. G. Altman, "Diagnostic tests 4: likelihood ratios," Bmj, vol. 329, no. 7458, pp. 168–169, 2004.

[39] J. P. A. Ioannidis, R. Tarone, and J. K. McLaughlin, "The false-positive to false-negative ratio in epidemiologic studies," Epidemiology, vol. 22, no. 4, pp. 450–456, 2011.