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Electroencephalogram Based Biomarkers for Detection of Alzheimer's Disease

Ali H. Hussein Al-Nuaimi, Shaymaa Al-Juboori, Emmanuel Jammeh, Lingfen Sun and Emmanuel Ifeakor

Abstract

Alzheimer's disease (AD) is an age-related progressive and neurodegenerative disorder, which is characterized by loss of memory and cognitive decline. It is the main cause of disability among older people. The rapid increase in the number of people living with AD and other forms of dementia due to the aging population represents a major challenge to health and social care systems worldwide. Degeneration of brain cells due to AD starts many years before the clinical manifestations become clear. Early diagnosis of AD will contribute to the development of effective treatments that could slow, stop, or prevent significant cognitive decline. Consequently, early diagnosis of AD may also be valuable in detecting patients with dementia who have not obtained a formal early diagnosis, and this may provide them with a chance to access suitable healthcare facilities. An early diagnosis biomarker capable of measuring brain cell degeneration due to AD would be valuable. Potentially, electroencephalogram (EEG) can play a valuable role in the early diagnosis of AD. EEG is noninvasive and low cost, and provides valuable information about brain dynamics in AD. Thus, EEG-based biomarkers may be used as a first-line decision-support tool in AD diagnosis and could complement other AD biomarkers.

Keywords: EEG biomarkers, AD biomarkers, slowing of EEG, decrease in EEG coherence, reduction in EEG complexity, detection of Alzheimer's disease

1. Introduction

Alzheimer's disease (AD) is an age-related progressive neurodegenerative disorder characterized by cognitive impairment and memory loss [1, 2] and is the leading cause of elderly disability [3]. AD is categorized as the sixth major cause of death in the United States among older people [4]. Due to the aging population, the fast growth in the number of individuals living with AD and other kinds of dementia is a major challenge for health and social care systems around the world [5]. There are currently more than 46.8 million people with dementia around the world with an annual care cost estimated at US\$ 818 billion and an annual cost of US\$ 2 trillion is projected to reach 74.7 million by 2030 [6]. It is estimated that by 2050 the number of people with dementia around the world will exceed 131 million, which will have

an enormous financial. However, many dementia sufferers are not diagnosed early [7, 8]. It is estimated that up to 50% of individuals with dementia may not have been diagnosed formally [8, 9]. In 2011, 28 million people out of 36 million people with dementia were not diagnosed worldwide [10].

Degeneration of brain cells due to AD begins many years before clinical manifestations become noticeable [5, 11–15]. Early diagnosis of AD will help to the development of efficient treatments that could mitigate, stop, or prevent significant cognitive impairment [14, 16, 17]. Early diagnosis of AD may also be valuable in detecting patients with dementia who have not obtained a formal early diagnosis, and this may provide them with a chance to access suitable healthcare facilities [18–20].

An early diagnosis biomarker that can measure brain cell degeneration due to AD would be valuable [2, 21–23]. But this may involve dealing with an extremely large number of individuals, as up to 50% of individuals with dementia may not have been diagnosed formally. Therefore, Simple, non-invasive, low-cost and reliable biomarkers are necessary for early diagnosis that can be accessed in clinical practice [5, 24, 25]. Recent guidelines support the use of biomarkers for biochemical and neuroimaging to promote AD diagnosis. AD testing of cerebral spinal fluid (CSF) is not commonly used in clinical practice as it involves lumbar puncture, an invasive procedure [2, 26, 27]. Neuroimaging is expensive, accessible only in specialized centers [28], and may not be appropriate for patients with pacemakers or certain implants [29]. Blood-based biomarkers have shown promising results in the diagnosis of AD but are not yet fully developed and there are currently no low-cost biosensors available for the detection of AD biomarkers in the blood [2, 24, 30].

EEG can play a potential role in early diagnosis of AD [11, 19, 20, 23, 31–33] EEG is non-invasive, low-cost, has a high temporal resolution, and provides valuable information about brain dynamics in AD [19, 20, 32, 34, 35]. The essential utility of EEG in detecting brain signal changes has been proved even at the preclinical stage of the disease [32, 36, 37]. EEG biomarkers can, therefore, be used in the diagnosis of AD as a first-line decision support tool [11, 34] and could supplement other AD biomarkers [25].

As a consequence of brain cell damage that affects brain activity, AD is characterized by memory loss and cognitive impairment [37]. AD leads changes in EEG characteristics [34, 37, 38] and EEG analysis may provide useful information about brain dynamics caused by AD [19, 20, 32, 34]. The most characteristic features in EEG caused by AD are slowing of EEG, a decrease in EEG coherence, and reduction in EEG complexity [32–34, 36–39]. These changes in the EEG can be quantified as a biomarker of AD. In order to quantify EEG changes as AD biomarkers, a range of linear and nonlinear techniques are being developed [40, 41]. AD biomarkers based on EEG slowing and reducing EEG coherence are often produced using linear methods of analysis (i.e. EEG signal spectral analysis) [36, 42, 43]. While biomarkers derived from the EEG complexity analysis are based on non-linear methods (e.g. entropy methods, fractal dimension, and Lempel-Ziv complexity) [44–47].

This chapter describes research into the development of EEG biomarkers that detect AD based on analysis of changes in the EEG. These changes can be quantified as a biomarker of AD. The most characteristic features in EEG caused by AD are slowing of EEG, a decrease in EEG coherence, and reduction in EEG complexity were reviewed in this chapter.

The chapter is arranged as follows. In Section 2, the EEG characteristic features of AD detection. In Section 3, the discussions are presented and the conclusions are presented in Section 4.

2. EEG characteristic features of AD detection

The most characteristic features evident in an EEG that detects AD are slowing of the EEG, a reduction in EEG complexity, and a decrease in EEG coherence [32, 34, 36–39]. These changes can thus be quantified as biomarkers of AD. EEG based biomarkers can therefore be divided into three main categories: the slowing of the EEG, reduction in complexity, and a decrease in the coherence between cortical regions [32–34, 36–39, 48]. The slowing of the EEG and reduction in complexity were reviewed in this chapter.

2.1 Reduction in EEG complexity

Approaches to EEG complexity showed promising results in the diagnosis of AD [11, 34, 49] and seemed suitable for the diagnosis of AD [37, 50, 51]. Complexity is a measure of how random the dynamic behavior of a particular sequence is [52]. The cortical regions of the brain are spontaneously fired, and this dynamic behavior is complex [53, 54]. AD causes a reduction in the neuronal activity of the brain [55] resulting in a decreased ability to process information [56–58] which may be reflected in EEG signals [55]. Several studies have investigated EEG complexity as a potential AD biomarker using whole EEG record with the objective of achieving a high performance. Given the association of EEG activities (e.g., alpha, delta activities) with AD, Al-nuaimi et al. [49] they proved that the derivation of EEG complexity based on EEG activities should lead to enhanced performance. This reduction can be measured using different methods e.g., Tsallis entropy (TsEn) [34, 59, 60], Higuchi Fractal Dimension (HFD) [61], and Lempel Ziv Complexity (LZC) [41, 47]. Consequently, EEG complexity can potentially be a good biomarker for AD diagnosis [37] as AD patients exhibit a significant reduction in EEG complexity [37–39, 48, 55, 62, 63].

In particular, TsEn approach has been shown to be one of the most promising information-theoretic methods for quantifying EEG complexity [34, 59, 60, 64, 65]. It has also been shown to be a reliable analysis tool to use with working memory tasks. Its capacity for rapid computation may serve as the basis for real-time decision support tools for diagnosing AD [34, 59, 65–67]. Sneddon et al. [68] analyzed EEG TsEn and found that it was capable of detecting mild dementia due to AD with 88% for sensitivity and 94% for specificity. De Bock et al. [60] concluded that EEG TsEn was an extremely promising potential diagnostic tool for mild cognitive impairment (MCI) and early dementia with 82% for sensitivity and 73% for specificity. Al-Nuaimi et al. [34] discriminated AD patients with a sensitivity and specificity of 85.8 and 70.9% respectively from normal subjects using the TsEn method. Garn et al. [69] investigated the use of TsEn for the diagnosis of AD on the basis of an EEG analysis and obtained p -value < 0.0036 for T7 and T8 channels for discrimination between AD patients and normal subjects.

HFD is a fast computing approach to obtain the fractal dimension of time series signals [70–72] even though there are very few data points available [70]. It can track changes in a biosignal from measuring its complexity [70, 71] and is appropriate for capturing region-specific neural changes due to AD [43, 72]. Furthermore, HFD offers a precise measure of the complexity of the signal compared to other methods [44, 70, 73] and has been shown to be an effective approach to discriminate between AD patients and normal subjects [30, 61]. HFD of the EEG is potentially a useful biomarker of AD diagnosis as it is significantly smaller in AD patients than in normal subjects [49, 61, 74]. Smits et al. [61] discovered that HFD

is sensitive to neural changes selectively related in patients with AD and normal subjects. Al-nuaimi et al. [49] analyzed HFD of EEG for AD detection and discovered that HFD is a promising EEG biomarker that captures changes in brain areas thought to be first affected by AD and could be used to identify AD with sensitivity and specificity values of 100 and 80% respectively.

LZC is a nonparametric and nonlinear method that provides a powerful method for quantifying the complexity of finite length sequences [75, 76]. It has previously been used to analyze EEG complexity in patients with AD [41, 77]. The reduction of LZC values may therefore be a good biomarker for AD [41, 77, 78]. It is a simple and powerful approach used in a number of biomedical applications [76]. LZC relies on coarse-grain measurement processing [77], and can be directly applied to the physiological signal without pre-processing [78]. LZC has been extensively used to measure the complexity of discrete-time physiological signals in the analysis of biomedical signals (e.g. EEG) [75]. It is also used in patients with AD to analyze brain function, transmission of brain information, and EEG complexity in patients with AD [41]. The LZC method produces a good biomarker for AD detection [78, 79]. Using LZC in AD patients, Hornero et al. [80] analyzed EEG and magnetoencephalogram (MEG). They discovered that LZC provides a useful insight into the EEG background activity features and the changes related to AD. Hornero et al. [81] discovered that LZC values were smaller in AD patients and proposed that the most significant differences were in the posterior region. In addition, they proposed that a reduced degree of irregularity and complexity characterize the MEG activity of AD patients and that LZC measurements can be used to identify AD patients with a sensitivity and specificity of 65 and 76.2% respectively. McBride et al. [62] investigated the complexity of EEG based on LZC approach for discriminating between patients with early cognitive impairment (MCI), AD patients and normal subjects. They discovered EEG complexity characteristics to provide promising results in discriminating between MCI, AD, and normal subjects for particular EEG frequency bands with regional electrical activity. The complexity of MEG in MCI patients, AD patients and normal subjects was investigated by Fernandez et al. [82] based on the LZC approach of discriminating between the three groups. They discovered that they could differentiate between AD patients and MCI patients with 94.4% for sensitivity and specificity by combining age and posterior LZC scores.

2.2 Slowing of EEG

The slowing of the EEG is one of the most consistent features relating to the detection of AD. Slowing may therefore be quantified as a biomarker of AD [11, 37, 83]. It can be measured in several ways such as changes in EEG amplitude (ΔEEG_A), zero-crossing intervals (ZCI) [11], and changes in the power spectrum (ΔPS) of the EEG signal [11, 32, 33, 37, 39, 84–91]. Al-nuaimi et al. [5] quantified slowing in EEG by measuring the ΔEEG_A . Their results showed that ΔEEG_A is a promising nonlinear EEG marker in the time domain. It can be measured through changes in EEG amplitude and can track changes in the EEG over time [5]. Their results showed that a gradual change in EEG amplitude is a marker for the subsequent rate of cognitive and functional decline in AD patients [5]. The reduction of ZCI of an EEG signal has also been shown to be a promising biomarker of AD [11, 74]. The slowing of the EEG can also be quantified by the power of the EEG signal in different frequency bands (i.e., delta, theta, alpha, beta, and gamma) where slowing is manifest in a decrease in power of high-frequency bands (alpha and beta) and an increase in power of low-frequency bands (delta and theta). These changes can be used to distinguish AD patients from those with other types of dementia [11, 32, 33, 37, 39].

An increase in the power ratio of the alpha/middle alpha bands is an indicator of mild cognitive impairment (MCI) in people who may go on to develop AD [87]. Conversely, an increase in the power ratio of theta/gamma bands has been associated with MCI patients who may not develop AD [92]. This increase was related to a decline in memory and can therefore be used to identify MCI patients in a cohort of normal people [36]. Numerous studies have shown that power changes in the EEG frequency bands are promising markers of AD [84–91].

2.3 Reduction in EEG coherence

AD causes changes in the cortical activity of the brain [93] which impacts the connectivity among cortical regions of the brain [37], which can be reflected in the EEG coherence. EEG coherence can be quantified by assessing the functional coupling between brain regions [37, 94]. Coherence measures depend on channel location and the frequency bands of the EEG signal [93, 95–98]. Studies have shown that AD patients have a significant reduction in the coherence in the alpha band especially in the temporo-parieto-occipital regions and an increase in the coherence in the delta band [93]. Furthermore, AD patients have a significant increase in the high beta band and a decrease in the delta band [99]. AD patients have also a reduction in both the left temporal alpha band and interhemispheric theta band compared to normal [97]. In addition, a positive association has been shown in EEG coherence in the frontal region for delta and beta bands [96]. The EEG coherence has been shown to be a sensitive and selective method for assessing the integrity of structural connections between brain areas in AD patients [98].

3. Discussions

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. Therefore, each analysis technique of EEG signal may capture a different characteristic e.g., complexity, slowing, and coherence of the EEG signal. However, for each technique, there are different analysis methods and each method may measure a different feature that related to cognitive decline in the brain due to AD. Therefore, each method has a different performance. High-performance result referring the used techniques and biomarkers were accurate enough, this provides an indicator for using them in the future studies, and may also be possible to test the candidate biomarkers and techniques in regular health checkup performed by clinicians.

Unlike previous researches, Al-Nuaimi et al. [48], concluded that the complexity measures extracted from the EEG frequency bands (i.e. delta, theta, alpha, beta, and gamma) provide significantly better efficiency in the detection of AD than those extracted from the entire EEG record. This is due to the significant differences between the complexity measurements for AD patients and normal subjects when extracted from the frequency bands compared to the entire record, which is the desirable property of a good biomarker. In particular, they discovered that the best performance was provided by the complexity measurements extracted from the delta and gamma bands for TsEn and HFD. Three EEG channels (T4, O1, and O2) have provided the best performance for the delta band. While F4 has provided the best performance for the theta band.

Similar results for the LZC's complexity measures were achieved, except that C3 was the best EEG channel for the theta band. This is consistent with the results of

other researches proposing that AD starts at the back of the brain and then gradually extends to other areas of the brain [5, 49, 83, 100, 101]. This means that AD can be detected using only a small number of EEG channels.

Their results suggest that the three EEG complexity measures, derived from the EEG frequency bands, can detect AD reliably (with sensitivity and specificity of >90%). Thus, EEG complexity measures could provide a basis for developing an accurate, low-cost and easy use tool to detect AD.

They found that AD patients have significantly lower complexity measures for specific EEG frequency bands and for specific EEG channels than normal subjects. This is consistent with findings of in previous studies [32–34, 36–39]. Thus, specific EEG channels and specific frequency bands can be identified which can provide the best biomarkers for the detection of AD. This can be used to achieve good performance in situations where the number of channels available is limited (e.g. when portable EEG systems are used outside specialist centers).

Al-nuaimi et al. [5] developed a new approach for detecting AD based on analyzing changes in EEG amplitude (ΔEEG_A). Their results suggested that 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 normal subjects. 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 [102].

The findings of their studies have a number of implications for research to develop new and robust techniques for the analysis of EEG to increase the contributions EEG makes to the diagnosis of AD.

Several biomarkers were developed for AD diagnosis. However, some of these studies investigated the rationality of combining multiple biomarkers in one diagnostic index [2, 103–105]. Poil et al. [104] investigated the performance of six EEG based biomarkers separately and they combined them in one diagnostic model. They found, combining multiple biomarkers could be more sensitive for early diagnosis of AD. Polikar et al. [106] combined EEG, MRI and PET biomarkers. They suggested the combination of different biomarkers could improve the diagnostic accuracy over any of the individual data sources. Walhovd et al. [107] found combining MR and CSF biomarkers can improve diagnostic classification of AD. Consequently, combining multiple biomarkers from different analysis methods in one diagnostic index may assist to increase the diagnostic performance.

AD is the most common form of dementia and many dementia sufferers do not receive an early diagnosis. Currently, no specific device is available to diagnose AD. Therefore, developing new biomarkers or combining multiple biomarkers to produce a new biomarker with high performance may contribute to the development of robust diagnosis methods that can be used to develop a new specific application for AD diagnosis in its early stages. Furthermore, early diagnosis of AD will contribute to the development of effective treatments that could slow, stop or prevent significant cognitive decline.

4. Conclusions

AD causes changes in the EEG due to memory loss and cognitive impairment, and these changes are thought to be associated with functional disconnections between cortical regions caused by brain cell death [37]. EEG assessment can, therefore, provide useful information on brain dynamics in AD. AD causes a decrease in brain neuronal activity that can be reflected in EEG signals. Non-linear

approaches based on EEG complexity methods showed promising results in the detected EEG changes that were thought to be due to AD [5, 34, 48, 49].

EEG based biomarkers can be used as the first line of decision making because these biomarkers are non-invasive, and low cost compared to others e.g., CSF, MRI or PET. However, EEG based biomarkers can complement other biomarkers [25, 106, 108].

EEG based biomarkers to detect AD have some limitations such as the size of samples were used in each study. Most of the EEG studies used a data sized between 10 and 100 of samples [109], unlike the MRI biomarkers, have thousands of samples available with free access as shown in ADNI dataset [4]. Most of the used EEG samples are cross-section, not a longitudinal dataset, and not free access to EEG datasets of AD. To overcome those limitations, longitudinal EEG dataset of AD may assist to track the dynamic changes in the brain which caused by AD, a large number of EEG sample may help to add more reality to the results, and free access to EEG dataset of AD will minimize the burden that researchers spent in collecting the dataset.

In this study, we reviewed an important class of complexity measures, information-theoretic methods, which offers a potentially powerful approach for quantifying changes in the EEG due to AD [59]. Information-theoretic methods have emerged as a potentially useful complexity-based approach to derive robust EEG biomarkers of AD [50, 59, 60, 65, 110, 111]. They are attractive due to the potential natural connection between biomarkers based on information theory and brain changes induced by AD [59]. Conceptually, information-processing activities in the brain are considered to be reflected in the information content of the EEG.

As a result, EEG complexity can potentially be a useful biomarker for the diagnosis of AD. We examined the three complexity measures approached by TsEn, HFD, and LZC extracted from the EEG frequency bands. TsEn, HFD, and LZC values in AD patients were found to be significantly lower in AD patients than in normal subjects for specific EEG frequency bands and specific EEG channels.

This study demonstrates that the complexity measures can detect the abnormalities induced by AD. However, other neurodegenerative diseases, such as other kinds of dementia, may cause similar changes. To improve the diagnostic usefulness of the methods, further development may be necessary to distinguish between dementias.

The slowing of the EEG was also reviewed. It is one of the most consistent features relating to the detection of AD. The slowing of EEG may therefore be quantified as a biomarker of AD [11, 37, 83].

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Author details


Ali H. Hussein Al-Nuaimi^{1*}, Shaymaa Al-Juboori², Emmanuel Jammeh²,
Lingfen Sun² and Emmanuel Ifeakor²

1 College of Education for Pure Science (Ibn Al-Haitham), University of Baghdad,
Baghdad, Iraq

2 School of Engineering, Computing and Mathematics, Faculty of Science and
Engineering, University of Plymouth, Plymouth, United Kingdom

*Address all correspondence to: ali.al-nuaimi@plymouth.ac.uk

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References

- [1] Harmony T, Fernández T, Gersenowies J, Galán L, Fernández-Bouzas A, Aubert E, et al. Specific EEG frequencies signal general common cognitive processes as well as specific task processes in man. *International Journal of Psychophysiology*. 2004;**53**(3):207-216
- [2] Humpel C. Identifying and validating biomarkers for Alzheimer's disease. *Trends in Biotechnology*. 2011;**29**(1):26-32
- [3] World Health Organization. WHO Mental Health Gap Action Programme (mhGAP) 2008. 2014
- [4] ADNI, Alzheimer's Disease Neuroimaging Initiative [Internet]. Available from: <http://www.adni-info.org/Home.html>
- [5] Al-nuaimi AH, Jammeh E, Sun L, Ifeachor E. 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 International Conference of the IEEE*. 2016. pp. 993-996
- [6] Prince M, Anders W, Maëlen G, Ali G-C, Yu-Tzu W, Matthew P. World Alzheimer Report [Internet]. 2015. Available from: <https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf>
- [7] Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M. World Alzheimer Report 2016 Improving Healthcare for People Living with Dementia. Coverage, Quality and Costs Now and in the Future 2016. pp. 1-140. Available from: <https://www.alz.co.uk/research/world-report-2016>
- [8] Jammeh E, Carroll C, Pearson S, Escudero J, Anastasiou A, Zajicek J, et al. Using NHS primary care data to identify undiagnosed dementia. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2015;**86**(11):e4-e4
- [9] Michalowsky B, Eichler T, Thyrian JR, Hertel J, Wucherer D, Hoffmann W, et al. Healthcare resource utilization and cost in dementia: Are there differences between patients screened positive for dementia with and those without a formal diagnosis of dementia in primary care in Germany? *International Psychogeriatrics*. 2016;**28**(03):359-369
- [10] Prince M, Bryce R, Ferri C. World Alzheimer Report 2011: The Benefits of Early Diagnosis and Intervention. Alzheimer's Disease International; 2011
- [11] Henderson G, Ifeachor E, Hudson N, Goh C, Outram N, Wimalaratna S, et al. Development and assessment of methods for detecting dementia using the human electroencephalogram. *IEEE Transactions on Biomedical Engineering*. 2006;**53**(8):1557-1568
- [12] AL S, editor. *Alzheimer Disease Sourcebook*. 5th ed. Detroit, Omnigraphics: Peter E. Ruffner; 2011
- [13] Galimberti D, Scarpani E, editors. *Biomarkers for Early Diagnosis of Alzheimer's Disease*. Galimberti: Nova Biomedical Books; 2008
- [14] Association A. 2016 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*. 2017;**12**(4):459-509
- [15] Jellinger KA, Janetzky B, Attems J, Kienzl E. Biomarkers for early diagnosis of Alzheimer disease: 'Alzheimer Associated gene'—a new blood biomarker? *Journal of Cellular and Molecular Medicine*. 2008;**12**(4):1094-1117
- [16] Ritchie K, Lovestone S. The dementias. *The Lancet*. 2002;**360**(9347):1759-1766

- [17] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*. 2011;7(3):280-292
- [18] Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences*. 2003;100(1):253-258
- [19] Gevins A, Smith ME, McEvoy L, Yu D. High-resolution EEG mapping of cortical activation related to working memory: Effects of task difficulty, type of processing, and practice. *Cerebral Cortex*. 1997;7(4):374-385
- [20] Sasaki K, Nambu A, Tsujimoto T, Matsuzaki R, Kyuhou S, Gemba H. Studies on integrative functions of the human frontal association cortex with MEG. *Cognitive Brain Research*. 1996;5(1):165-174
- [21] Abeel T, Helleputte T, Van de Peer Y, Dupont P, Saeys Y. Robust biomarker identification for cancer diagnosis with ensemble feature selection methods. *Bioinformatics*. 2010;26(3):392-398
- [22] Boucheham A, Batouche M. Robust biomarker discovery for cancer diagnosis based on meta-ensemble feature selection. In: *Science and Information Conference (SAI)*, 2014. IEEE. 2014. pp. 452-560
- [23] Al-nuaimi AH, Jammeh E, Sun L, Ifeachor E. Changes in the electroencephalogram as a biomarker of Alzheimer's disease. In: *Biosense Dementia 2017 – International Workshop on Biosensors for Dementia from 13 – 14 June 2017 – Plymouth University*. Plymouth, UK: International Workshop on Biosensors for Dementia; 2017. p. 40. Available from: <https://www.plymouth.ac.uk/whats-on/biosense-dementia>
- [24] Cedazo-Minguez A, Winblad B. Biomarkers for Alzheimer's disease and other forms of dementia: Clinical needs, limitations and future aspects. *Experimental Gerontology*. 2010;45(1):5-14
- [25] Ferreira D, Jelic V, Cavallin L, Oeksengaard A-R, Snaedal J, Høgh P, et al. Electroencephalography is a good complement to currently established dementia biomarkers. *Dementia and Geriatric Cognitive Disorders*. 2016;42(1-2):80-92
- [26] Blennow K, Hampel H. CSF markers for incipient Alzheimer's disease. *Lancet Neurology*. 2003;2(10):605-613
- [27] O'Bryant SE, Mielke MM, Rissman RA, Lista S, Vanderstichele H, Zetterberg H, et al. Blood-based biomarkers in Alzheimer disease: Current state of the science and a novel collaborative paradigm for advancing from discovery to clinic. *Alzheimer's & Dementia*. 2017;13(1):45-58
- [28] Ferreira D, Perestelo-Pérez L, Westman E, Wahlund L-O, Sarría A, Serrano-Aguilar P. Meta-review of CSF core biomarkers in Alzheimer's disease: The state-of-the-art after the new revised diagnostic criteria. *Frontiers in Aging Neuroscience*. 2014;6:47
- [29] Weiner M, Khachaturian Z. The Use of MRI and PET for Clinical Diagnosis of Dementia and Investigation of Cognitive Impairment: A Consensus Report. *Alzheimer's Assoc Chicago*; 2005
- [30] Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, et al. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimer's & Dementia*. 2016;12(3):292-323

- [31] Jiang H, White MP, Greicius MD, Waelde LC, Spiegel D. Brain activity and functional connectivity associated with hypnosis. *Cerebral Cortex*. 2016;**27**(8):4083-4093
- [32] Signorino M, Pucci E, Belardinelli N, Nolfe G, Angeleri F. EEG spectral analysis in vascular and Alzheimer dementia. *Electroencephalography and Clinical Neurophysiology*. 1995;**94**(5):313-325
- [33] Besthorn C, Zerfass R, Geiger-Kabisch C, Sattel H, Daniel S, Schreiter-Gasser U, et al. Discrimination of Alzheimer's disease and normal aging by EEG data. *Electroencephalography and Clinical Neurophysiology*. 1997;**103**(2):241-248
- [34] Al-Nuaimi AH, Jammeh E, Sun L, Ifeachor E. Tsallis entropy as a biomarker for detection of Alzheimer's disease. In: *Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual International Conference of the IEEE*. IEEE; 2015. pp. 4166-4169
- [35] Horvath A, Szucs A, Csukly G, Sakovics A, Stefanics G, Kamondi A. EEG and ERP biomarkers of Alzheimer's disease: a critical review. *Frontiers in Bioscience*. 2018;**23**:183-220
- [36] Moretti DV, Fracassi C, Pievani M, Geroldi C, Binetti G, Zanetti O, et al. Increase of theta/gamma ratio is associated with memory impairment. *Clinical Neurophysiology*. 2009;**120**(2):295-303
- [37] Jeong J. EEG dynamics in patients with Alzheimer's disease. *Clinical Neurophysiology*. 2004;**115**(7):1490-1505
- [38] Latchoumane C-FV, Ifeachor E, Hudson N, Wimalaratna S, Jeong J. Dynamical nonstationarity analysis of resting EEGs in Alzheimer's disease. In: *International Conference on Neural Information Processing*. Springer; 2007. pp. 921-929
- [39] Dauwels J, Vialatte F-B, Cichocki A. On the early diagnosis of Alzheimer's disease from EEG signals: A mini-review. In: *Advances in Cognitive Neurodynamics (II)*. Dordrecht: Springer; 2011. pp. 709-716
- [40] Babiloni C, Binetti G, Cassetta E, Dal Forno G, Del Percio C, Ferreri F, et al. Sources of cortical rhythms change as a function of cognitive impairment in pathological aging: A multicenter study. *Clinical Neurophysiology*. 2006;**117**(2):252-268
- [41] Abásolo D, Hornero R, Gómez C, García M, López M. Analysis of EEG background activity in Alzheimer's disease patients with Lempel–Ziv complexity and central tendency measure. *Medical Engineering & Physics*. 2006;**28**(4):315-322
- [42] Babiloni C, Del Percio C, Vecchio F, Sebastiano F, Di Gennaro G, Quarato PP, et al. Alpha, beta and gamma electrocorticographic rhythms in somatosensory, motor, premotor and prefrontal cortical areas differ in movement execution and observation in humans. *Clinical Neurophysiology*. 2016;**127**(1):641-654
- [43] Yener GG, Emek-Savaş DD, Lizio R, Çavuşoğlu B, Carducci F, Ada E, et al. Frontal delta event-related oscillations relate to frontal volume in mild cognitive impairment and healthy controls. *International Journal of Psychophysiology*. 2016;**103**:110-117
- [44] Gómez C, Mediavilla Á, Hornero R, Abásolo D, Fernández A. Use of the Higuchi's fractal dimension for the analysis of MEG recordings from Alzheimer's disease patients. *Medical Engineering & Physics*. 2009;**31**(3):306-313
- [45] Labate D, La Foresta F, Morabito G, Palamara I, Morabito FC. Entropic measures of EEG complexity in Alzheimer's disease through a

multivariate multiscale approach. *IEEE Sensors Journal*. 2013;**13**(9):3284-3292

[46] Lin P-F, Lo M-T, Tsao J, Chang Y-C, Lin C, Ho Y-L. Correlations between the signal complexity of cerebral and cardiac electrical activity: A multiscale entropy analysis. *PLoS One*. 2014;**9**(2):e87798

[47] Simons S, Abasolo D, Hughes M. Investigation of Alzheimer's disease EEG frequency components with Lempel-Ziv complexity. In: 6th European Conference of the International Federation for Medical and Biological Engineering. Springer; 2015. pp. 46-49

[48] Al-Nuaimi AHH, Jammeh E, Sun L, Ifeachor E. Complexity measures for quantifying changes in electroencephalogram in Alzheimer's disease. *Complexity*. 2018;**2018**:1-12. Available from: <https://www.hindawi.com/journals/complexity/2018/8915079/>

[49] Al-nuaimi AH, Jammeh E, Sun L, Ifeachor E. Higuchi fractal dimension of the electroencephalogram as a biomarker for early detection of Alzheimer's disease. In: *Engineering in Medicine and Biology Society (EMBC), 2017 IEEE 39th Annual International Conference of the IEEE*. IEEE; 2017. pp. 2320-2324

[50] Abásolo D, Hornero R, Espino P, Poza J, Sánchez CI, de la Rosa R. Analysis of regularity in the EEG background activity of Alzheimer's disease patients with approximate entropy. *Clinical Neurophysiology*. 2005;**116**(8):1826-1834

[51] Kantz H, Schreiber T. *Nonlinear Time Series Analysis*. 2nd ed. Cambridge, UK: Cambridge University Press; 2004

[52] Lempel A, Ziv J. On the complexity of finite sequences. *IEEE*

Transactions on Information Theory. 1976;**22**(1):75-81

[53] Tononi G, Edelman GM, Sporns O. Complexity and coherency: Integrating information in the brain. *Trends in Cognitive Sciences*. 1998;**2**(12):474-484

[54] Wackerbauer R, Witt A, Atmanspacher H, Kurths J, Scheingraber H. A comparative classification of complexity measures. *Chaos, Solitons & Fractals*. 1994;**4**(1):133-173

[55] Besthorn C, Sattel H, Geiger-Kabisch C, Zerfass R, Förstl H. Parameters of EEG dimensional complexity in Alzheimer's disease. *Electroencephalography and Clinical Neurophysiology*. 1995;**95**(2):84-89

[56] Burgess AP, Rehman J, Williams JD. Changes in neural complexity during the perception of 3D images using random dot stereograms. *International Journal of Psychophysiology*. 2003;**48**(1):35-42

[57] Gu F, Meng X, Shen E, Cai Z. Can we measure consciousness with EEG complexities? *International Journal of Bifurcation and Chaos*. 2003;**13**(03):733-742

[58] Adeli H, Ghosh-Dastidar S. *Automated EEG-Based Diagnosis of Neurological Disorders: Inventing the Future of Neurology*. Boca Raton: CRC Press; 2010

[59] Zhao P, Van-Eetvelt P, Goh C, Hudson N, Wimalaratna S, Ifeachor E. Characterization of EEGs in Alzheimer's disease using information theoretic methods. In: *Engineering in Medicine and Biology Society, 2007 EMBS 2007 29th Annual International Conference of the IEEE*. IEEE; 2007. pp. 5127-5131

[60] De Bock TJ, Das S, Mohsin M, Munro NB, Hively LM, Jiang Y, et al.

Early detection of Alzheimer's disease using nonlinear analysis of EEG via Tsallis entropy. In: Biomedical Sciences and Engineering Conference (BSEC), 2010. IEEE; 2010. pp. 1-4

[61] Smits FM, Porcaro C, Cottone C, Cancelli A, Rossini PM, Tecchio F. Electroencephalographic fractal dimension in healthy ageing and Alzheimer's disease. *PLoS One*. 2016;**11**(2):e0149587

[62] McBride JC, Zhao X, Munro NB, Smith CD, Jicha GA, Hively L, et al. Spectral and complexity analysis of scalp EEG characteristics for mild cognitive impairment and early Alzheimer's disease. *Computer Methods and Programs in Biomedicine*. 2014;**114**(2):153-163

[63] Dauwels J, Srinivasan K, Ramasubba Reddy M, Musha T, Vialatte F-B, Latchoumane C, et al. Slowing and loss of complexity in Alzheimer's EEG: Two sides of the same coin? *International Journal of Alzheimer's Disease*. 2011;**2011**:539621

[64] Dauwels J, Vialatte F, Cichocki A. Diagnosis of Alzheimer's disease from EEG signals: Where are we standing? *Current Alzheimer Research*. 2010;**7**(6):487-505

[65] Hamadicharef B, Guan C, Ifeakor E, Hudson N, Wimalaratna S. Performance evaluation and fusion of methods for early detection of Alzheimer disease. In: *BioMedical Engineering and Informatics, 2008 BMEI 2008 International Conference on IEEE*. 2008. pp. 347-351

[66] Al-Qazzaz NK, Ali S, Ahmad SA, Islam MS, Escudero J. Entropy-based markers of EEG background activity of stroke-related mild cognitive impairment and vascular dementia patients. In *Sensors and electronic instrumentation advances: proceedings of the 2nd international conference on*

sensors and electronic instrumentation advances 2016. pp. 22-23

[67] Coronel C, Garn H, Waser M, Deistler M, Benke T, Dal-Bianco P, et al. Quantitative EEG markers of entropy and auto mutual information in relation to MMSE scores of probable Alzheimer's disease patients. *Entropy*. 2017;**19**(3):130

[68] Sneddon R, Shankle WR, Hara J, Rodriguez A, Hoffman D, Saha U. EEG detection of early Alzheimer's disease using psychophysical tasks. *Clinical EEG and Neuroscience*. 2005;**36**(3):141-150

[69] Garn H, Waser M, Deistler M, Benke T, Dal-Bianco P, Ransmayr G, et al. Quantitative EEG markers relate to Alzheimer's disease severity in the prospective dementia registry Austria (PRODEM). *Clinical Neurophysiology*. 2015;**126**(3):505-513

[70] Accardo A, Affinito M, Carrozzi M, Bouquet F. Use of the fractal dimension for the analysis of electroencephalographic time series. *Biological Cybernetics*. 1997;**77**(5):339-350

[71] Preißl H, Lutzenberger W, Pulvermüller F, Birbaumer N. Fractal dimensions of short EEG time series in humans. *Neuroscience Letters*. 1997;**225**(2):77-80

[72] Higuchi T. Approach to an irregular time series on the basis of the fractal theory. *Physica D: Nonlinear Phenomena*. 1988;**31**(2):277-283

[73] Esteller R, Vachtsevanos G, Echaz J, Lilt B. A comparison of fractal dimension algorithms using synthetic and experimental data. In: *Circuits and Systems, 1999 ISCAS'99 Proceedings of the 1999 IEEE International Symposium on IEEE*. 1999. pp. 199-202

- [74] Staudinger T, Polikar R. Analysis of complexity based EEG features for the diagnosis of Alzheimer's disease. In: Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE. IEEE; 2011. pp. 2033-2036
- [75] Abásolo D, Simons S, da Silva RM, Tononi G, Vyazovskiy VV. Lempel-Ziv complexity of cortical activity during sleep and waking in rats. *Journal of Neurophysiology*. 2015;**113**(7):2742-2752
- [76] Rivolta MW, Migliorini M, Aktaruzzaman M, Sassi R, Bianchi AM. Effects of the series length on Lempel-Ziv complexity during sleep. In: Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE. IEEE; 2014. pp. 693-696
- [77] Zhang X-S, Roy RJ, Jensen EW. EEG complexity as a measure of depth of anesthesia for patients. *IEEE Transactions on Biomedical Engineering*. 2001;**48**(12):1424-1433
- [78] Aboy M, Hornero R, Abásolo D, Álvarez D. Interpretation of the Lempel-Ziv complexity measure in the context of biomedical signal analysis. *IEEE Transactions on Biomedical Engineering*. 2006;**53**(11):2282-2288
- [79] Simons S, Abásolo D. Distance-based Lempel-Ziv complexity for the analysis of electroencephalograms in patients with Alzheimer's disease. *Entropy*. 2017;**19**(3):129
- [80] Hornero R, Abásolo D, Escudero J, Gómez C. Nonlinear analysis of electroencephalogram and magnetoencephalogram recordings in patients with Alzheimer's disease. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*. 2009;**367**(1887):317-336
- [81] Hornero R, Escudero J, Fernández A, Poza J, Gómez C. Spectral and nonlinear analyses of MEG background activity in patients with Alzheimer's disease. *IEEE Transactions on Biomedical Engineering*. 2008;**55**(6):1658-1665
- [82] Fernandez A, Hornero R, Gomez C, Turrero A, Gil-Gregorio P, Matías-Santos J, et al. Complexity analysis of spontaneous brain activity in Alzheimer disease and mild cognitive impairment: An MEG study. *Alzheimer Disease and Associated Disorders*. 2010;**24**(2):182-189
- [83] Babiloni C, Ferri R, Binetti G, Vecchio F, Frisoni GB, Lanuzza B, et al. Directionality of EEG synchronization in Alzheimer's disease subjects. *Neurobiology of Aging*. 2009;**30**(1):93-102
- [84] Babiloni C, Del Percio C, Capotosto P, Noce G, Infarinato F, Muratori C, et al. Cortical sources of resting state electroencephalographic rhythms differ in relapsing-remitting and secondary progressive multiple sclerosis. *Clinical Neurophysiology*. 2016;**127**(1):581-590
- [85] Moretti DV. Electroencephalography-driven approach to prodromal Alzheimer's disease diagnosis: From biomarker integration to network-level comprehension. *Clinical Interventions in Aging*. 2016;**11**:897
- [86] Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain Research Reviews*. 1999;**29**(2):169-195
- [87] Moretti DV. Association of EEG, MRI, and regional blood flow biomarkers is predictive of prodromal Alzheimer's disease. *Neuropsychiatric Disease and Treatment*. 2015;**11**:2779

- [88] Moretti DV, Frisoni GB, Binetti G, Zanetti O. Comparison of the effects of transdermal and oral rivastigmine on cognitive function and EEG markers in patients with Alzheimer's disease. *Frontiers in Aging Neuroscience*. 2014;**6**:179
- [89] Kanda PAM, Oliveira EF, Fraga FJ. EEG epochs with less alpha rhythm improve discrimination of mild Alzheimer's. *Computer Methods and Programs in Biomedicine*. 2017;**138**:13-22
- [90] Babiloni C, Lizio R, Del Percio C, Marzano N, Soricelli A, Salvatore E, et al. Cortical sources of resting state EEG rhythms are sensitive to the progression of early stage Alzheimer's disease. *Journal of Alzheimer's Disease*. 2013;**34**(4):1015-1035
- [91] Babiloni C, Lizio R, Marzano N, Capotosto P, Soricelli A, Triggiani AI, et al. Brain neural synchronization and functional coupling in Alzheimer's disease as revealed by resting state EEG rhythms. *International Journal of Psychophysiology*. 2016;**103**:88-102
- [92] Moretti DV, Paternicò D, Binetti G, Zanetti O, Frisoni GB. EEG markers are associated to gray matter changes in thalamus and basal ganglia in subjects with mild cognitive impairment. *NeuroImage*. 2012;**60**(1):489-496
- [93] Locatelli T, Cursi M, Liberati D, Franceschi M, Comi G. EEG coherence in Alzheimer's disease. *Electroencephalography and Clinical Neurophysiology*. 1998;**106**(3):229-237
- [94] Aftanas LI, Lotova NV, Koshkarov VI, Popov SA. Non-linear dynamical coupling between different brain areas during evoked emotions: An EEG investigation. *Biological Psychology*. 1998;**48**(2):121-138
- [95] Gudmundsson S, Runarsson TP, Sigurdsson S, Eiriksdottir G, Johnsen K. Reliability of quantitative EEG features. *Clinical Neurophysiology*. 2007;**118**(10):2162-2171
- [96] Fleck JI, Kuti J, Brown J, Mahon JR, Gayda-Chelder C. Frontal-posterior coherence and cognitive function in older adults. *International Journal of Psychophysiology*. 2016;**110**:217-230
- [97] Adler G, Brassens S, Jajcevic A. EEG coherence in Alzheimer's dementia. *Journal of Neural Transmission*. 2003;**110**(9):1051-1058
- [98] Leuchter AF, Newton TF, IANA C, Walter DO, Rosenberg-Thompson S, Lachenbruch PA. Changes in brain functional connectivity in Alzheimer-type and multi-infarct dementia. *Brain*. 1992;**115**(5):1543-1561
- [99] Musaeus CS, Shafi MM, Santarnecchi E, Herman ST, Press DZ. Levetiracetam alters oscillatory connectivity in Alzheimer's disease. *Journal of Alzheimer's Disease*. 2017;**58**(4):1065-1076
- [100] Moretti DV. Theta and alpha EEG frequency interplay in subjects with mild cognitive impairment: Evidence from EEG, MRI, and SPECT brain modifications. *Frontiers in Aging Neuroscience*. 2015;**7**:31
- [101] Khan UA, Liu L, Provenzano FA, Berman DE, Profaci CP, Sloan R, et al. Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer's disease. *Nature Neuroscience*. 2014;**17**(2):304-311
- [102] Babiloni C, Ferri R, Binetti G, Cassarino A, Dal Forno G, Ercolani M, et al. Fronto-parietal coupling of brain rhythms in mild cognitive impairment: A multicentric EEG study. *Brain Research Bulletin*. 2006;**69**(1):63-73
- [103] Sonnen JA, Montine KS, Quinn JF, Kaye JA, Breitner JCS,

Montine TJ. Biomarkers for cognitive impairment and dementia in elderly people. *Lancet Neurology*. 2008;7(8):704-714

[104] Poil S-S, De Haan W, van der Flier WM, Mansvelder HD, Scheltens P, Linkenkaer-Hansen K. Integrative EEG biomarkers predict progression to Alzheimer's disease at the MCI stage. *Frontiers in Aging Neuroscience*. 2013;5:58

[105] Lista S, Garaci FG, Ewers M, Teipel S, Zetterberg H, Blennow K, et al. CSF A β 1-42 combined with neuroimaging biomarkers in the early detection, diagnosis and prediction of Alzheimer's disease. *Alzheimer's & Dementia*. 2014;10(3):381-392

[106] Polikar R, Tilley C, Hillis B, Clark CM, Multimodal EEG. MRI and PET data fusion for Alzheimer's disease diagnosis. In: 2010 Annual International Conference of the IEEE Engineering in Medicine and Biology. IEEE. 2010. pp. 6058-6061

[107] Walhovd KB, Fjell AM, Brewer J, McEvoy LK, Fennema-Notestine C, Hagler DJ, et al. Combining MR imaging, positron-emission tomography, and CSF biomarkers in the diagnosis and prognosis of Alzheimer disease. *American Journal of Neuroradiology*. 2010;31(2):347-354

[108] Nielsen MS, Simonsen AH, Siersma V, Engedal K, Jelic V, Andersen BB, et al. Quantitative electroencephalography analyzed by statistical pattern recognition as a diagnostic and prognostic tool in mild cognitive impairment: Results from a Nordic multicenter cohort study. *Dementia and Geriatric Cognitive Disorders Extra*. 2018;8(3):426-438

[109] Houmani N, Vialatte F, Gallego-Jutglà E, Dreyfus G, Nguyen-Michel V-H, Mariani J, et al. Diagnosis of Alzheimer's disease

with electroencephalography in a differential framework. *PLoS One*. 2018;13(3):e0193607

[110] Escudero J, Abásolo D, Hornero R, Espino P, López M. Analysis of electroencephalograms in Alzheimer's disease patients with multiscale entropy. *Physiological Measurement*. 2006;27(11):1091

[111] Zanin M, Zunino L, Rosso OA, Papo D. Permutation entropy and its main biomedical and econophysics applications: A review. *Entropy*. 2012;14(8):1553-1577