Use of the Higuchi's fractal dimension for the analysis of MEG recordings from Alzheimer's disease patients

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Abstract

Alzheimer's disease (AD) is an irreversible brain disorder of unknown aetiology that gradually destroys brain cells and represents the most prevalent form of dementia in western countries. The main aim of this study was to analyse the magnetoencephalogram (MEG) background activity from 20 AD patients and 21 elderly control subjects using Higuchi's fractal dimension (*HFD*). This non-linear measure can be used to estimate the dimensional complexity of biomedical time series. Before the analysis with *HFD*, the stationarity and the non-linear structure of the signals were proved. Our results showed that MEG signals from AD patients had lower *HFD* values than control subjects' recordings. We found significant differences between both groups at 71 of the 148 MEG channels ($p < 0.01$; Student's *t*-test with Bonferroni's correction). Additionally, five brain regions (anterior, central, left lateral, posterior and right lateral) were analysed by means of receiver operating characteristic curves, using a leave-one-out cross-validation procedure. The highest accuracy (87.8%) was achieved when the mean *HFD* over all channels was analysed. To sum up, our results suggest that spontaneous MEG rhythms are less complex in AD patients than in healthy control subjects, hence indicating an abnormal type of dynamics in AD.

Keywords: Alzheimer's disease; magnetoencephalogram; fractal dimension; Higuchi's algorithm; surrogate data; stationarity.

1. Introduction

Alzheimer's disease (AD) is considered the main cause of dementia in western countries [1]. It affects 1% of population aged 60-64 years, but the prevalence increases exponentially with age, so about 30% of people over 85 years suffer from this disease [2]. Additionally, as life expectancy has improved significantly in western countries in the last decades, it is expected that the number of people with dementia increase up to 81 millions in 2040 [2]. This degenerative disease is characterized by neuronal loss and the appearance of neurofibrillary tangles and senile plaques. AD symptoms are memory loss, confusion, disorientation and speech problems [3]. Although a definite diagnosis is only possible by necropsy, a differential diagnosis with other types of dementia and with major depression should be attempted. The differential diagnosis includes medical history studies, physical and neurological evaluation and neuroimaging techniques. Mental status tests are also used to assess the severity of cognitive deficit.

Magnetoencephalography is a non-invasive technique that allows to record the magnetic fields generated by the human brain. The use of magnetoencephalograms (MEGs) to study the brain background activity offers some advantages over electroencephalograms (EEGs). Firstly, electrical activity is more affected than magnetic oscillations by skull and extracerebral brain tissues [4, 5]. Moreover, EEG acquisition can be significantly influenced by technical and methodological issues, like distance between electrodes and the sensor placement. In addition to this, MEG provides reference-free recordings. On the other hand, the magnetic fields generated by the brain are extremely weak. Thus, large arrays of superconducting quantum interference devices (SQUIDs), immersed in liquid helium at 4.2 K, are necessary to detect them. Liquid helium temperatures can be achieved either with cryocoolers or with a cryogenic bath [6]. Additionally, MEGs must be recorded in a

magnetically shielded room to reduce the environmental noise [5]. These issues increase the economical cost of MEG acquisition and reduce its availability [5].

EEG and MEG recordings have been analysed in the last decades by means of chaos theory [7]. Due to the fact that non-linearity is present at the brain, even at cellular level [8], the use of methods derived from chaos theory has offered valuable information to study different pathological states [7]. When chaos theory has been applied to EEG/MEG signals, the dimensional complexity has mainly been used to study changes in the dynamical behaviour of the brain [9]. Two approaches are feasible to calculate the dimensional complexity of a signal: estimate the fractal dimension (FD) of the time series directly in the time domain or reconstruct the attractor in a multi-dimensional phase space. The method most widely used to estimate the dimensional complexity is the correlation dimension (D_2), which computes the geometric complexity of the reconstructed attractor [10]. D_2 is considered to be a reflection of the complexity of the cortical dynamics underlying the electromagnetic brain signal [3]. This measure has shown changes of the cerebral dynamics in different brain pathologies such as schizophrenia [11], vascular dementia [12], Parkinson's disease [13, 14], epilepsy [15], alpha coma [16], depression [17] or Creutzfeldt-Jakob disease [18].

D_2 has also been used to differentiate EEG/MEG recordings from AD patients and controls subjects [12, 19-21]. For instance, Jeong *et al.* [12] showed that AD patients exhibit significantly lower D_2 values than control subjects in many EEG channels. Abatzoglou *et al.* [19] reported lower D_2 for AD patients' MEGs. Van Cappellen van Walsum *et al.* [20] analysed AD patients' MEG signals in different frequency bands. Statistical differences between both groups were found in delta, theta and beta bands [20]. Finally, Besthorn *et al.* [21] suggested that a D_2 decrease was correlated with an increase in dementia severity. Nevertheless, this measure has some drawbacks: reliable estimation of D_2 requires a large quantity of data and stationary and noise free time series [22, 23]. As these assumptions

cannot be achieved for physiological data, other measures are needed to estimate the dimensional complexity of EEG/MEG data.

As we have previously mentioned, the dimensional complexity of a signal can also be calculated directly in the time domain using the *FD*. The term *FD* was introduced by Mandelbrot to study temporal or spatial continuous phenomena that show correlation into a range of scales [24]. Applied to MEG time series, *FD* quantifies the complexity and self-similarity of these signals [9]. Many algorithms are available to compute *FD*, like those proposed by Higuchi [25], Maragos and Sun [26], Katz [27] and Petrosian [28], or the box counting method [29]. Higuchi's fractal dimension (*HFD*) is an appropriate method for analysing the *FD* of biomedical signals [9], as MEG recordings, due to the following reasons. Compared with Petrosian's algorithm, Higuchi's one does not depend on a binary sequence and, in many cases, it is less sensitive to noise [30]. Box counting has a high computational burden in time and memory [31], so it is less efficient than *HFD*. Moreover, Higuchi's algorithm provides more accurate estimation of the *FD* than the methods proposed by Maragos and Sun, Katz and Petrosian [9, 30]. On the other hand, *HFD* is more sensitive to noise than Katz's *FD* [30]. Additionally, Petrosian and Katz's methods are faster than Higuchi's, although this is not a problem since the three algorithms can be run in real time [30].

In this study, we examined the MEG background activity in AD patients and elderly control subjects using *HFD*. The main aim of this work was to test the hypothesis that *HFD* values are lower in the AD patients' MEGs than in controls' ones, hence indicating an abnormal type of dynamics in AD.

2. Materials and methods

2.1. Subjects and MEG recording

MEGs were recorded using a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) located in a magnetically shielded room. The subjects lay comfortably on a patient bed, in a relaxed state and with their eyes closed. They were asked to stay awake and to avoid eye and head movements. For each subject, five minutes of recording were acquired at a sampling frequency of 678.17 Hz, using a hardware band-pass filter from 0.1 to 200 Hz. Then, the equipment decimated each 5 minutes data set. This process consisted of filtering the data to respect Nyquist criterion, following by a down-sampling by a factor of four, thus obtaining a sampling rate of 169.55 Hz. Finally, artefact-free epochs of 5 seconds (848 samples) were digitally filtered between 0.5 and 40 Hz and copied as ASCII files for off-line analysis. Fig. 1 shows an example of an AD patient's MEG epoch.

INSERT FIGURE 1 AROUND HERE

MEG data were acquired from 41 subjects: 20 patients with probable AD and 21 elderly control subjects. Cognitive status was screened in both groups with the Mini Mental State Examination (MMSE) of Folstein *et al.* [32]. The AD group consisted of 20 patients (7 men and 13 women; age = 73.05 ± 8.65 years, mean $\pm$ standard deviation, SD) fulfilling the criteria of probable AD, according to the criteria of the *National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's and Related Disorders Association* (NINCDS-ADRDA). The mean MMSE score for the patients was 17.85 ± 3.91 points. Patients were free of other significant medical, neurological and psychiatric diseases than AD. Moreover, none of the participants in the study used medication that could affect the MEG activity.

MEGs were also obtained from 21 elderly control subjects without past or present neurological disorders (9 men and 12 women; age = 70.29 ± 7.07 years, MMSE score = 29.10 ± 1.00 points). The difference in the mean age of both populations is not statistically significant ($p = 0.26 > 0.01$, Student's t -test). The local ethics committee approved this study. All control subjects and all caregivers of the patients gave their informed consent for the participation in the current study.

2.2. Testing for stationarity

To estimate the FD appropriately, stationary MEG epochs are necessary. Some algorithms for dimensional complexity estimation, such as Katz's one or D_2 , require a large number of samples to obtain reliable values [9]. For this reason, it is necessary that the signal remains stationary during long duration intervals. This assumption is very difficult to achieve for physiological data, as MEG signals. Nevertheless, Higuchi's algorithm can be applied to shorter time series [25]. Therefore, recordings of five seconds duration (848 data points) from brain background activity have been analysed in our study. To guarantee that the aforementioned epochs remain stationary, Bendat and Piersol's runs test [33], a general non-parametric test for weak or wide sense stationarity, was used.

2.3. Surrogate data

Although it is commonly accepted that non-linearity is present at the brain, even at cellular level [8], we cannot guarantee that MEG signals reflect the non-linear features of the brain. Therefore, a surrogate data method is necessary to test the non-linearity of our time series to determine if HFD could be appropriately applied [34]. In the present paper, surrogate data were generated with the amplitude adjusted Fourier transform algorithm. A detailed description of the aforementioned algorithm can be found in [35]. Using this procedure,

original and surrogate data have the same amplitude distribution and Fourier power spectra [35]. Hence, surrogate data have the same linear properties than the original recordings, but not the possible non-linear ones. Significant differences between the *HFD* values obtained from the two data sets indicate that the signals are non-linear [36].

2.4. Higuchi's fractal dimension (*HFD*)

Higuchi proposed in 1988 an efficient algorithm for measuring the *FD* of discrete time sequences [25]. Higuchi's algorithm calculates the *FD* directly from time series. As the reconstruction of the attractor phase space is not necessary, this algorithm is simpler and faster than D_2 and other classical measures derived from chaos theory. *FD* can be used to quantify the complexity and self-similarity of a signal [9]. *HFD* has already been used to analyse the complexity of brain recordings [9, 37] and other biological signals [34, 38].

Given a one dimensional time series $X = x[1], x[2], \dots, x[N]$, the algorithm to compute the *HFD* can be described as follows [25]:

1. Form k new time series X_k^m defined by:

$$X_k^m = \left\{ x[m], x[m+k], x[m+2k], \dots, x\left[m + \text{int}\left(\frac{N-m}{k}\right) \cdot k\right] \right\}$$

where k and m are integers, and $\text{int}(\bullet)$ is the integer part of $\bullet$. k indicates the discrete time interval between points, whereas $m = 1, 2, \dots, k$ represents the initial time value.

2. The length of each new time series can be defined as follows:

$$L(m, k) = \frac{\left\{ \left(\sum_{i=1}^{\text{int}\left(\frac{N-m}{k}\right)} |x[m+ik] - x[m+(i-1) \cdot k]| \right) \frac{N-1}{\text{int}\left(\frac{N-m}{k}\right) \cdot k} \right\}}{k}$$

where N is length of the original time series X and $(N-1)/\{\text{int}[(N-m)/k] \cdot k\}$ is a normalization factor.

3. Then, the length of the curve for the time interval k is defined as the average of the k values $L(m,k)$, for $m = 1, 2, \dots, k$:

$$L(k) = \frac{1}{k} \cdot \sum_{m=1}^k L(m,k)$$

4. Finally, when $L(k)$ is plotted against $1/k$ on a double logarithmic scale, with $k = 1, 2, \dots, k_{\max}$, the data should fall on a straight line, with a slope equal to the FD of X . Thus, HFD is defined as the slope of the line that fits the pairs $\{\ln[L(k)], \ln(1/k)\}$ in a least-squares sense. In order to choose an appropriate value of the parameter $k_{\max}$, HFD values were plotted against a range of $k_{\max}$. The point at which the FD plateaus is considered a saturation point and that $k_{\max}$ value should be selected [34, 39]. A value of $k_{\max} = 48$ was chosen for our study.

3. Results

Before the analysis of the recordings with HFD , the stationarity of the MEG epochs was investigated using the Bendat and Piersol's runs test [33]. The assessment of stationarity with this method depends on the window length [40], a parameter that can be determined estimating the dominant low frequency band in terms of energy distribution [41]. We found that 72% of the MEG epochs retained the majority of the signal energy below 10.6 Hz. Thus, a window of at least 94.3 ms is necessary. As a conservative estimate, the window length should be more than three times this value [41]. Thus, in our study, a window of 300 ms, i.e. 50 samples, was employed. Using the aforementioned test, we found that 59.53% of the epochs were stationary. These epochs were selected for further analysis with HFD and the remainders were discarded.

A surrogate data method was used to detect the non-linearity in the MEGs. To generate these artificial data, the amplitude adjusted Fourier transform algorithm [35] was

chosen. Our results showed statistically significant differences ($p < 0.01$, Student's t -test) between the HFD values obtained from the original and the surrogate data sets. Thus, we can assume that the MEG time series used in our study contain non-linear features. These results confirm the suitability of MEG analysis with HFD .

After testing the stationarity and non-linearity of the recordings, Higuchi's algorithm was applied. The average HFD value for the control group was 1.89 ± 0.03 (mean $\pm$ SD), whereas it reached 1.81 ± 0.07 for AD patients. Our results showed that FD values were higher in the control group than in the AD group for all channels (Fig. 2), which suggests that AD is accompanied by a MEG complexity decrease. Additionally, differences between AD patients and elderly control subjects were statistically significant in 71 channels ($p < 0.01$, Student's t -test with Bonferroni's correction), specially in the temporal regions.

INSERT FIGURE 2 AROUND HERE

Furthermore, we evaluated the ability of HFD to discriminate AD patients from elderly control subjects by means of receiver operating characteristic (ROC) curves. A ROC curve is a graphical representation of the trade-offs between sensitivity and specificity. We define sensitivity as the rate of AD patients who test positive, whereas specificity represents the fraction of controls correctly recognized. Accuracy quantifies the total number of subjects precisely classified. The area under the ROC curve (AROC) is a single number summarizing the performance. AROC indicates the probability that a randomly selected AD patient has a HFD value lower than a randomly chosen control subject. In order to calculate these values, a leave-one-out cross-validation procedure was used. In the leave-one-out method, the results from one subject are excluded from the training set one at a time. Afterwards, the results of this subject are classified on the basis of the threshold calculated from the results obtained

from all other subjects. The leave-one-out cross-validation procedure provides a nearly unbiased estimate of the true error rate of the classification procedure [42]. To simplify the analyses, the *HFD* results were averaged over all channels. We also grouped the channels in five brain areas (anterior, central, left lateral, posterior and right lateral), as Fig. 3 shows. Fig. 4 represents the ROC curves obtained at each region. The highest accuracy (87.8%) and AROC (0.8952) values were achieved when the mean *HFD* over all channels was analysed. Table 1 shows the sensitivity, specificity and accuracy values obtained at each region. The AROC values and their 95% confidence intervals (CIs) are also presented.

INSERT FIGURES 3 AND 4 AROUND HERE

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4. Discussion and conclusions

We explored the ability of *HFD* to discriminate between spontaneous MEG rhythms of 20 AD patients and 21 control subjects. Before the complexity analysis with *HFD*, the stationarity and the non-linear structure of the recordings were tested.

HFD has proven to be effective in discriminating AD patients from elderly controls. Values were lower in AD patients at all MEG channels. Given the fact that *FD* can be used to quantify the signal complexity [9], our study suggests that brains affected by AD show a less complex behaviour. Additionally, the differences between both groups were statistically significant in 71 channels ($p < 0.01$; Student's *t*-test with Bonferroni's correction). Our results agree with previous studies that have analysed electromagnetic brain recordings with different complexity measures. For instance, Jeong *et al.* [43] demonstrated that D_2 values, calculated

from EEG, were significantly lower in AD patients than in controls. These results were confirmed by Jelles *et al.* [10]. Abatzoglou *et al.* [19] showed that AD is associated with a decrease in the dimensional complexity of MEG activity. Nevertheless, other MEG study found that the variations reflected by D_2 were in opposite directions in different frequency bands [20]. Besthorn *et al.* [21] suggested that the dimensional complexity reduction is correlated with the severity dementia. In other research work, EEGs obtained from probable AD patients, autopsy-confirmed AD patients and controls were analysed by means of FD [44]. Significant differences were found between the AD groups and the control group, and also between probable and autopsy-confirmed patients [44]. Finally, Lempel-Ziv complexity provided lower values in AD patients' MEGs [45]. This complexity decrease may be due to two cerebral mechanisms: a general effect of neurotransmitter deficiency and connectivity loss of local neural networks as a result of nerve cell death [10].

The mean HFD values averaged over all channels were analysed by means of a ROC curve, using a leave-one-out cross-validation procedure. An accuracy of 87.8% (80% sensitivity; 95.24% specificity) was reached. Additionally, we explored the ability of HFD to classify the MEGs from AD patients and controls at five brain areas (anterior, central, left lateral, posterior and right lateral). In previous papers, non-linear methods and ROC curves have been employed to classify MEG signals from AD patients and control subjects. For instance, an accuracy of 83.3% was obtained with Lempel-Ziv complexity [45]. The accuracy was slightly lower (82.9%) when the auto-mutual information decrease rate was analyzed [46]. Despite the highest precision was achieved with HFD , all these values should be taken with caution due to the small sample sizes.

Some limitations of our study merit consideration. Firstly, the sample size is small. To prove the usefulness of HFD as a diagnostic tool, this approach should be extended on a larger patient population before any conclusion can be made of its clinical diagnostic value.

Moreover, the detected decreased in complexity is not specific to AD and it appears in other neurodegenerative diseases. Future efforts will be addressed to characterize the MEG background activity in AD and in other types of dementia. Additionally, the results obtained were averaged grouping the sensors in five brain areas to simplify the analyses. This issue involves a loss of spatial information. Finally, Higuchi's algorithm requires stationary MEG epochs to estimate the *FD* appropriately. However, *HFD* may be a suitable method to analyse physiological signals, since it can be applied to relatively short time series.

In summary, non-linear analysis of the MEG background activity with *HFD* showed a decrease in the dimensional complexity of AD patients' MEGs. The differences between AD patients and elderly control subjects were statistically significant in 71 channels. Our findings suggest that neuronal dysfunction in AD is associated with a decrease dimensional complexity in MEG signals.

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Tables

Table 1. Sensitivity, specificity and accuracy values obtained at each brain region with *HFD*, using a leave-one-out cross-validation procedure. The areas under the ROC curves (AROCs) and their respective 95% confidence intervals (CIs) are also showed.

Brain region	Sensitivity	Specificity	Accuracy	AROC	AROC CI (95%)
All channels	80.00%	95.24%	87.80%	0.90	0.79-1.00
Anterior	85.00%	76.19%	80.49%	0.86	0.74-0.98
Central	70.00%	90.48%	80.49%	0.87	0.75-0.99
Right lateral	85.00%	80.95%	82.93%	0.89	0.77-1.00
Posterior	70.00%	80.95%	75.61%	0.89	0.78-0.99
Left lateral	75.00%	76.19%	75.61%	0.89	0.79-0.99

Figure legends

Fig. 1. Example of MEG time series from an AD patient.

Fig. 2. Average *HFD* values from MEGs in AD patients and control subjects.

Fig. 3. Illustration of sensor grouping into five brain regions: anterior, central, left lateral, posterior and right lateral.

Fig. 4. ROC curves showing the discrimination between AD patients and controls with the *HFD* mean values (a) over all channels and at the following brain regions: (b) anterior, (c) central, (d) left lateral, (e) posterior and (f) right lateral.

FIGURE 1

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