Measurement 225 (2024) 114040

Contents lists available at ScienceDirect

Measurement

journal homepage: www.elsevier.com/locate/measurement

EEG complexity-based algorithm using Multiscale Fuzzy Entropy: Towards a detection of Alzheimer's disease

Andrea Cataldo [a,*], Sabatina Criscuolo [b], Egidio De Benedetto [b], Antonio Masciullo [a], Marisa Pesola [b], Joseph Picone [c], Raissa Schiavoni [a]

[a] University of Salento - Department of Engineering for Innovation, Lecce, Italy
[b] University of Naples Federico II - Department of Information Technology and Electrical Engineering, Naples, Italy
[c] Department of Electrical and Computer Engineering, Temple University, Philadelphia, PA, USA

ARTICLE INFO

Keywords:
Alzheimer's disease
Complexity
Measures
Electroencephalography
Multiscale fuzzy entropy
Neurodegenerative diseases

ABSTRACT

Alzheimer's Disease (AD) is a progressive neurodegenerative condition causing memory, attention, and language decline. Current AD diagnostic methods lack objectivity and non-invasiveness. While electroencephalography (EEG) holds promise for AD research, conventional EEG analysis methods have proven unsatisfactory. Non-linear dynamical approaches are considered more effective in assessing the brain's complex nature. Starting from these considerations, this study presents an entropy-based algorithm utilizing Multiscale Fuzzy Entropy (MFE) as a promising, effective AD diagnostic method. Computed across 20 different time scales for a public dataset, MFE showed a significant discriminative power. Notably, a trend inversion was observed in the results: AD subjects displayed higher complexity values for slow frequency bands compared to healthy controls, while the opposite was found in fast frequency bands. These findings underscore the potential of MFE in effectively distinguishing AD patients from healthy individuals, marking a significant advance towards more objective and reliable AD diagnosis strategies.

1. Introduction

Electroencephalography (EEG) is a non-invasive and low-cost method widely used both in clinical and research environments [1] for detecting and monitoring the electrical activity of the brain in order to diagnose neurological disease [2], to study neural responses to different types of stimulation [3–5], the execution of motor movements, and brain–computer interfaces [6,7]. By applying electrodes to the scalp and properly processing the obtained signals [8], the EEG recording allows the investigation of the temporal dynamics of the brain at a high temporal resolution. However, conventional EEG analysis methods (e.g. event-related potential, time analysis, and frequency analysis) assume the stationarity of the system, thus disregarding the non-stationary nature and temporally intricate behavior of neuronal processes. Indeed, brain processes are not purely regular but neither totally random [9]; for this reason, complexity measures of EEG signals may offer a novel understanding of physiological processes in both normal and abnormal conditions. In general, non-linear dynamical analysis is expected to be more appropriate for exploring brain activity and for a detailed comprehension of neural phenomena, particularly in neurodegenerative disorders such as Alzheimer's disease (AD), which impairs the connections between neurons [10]. AD is the most common age-related form of dementia according to the World Health Organization [11], and its onset typically occurs after the age of 60 [12]. It is characterized by a widespread loss of functional neuronal interaction and progressive impairment of memory. Currently, there is no reliable biochemical marker for the diagnosis of AD, and it can only be considered 'possible' or 'probable' based on the outcome of neuropsychological tests that evaluate memory, language, and attention-related issues, such as the Mini-Mental State Examination (MMSE) [13]. The current limitations in diagnostic approaches highlight the necessity for an early and objective method for detecting AD. In this regard, EEG has emerged as a promising solution [1,14]. In fact, the quantitative analysis of EEG signals has the potential for identifying biomarkers for AD diagnosis. Studies based on frequency methods show that an EEG signal of patient with AD presents an increase in the relative power of low-frequency bands (delta, 0.5–4 Hz, and theta, 4–8 Hz), combined with a reduction in the mean alpha frequency 8–13 Hz [15–17]. Furthermore, synchronization could be a useful indicator for AD, revealing variations in functional connectivity, especially within the beta and theta frequency bands, when contrasted with healthy subjects [18–20]. Recently, there has been a growing interest in applying complexity

* Corresponding author.
E-mail address: andrea.cataldo@unisalento.it (A. Cataldo).

https://doi.org/10.1016/j.measurement.2023.114040
Received 22 August 2023; Received in revised form 25 November 2023; Accepted 13 December 2023
Available online 15 December 2023

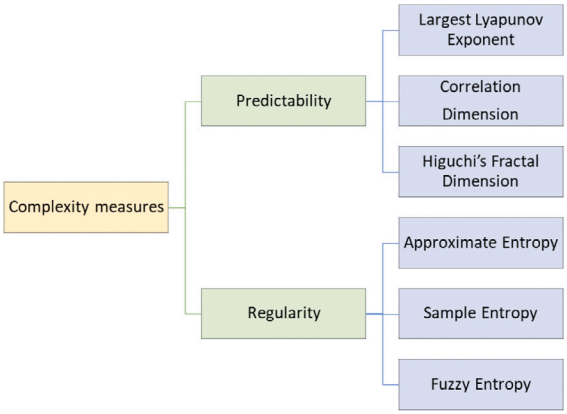

Fig. 1. Taxonomy of complexity measures mostly used in the analysis of EEG signal predictability and regularity.

analysis to EEG signals in individuals with AD, reporting a reduction in complexity and an increase in signal regularity [21–24]. By combining the evaluation of EEG signals' complexity with the measurement of frequency band powers, the EEG analysis can assume a great potential for AD diagnosis, especially for the timely detection of the so-called Mild Cognitive Impairment (MCI) i.e., the early stage of AD [25].

On such basis, this study proposes a specific procedure based on Multiscale Fuzzy Entropy (MFE) for analyzing the complexity of the EEG traces of a set of AD and healthy subjects. The aim is to identify particular channels and frequency bands that facilitate discrimination between healthy individuals and patients with AD through EEG complexity analysis. This objective falls within the larger scope of enhancing healthcare through the adoption of advanced processing techniques that enable periodic screening, diagnosis, and prevention of AD [10,15].

The remainder of the paper is organized as follows. Section 2 provides an overview of state-of-the-art methods based on entropy analysis for the monitoring and diagnosis of AD. Section 3 addresses the basic theoretical concepts of the proposed technique, the dataset adopted in this work, the implementation of the method, and the statistical analysis performed on the data. Section 4 describes the experimental results and addresses the discussions. Finally, conclusions are reported in Section 5.

2. Related works

Complexity science focuses on investigating and describing systems composed of various interconnected components that function and interact at various levels. These systems exhibit chaotic behavior, characterized by unpredictability and irregularities that arise from nonlinear interactions. Indeed, a complex system exhibits two distinct features: *predictability* and *regularity* [10,23]. The former refers to the temporal evolution of the system states into spatial and/or temporal dimensionality. On the other hand, regularity refers to the number of pattern repetitions in the system. However, a full reconstruction of the spatio-temporal dimensionality of the signal is required for predictability calculations, whereas regularity measures explore fewer details in the time–frequency domain, resulting in greater robustness. Therefore, since brain processes are characterized by the interchange of noisy and low-amplitude signals, in this case, regularity measures are more appropriate to fully investigate the complexity of bio-signals compared to predictability measures that may be less reliable [23].

In recent years, the analysis of non-linear systems through complexity has emerged as a prominent approach for studying electrophysiological signals, investigating neurodegenerative diseases and mental states [26,27]. Several metrics have been proposed to evaluate the predictability and regularity of the brain. Fig. 1 shows the most commonly used. *Entropy* has emerged as the predominant metric employed for quantifying brain complexity [28–30], with particular attention to Approximate Entropy (ApEn), Sample Entropy (SampEn), and Fuzzy Entropy (FuzzyEn) [31,32]. These measures allow for the evaluation of similarities between patterns of signals, identifying repeated sequences in the time series. More in detail, for doing that, ApEn and SampEn use a binary mechanism (Heaviside function) with a threshold value, whereas FuzzyEn uses a fuzzy membership function by returning a real number between 0 and 1. Typically, these metrics are applied to the signal at its original time scale, the reason why they are called single-scale metrics. On the other hand, it is worth noting that EEG signals can provide different and extremely useful information for the purpose of understanding brain dynamics when they are analyzed at different spatial and temporal scales [33]. More specifically, at the spatial dimension, brain complexity can be defined by the intricacy of activities within specific brain regions or individual neurons and groups of neural cells. Meanwhile, at the temporal dimension, neural complexity can be ascertained by the intricacy of activity patterns over time. Hence, single-scale methods may not be adequate for accurately characterizing EEG complexity. Instead, a multiscale approach is necessary to fully capture the EEG brain signal complexity in space and time [23].

The multiscale entropy concept is schematized in Fig. 2. As a matter of fact, the multiscale entropy measures [38], evaluating signal complexity at varying resolution scales, are especially valuable for investigating the brain and the association between EEG signals complexity and neuro-degenerative disorders, in particular for AD. In the literature, several studies have been dedicated to the investigation into Multiscale Sample Entropy (MSE) of EEG signals from patients diagnosed with different degrees of AD [34,35,39]. The findings demonstrate that the quantification of complexity levels at multiple temporal scales provides a dynamic representation of the progression of AD. Notably, it appears that entropy significantly decreased from moderate to severe stages of AD, as opposed to the early stage of AD, where entropy levels were comparable to those of healthy controls. These reductions in complexity may indicate deficits in thought-processing capacity and/or reduced responsiveness to an external stimulus.

Mizuno et al. [34] observed a decrease of MSE at small time scales in frontal regions, while the brain complexity increased at larger time scales in many different brain areas, which could be associated with phenomena of incorrect connection between the regions. Sun et al. [40] showed a statistically significant difference in the MSE of the temporal, occipito-parietal, and right frontal lobes between AD, MCI, and healthy individuals. More specifically, healthy individuals exhibited higher entropy than MCI and AD patients at short-scale factors, while the opposite trend was observed at long-scale factors. More recently, Su et al. [37] utilized multiscale fuzzy entropy (MFE) to enable early diagnosis of MCI patients. Their findings indicated that the prefrontal lobe may be a particularly sensitive brain area. Specifically, the MFE of normal controls was greater than that of individuals with MCI in the Fp1 and Fp2 channels.

Table 1 provides a summary of findings from the referenced literature. Across the considered studies, multiscale entropy calculations were exclusively conducted on wide frequency ranges, lacking differentiation for single EEG bands. Notably, these studies reflect some challenges related to the lack of standardized approaches. The inherent complexity and variability of brain signals, combined with the absence of a definitive gold standard for metrics and parameters, complicate direct comparisons with existing literature.

Based on these considerations, this study focuses on an MFE algorithm for analyzing the complexity of EEG signals in AD and healthy subjects, identifying channels and frequency bands that facilitate discrimination between the two groups.

Table 1
Multiscale Entropy Analysis in EEG Data for distinguishing Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) in existing literature.

Study	Method	Subjects	Frequency range	Findings
Mizuno et al. [34]	MSE (20 time scales)	15 AD + 18 HS	1.5 Hz to 60 Hz	Trend inversion with decreased complexity for short-time scales and increased complexity for long-time scales in AD subjects.
Yang et al. [35]	MSE (20 time scales)	108 AD + 15 HS	0.05 Hz to 70 Hz	Trend inversion with decreased complexity for short-time scales and increased complexity for long-time scales in subjects with severe AD.
Fan et al. [36]	MSE (20 time scales) for ML algorithm	108 AD + 15 HS	0.05 Hz to 70 Hz	Maximum classification accuracy of about 80 % between normal controls and subjects with severe AD.
Su et al. [37]	MFE (15 time scales) + Phase Lag Value (PLV) for ML algorithm	28 MCI + 21 HS	1 Hz to 45 Hz	Maximum classification accuracy of about 83 % between normal controls and subjects with MCI.

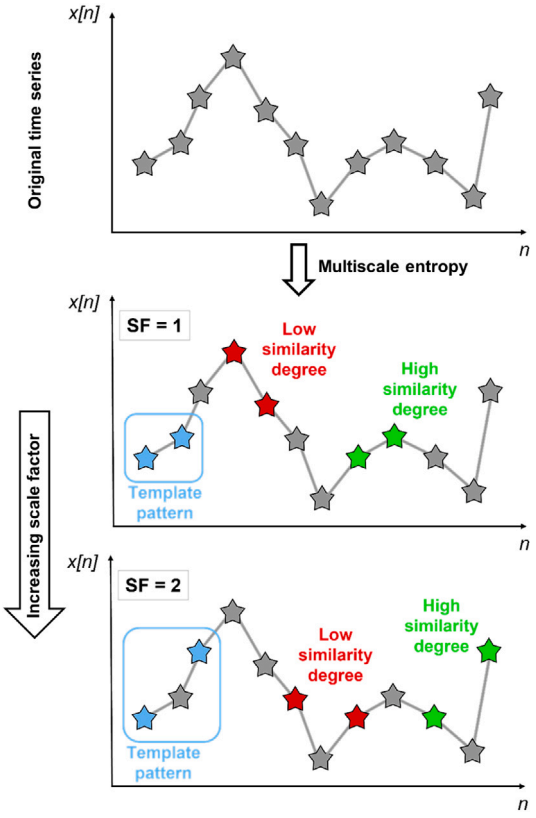

Fig. 2. Multiscale entropy concept. Multiscale entropy is an information-theoretic metric to describe the temporal irregularity of time series data. It measures the probability that two patterns of sequence length m (here, 2) remain similar when the next sample $m+1$ is included in the sequence.

3. Materials and methods

As mentioned in Section 1, this study aims to develop a procedure based on MFE to analyze the complexity of EEG traces and identify the channels and frequency bands that allow distinguishing between healthy individuals and patients with AD. In this regard, a set of data was selected from an extensive publicly available archive of clinical EEG recordings collected at Temple University Hospital (TUH) [41]. The utilization of these public data has allowed the validation of the method on real subjects, whose pathological condition was determined by medical personnel. The data were appropriately preprocessed, and the MFE-based algorithm was applied.

In the following sections, after outlining the theoretical foundations for the MFE, the proposed method is described in detail.

3.1. Multiscale Fuzzy Entropy (MFE)

MFE was recently introduced as an evolution of the more traditional entropy-based techniques such as Approximate Entropy (ApEn) and Sample Entropy (SampEn) [42]. These techniques try to quantify how regular or chaotic a time series is by analyzing the signal through a sliding window that searches for similar patterns. However, ApEn and SampEn make matching vectors with either 1 or 0 values; this is a non-real situation for biological signals when there may be uncertainty about sharing between classes.

Conversely, FuzzyEn overcomes this limitation since it relies on the theory of fuzzy logic, which accepts the concept of partial truth. Unlike Boolean logic, which employs only binary values, fuzzy logic grants a continuous degree of truth with values ranging from 0 (representing "totally false") to 1 (representing "totally true"). Interpreting these real values as a degree of belonging to a set of similar patterns, this function is also known as the membership function.

In EEG analysis, FuzzyEn is employed to assign a certain degree of similarity among patterns throughout the entire time series. Then, the total contribution of all values between 0 and 1 computed for each template will represent a measure of the complexity of the brain waveforms.

In addition, FuzzyEn shows a weaker dependence on record length than ApEn and SampEn [42], and it reduces the impact of the variation of some arbitrary parameters in the formulations (such as the sample length m and the threshold r for calculating distance) on results. Indeed, it has been shown how ApEn and SampEn lack consistency when slightly different values for input parameters are used to evaluate the same EEG record [43]. For all these reasons, in this work, FuzzyEn was selected for calculating entropy. Furthermore, a multiscale strategy is required in order to broaden the search for patterns of different time resolutions. This more comprehensive approach is particularly valuable for EEG signals [10], as it offers insights into the organization of brain processes with diverse temporal dynamics. In light of these considerations, MFE was selected for this investigation and the related mathematical framework will now be explained in more detail.

As aforementioned, FuzzyEn relies on a fuzzy membership function to compare two vectors and determine their degree of similarity as a real number in the range $[0, 1]$.

Given a discrete time series $x[n]$ consisting of N samples, a first vector $\mathbf{X}_i^m$ of m consecutive samples is collected:

$$\mathbf{X}_i^m = \{x[i], x[i+1], \ldots, x[i+m-1]\} - x_0[i], \tag{1}$$

where i is the starting time point of the generic pattern and $x_0[i]$ is the mean value of all m-selected samples. Then, a shifted version $\mathbf{X}_j^m$, with $i \neq j$, is moved along the trace and compared to the first vector $\mathbf{X}_i^m$. The similarity degree D_{ij}^m of $\mathbf{X}_j^m$ to $\mathbf{X}_i^m$ is calculated as

$$D_{ij}^m = \mu(d_{ij}^m, n, r) = \exp\left(\frac{-(d_{ij}^m)^n}{r}\right), \tag{2}$$

where d_{ij}^m is the maximum absolute difference between the two vectors and μ stands for the fuzzy membership function. As can be seen

Table 2
Summarized characteristics of the selected subjects.

Diagnosis	Sex	Number of subjects	Age (mean ± std)
AD	F	9	78.5 ± 11.7
HS	F	9	78.4 ± 8.1
AD	M	8	84.7 ± 4.5
HS	M	8	68.8 ± 3.1

from Eq. (2), an exponential function is a typical choice for μ in order to meet two requirements: it should be continuous to avoid abrupt fluctuations and it should maximize self-similarity [44]. The smoothness of the exponential fuzzy function is adjusted by two arbitrarily assigned parameters, namely n and r shown in (2). Consequently, the mean over all of the different sequences of length m is computed as follows:

$$\phi^m = \frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m-1}\sum_{j\neq i,j=1}^{N-m-1} D_{ij}^m\right). \tag{3}$$

Similarly, computations are repeated for a second vector $\mathbf{X}_i^{m+1}$ of length $m+1$, obtaining the mean ϕ^{m+1} from Eq. (3). Finally, FuzzyEn can be estimated as the negative natural logarithm of the deviation between ϕ^m and ϕ^{m+1}:

$$FuzzyEn(m,n,r) = \ln\phi^m - \ln\phi^{m+1}. \tag{4}$$

As a result, FuzzyEn is the conditional probability that trends observed for m points are the same for $(m+1)$ points. On such basis, FuzzyEn represents a single-scale measure that is characterized by a not adequate sensitivity in order to understand the brain's dynamic complex mechanisms. For these reasons, as aforementioned, a *multiscale* approach based on FuzzyEn is much more suitable. In this way, MFE enables the estimation of the brain processes complexity over a time-scale interval [37], in order to obtain more useful information that would otherwise be lost. The idea behind the multiscale approach is to recalculate the selected entropy method on the original signal $x[n]$ whenever the time scale is varied:

$$y_s[n] = \sum_{i=j}^{j+s-1} x[n], \text{ for } 1 \le j \le N-s+1, \tag{5}$$

where $y_s[n]$ is the new time series at the sth scale factor. A scaling factor of at least 15 is recommended [37].

3.2. Dataset description

The dataset consists of a large archive of 26.846 clinical EEG recordings collected at Temple University Hospital (TUH) of Philadelphia from 2002 to 2017 [45], including a variety of seizure types and other neurological disorders. Each EEG record, in *EDF* standard format, is associated with a textual clinician report generated by the neurologist following EEG analysis. These documents reported, for each patient, personal data such as age and sex, full medical history with the diseases the subject suffering from, and medications. The corpus is publicly available from the Neural Engineering Data Consortium [41].

For the present study, on the basis of clinical reports, a total of 17 subjects with a diagnosis of AD were selected, being careful not to consider subjects suffering from other neurological diseases in addition to AD. On the other hand, 17 healthy subjects (HS) were extracted from a subset of the main one called TUH Abnormal EEG Corpus (TUAB) [41], considering EEGs that have been annotated as normal by neurologists. Information on the number of subjects, sex, and range of ages is detailed in Table 2. For patients with multiple EEG records, the more recent was used. The selected data were re-sample at 250 Hz and 19 EEG channels were selected according to the 10-20 electrode placement system, specifically Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz.

3.3. Implementation

Fig. 3 describes the steps of the proposed methodology. As aforementioned, the EEG signals of selected groups of subjects were considered. For each subject, 60 s of clean signal were manually selected from the closed-eyes trace. Then, a standardized preprocessing pipeline (see Fig. 3) was applied to the selected traces. In particular, the main preprocessing steps applied to the selected data were: epoching, amplitude scaling, and band filtering.

1. *Epoching* consists of splitting the continuous EEG trace into shorter segments called "epochs", typically ranging from a few hundred milliseconds to a few seconds in length. Each epoch represents a discrete time window of the signal and can be used for further analysis, such as averaging across multiple epochs to reduce noise and enhance the signal of interest. As mentioned earlier, the available data were resting state and no stimulus was administered, hence the choice of epoch duration was arbitrary. Inspired by previous works in the literature [35], the total 60-second EEG trace was divided into 20 epochs of 3-second duration. Given the sampling frequency of 250 Hz, each epoch consisted of 750 samples.
2. *Amplitude scaling* denotes the procedure of adapting all the raw EEG signals to a standardized scale, with the aim of ensuring amplitude consistency across different recording configurations and individuals [46]. In the context of this study, scaling assumes particular relevance, given that the EEG data were recorded over a wide span of years and with possibly different instrumentation. Therefore, to make the MFE results as independent as possible from inter-individual variability, each trace was scaled channel by channel. A maximum-minimum normalization was chosen for these data, using the following formula:
$$x_{norm,i} = \frac{x_i - x_{min,i}}{x_{max,i} - x_{min,i}} \cdot (A_{max} - A_{min}) + A_{min}, \tag{6}$$
where i is the channel index, while A_{max} and A_{min} define the extremes of the output amplitude range. Maxima and minima were calculated for each epoch, then the relative median values $x_{max,i}$ and $x_{min,i}$ of the two vectors were identified and used as reference values of the normalization.
3. *Band filtering* served the purpose of restricting the investigation to the frequency range of interest. Specifically, the signal was band-pass filtered between 0.5 to 30 Hz for considering the most significant part of EEG signals, and then the data was filtered for the four main bands of the EEG signal: delta (0.5 to 4 Hz), theta (4 to 8 Hz), alpha (8 to 13 Hz), and beta (13 to 30 Hz). A finite impulse response (FIR) filter with an order equal to the number of samples in a single epoch was applied. Consequently, the first epoch related to the transient was excluded from each time series.

Finally, the preprocessed EEG data were analyzed epoch-wise to calculate the Multiscale Fuzzy Entropy (MFE) values. Due to the lack of established guidelines for parameters selection in MSE calculation, values of m and r were set to 2 and 0.20, respectively, based on existing literature [35,40]. A range of scale factors from 1 to 20 was chosen to effectively discriminate between the AD and control groups, as reported in the literature [35,38,40]. Moreover, experimental findings from preliminary investigation suggested that the use of at least 20 scale factors ensures a sufficient number to capture the whole dynamics. The MFE values for each subject and EEG channel in the specific frequency range were obtained by averaging across all 19 epochs.

The implementation of the methods described above was carried out through *MATLAB* ©.

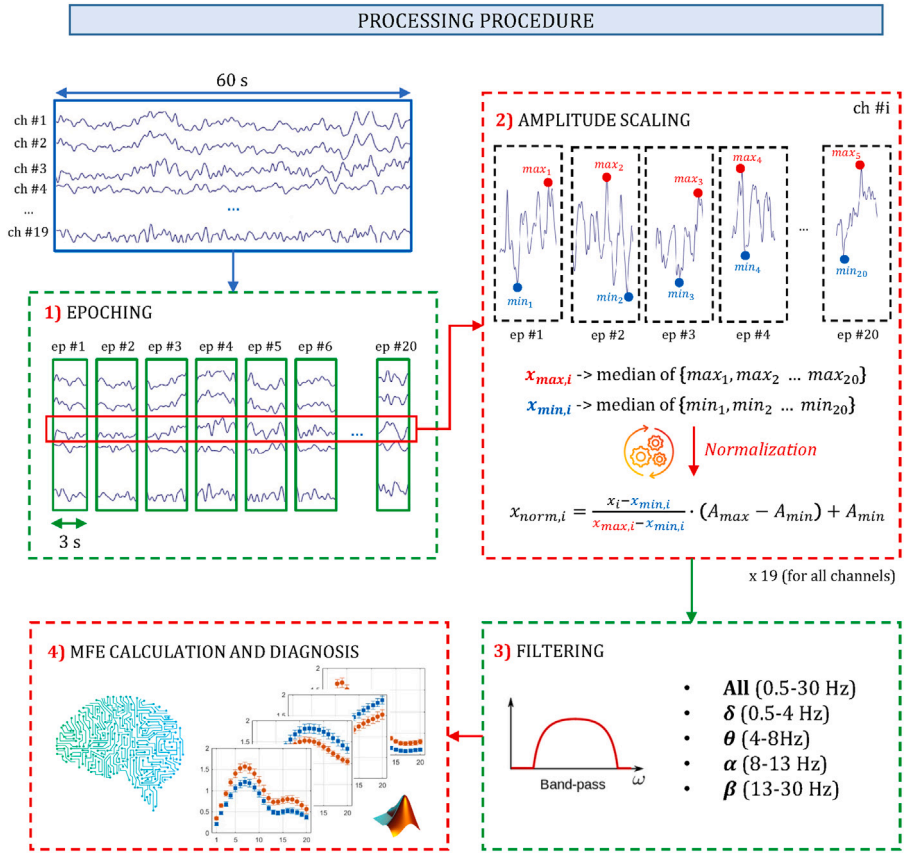

Fig. 3. Proposed methodology. For each subject, 60 s of clean EEG signal were selected. Then, the EEG traces were (1) epoched into 3-second segments, (2) normalized, and (3) filtered. Finally, (4) epoch-wise analysis of processed EEG data was conducted to determine Multiscale Fuzzy Entropy (MFE) values, obtained by averaging across all 19 epochs for each subject and EEG channel in the specific frequency range.

3.4. Statistical analysis

The two-sided Mann–Whitney U-test [47] was employed to assess differences for each channel, each band, and each scale factor between the AD group and the HS group. This test is a non-parametric statistical test used to compare two independent groups when normal distributions cannot be assumed. A significance level equal to 0.05 was chosen for this analysis. Hence, MFE differences between the two groups will be considered significant when associate p-values < 0.05.

3.5. Cluster analysis

The *k*-means algorithm [48] was employed to assess the detection efficacy of the proposed method, specifically to analyze the presence of two well-defined clusters (AD and HS) in our MFE data. In greater detail, *k*-means clustering facilitates the grouping of similar data points and the identification of underlying patterns solely based on input vectors, without relying on known or labeled outcomes. Consequently, data points are clustered based on shared similarities. To quantitatively evaluate the clustering results, the Silhouette Score (S) was employed. It measures the cohesion and separation of data points within clusters and helps determine whether the clusters are well-separated and internally homogeneous. This score, ranging from −1 to +1, is computed using the formula:

$$S = \frac{1}{N}\sum_{i=1}^{N}\frac{max(a_i b_i)}{b_i - a_i} \tag{7}$$

where N is the number of data points, ai is the average distance of data point i to all other data points in the same cluster (intra-cluster distance) and, bi is the average distance of data point i to all other data points in the nearest cluster (inter-cluster distance). A positive score denotes appropriate clustering, with the data point being closer to its assigned cluster than the nearest neighboring cluster.

4. Results and discussion

As aforementioned, the experimental procedure was carried out on data selected from a publicly-available dataset. More in detail, 17 subjects with AD and 17 control HS were considered. The obtained results in terms of mean (dots) and standard deviation (bars) are reported in Fig. 4, which shows the comparison between the MFE values of the AD subjects and those of the HS, depending on the scale factors. In this regard, MFE profile could provide useful information about the level of randomness/entropy in each time scale of the signal. Specifically, the MFE trends are shown for the whole frequency range and for the delta, theta, alpha, and beta bands. For the sake of brevity, only the results obtained when the electrodes are placed on the sagittal line (Fz, Cz, Pz) are presented, since the curves obtained from the other channels exhibit a similar trend.

As a first observation, it is clear that, over the whole considered frequency range (0.5–30 Hz), the MFE curves exhibit a different behavior between HS and patients with AD for short- and long-time scale factors. Notably, the MFE curve of AD subjects is systematically lower on the short-time scales and significantly higher on the long-time scales compared to HS. These results suggest that different trends between short- and long-time scales were probably due to different pathophysiologic mechanisms of brain activity in AD or HS subjects. As per the short-time scales, the lower MFE observed in AD patients suggests a shift in brain activity towards regularity with a loss of physiologic complexity and dynamic mechanisms. In addition, with

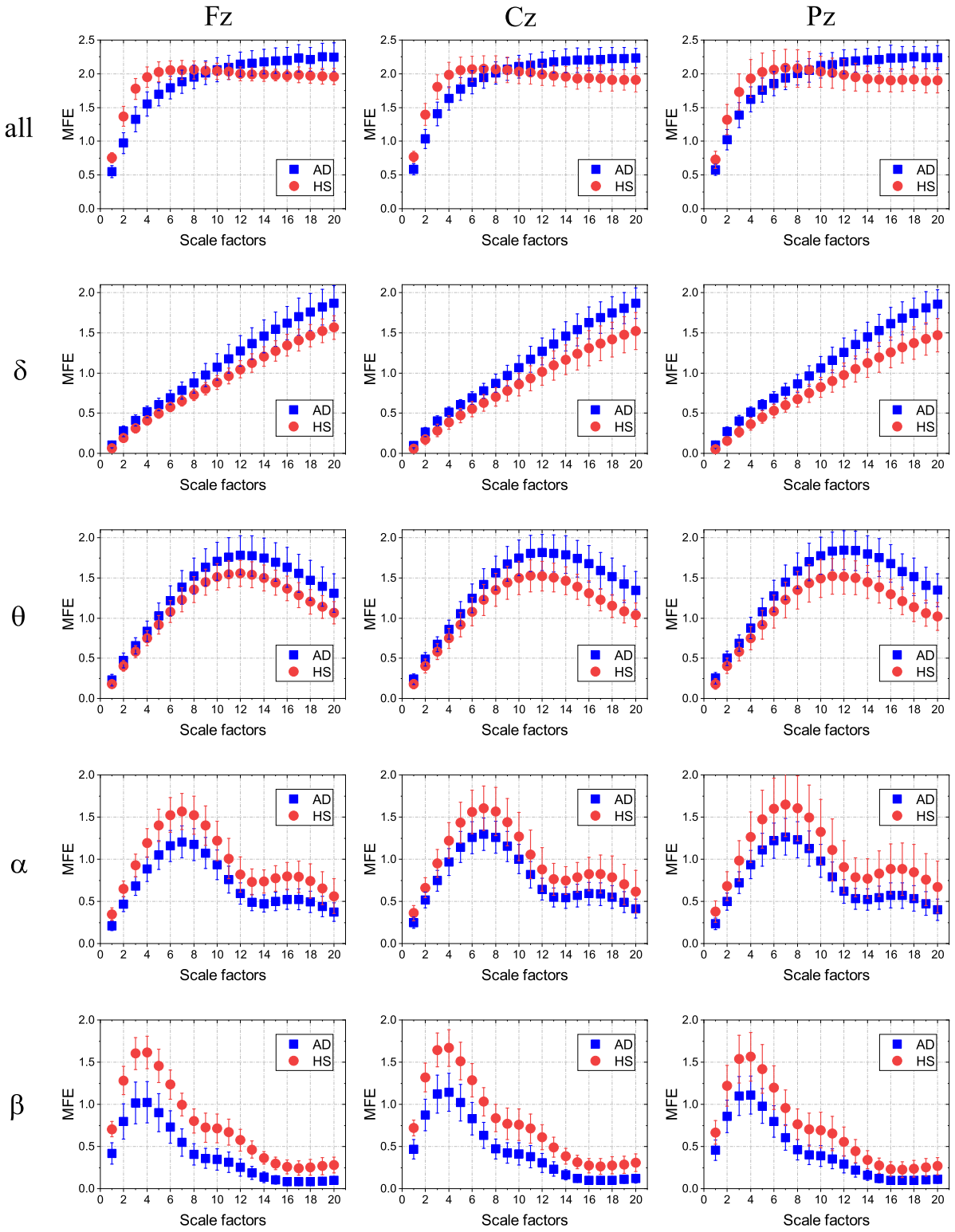

Fig. 4. Comparison between the MFE values of the AD patients and HS, depending on the scale factors. The results are reported in terms of mean (dots) and standard deviation (bars). The rows show the frequency ranges: all (0.5–30 Hz), delta δ (0.5–4 Hz), theta θ (4–8 Hz), alpha α (8–13 Hz), and beta β (13–30 Hz). On the columns, sagittal-line electrodes Fz, Cz, Pz are presented.

regard to long-time scales, the finding of higher MFE values in patients with AD could suggest that their brain activity may be more complex or less predictable than that of healthy controls. However, this is not exactly correct since, based on the hypothesis introduced by Costa et al. [38] and Goldberger et al. [49], and increased irregularity (therefore an increased entropy) does not imply increased physiologic dynamical complexity. On the contrary, this phenomenon could indicate a chaotic and nonfunctional system characterized by a non-stationary brain activity associated with aging or illness. Both findings support the assumption of loss of physiological complexity.

Moreover, as illustrated in Fig. 4, the impact of cognitive impairment in individuals with AD is more evident from the analysis of the

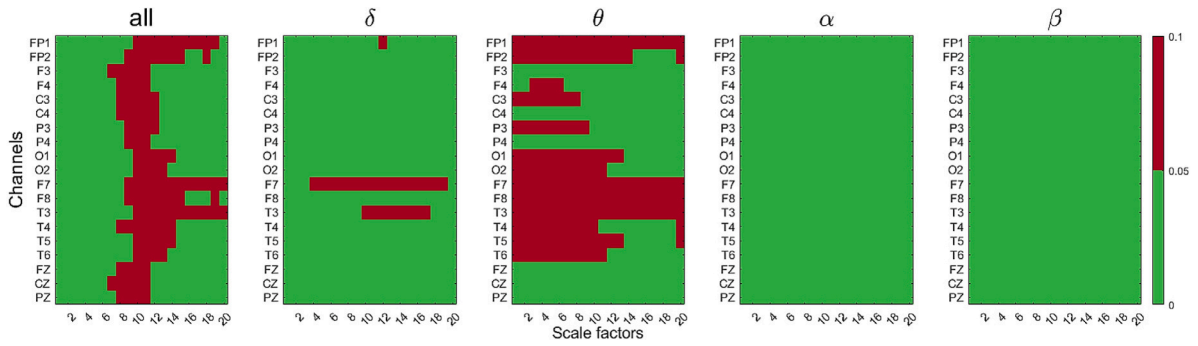

Fig. 5. Statistical significance of the MFE results assessed using the Mann–Whitney U-test: p-values. Each subplot represents a frequency range: all (0.5–30 Hz), delta δ (0.5–4 Hz), theta θ (4–8 Hz), alpha α (8–13 Hz), and beta β (13–30 Hz). Given a significance level of 0.05, green pixels indicate significant median differences between AD and HS groups for each EEG channel and scale factor.

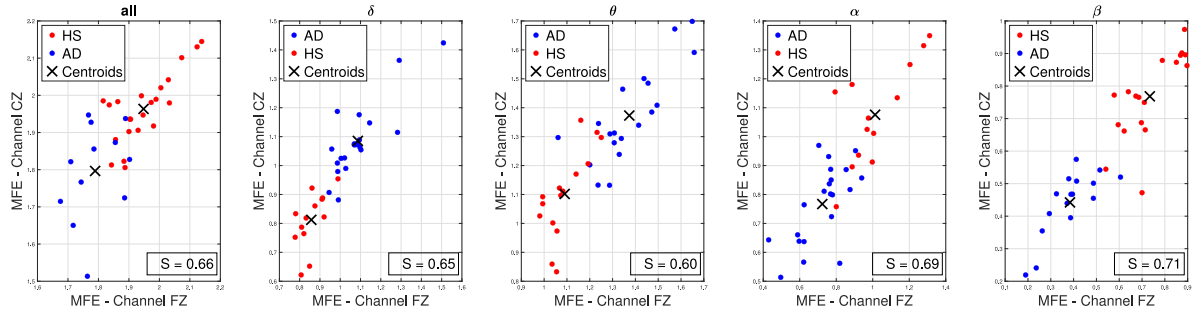

Fig. 6. K-means clustering results for each EEG frequency band. For visualization clarity, each dot represents the average MFE value on scale factors.

Table 3
Summary of the obtained results.

Band	MFE	Notes
All	$AD < HS$ on the short time scales $AD > HS$ on the long time scales	At short time scales there is a shift in AD brain activity towards regularity with a loss of physiologic complexity and dynamic mechanisms. At long time scales there is a chaotic and nonfunctional behavior characterized by a non-stationary brain activity.
δ θ	$AD > HS$ $AD > HS$	This phenomenon can be attributed to the pathological decline that is observed in individuals with AD, since cognitive impairment is accompanied by changes in frequency-specific neural activity with a shift of brain activities to lower frequencies.
α β	$AD < HS$ $AD < HS$	Also in this case, the behavior is due to the shift in brain activity from higher to lower frequencies. Therefore, at the higher frequency bands (α and β) the MFE values of the AD group are lower than those of the HS group.

specific frequency bands. Specifically, it is worth noting that at the lower frequency bands (delta and theta), the MFE curves of the two groups exhibit an opposite behavior compared to that at the higher frequency bands (alpha and beta). More in detail, the analysis of delta and theta frequency bands reveals that the MFE values of the AD group systematically exceed those of the HS group, with this difference becoming more pronounced at larger scale factor values. In contrast, in the alpha and beta frequency bands, the MFE values of the AD group are lower than those of the HS group.

This phenomenon can be attributed to the pathological decline that is observed in individuals with AD. Indeed, in the literature, it is agreed upon that cognitive impairment is accompanied by changes in frequency-specific neural activity.

Specifically, conventional EEG power analysis conducted on AD patients typically reveals a slowing EEG pattern characterized by increased delta band power and decreased alpha activity [50–52], and this is also reflected in the complex activity of the brain. Moreover, the evidence of different behavior in MFE for AD patients and HS in frontal-central position both for short- and long-time scale could be correlated with fast and slow EEG oscillations, providing evidence for this association [34,35]. Finally, these findings are predictive of cognitive deterioration in patients with AD and can be a useful index to identify also the condition of mild cognitive impairment, so as to achieve an early diagnosis with the potential to increase the effectiveness of therapy. Table 3 summarizes the obtained results.

Statistical tests described in Section 3.4 were performed to assess the discrimination power of MFE and the results are presented in Fig. 5. The differences between AD and HS groups result in statistically significant (green pixels) across all the frequency ranges, with a few exceptions. Notably, considering the overall band, a loss of significance is mainly observed at the central scale factors (red pixels around scales 8-12), attributable to the inversion of trends between the two groups. Within the delta band, diminished discrimination power is evident in only channels F7 and T3. As for the theta band, the most significant channels are found to be F3, C4, and P4, along with the three sagittal channels Fz, Cz, and Pz. Finally, in alpha and beta bands, the MFE is statistically significant across all channels and scale factors.

Cluster analysis described in Section 3.5 was performed to assess the power of MFE in AD detection. The *k*-means analysis was conducted by considering all the MFE values on scale factors. The obtained results are shown in Fig. 6. Specifically, for the sake of clarity, Fig. 6 presents the obtained clusters for AD (blue) and HS (red) for all the frequency ranges

by considering MFE values in Fz and Cz (x- and *y*-axis, respectively). For each plot, a silhouette score (S) is also reported. Silhouette scores exceeding 0.60 are evidently obtained for all frequency bands, confirming appropriate clusters. The MFE values in the alpha and beta bands allow for better discrimination between AD and HS, as also observed by the statistical test.

This exploratory investigation represents a step towards the development of a tool for diagnosing Alzheimer's disease based on EEG signals and neural complexity. In a long-term view, the obtained results can potentially aid in early diagnosis and improve the effectiveness of therapy for AD patients. Differently from some conventional techniques [53], EEG is non-invasive and cost-effective; it can capture real-time neural activity, making it a practical and advantageous tool for routine clinical assessments. To achieve this goal, however, some aspects still need to be addressed. Firstly, it is important to extend the number of subjects (also with individuals with other pathologies). This would allow to establish the applicability and generalizability of the current findings. Moreover, additional analyses should be conducted using other publicly available datasets (e.g., CAUEEG dataset [54]) and self-collected data through an experimental campaign conducted under resting-state conditions as well as in the presence of different stimuli (e.g. olfactory stimuli, given that individuals with cognitive impairment often exhibit anosmia [10,14]). As aforementioned, this study addressed the possibility of discerning potential differences in complexity between individuals with AD and healthy subjects by using MFE. In fact, the literature reveals some challenges related to the lack of standardized approaches and of an absolute "truth" in EEG-complexity based analysis for AD. Numerous factors, including age, gender, disease severity, and test execution conditions, likely contribute to this variability. Based on these considerations, subjects were selected carefully, so as to have a well-balanced group of healthy individuals and patients with Alzheimer's disease. Furthermore, individuals with other known medical conditions were excluded to minimize potential confounding factors. However, in future research, it will be useful to explore the comorbidities, so as to provide a more comprehensive understanding for clinical practice. Finally, it could be of interest to combine EEG complexity analysis with signal coherence and synchronization analysis, like functional analysis [19] and phase lag index [55,56] to gain further insights into the neural mechanisms underlying cognitive decline in patients.

5. Conclusions

In this work, an entropy-based algorithm using MFE as a method to quantify the complexity of EEG signals was presented. The multiscale approach for computing FuzzyEn allows the analysis of neural signals complexity over a time-scale interval obtaining more useful information about the brain processes. The proposed method was applied to EEG data of 17 AD and 17 healthy subjects from a public dataset. The results showed that AD patients exhibit different MFE profiles compared to healthy controls. In particular, AD patients presented lower MFE values at short-time scales and higher values at long-time scales, indicating a shift towards regularity and randomness, respectively, in brain activity. Furthermore, the impact of cognitive impairment in AD patients was more evident in the analysis of specific frequency bands, with higher MFE values in delta and theta bands and lower values in alpha and beta bands. It is clear that, in AD subjects, the brain processes on short- and long-time scales could depend on the effects of an underlying pathology.

The obtained results can potentially aid in early diagnosis and improve the effectiveness of therapy for AD patients. The MFE-based complexity analysis could play a pivotal role in advancing early diagnosis and enhancing the efficacy of therapy for individuals affected by AD. The integration of this novel approach with existing diagnostic methods has the potential to unveil early signs of AD in patients manifesting mild or non-specific symptoms, thereby facilitating prompt diagnosis and timely intervention. The non-invasive nature, cost-effectiveness, and real-time capturing of neural activity through EEG render it a practical and advantageous tool for routine clinical assessments, for longitudinal studies and continuous monitoring, providing insights into the progression of the pathology. While further work is needed, the obtained results represent an important step forward for the development of an MFE-based metric for AD diagnosis.

CRediT authorship contribution statement

Andrea Cataldo: Conceptualization, Funding acquisition, Supervision, Writing – review & editing, Methodology. **Sabatina Criscuolo:** Data curation, Investigation, Software, Validation, Visualization, Writing – original draft. **Egidio De Benedetto:** Conceptualization, Methodology, Supervision, Writing – review & editing, Funding acquisition. **Antonio Masciullo:** Formal analysis, Investigation, Methodology, Supervision, Writing – original draft. **Marisa Pesola:** Data curation, Investigation, Software, Writing – original draft, Validation, Visualization. **Joseph Picone:** Methodology, Writing – review & editing, Data curation, Investigation. **Raissa Schiavoni:** Data curation, Investigation, Software, Writing – original draft, Validation, Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

This work was supported in part by the INTENSE project (F/310148/01-05/X56)— Italian Ministry of Economic Development Accordo Innovazione DM 31/12/2021.

This work was supported by the PNRR DM 351/2022 - M4C1, by the European Union - FSE-REACT-EU, PON Research and Innovation 2014–2020, DM 1061/2021 contract number DOT19X7NYL-2.

References

[1] G.R. Müller-Putz, Electroencephalography, Handb. Clin. Neurol. 168 (2020) 249–262.
[2] W.O. Tatum IV, Handbook of EEG Interpretation, Springer Publishing Company, 2021.
[3] H. Yu, X. Wu, L. Cai, B. Deng, J. Wang, Modulation of spectral power and functional connectivity in human brain by acupuncture stimulation, IEEE Trans. Neural Syst. Rehabil. Eng. 26 (5) (2018) 977–986.
[4] H. Yu, X. Li, X. Lei, J. Wang, Modulation effect of acupuncture on functional brain networks and classification of its manipulation with EEG signals, IEEE Trans. Neural Syst. Rehabil. Eng. 27 (10) (2019) 1973–1984.
[5] H. Yu, Z. Meng, H. Li, C. Liu, J. Wang, Intensity-varied closed-loop noise stimulation for oscillation suppression in the parkinsonian state, IEEE Trans. Cybern. 52 (9) (2021) 9861–9870.
[6] P. Arpaia, D. Coyle, F. Donnarumma, A. Esposito, A. Natalizio, M. Parvis, Visual and haptic feedback in detecting motor imagery within a wearable brain–computer interface, Measurement 206 (2023) 112304.
[7] P. Arpaia, E. De Benedetto, L. Duraccio, Design, implementation, and metrological characterization of a wearable, integrated AR-BCI hands-free system for health 4.0 monitoring, Measurement 177 (2021) 109280.
[8] A. Cataldo, S. Criscuolo, E. De Benedetto, A. Masciullo, M. Pesola, R. Schiavoni, S. Invitto, A method for optimizing the artifact subspace reconstruction performance in low-density EEG, IEEE Sens. J. 22 (21) (2022) 21257–21265.
[9] G. Tononi, G.M. Edelman, O. Sporns, Complexity and coherency: integrating information in the brain, Trends Cogn. Sci. 2 (12) (1998) 474–484, http://dx.doi.org/10.1016/s1364-6613(98)01259-5.
[10] A. Cataldo, S. Criscuolo, E. De Benedetto, A. Masciullo, M. Pesola, R. Schiavoni, Uncovering the correlation between COVID-19 and neurodegenerative processes: Toward a new approach based on EEG entropic analysis, Bioengineering 10 (4) (2023) 435.

[11] Ministero della Salute - Italy, World Alzheimer's Day, 21 September 2022, 2022, [Online]. https://www.salute.gov.it/portale/demenze/dettaglioNotizieDemenze.jsp?lingua=italiano&menu=notizie&p=dalministero&id=5998#:~:text=Nel%20mondo%2C%20secondo%20i%20dati,78%20milioni%20entro%20il%202030. (Accessed 28 April 2023).
[12] R. Castellani, R. Rolston, M. Smith, Alzheimer disease, Dis. Mon. 56 (9) (2010) 484–546.
[13] I. Arevalo-Rodriguez, N. Smailagic, M. Roqué-Figuls, et al., Mini-Mental State Examination (MMSE) for the early detection of dementia in people with mild cognitive impairment (MCI), Cochrane Database Syst. Rev. 7 (7) (2021).
[14] P. Arpaia, A. Cataldo, S. Criscuolo, E. De Benedetto, A. Masciullo, R. Schiavoni, Assessment and scientific progresses in the analysis of olfactory evoked potentials, Bioengineering 9 (6) (2022) 252.
[15] B. Czigler, D. Csikós, Z. Hidasi, Z.A. Gaál, É. Csibri, É. Kiss, P. Salacz, M. Molnár, Quantitative EEG in early Alzheimer's disease patients—power spectrum and complexity features, Int. J. Psychophysiol. 68 (1) (2008) 75–80.
[16] U. Smailovic, V. Jelic, Neurophysiological markers of Alzheimer's disease: quantitative EEG approach, Neurol. Ther. 8 (2019) 37–55.
[17] A. Modir, S. Shamekhi, P. Ghaderyan, A systematic review and methodological analysis of EEG-based biomarkers of Alzheimer's disease, Measurement (2023) 113274.
[18] C.J. Stam, Y. Van Der Made, Y.A. Pijnenburg, P. Scheltens, EEG synchronization in mild cognitive impairment and Alzheimer's disease, Acta Neurol. Scand. 108 (2) (2003) 90–96.
[19] H. Yu, X. Lei, Z. Song, C. Liu, J. Wang, Supervised network-based fuzzy learning of EEG signals for Alzheimer's disease identification, IEEE Trans. Fuzzy Syst. 28 (1) (2019) 60–71.
[20] K. Li, J. Wang, S. Li, H. Yu, L. Zhu, J. Liu, L. Wu, Feature extraction and identification of Alzheimer's disease based on latent factor of multi-channel EEG, IEEE Trans. Neural Syst. Rehabil. Eng. 29 (2021) 1557–1567.
[21] J. Dauwels, K. Srinivasan, M. Ramasubba Reddy, T. Musha, F.-B. Vialatte, C. Latchoumane, J. Jeong, A. Cichocki, et al., Slowing and loss of complexity in Alzheimer's EEG: two sides of the same coin? Int. J. Alzheimer's Dis. 2011 (2011).
[22] D. Labate, F. La Foresta, G. Morabito, I. Palamara, F.C. Morabito, Entropic measures of EEG complexity in Alzheimer's disease through a multivariate multiscale approach, IEEE Sens. J. 13 (9) (2013) 3284–3292.
[23] Z.J. Lau, T. Pham, S.A. Chen, D. Makowski, Brain entropy, fractal dimensions and predictability: A review of complexity measures for EEG in healthy and neuropsychiatric populations, Eur. J. Neurosci. 56 (7) (2022) 5047–5069.
[24] F. Li, L. Jiang, Y. Liao, Y. Si, C. Yi, Y. Zhang, X. Zhu, Z. Yang, D. Yao, Z. Cao, et al., Brain variability in dynamic resting-state networks identified by fuzzy entropy: a scalp EEG study, J. Neural Eng. 18 (4) (2021) 046097.
[25] H. Garn, M. Waser, M. Deistler, R. Schmidt, P. Dal-Bianco, G. Ransmayr, J. Zeitlhofer, H. Schmidt, S. Seiler, G. Sanin, et al., Quantitative EEG in Alzheimer's disease: cognitive state, resting state and association with disease severity, Int. J. Psychophysiol. 93 (3) (2014) 390–397.
[26] S.M.G. Beyrami, P. Ghaderyan, A robust, cost-effective and non-invasive computer-aided method for diagnosis three types of neurodegenerative diseases with gait signal analysis, Measurement 156 (2020) 107579.
[27] P. Ghaderyan, F. Moghaddam, S. Khoshnoud, M. Shamsi, New interdependence feature of eeg signals as a biomarker of timing deficits evaluated in attention-deficit/hyperactivity disorder detection, Measurement 199 (2022) 111468.
[28] D. Abásolo, R. Hornero, P. Espino, D. Alvarez, J. Poza, Entropy analysis of the EEG background activity in Alzheimer's disease patients, Physiol. Meas. 27 (3) (2006) 241.
[29] X. Li, Z. Zhu, W. Zhao, Y. Sun, D. Wen, Y. Xie, X. Liu, H. Niu, Y. Han, Decreased resting-state brain signal complexity in patients with mild cognitive impairment and Alzheimer's disease: a multi-scale entropy analysis, Biomed. Opt. Express 9 (4) (2018) 1916–1929.
[30] S. Keshmiri, Entropy and the brain: An overview, Entropy 22 (9) (2020) 917.
[31] Z. Cao, C.T. Lin, Inherent fuzzy entropy for the improvement of EEG complexity evaluation, IEEE Trans. Fuzzy Syst. 26 (2) (2017) 1032–1035.
[32] S. Simons, P. Espino, D. Abásolo, Fuzzy entropy analysis of the electroencephalogram in patients with Alzheimer's disease: is the method superior to sample entropy? Entropy 20 (1) (2018) 21.
[33] C. Chen, J. Li, X. Lu, Multiscale entropy-based analysis and processing of EEG signal during watching 3DTV, Measurement 125 (2018) 432–437.
[34] T. Mizuno, T. Takahashi, R.Y. Cho, M. Kikuchi, T. Murata, K. Takahashi, Y. Wada, Assessment of EEG dynamical complexity in Alzheimer's disease using multiscale entropy, Clin. Neurophysiol. 121 (9) (2010) 1438–1446.
[35] A.C. Yang, S.J. Wang, K.L. Lai, C.F. Tsai, C.H. Yang, J.P. Hwang, M.T. Lo, N.E. Huang, C.K. Peng, J.L. Fuh, Cognitive and neuropsychiatric correlates of EEG dynamic complexity in patients with Alzheimer's disease, Prog. Neuropsychopharmacol. Biol. Psych. 47 (2013) 52–61.
[36] M. Fan, A.C. Yang, J.L. Fuh, C.A. Chou, Topological pattern recognition of severe Alzheimer's disease via regularized supervised learning of EEG complexity, Front. Neurosci. 12 (2018) 685.
[37] R. Su, X. Li, Z. Li, Y. Han, W. Cui, P. Xie, Y. Liu, Constructing biomarker for early diagnosis of aMCI based on combination of multiscale fuzzy entropy and functional brain connectivity, Biomed. Signal Process. Control 70 (2021) 103000.
[38] M. Costa, A.L. Goldberger, C.K. Peng, Multiscale entropy analysis of complex physiologic time series, Phys. Rev. Lett. 89 (6) (2002) 068102.
[39] J.H. Park, S. Kim, C.H. Kim, A. Cichocki, K. Kim, Multiscale entropy analysis of EEG from patients under different pathological conditions, Fractals 15 (04) (2007) 399–404.
[40] J. Sun, B. Wang, Y. Niu, Y. Tan, C. Fan, N. Zhang, J. Xue, J. Wei, J. Xiang, Complexity analysis of EEG, MEG, and fMRI in mild cognitive impairment and Alzheimer's disease: a review, Entropy 22 (2) (2020) 239.
[41] Neural Engineering Data Consortium, [Online]. https://isip.piconepress.com/projects/nedc/. (Accessed 11 May 2023),
[42] A. Humeau-Heurtier, Multiscale entropy approaches and their applications, Entropy 22 (6) (2020) 644.
[43] J. Richman, J. Moorman, Physiological time-series analysis using approximate entropy and sample entropy, Am. J. Physiol. Heart Circ. Physiol. 278 (6) (2000) 2039–2049.
[44] W. Chen, Z. Wang, H. Xie, W. Yu, Characterization of surface EMG signal based on fuzzy entropy, IEEE Trans. Neural Syst. Rehabil. Eng. 15 (2) (2007) 266–272.
[45] I. Obeid, J. Picone, The temple university hospital EEG data corpus, Front. Neurosci. 10 (2016).
[46] L. Logesparan, E. Rodriguez-Villegas, A.J. Casson, The impact of signal normalization on seizure detection using line length features, Med. Biol. Eng. Comput. 53 (2015) 929–942.
[47] D.C. Montgomery, G.C. Runger, Applied Statistics and Probability for Engineers, John wiley & sons, 2010.
[48] M. Ahmed, R. Seraj, S.M.S. Islam, The k-means algorithm: A comprehensive survey and performance evaluation, Electronics 9 (8) (2020) 1295.
[49] A.L. Goldberger, C.-K. Peng, L.A. Lipsitz, What is physiologic complexity and how does it change with aging and disease? Neurobiol. Aging 23 (1) (2002) 23–26.
[50] J.J. Claus, V.I. Kwa, S. Teunisse, G.J. Walstra, W.A. van Gool, J.H.T. Koelman, L.J. Bour, B.W.O. de Visser, Slowing on quantitative spectral EEG is a marker for rate of subsequent cognitive and functional decline in early alzheimer disease, Alzheimer Dis. Assoc. Disord. 12 (3) (1998) 167–174.
[51] C. Babiloni, G. Binetti, E. Cassetta, D. Cerboneschi, G. Dal Forno, C. Del Percio, F. Ferreri, R. Ferri, B. Lanuzza, C. Miniussi, D. Moretti, F. Nobili, R. Pascual-Marqui, G. Rodriguez, G. Romani, S. Salinari, F. Tecchio, P. Vitali, O. Zanetti, F. Zappasodi, P. Rossini, Mapping distributed sources of cortical rhythms in mild Alzheimer's disease. A multicentric EEG study, NeuroImage 22 (1) (2004) 57–67.
[52] K. Bennys, G. Rondouin, C. Vergnes, J. Touchon, Diagnostic value of quantitative EEG in Alzheimer's disease, Neurophysiol. Clin. 31 (3) (2001) 153–160.
[53] R.S. Turner, T. Stubbs, D.A. Davies, B.C. Albensi, Potential new approaches for diagnosis of Alzheimer's disease and related dementias, Front. Neurol. 11 (2020) 496.
[54] M.j. Kim, Y.C. Youn, J. Paik, Deep learning-based EEG analysis to classify normal, mild cognitive impairment, and dementia: Algorithms and dataset, NeuroImage 272 (2023) 120054.
[55] S.J. Ruiz-Gómez, R. Hornero, J. Poza, A. Maturana-Candelas, N. Pinto, C. Gómez, Computational modeling of the effects of EEG volume conduction on functional connectivity metrics. Application to Alzheimer's disease continuum, J. Neural Eng. 16 (6) (2019) 066019.
[56] P. Núnez, J. Poza, C. Gómez, V. Rodríguez-González, A. Hillebrand, M.A. Tola-Arribas, M. Cano, R. Hornero, Characterizing the fluctuations of dynamic resting-state electrophysiological functional connectivity: reduced neuronal coupling variability in mild cognitive impairment and dementia due to Alzheimer's disease, J. Neural Eng. 16 (5) (2019) 056030.