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Electroencephalogram Hybrid Method for Alzheimer Early Detection

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Abstract

Alzheimer's disease (AD) is a neurocognitive illness that leads to dementia and mainly affects the elderly. As the percentage of old people is strongly increasing worldwide, it is urgent to develop contributions to solve this complex problem. The early diagnosis at AD first stage known as Mild Cognitive Impairment (MCI) needs a better accuracy and there is not a biomarker able to detect AD without invasive tests. In this study, Electroencephalogram (EEG) signals have been used to serve as a way of finding parameters to improve AD diagnosis in first stages. For that, a hybrid method based on a Cepstral analysis of EEG Discrete Wavelet Transform (DWT) multiband decomposition was developed. Several Cepstral Distances (*CD*) were extracted to verify the lag between cepstra of conventional bands signals. The results showed that this hybrid method is a good tool for describing and distinguishing the AD EEG activity along its different stages because several statistically significant parameters variations were found between controls, MCI, moderate AD and advanced AD (the lowest p-value=0.003<0.05).

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Keywords: Alzheimer's Diasease; Early Diagnosis, Cepstral Analisys; Wavelet Transform; Electroencephalogram signals; Cepstral distances;

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1. Introduction

Alzheimer's disease (AD) is a neurodegenerative and progressive illness. This until now incurable disease mostly affects adults over the age of 60 and is the main cause of dementia among old people. Nowadays, it is estimated that there are 46.8 million people with dementia in the world [1]. But, also according to [1], this number will double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050, and the majority of those cases will come from AD cases. A characteristic of AD is that it progresses inexorably. Once its diagnosis is established, the patient's life expectancy is usually around 8 to 10 years [2]. The patients' memory, cognition, language, learning, judgment and behaviour are progressively destroyed. Neurons and their connections degenerate and die, causing brain atrophy and overall decline in mental functions [3]. Its cause is unknown but it is believed that accumulation of a protein called β-amyloid and another called tau in neurons is the factor responsible for triggering the disease [4].

The AD diagnosis accuracy at its first stage - Mild Cognitive Impairment (MCI) - has been relatively low. Furthermore, the current diagnosis exams available in the clinical environment are invasive and present secondary harmful effects to the patients' health. However, it is known that an effective diagnosis can support early treatments and preserve the intellectual capacities for much longer [4] so research for improvement of early detection accuracy is needed. As EEG is a non-invasive and relatively cheap technique, it would be convenient that a more preponderant role could be established for its use in AD diagnosis than has been observed in the last decades. Conventionally, the EEG is divided in 5 different frequency bands: delta (δ, 1-4 Hz), theta (θ, 4-8 Hz), alpha (α, 8-16 Hz), beta (β, 16-32 Hz), and gamma (γ, >32 Hz) and AD seems to affect the signal energy in all these different bands [5]. The major effect is known as the EEG "slowing", that means an increase of power in low frequency bands such as δ and θ, and a decrease of power in higher frequency bands such as α, β and γ [5]. Therefore, the potential of use of EEG signals in support of AD diagnosis lies in the enhancement of the detection capacity of this phenomenon.

From the previous results in advanced AD identification [6], in the present study, the authors intend to verify the power of the combination of the Wavelet Transform (WT) and the Cepstral analysis, as a hybrid tool, for describing and distinguishing the abnormalities in EEG activity associated with AD in early stages.

This paper is organized as follows: in section 2, the study participant's selection, the EEG recording, the applied signal processing technique and the extracted features are detailed and it ends with the statistical description and analysis of the results. Section 3 presents the study conclusions.

2. Dataset and Methodology

A set of 38 subjects participated in this study: 11 as Controls (C), 8 with MCI, 11 with moderate AD (ADM) and 8 with advanced AD (ADA). EEGs were recorded from the 19 scalp loci of the International 10-20 configuration using a digital electroencephalograph and with the eyes closed in Hospital de São João - Porto, Portugal and all participants gave their consent prior to participating in this study. The protocol was approved by the local Ethics Committee. The sampling frequency was 256 Hz, and all recordings were digitally filtered with a band-pass filter with cut-off frequencies of 1 and 40Hz. In Table 1, additional information is provided regarding the participants in each group, including the average age and the average result of Mini-Mental State Examination (MMSE). All EEG were organized in segments of 5s (1280 epochs).

Table 1. *The dataset used in this study*

	Control Subjects	**MCI Patients**	**ADM Patients**	**ADA Patients**
#	11	8	11	8
Age (average)	74	80	79	79
MMSE (average)	28,68	26,29	18,89	11,50

The proposed methodology consists of four steps, as illustrated in Fig 1. The first two steps comprise the EEG signal processing hybrid method, which performs a cepstral analysis over a DWT decomposition. The WT is a processing tool that provides a good time resolution for the high frequencies and good frequency resolution for low frequencies, aspects that are very welcome for processing EEG signals because the target frequencies bands are localized in low frequencies, while the *Cepstrum* is a good tool for checking the time lags between replicas in conventional frequency bands. The last two steps perform the features extraction and the statistical analysis between study groups.

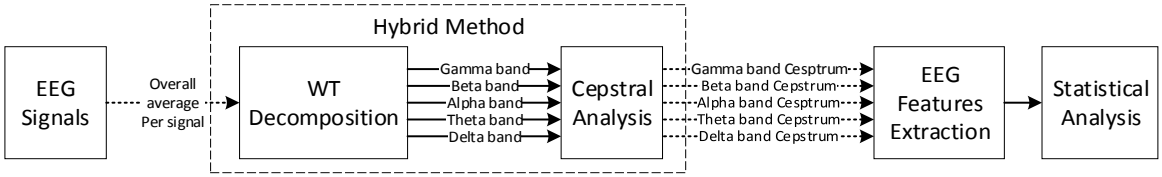

Fig. 1. Methodology description

2.1. The Discrete Wavelet Transform

The Discrete Wavelet Transform (*DWT*) provides a multiresolution analysis that consists in obtaining progressively, by successive filtering, smaller signal resolution versions. The *DWT* uses a set of two functions: a scale function ($\varphi[n]$) and a Wavelet function ($\psi[n]$) [7].

$$\varphi[n]=\sum_k h[k]\cdot\varphi[2\cdot n-k] \tag{1}$$

$$\psi[n]=\sum_k g[k]\cdot\varphi[2\cdot n-k] \tag{2}$$

where k is the discrete translation parameter, and $h[k]$ and $g[k]$ are, respectively, the impulse responses of the low-pass and high-pass filters used in the *WT* analysis. The signal decomposition into different frequency bands is achieved by successive low-pass filters and high-pass filters applied in the time domain, followed by subsampling by a factor of two until the maximum level of decomposition ($\log_2(N)$) is reached, as is indicated in equations 3 and 4 [7].

$$DWT_A^{\varphi}[j,k]=\sum_{n=0}^{\frac{N}{2^{(j-1)}}} DWT_A^{\varphi}[j-1,n]\cdot h[2\cdot k-n] \tag{3}$$

$$DWT_D^{\psi}[j,k]=\sum_{n=0}^{\frac{N}{2^{(j-1)}}} DWT_A^{\psi}[j-1,n]\cdot g[2\cdot k-n] \tag{4}$$

where k=0, ..., N/(2^j); j=0, ..., $log_2(N)$, N is the signal length, and A and D represent the DWT approximated and detail coefficients [7], respectively.

2.2. Cepstral Analysis

Cepstral analysis is a signal analysis technique based on a homomorphic transformation called cepstrum. The cepstrum enables two or more signals deconvolution in the time-domain. It was proposed in 1963 by Bogert, Healy and Tukey for detecting echoes in seismic signals [8]. So, the cepstrum is useful to separate source and filter components which is one of the main reasons why it is highly applied for instance in speech signal processing.

The real cepstrum is defined as the inverse Discrete Fourier Transform (*DFT*) of the signal's *DFT* log magnitude, as defined in eq. (5),

$$c_i = c_j = IDFT(\log(|\,DFT(x_i(n))\,|)) \tag{5}$$

where $i=j=\{\delta,\theta,\alpha,\beta,\gamma\}$, $x_i(n)$ represents, in the actual application, each EEG conventional bands signals obtained by the WT multiband decomposition process [6].

2.3. EEG Features Extraction

Each EEG signal of the study participants was subjected to a global average (average between electrodes followed by a segments average) and the resulting signals (one for each study participant - 11 Controls, 8 MCI, 11 ADM and 8

ADA) were decomposed by 4 different kinds of WT families bases (Biorthogonal 3.5, Symlet6, Coiflet6 and Daubechies6). The WT decomposition was made until the level 5, which is the correct level of EEG signal decomposition to reach the conventional frequency bands of EEG (δ, θ, α, β and γ bands), as illustrated in the Fig. 2.

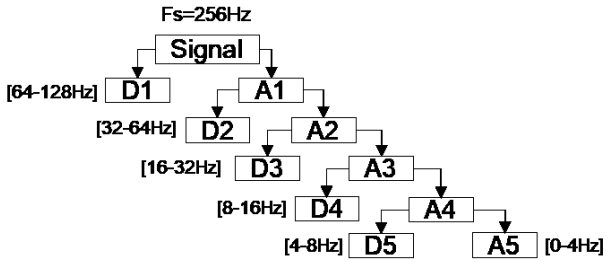

Fig. 2. EEG Wavelet Multiband Decomposition

The signals resulting from the decomposition in the bands δ, θ, α, β and γ correspond to the coefficients $A5$, $D5$, $D4$, $D3$ and $D2$ of the DWT decomposition, respectively. Each EEG conventional signal band was reconstructed in time domain with the same length of the original EEG signal segment through the Wavelet Based Interpolation Method. After computed the real cepstrum of each EEG conventional band, the following cepstral distances (*CD*) were calculated as features:

- The smoothed distance between two cepstra [6]:

$$CD1_{i,j} = l * \sqrt{\left(\left(c_i(1) - c_j(1)\right)^2 + p * \sum_{n=2}^{N} \left(c_i(n) - c_j(n)\right)^2 \right)}; \quad (6)$$

where, l and p are the smoothed distance normalization factors, N is the cepstral signal length, c_i and c_j are the cepstra signals and $i=j=\{\delta,\theta,\alpha,\beta,\gamma\}$;

- The smoothed distance between two cepstra without the first cepstral coefficient [6]:

$$CD2_{i,j} = l * \sqrt{\left(p * \sum_{n=2}^{N} \left(c_i(n) - c_j(n)\right)^2 \right)}; \quad (7)$$

- The Euclidian distance between two cepstra vectors [6]:

$$CD3_{i,j} = \sqrt{\sum_{n=1}^{N} \left(c_i(n) - c_j(n)\right)^2}; \quad (8)$$

- Weighted Euclidian distance between two cepstra vectors [6]:

$$CD4_{i,j} = \sqrt{\left(\sum_{n=1}^{N} w(n) * \left(c_i(n) - c_j(n)\right)^2 \right)}; \text{where } w = [1, N] \quad (9)$$

- Non-linear weighted distance of two cepstra vectors [6]:

$$CD5_{i,j} = \sqrt{\left(\sum_{n=1}^{N} \sqrt{w(n)} * \left(c_i(n) - c_j(n)\right)^2 \right)}; \text{where } w = [1, N] \quad (10)$$

- Exponentially weighted distance of two cepstra vectors [6]:

$$CD6_{i,j} = \sqrt{\left(\sum_{n=1}^{N} w(n) * w(n) * \left(c_i(n) - c_j(n)\right)^2 \right)}; \text{where } w = [1, N] \quad (11)$$

All the features vectors (V) were normalized as follows:

$$V(i) = \frac{V(i) - med}{std} \quad (12)$$

where,

$$std = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(V(i) - med)^2} \quad (13)$$

$$med = \frac{\sum_{i=1}^{N} V(i)}{N} \quad (14)$$

std is the sample standard deviation; *med* is the V mean value and N is the V samples number.

2.4. Statistical Analysis and results

The *CD* parameters homoscedasticity was accessed with the Levene's test and the normality with the Kolmogorov-Smirnov test. As the data distributions did not meet the parametric tests hypotheses, the differences between groups were analyzed by using Kruskal-Wallis test (p<0.05). As statistical differences between groups were only found when δ/θ, θ/α and α/γ bands were compared, the analysis have been focused just in those bands (see Table 2, Table 3 and Table 4). For each feature, the best-achieved p-values are represented in bold in Tables 2, 3 and 4.

Despite the highly significant differences found in *CD* between the θ/α and α/γ, it can be seen that the lowest p-value was reached with *CD* between band δ and band θ ($CD2_{\delta,\theta}$ and $CD3_{\delta,\theta}$). The "*shift-to-the-left*" effect, also known as the "EEG slowdown" phenomenon, can be a possible hypothesis to explain those results because, as the disease progresses, the power in high frequencies tends to be progressively transmitted to the low frequencies, thereby increasing the energy in lower frequencies and decreasing the energy in higher frequencies. This phenomenon involves a loss of neurotransmitter acetylcholine and it is detected since AD appears (MCI). As in previous studies [6, 9], the Biorthogonal *WT* showed the highest performance to emphasize the EEG AD activity and its combination with the cepstrum demonstrated to provide higher discrimination parameters than in a previous study [9] (p=0.0030 *vs.* p=0.0035). Therefore, these results show that the cepstrum has the propriety to emphasize the differences between groups separated by the *WT*. It was also found that *CD*4 and *CD5* do not allow to identify AD in different stages (p>0.05 in all statistical tests). The *CD2* and *CD*3 proved to be promising parameters to identify AD in different stages as they provided the lowest p-values. However, *CD1* and *CD6* are also good parameters as a p<0.05 was found for those distributions. Differences between groups, in α/γ bands comparisons, were only achieved in *CD6* parameters distributions. This demonstrates that *CD*6 is useful to find differences in AD activity over different stages in higher frequencies.

Table 2. Kruskal-Wallis test p-values for *CD* between δ and θ bands

WT base family band reconstruction	**Features**					
	$CD1_{\delta,\theta}$	$CD2_{\delta,\theta}$	$CD3_{\delta,\theta}$	$CD4_{\delta,\theta}$	$CD5_{\delta,\theta}$	$CD6_{\delta,\theta}$
Biorthogonal 3.5	**0,0051**	**0,0030**	**0,0030**	N.S	N.S	**0,0041**
Symlet6	0,0272	0,0099	0,0099	N.S	N.S	0,0171
Coiflet6	0,0252	0,0148	0,0148	N.S	N.S	0,0129
Daubechies6	0,0494	0,0242	0,0242	N.S	N.S	0,0213

N.S. – Not significant

Table 3 Kruskal-Wallis test *p*-values for *CD* between θ and α bands

WT base family band reconstruction	**Features**					
	$CD1_{\theta,\alpha}$	$CD2_{\theta,\alpha}$	$CD3_{\theta,\alpha}$	$CD4_{\theta,\alpha}$	$CD5_{\theta,\alpha}$	$CD6_{\theta,\alpha}$
Biorthogonal 3.5	**0,0158**	**0,0084**	**0,0084**	N.S	N.S	**0,0048**
Symlet6	N.S.	N.S.	N.S.	N.S	N.S	0,0171
Coiflet6	0,0364	0,0203	0,0203	N.S	N.S	0,0102
Daubechies6	N.S.	0,0297	0,0297	N.S	N.S	0,0296

Table 4. Kruskal-Wallis test *p*-values for *CD* between α and γ bands

WT base family band reconstruction	**Features**					
	$CD1_{\alpha,\gamma}$	$CD2_{\alpha,\gamma}$	$CD3_{\alpha,\gamma}$	$CD4_{\alpha,\gamma}$	$CD5_{\alpha,\gamma}$	$CD6_{\alpha,\gamma}$
Biorthogonal 3.5	N.S	N.S	N.S	N.S	N.S	**0,0276**
Symlet6	N.S	N.S	N.S	N.S	N.S	0,0383
Coiflet6	N.S	N.S	N.S	N.S	N.S	0,4886
Daubechies6	N.S	N.S	N.S	N.S	N.S	0,1316

3. Conclusion

AD remains incurable until today and patients usually start treatments when they already have significant symptoms, because it is difficult to get an accurate early AD diagnosis that can raise the chances in order to reduce the effects of AD progresses.

This study presents a further contribution in the search for new parameters of AD detection based on the EEG in order to increase its value as a diagnosis tool in early stages. This work showed that the *WT* and cepstrum combination, as a hybrid method, provided a valuable tool to obtain good features for AD early detection in the EEG. In short, the authors of this study processed the global average of each EEG signal of the study groups with the *WT* to get each of that signal's reconstructed conventional bands components. After that, each conventional band component was submitted to a cepstral analysis in order to evaluate the lags between the conventional bands. Significant differences were found in *CD* between δ/θ, θ/α and α/γ bands, namely *CD1*, *CD2*, *CD3* and *CD6*. It was concluded that two features $CD2_{\delta/\theta}$ and $CD3_{\delta/\theta}$ have high discriminative power to identify AD over its different stages (p=0.003<0.05).

In a previous study [6], the cepstrum applied to the WT multiband decomposition showed already to be a good tool for helping in ADA identification. In the present study, the same hybrid tool was also applied, but this time with an AD early stages detection aim and it revealed capability to emphasize the AD activity over its different stages. Finally, the results should be extended to a larger population to ensure generalization.

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